

Validation methods to check the estimations with stochastic sampling approach

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Various estimation methods of pop PK/PD

There are several approaches to estimate parameters in population PK/PD model.

- based on approximation of the likelihood
 - FO / FOCE / Laplacian method
- based on the “exact” likelihood with stochastic sampling (MCMC)
 - IMP / IMPMAP / SAEM / BAYES

What is stochastic sampling?

- developed to sample from very complex distribution, like the posterior density $p(\theta|\text{data})$ in Bayesian analysis
- Markov Chain Monte Carlo (MCMC) is the most popular way
 - Metropolis-Hastings algorithm / Gibbs sampling algorithm
- very useful technique to solve complex integration form without linearization or to find optimal values of complex function
 - Monte Carlo integration / Monte Carlo optimization
- need to check convergence to stationarity distribution and convergence of average
- need to have multiple chain with different initial values.
- sometimes take every M samples for independency

How to check convergence to stationarity and convergence of average

1. Graphical diagnoses

- time series plot for randomness and stationarity, density plot for convergence of averages, ACF plot for dependency, confidence band plot for the stabilization of the empirical cdf.

2. Heidelberger and Welch test (Heidelberger and Welch, 1983)

- test whether the empirical distribution is stationarity using Carmer-von Mises statistic

3. Geweke statistic (Geweke, 1992)

- should follow $N(0,1)$ under stationarity condition

4. Effective size (Heidelberger and Welch, 1983 and Geweke, 1992)

- an indication about the loss in efficiency due to the use of a Markov chain

5. Shrink factor (Gelman and Rubin, 1992)

- check the dispersion of the initial distribution
- far from 1 shows that the chains have not yet covered the same region

6. Kolmogorov-Smirnov test

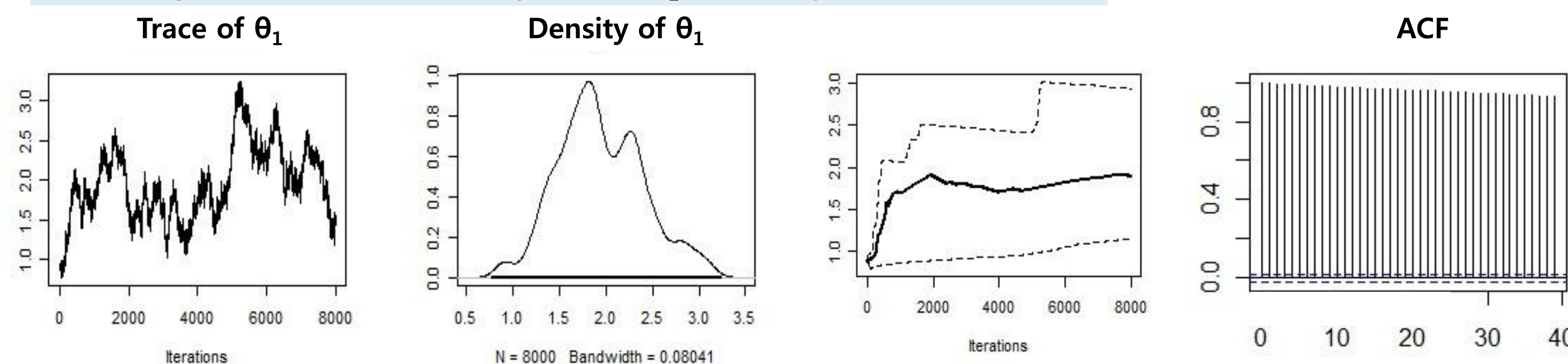
- compare the distributions of two sequences
- to remove dependency, compare the distributions of two following sequences $\{\theta_1^{(G)}, \theta_1^{(2G)}, \dots, \theta_1^{(MG)}\}$ and $\{\theta_2^{(G)}, \theta_2^{(2G)}, \dots, \theta_2^{(MG)}\}$

Example

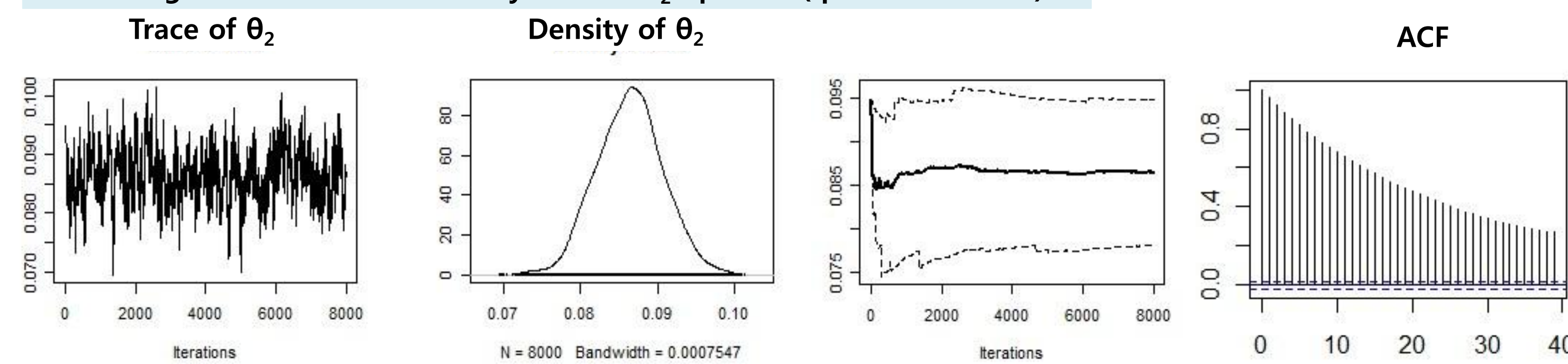
- Use CONTROL5 (Theophylline) in NONMEM
- \$EST METHOD=BAYES INTER PRINT=1

I. single chain

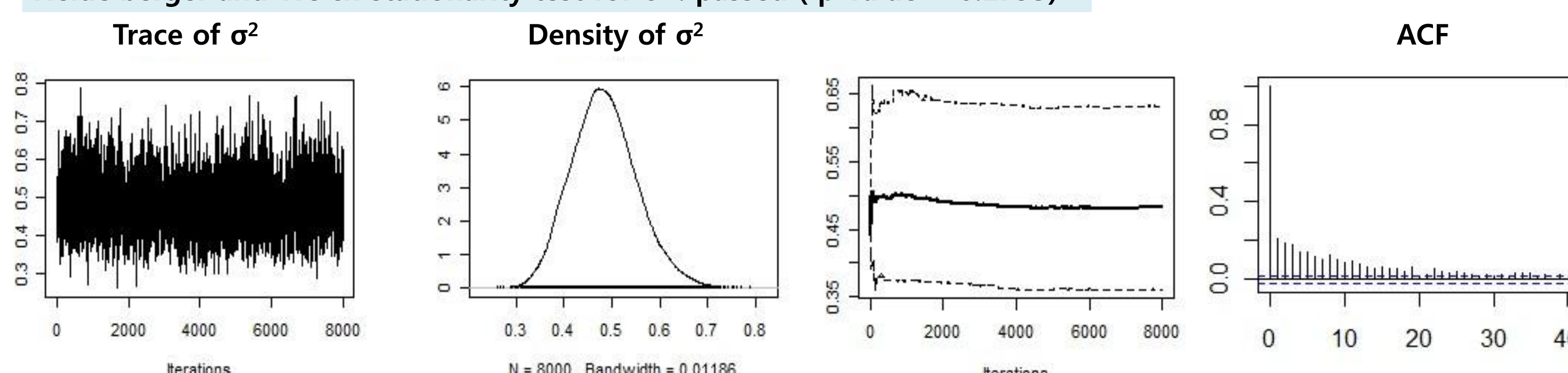
Heidelberger and Welch stationarity test for θ_1 : failed (p-value = 0.000012)



Heidelberger and Welch stationarity test for θ_2 : passed (p-value = 0.774)



Heidelberger and Welch stationarity test for σ^2 : passed (p-value = 0.1795)



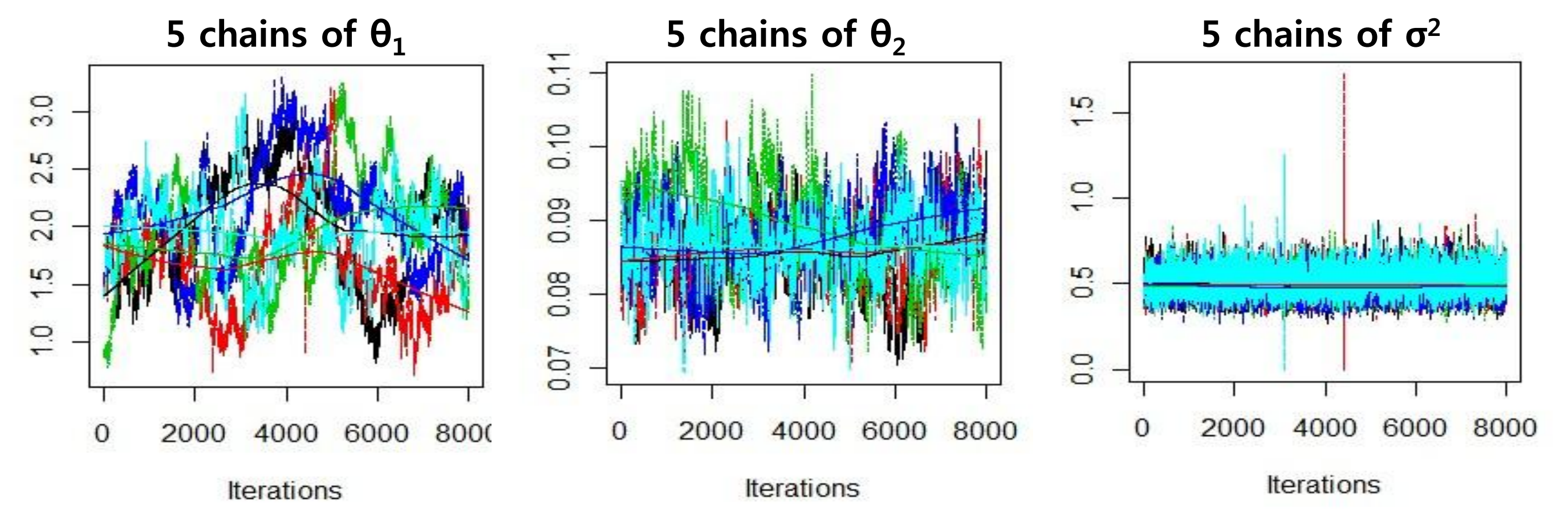
II. Multiple chains with different initial values

- use different seed in NONMEM

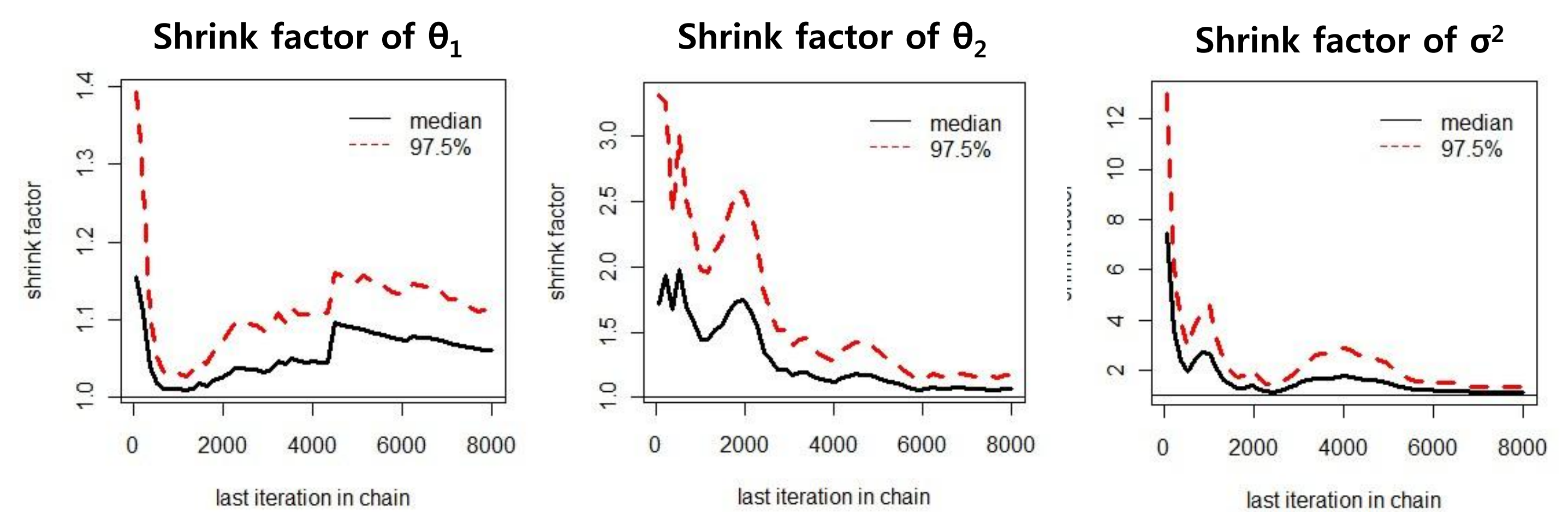
1. Numerical result

	θ_1			θ_2			σ^2		
	H-W stationarity test	Geweke statistic	Effective size	H-W stationarity test	Geweke statistic	Effective size	H-W stationarity test	Geweke statistic	Effective size
Chain1	Failed	NA	5.41	Passed	0.1563	88.09	passed	2.6795	1218.64
Chain2	Failed	1.044	10.74	Passed	-1.7601	127.54	passed	-0.3351	1714.93
Chain3	Failed	NA	7.39	Failed	9.2622	32.39	passed	0.5919	1051.27
Chain4	Failed	-1.649	5.97	Failed	-4.7658	90.51	passed	3.4833	1310.94
Chain5	passed	-2.076	25.47	passed	-0.2827	159.80	passed	-3.1138	2598.80

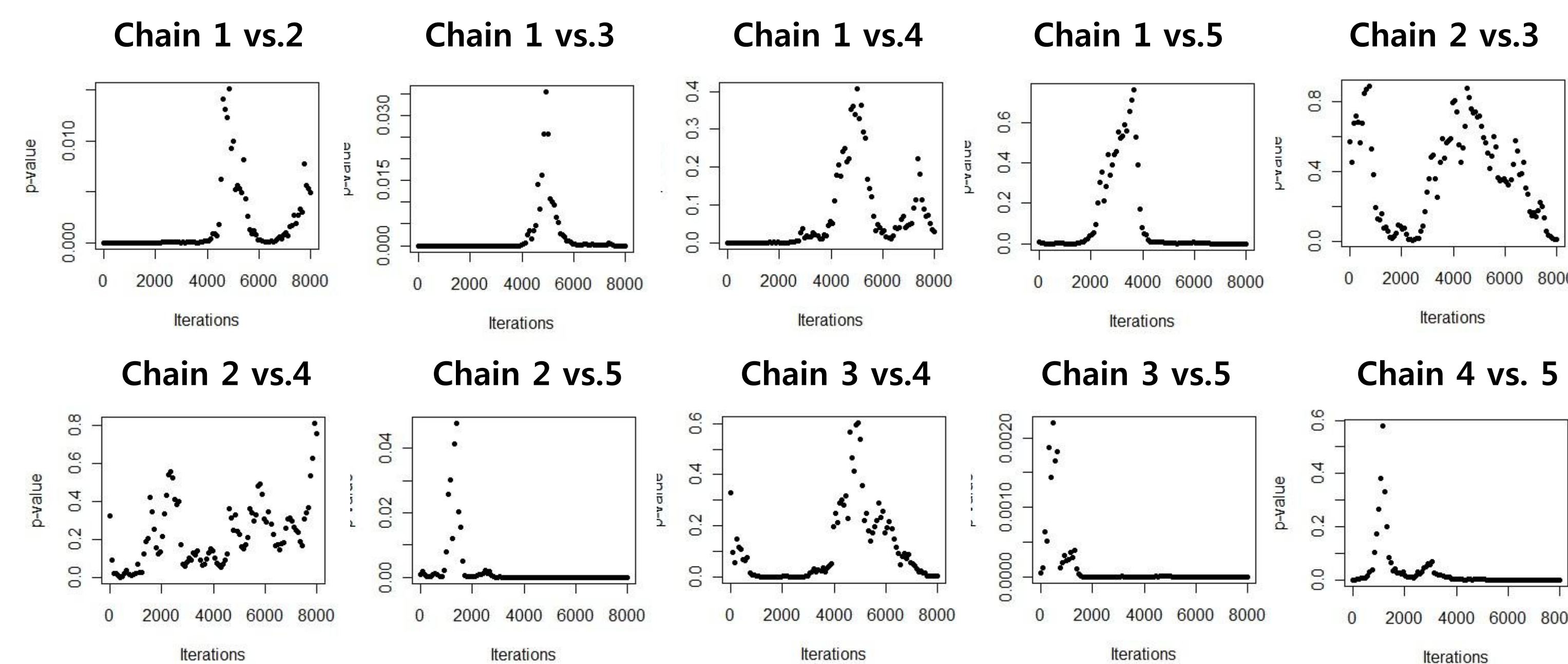
2. Graphical result



3. Shrink factor



4. Kolmogorov-Smirnov test



Discussion

- use coda package in R
- for stochastic sampling method, need to check sufficient burn in period, stationarity, and convergence for the estimations with various validation methods
- recommend to use multiple chains with different initial values

fit4NM

- fit4NM is a model building aid tool for population PK/PD analysis using NONMEM. It provide all the procedures for PKPD modeling, from data manipulation to model evaluation.
- It is written in R and available from <http://www.fit4NM.org>
- It provides its own GUI to help naïve user use this tool without any knowledge about R.
- Methods to check the estimations with stochastic sampling approach will be implemented in fit4NM.

References

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