Subspace MCMC algorithm for Bayesian parameter estimation of hierarchical PK/PD models in Pumas

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1. Objectives

To speed up the sampling from high-dimensional posteriors of hierarchical Pumas models with a high correlation between the variables' samples

2. Methods

The subspace inference method for PK/PD models implemented in two steps:

1. subspace construction by using principle component analysis(PCA) method
2. NUTS posterior sampling in a subspace (aka subspace inference).

2.1 Subspace Construction Algorithm

Algorithm 1 Subspace Construction

```
P_m ← P_0                 ▷ Initialize mean of parameters as pretrained value
for i=1:T do                          ▷ For every iteration
    for s=1:N do                      ▷ For every subjects
        gradient of log density w.r.t subject, Δ
        P_0 ← P_0 + Δ  ▷ Update parameter value
        P_m ← (i * P_m + P_0)/(i + 1)     ▷ Update mean of parameters
        push(P_dev, P_0 − P_m)             ▷ Push the parameter deviation to the deviation matrix
    end for
end for
U, S, Vt = svd(P_dev)          ▷ Do singular value decomposition
P_prj ← U[:, 1 : M] * S[:, 1 : M]       ▷ Calculate subspace
```

2.2 Subspace Inference

- Define log density function and log density gradient function to generate samples of subspace, z with size of M
- Generate random samples of z based on log density
- Calculate PK/PD model parameter,

$$Params = P_{prj} * z + P_m$$

3. Implementation

Implemented in a development version of Pumas.

4. Results

The experiments are conducted and compared with NUTS sampling method available in Pumas. The performance of subspace inference for PK/PD parameter estimation is analysed by comparing sampling time, effective sample size etc.

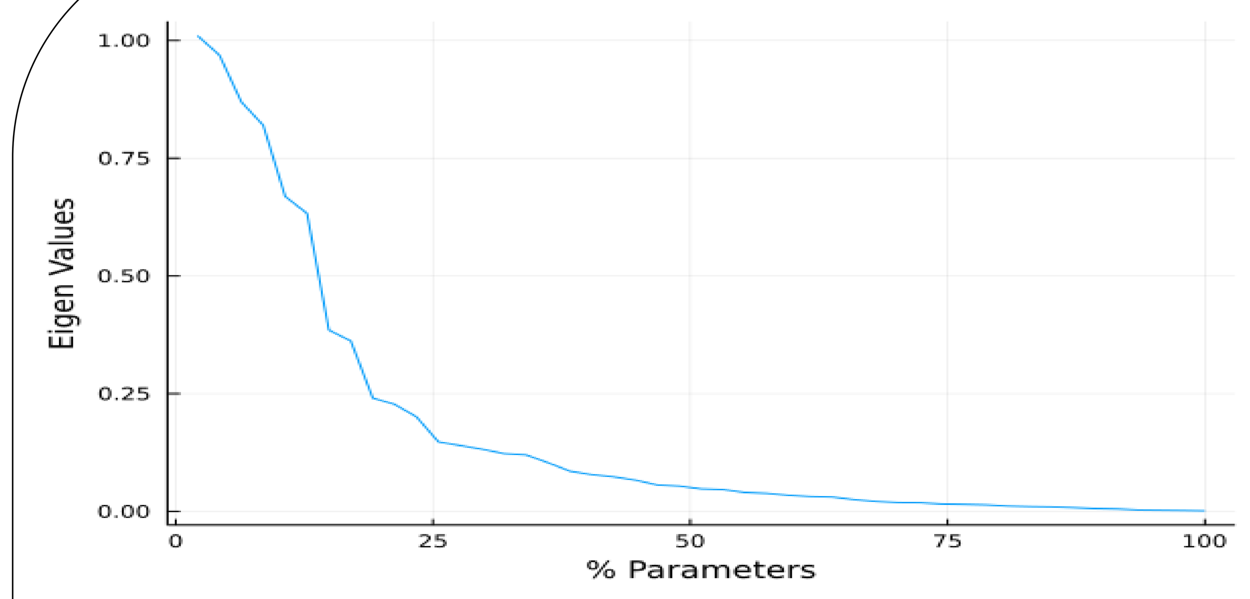

Figure 1: Eigenvalues of covariances of NUTS samples vs percentage of parameters

The Figure 1 shows that eigen values of sample covariance is quickly reducing, so only few variables contributes to whole variance. So, whole parameter space converges to a subspace.

Table 1: Effect of population size in sampling time

Population Size	120		30	
Algorithm	Sub	NUTS	Sub	NUTS
Sampling Time (s)	64	132	20	19
Mean θ_1	3.50	3.48	3.44	3.44
Std θ_1	0.07	0.11	0.16	0.203
Ess θ_1	199	34.90	226.7	107.7

Table 2: Sampling time, Effective sample size, mean and variance comparison

Algorithm	Subspace Inference		NUTS
Params	Rank = 20	Rank = 10	
Sampling Time	73s	29s	175s
Meanθ_1	2.02	2.26	1.846
Std θ_1	0.2332	0.128	0.498
Ess θ_1	2484.13	912.64	1622

5. Conclusion

The proposed method outperforms the NUTS-based method for PK/PD parameter estimation. When the subspace size increases then the mean value approaches the true value. However, increase in the subspace size increases the time for the parameter estimation.

References

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- Izmailov, Pavel, et al. "Subspace inference for Bayesian deep learning." Uncertainty in Artificial Intelligence. PMLR, 2020.