

A unified parametric/nonparametric approach to population PK/PD modeling

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Abstract

Currently the most popular computational methods for PK/PD population modeling are based on a parametric maximum likelihood (ML) approach that assumes normality or lognormality for the underlying population distribution. In order to reduce computational requirements to reasonable levels, these direct parametric methods make approximations in the computation of the likelihood function that significantly compromise statistical consistency. We have often observed, for example, that such methods introduce artificial correlations between population parameters.

Nonparametric ML methods, such as the NPEM and NPAG programs from our laboratory, have obvious advantages for situations where unimodal parametric distributions may be unrealistic, such as multimodal populations of fast and slow metabolizers. Here it is shown that nonparametric ML methods can also be advantageously applied to the unimodal parametric case to obtain consistent parametric estimators that avoid the difficulties caused by likelihood approximations.

Nonparametric ML methods produce distribution estimators that can be interpreted as a set of direct observations of the PK/PD parameters for a finite set of virtual subjects, even though there are no such direct observations in the available data. If the nonparametric ML problem is solved exactly, i.e. a global maximum to the likelihood function is found, then the means and covariances of these virtual direct observations are in fact consistent estimators of the means and covariances of an assumed normal or lognormal parametric distribution.

We have recently combined the use of adaptive grids with a primal-dual interior-point algorithm to obtain such globally optimal nonparametric solutions with no introduced approximations. In many cases this can now be done on a single-processor PC, whereas previous nonparametric methods based on the EM algorithm often required a supercomputer to obtain the necessary accuracy. By the simple extension mentioned above, a computationally efficient and statistically consistent common method for both the parametric and nonparametric PK/PD population problems is obtained.

Examples using both simulated and real data are given to illustrate the method.

Parametric Population Methods

- Assume normal or lognormal inter-individual population distribution $N(\mu, \Sigma)$ for PK parameters θ
- Estimate μ and Σ from observations Y_{obs} by maximizing parametric likelihood function

$$\int g(Y_{obs} - Y_{pred}(\theta)) dF(\theta | \mu, \Sigma)$$

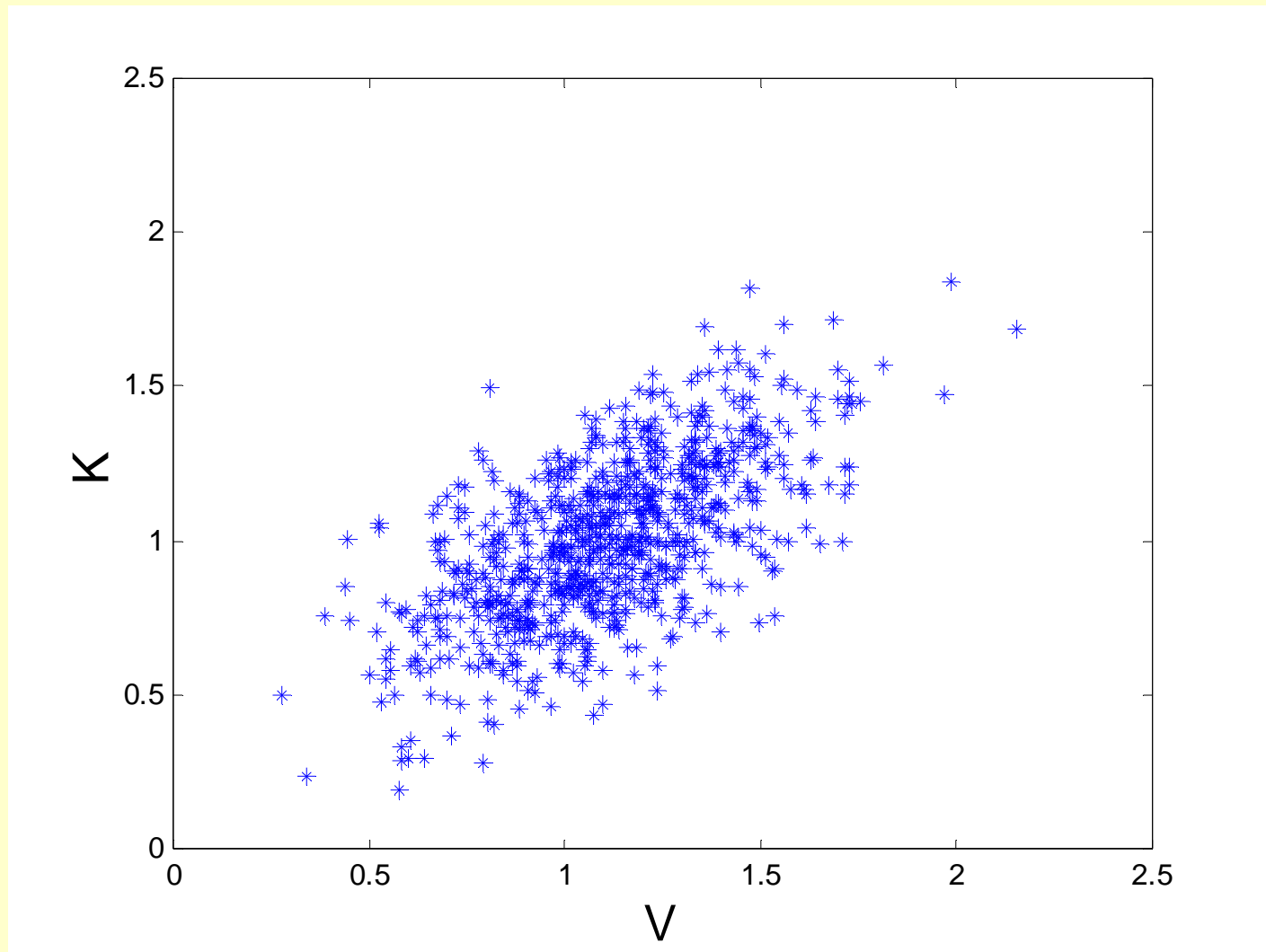
Parametric methods use approximate likelihood functions

- Integrals in parametric likelihood function cannot be evaluated analytically
- Approximation methods: - F. O. , F.O.C.E., Laplace – can adversely affect statistical consistency, bias, efficiency and asymptotic stochastic convergence rates

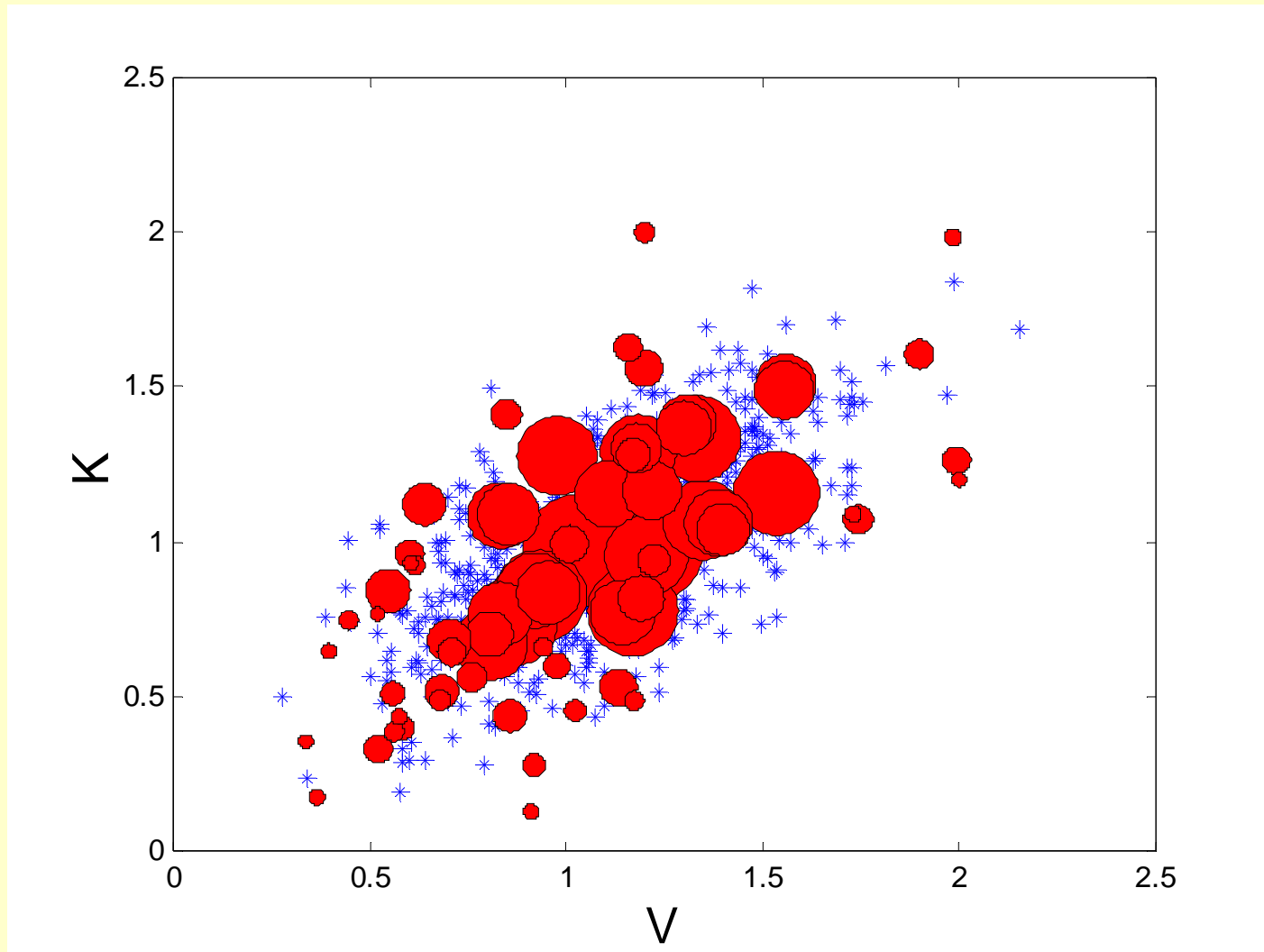
Nonparametric population methods use exact likelihood functions

- (Mallet) Maximum likelihood NP distribution estimate is a discrete distribution with at most N support points
- Likelihood integral reduces to a finite sum that can be evaluated exactly!

*800 Normally distributed (K, V) points,
correlation = +0.6*



800 normal points + 70 NPAG support points



*Recent advances in optimization technology
have dramatically improved the
computational performance of NP population
methods*

- NPAG – nonparametric adaptive grid algorithm (LAPK, 1999) for optimization of support point positions
- primal-dual interior point algorithm (Burke, RFPK, 2000) for optimization of support point probabilities

Recent advances, cont'd

	CPU TIME (HRS)	MEMORY (MB)	LOG-LIK
NPEM:	2037	10000	-433.1
NPAG:	1.7	6	-433.0

Potential advantages of applying NP method in a parametric context

- NP maximum likelihood function can be evaluated exactly – no approximations!
- Since the NP distribution estimate is consistent, so are derived estimates of population means, variances, and covariances
- But at what price in terms of statistical efficiency, bias, asymptotic convergence?

An encouraging observation – P and NP estimators are identical in data rich limit

In the data rich limit , we obtain precise estimates of the PK parameter vector θ_i for each subject i , and both P and NP case give the same estimates:

$$\hat{\mu} = \frac{1}{N} \sum_{i=1}^N \theta_i$$

$$\hat{\Sigma} = \frac{1}{N} \sum_{i=1}^N (\theta_i - \hat{\mu})(\theta_i - \hat{\mu})^T$$

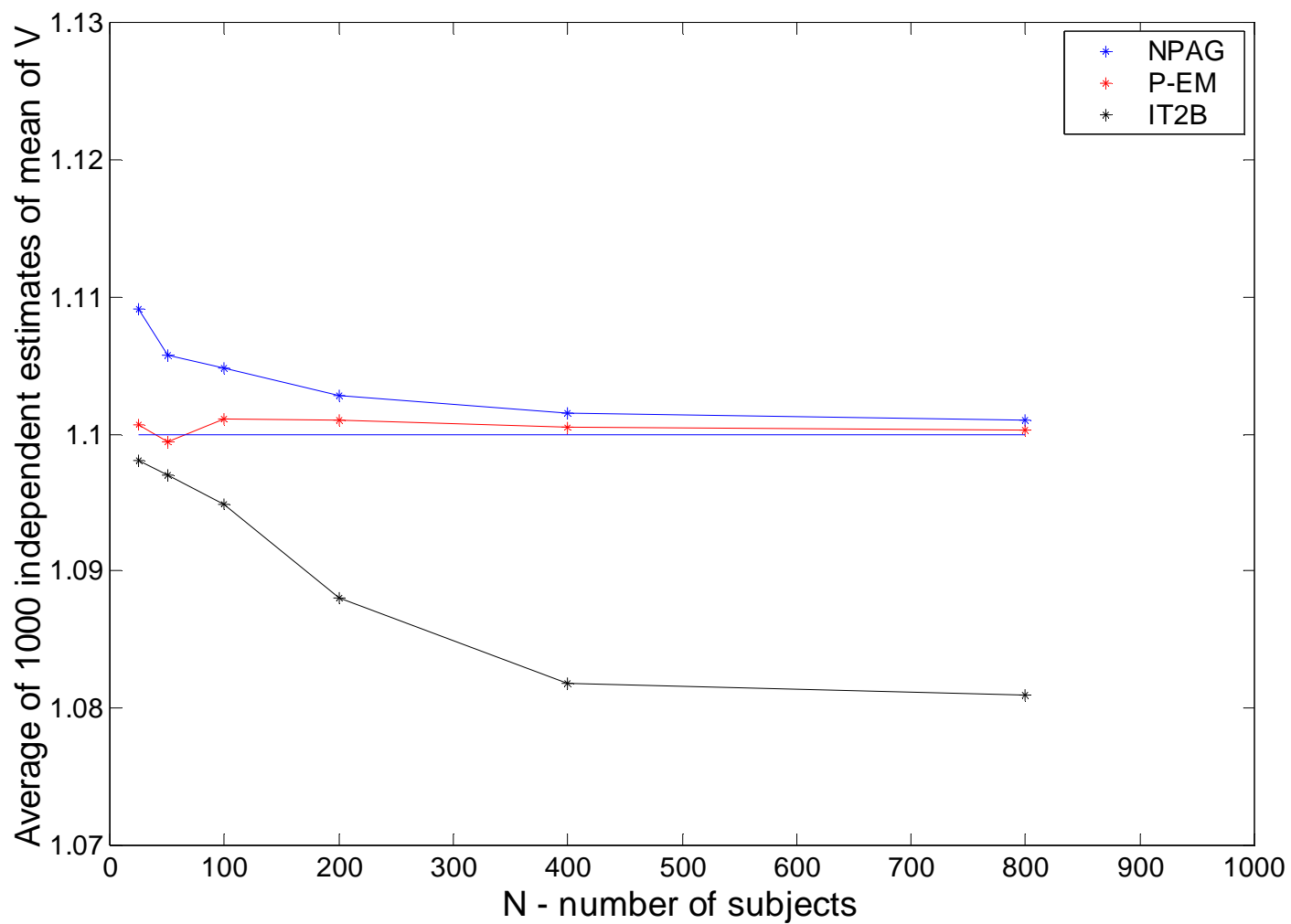
Study objectives

1. Evaluate statistical properties (bias, efficiency, asymptotic convergence rate) of NPAG estimator in a simple, controlled parametric setting
2. Compare to an approximate (F.O.C.E) parametric method (IT2B from LAPK, closely related to P-EM method below)
3. Compare to 'true' ML parametric method Schumitzky's parametric EM (P-EM) with Faure low discrepancy sequence integration

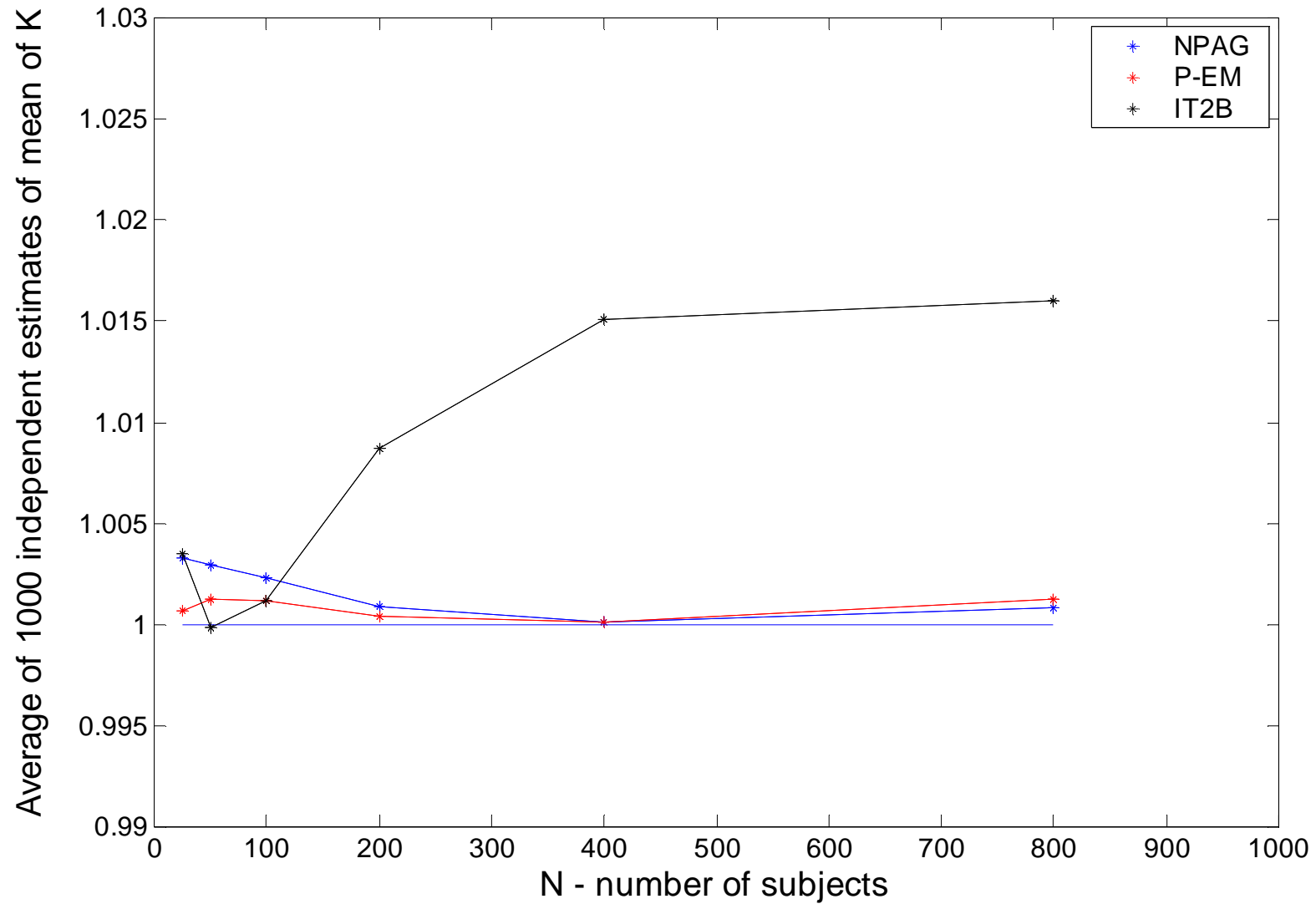
Simulation conditions

- One compartment model $h(V,K) = e^{-Kt}/V$ with unit intravenous bolus dose at $t=0$
- Five parameters in $N(\mu,\Sigma)$: $\mu_V=1.1$, $\mu_K=1.0$
 $\sigma_V=0.25$, $\sigma_K=0.25$, $\rho = -0.6, 0.0$, and $+0.6$
- 1000+ replications to evaluate bias and efficiency
- $N=25, 50, 100, 200, 400, 800$ sample sizes
- Two levels (moderately data poor) with 10% observational error

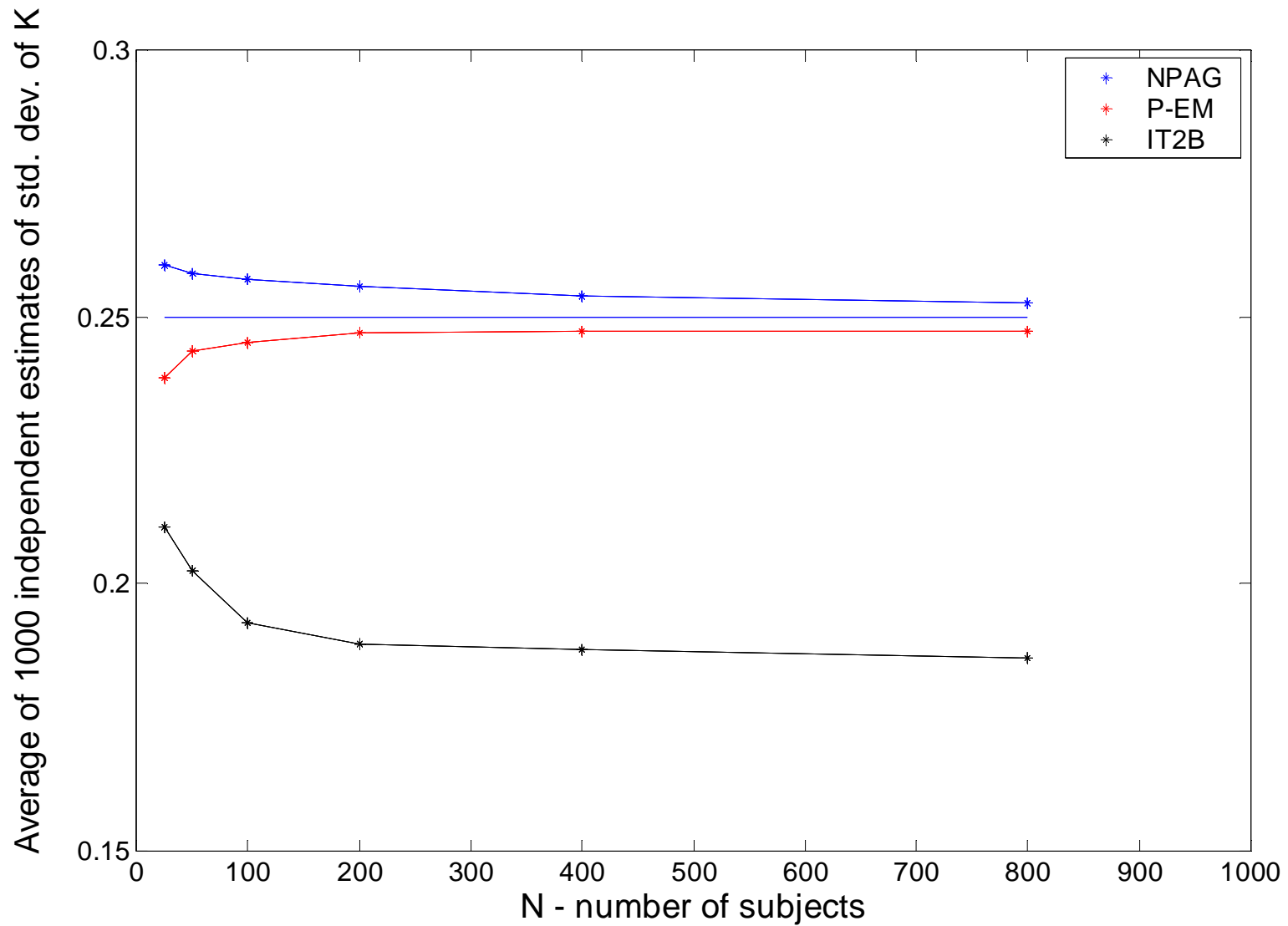
NPAG and P-EM are consistent
(true value of $\mu_V = 1.1$)



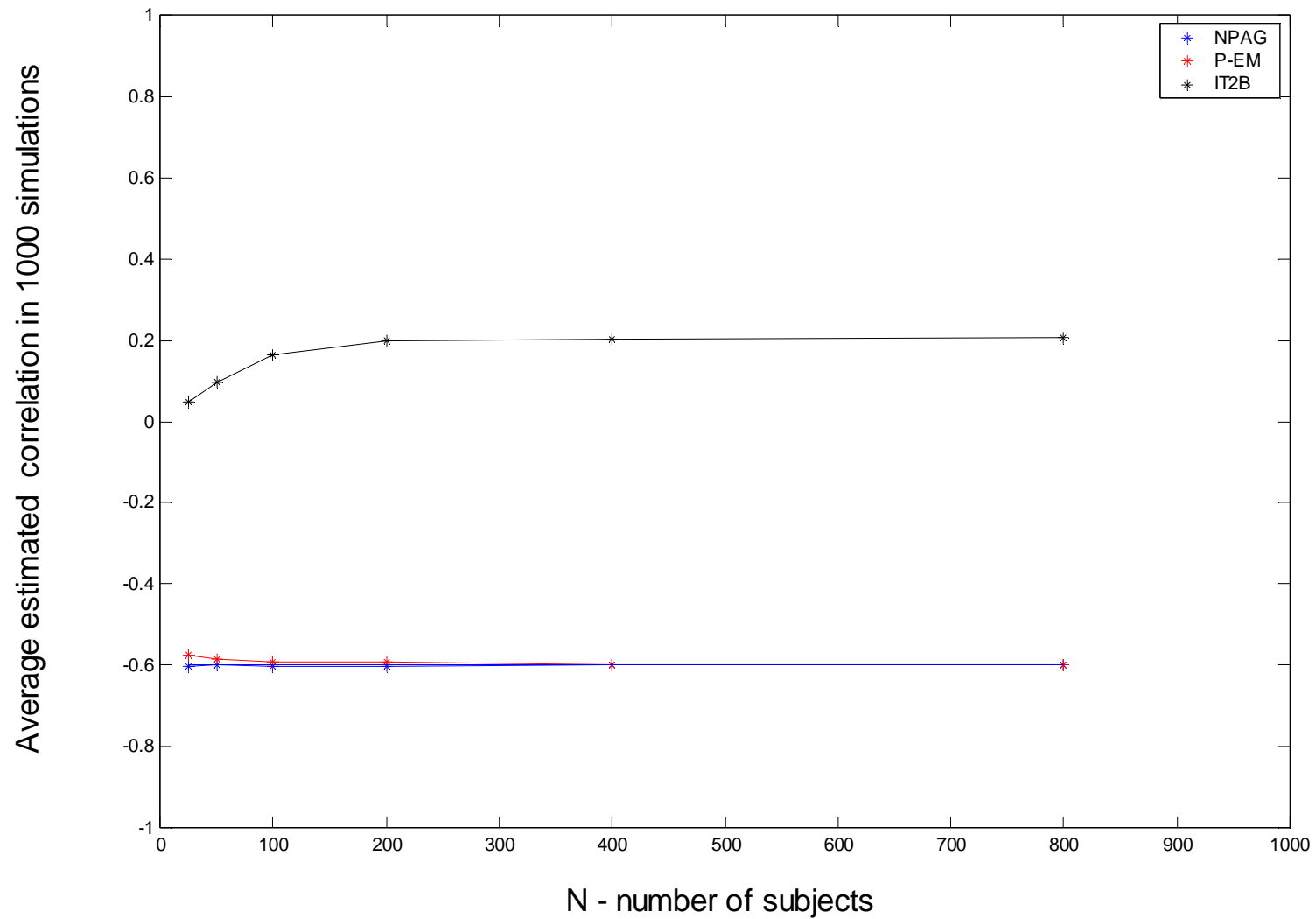
Consistency of estimators of μ_K
(true value of $\mu_K = 1.0$)



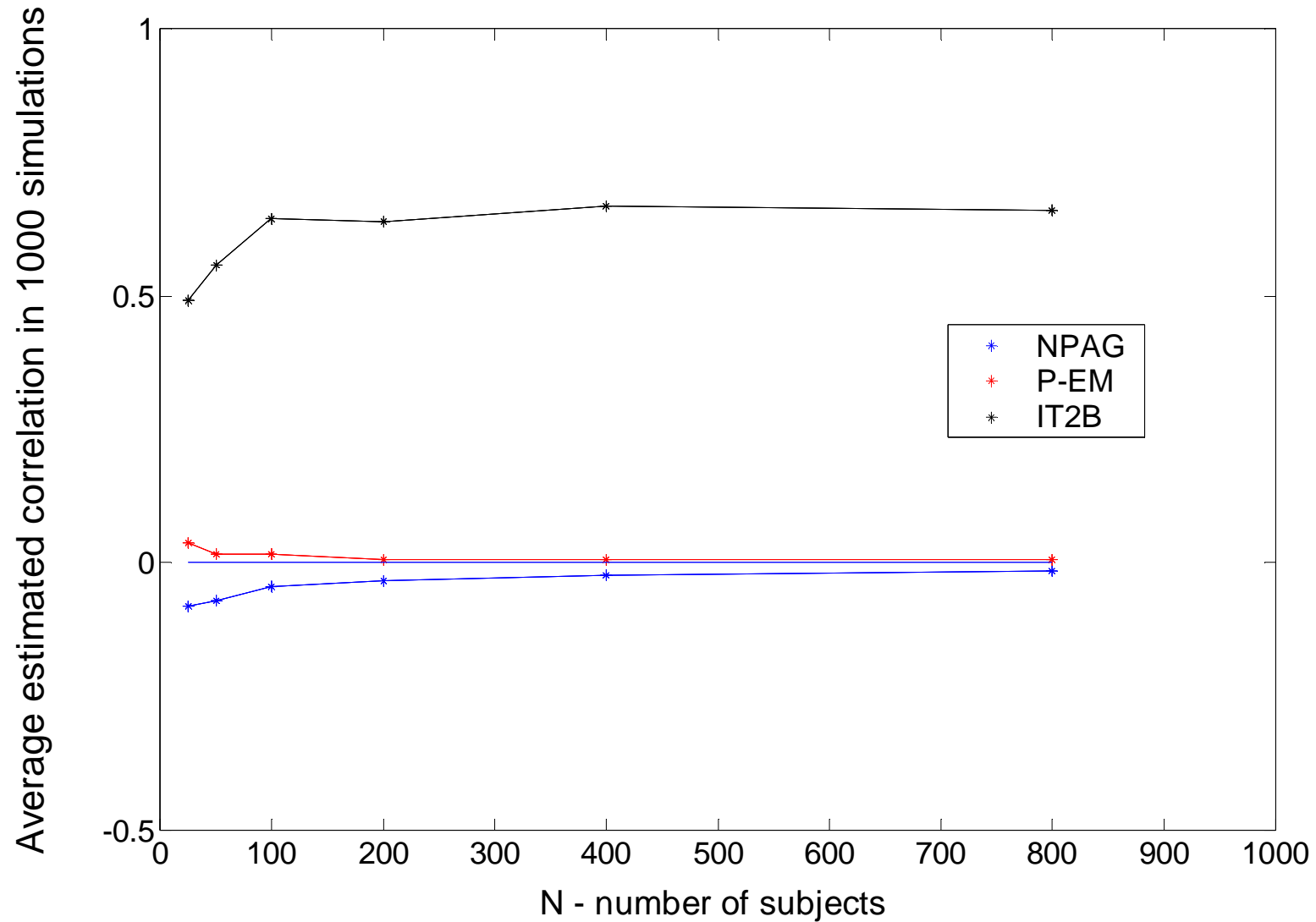
Consistency of estimators of σ_K
(true value of $\sigma_K=0.25$)



Consistency of estimators of V-K correlation coefficient (true value $\rho = -0.6$)



Consistency of estimators of V-K correlation coefficient (true value $\rho=0.0$)



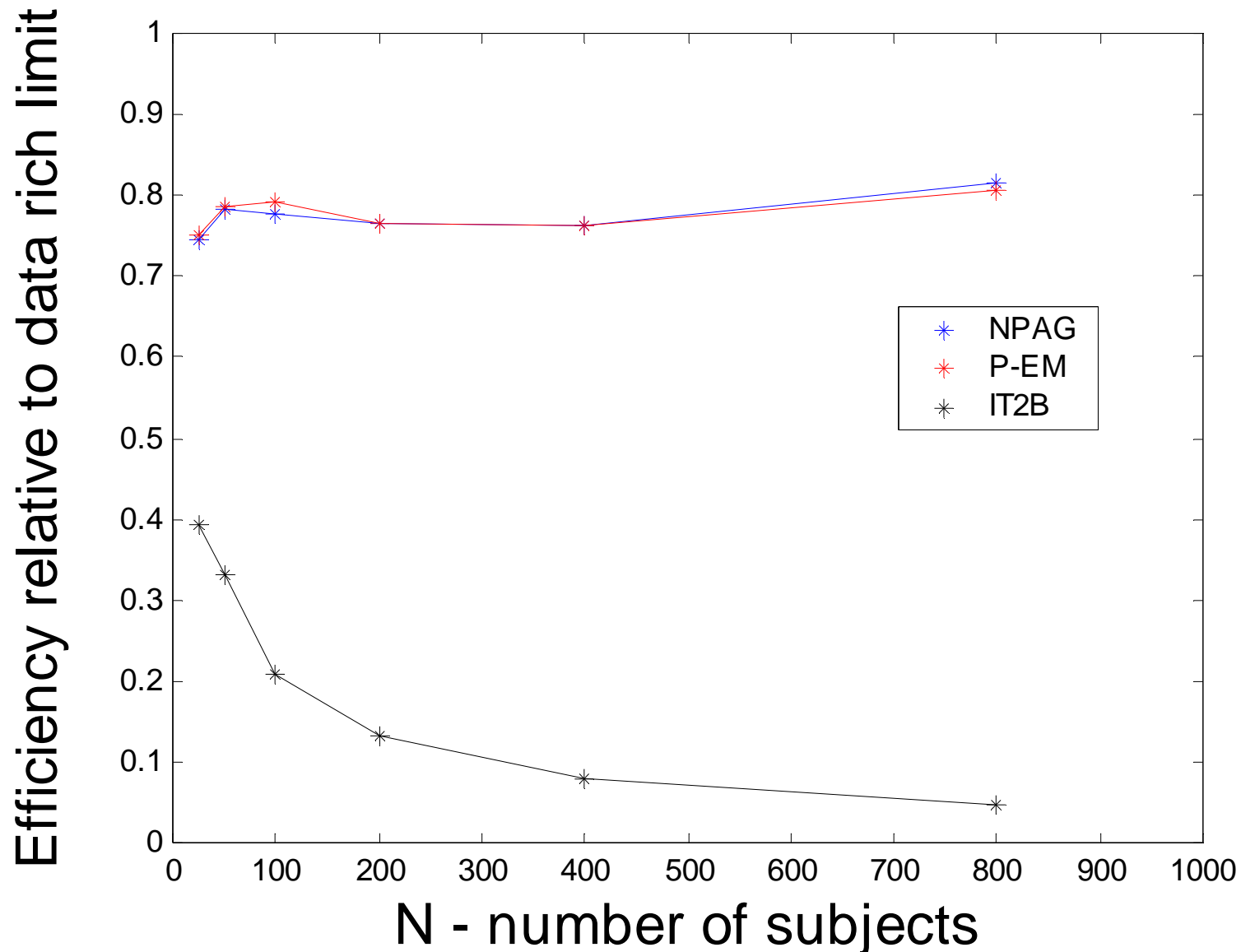
*Consequence #1 of using F.O.C.E approximation—
loss of consistency*

- small (1-2%) bias for μ_V, μ_K
- moderate (20 – 30%) bias for σ_V, σ_K
- severe bias for correlations

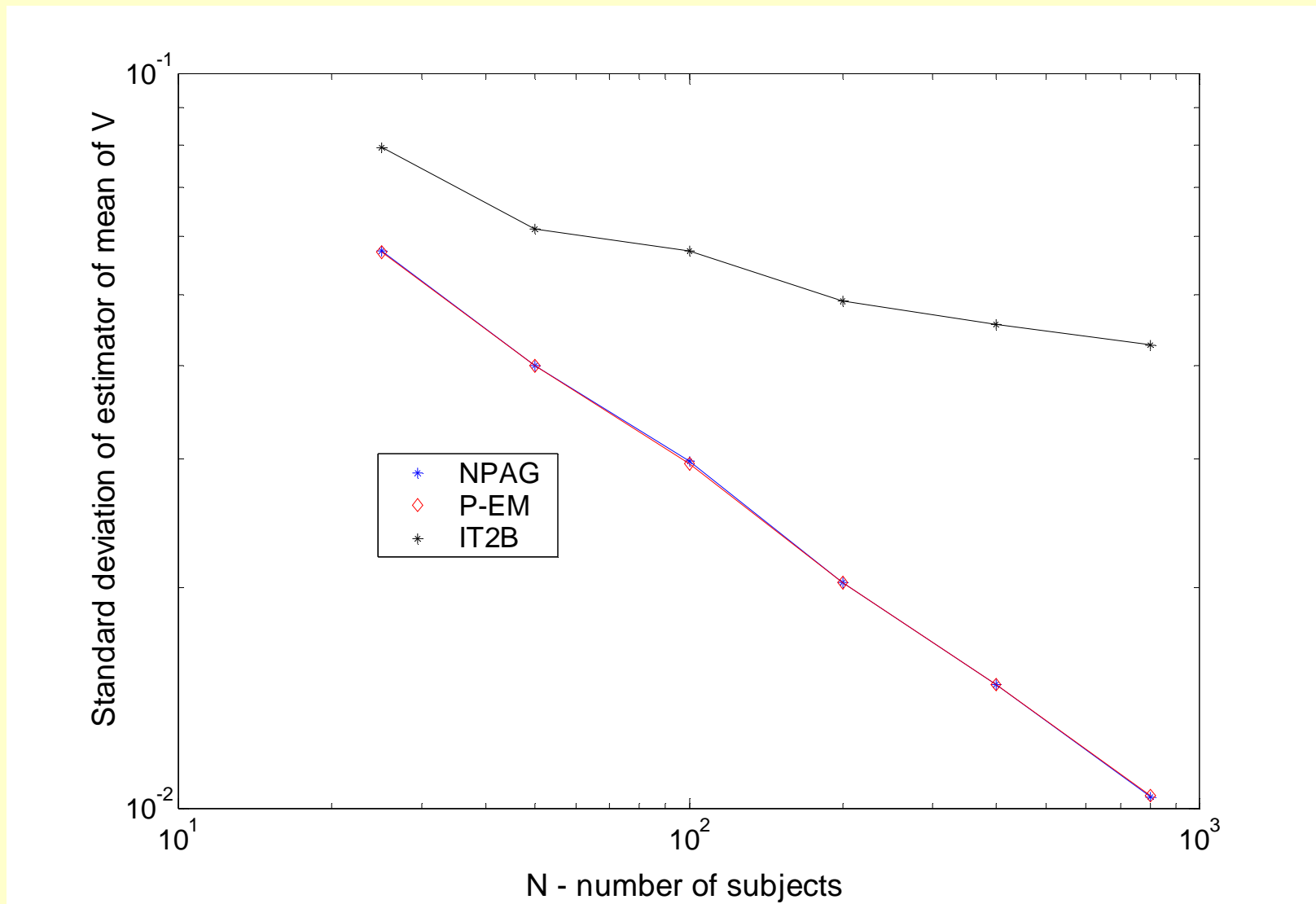
true value average estimate

-0.6	+0.2
0.0	+0.6
+0.6	+0.85

Statistical efficiencies of NPAG and P-EM are nearly identical and much higher than IT2B



Asymptotic stochastic convergence rate of IT2B is $1/N^{1/4}$ vs. $1/N^{1/2}$ for NPAG and P-EM



*Consequence #2 of using F.O.C.E approximation:
degradation of asymptotic behavior*

- Severe loss of statistical efficiency
- Severe reduction of asymptotic convergence rate :
 $N^{-1/4}$ (IT2B) vs. $N^{-1/2}$ (NPAG and P-EM)

(need 16 X the number of subjects to reduce standard deviation of IT2B estimator by factor of 2 vs. 4 X for NPAG and P-EM)

Conclusions (NPAG and P-EM)

- Both computational methods using accurate likelihoods (NPAG and P-EM) display statistical consistency, in agreement with ML theory.
- Biases, if any, are small and decay toward 0 with increasing N.
- The statistical quality of the NPAG and P-EM parameter estimates are equivalent, although the bias structures are different

Conclusions (NPAG and P-EM) cont' d

- Multidimensional numerical integration using low discrepancy sequences works well – much more efficient than Monte Carlo or rectangular grids
- P-EM can easily be extended to higher dimensions $d > 2$
- P-EM and NPAG share an initial stage of computing model predictions on a low discrepancy grid – can do both estimates in a single run as an integrated parametric/non-parametric method!

Conclusions (IT2B)

The F.O.C.E. approximation:

- results in loss of consistency - small bias for means, larger for standard deviations, very large for correlations
- significantly degrades statistical efficiency and asymptotic convergence behavior