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

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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.

$$X_t = R \cdot X_{t-1} \cdot (1-X_{t-1}) \qquad \text{Eq. 1}$$

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: $\varepsilon_t \sim N(0,\sigma^2)$.
- 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).

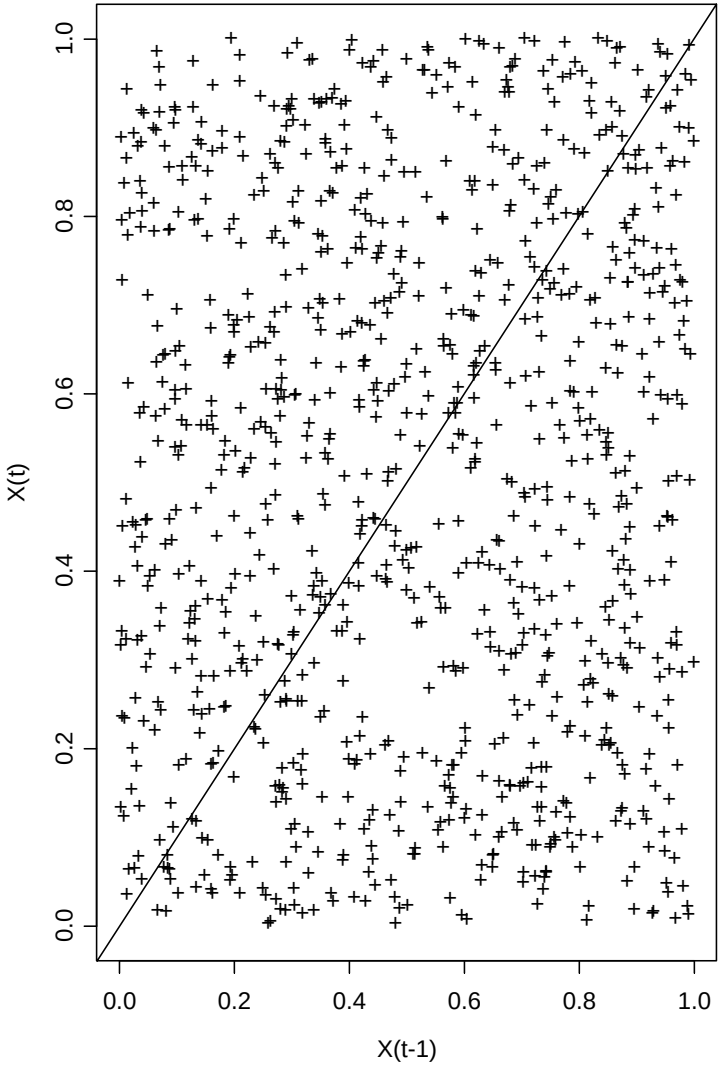
Simulation Results

- 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

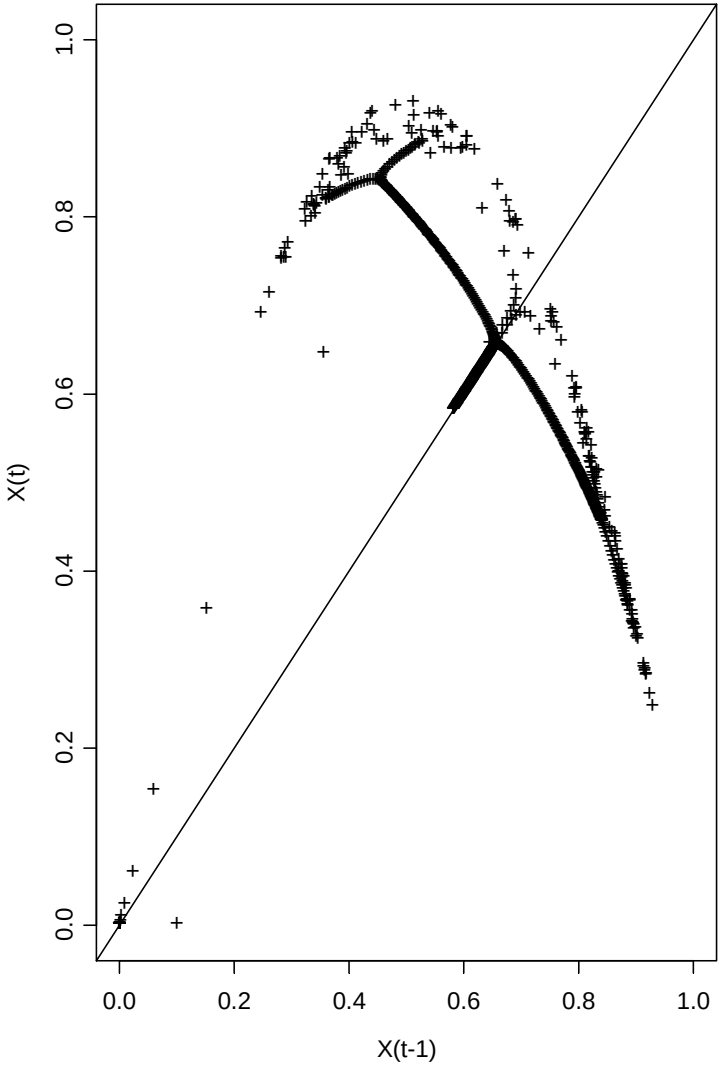
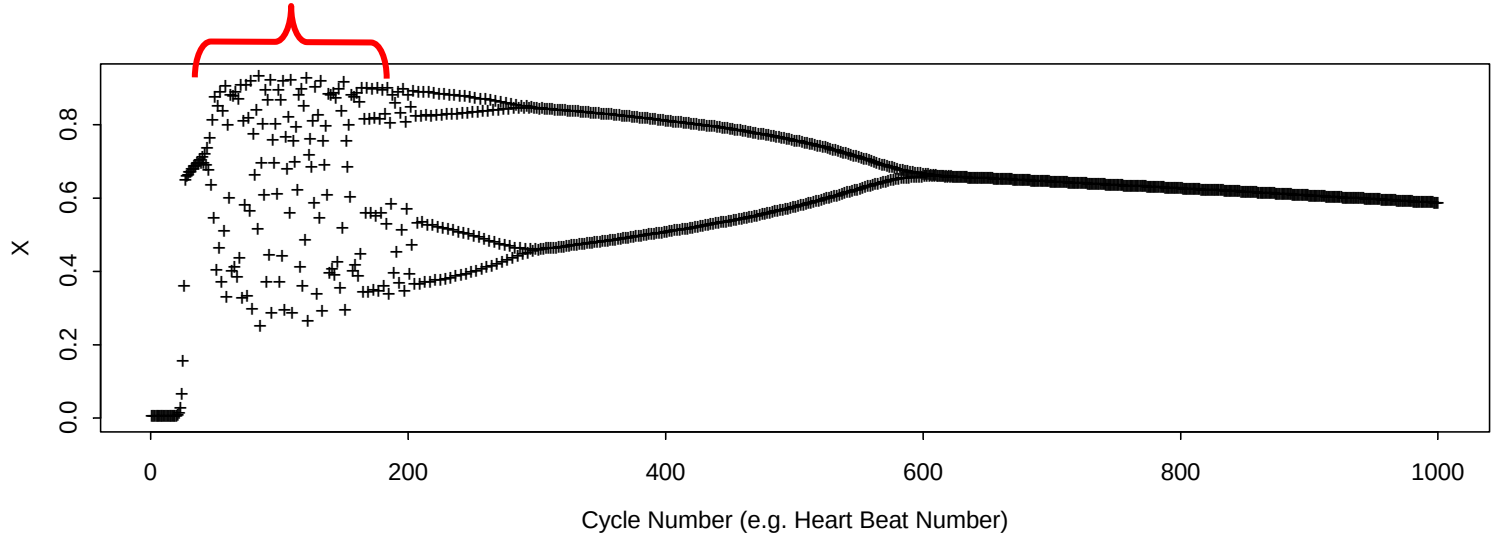
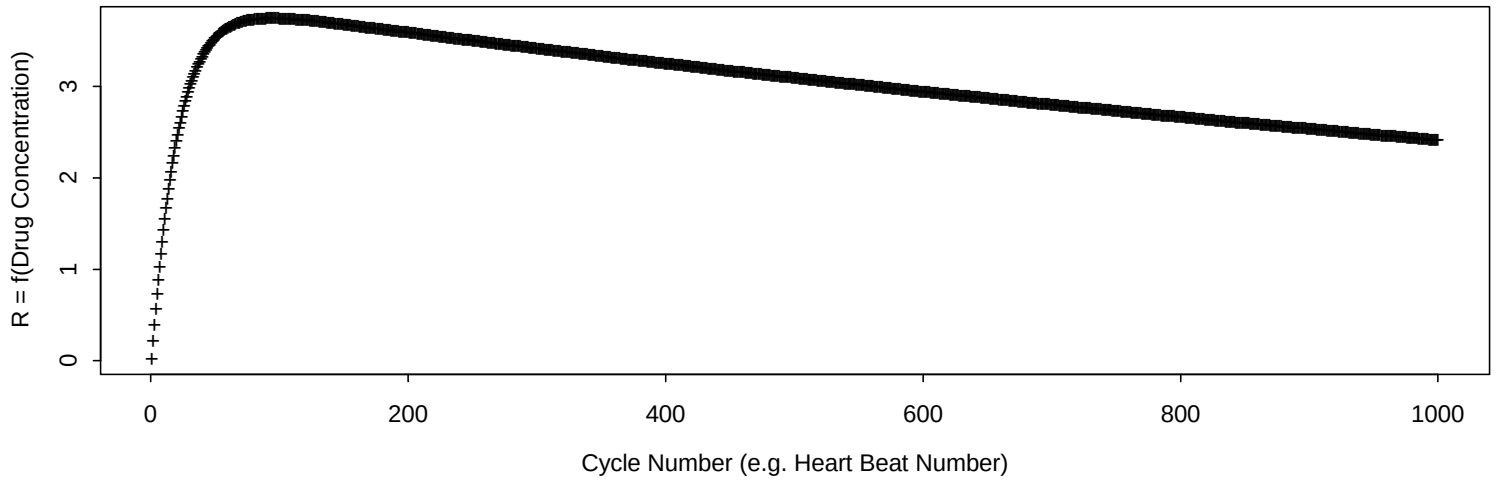


Figure 2: Simulated Data Without Noise

chaotic state (e.g. arrhythmia)





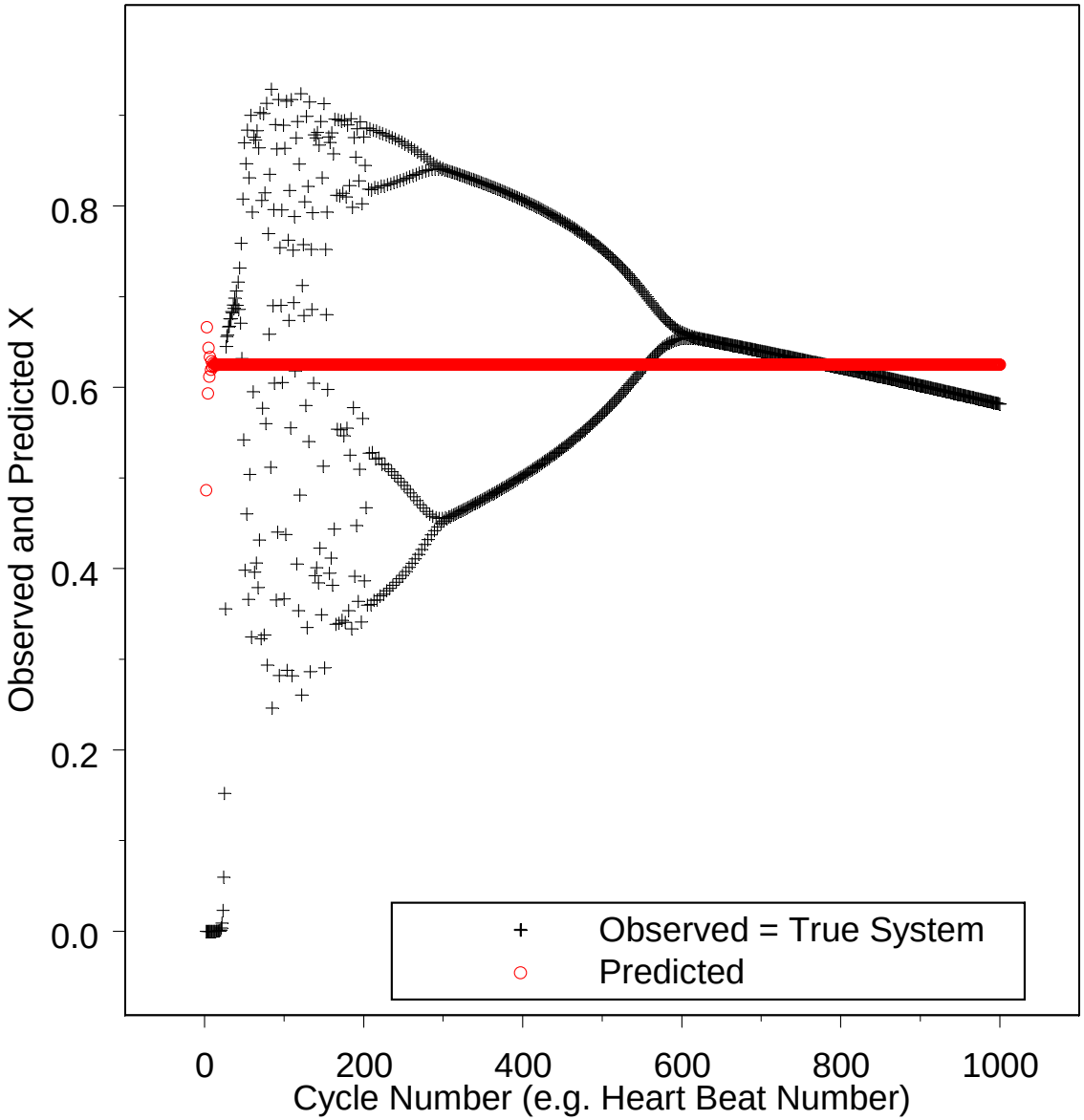
Estimation Results: Model Fit

- 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.

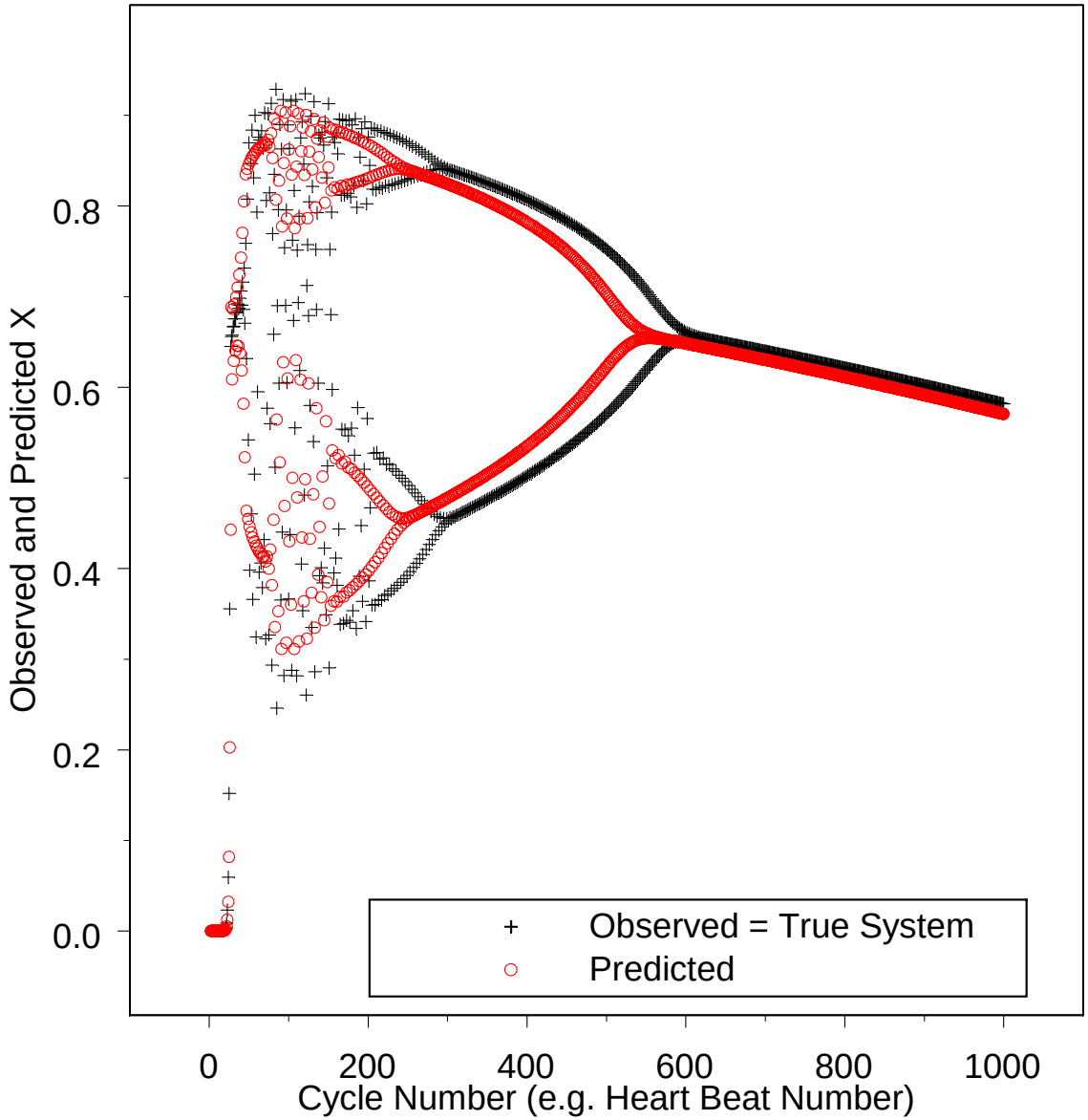
- The predicted response was generally in good agreement with the underlying system data at low to moderate levels of residual variability ($\sigma^2 \leq 0.01$), but the PD system behavior was lost in both the observed and predicted response when measurement noise was large ($\sigma^2 = 0.1$).

Figure 3: No Drug Effect ($\sigma^2 = 0$)



005dvpredvt.wmf

Figure 4: PD Model Fit ($\sigma^2 = 0$)



003dvpredvt.wmf

Figure 5: PD Model Fit ($\sigma^2 = 0.001$)

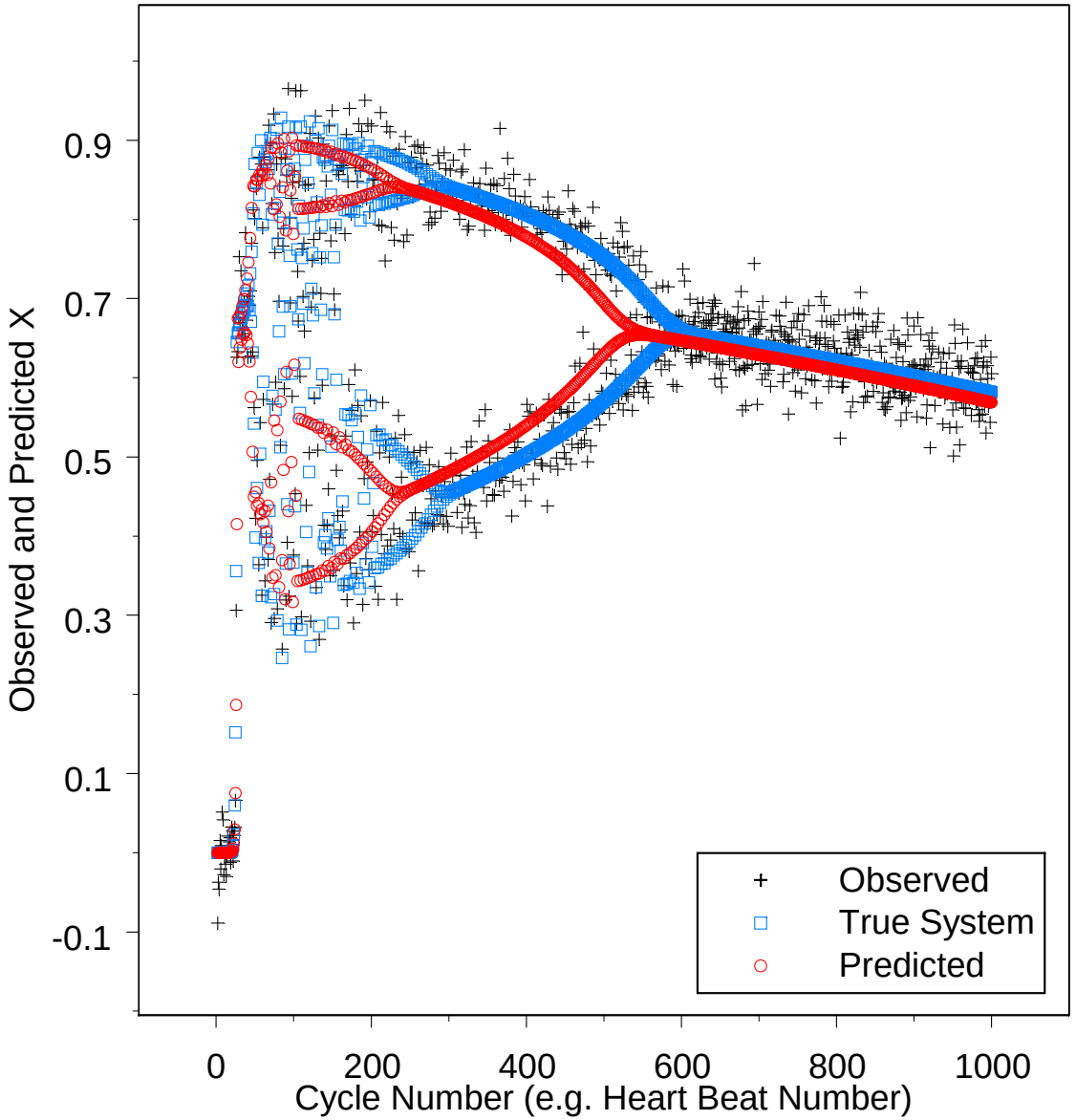


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Figure 6: PD Model Fit ($\sigma^2 = 0.01$)

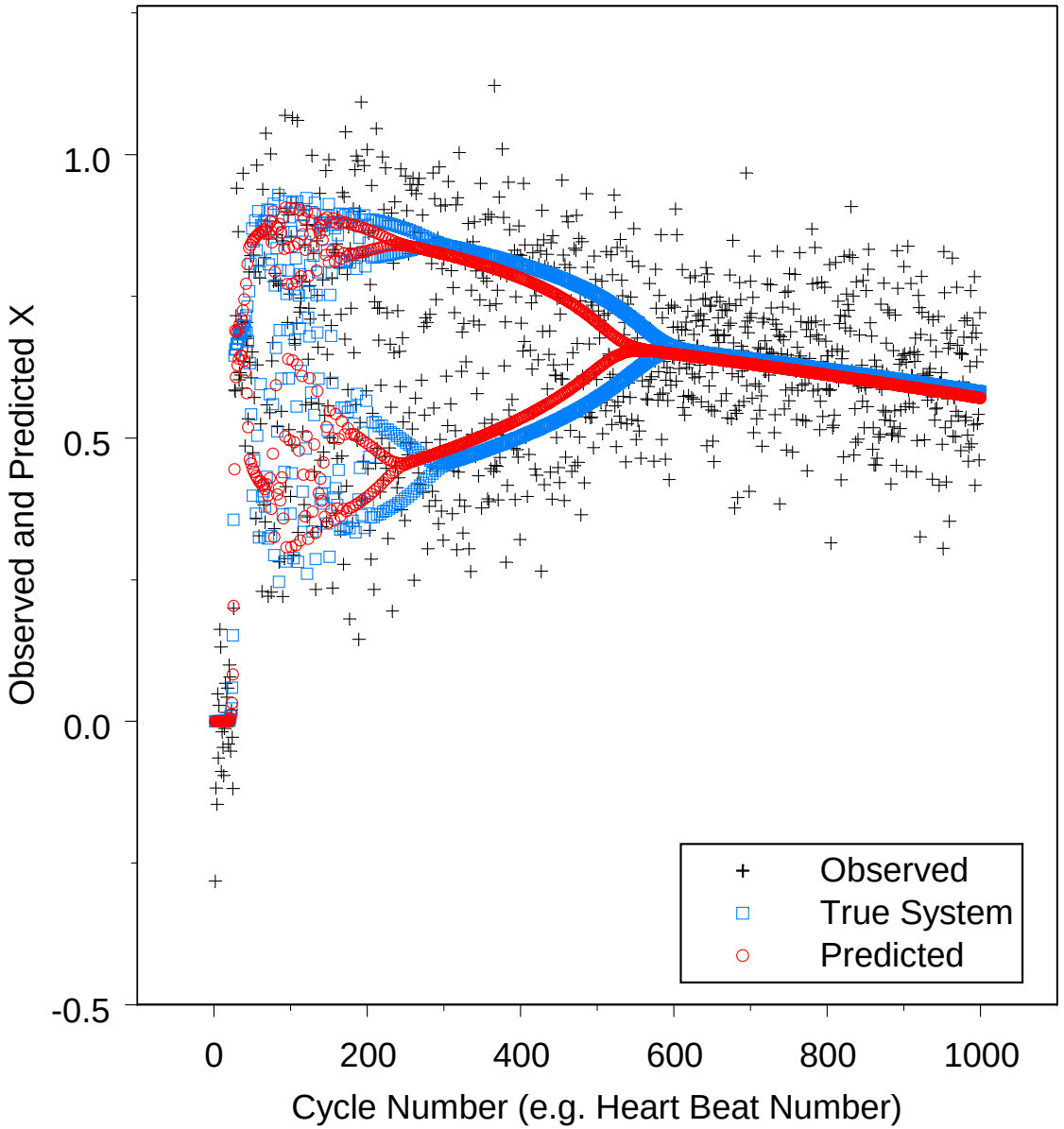

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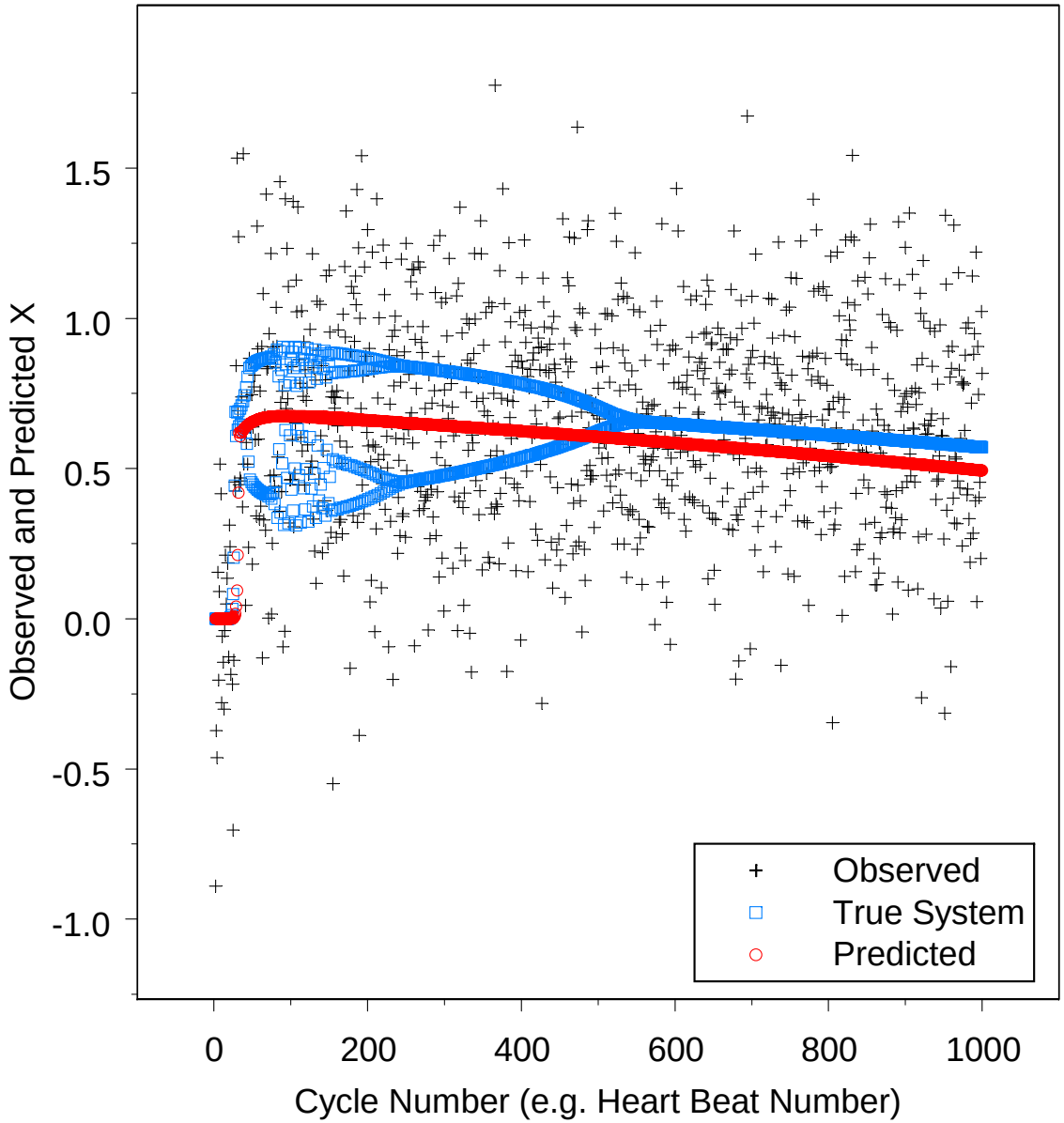
Figure 7: PD Model Fit ($\sigma^2 = 0.1$)



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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

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

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 (σ^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.

NMTRAN Control Stream

```
$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 …
```

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