When data in a population of interest is sparse due to practical constraints, it is occasionally difficult to estimate all the parameters of a model, specifically a complex model, with the sparse data alone. Use of priors for parameters which are difficult to estimate is one of the ways to analyze such limited data while borrowing information from the priors and stabilizing the estimation [1]. The analysis with priors can be performed by PRIOR functionality of NONMEM.

When analyzing a sparse data with priors, parameter estimates which incorporate corresponding priors depend on information of the priors as well as information of the data. Therefore, it is considered important to evaluate information of the priors relative to the data when interpreting the result. In addition, if use of priors for specific parameters is supposed in a future study, it is considered meaningful to evaluate optimal study designs which improve precision of parameter estimates in the analysis with priors.

In this work, 1) we present information of priors relative to sparse data based on variance of estimates from Fisher information with or without the priors. 2) We also show how information of the prior relative to sparse data can be evaluated to design studies for a future study as a similar approach to design optimization of experiments [2].

**Methods**

In this presentation, information of a prior relative to sparse data is defined as how many times the prior is as informative as the sparse data is. This idea is based on prior information of Bayes estimator [3]. To measure the relative strength of priors, we use variance of parameter estimates based on Fisher information matrix with or without priors. For example, as shown in Figure 1, when variance of an estimate (θ) obtained from FIM for a sparse data (FIMSP) is comparable to variance of the prior distribution (V0), strength of the prior is considered Nb-time of the sparse data. Since the Nb depends on information of both the data and the prior, the Nb is considered as an index of information of the prior relative to the sparse data. We describe below how to obtain the index through Fisher information matrix with priors.

![Figure 1. Information of a prior (Nb) is defined as the prior is Nb times as informative as sparse data (dS).](image)

The population Fisher information matrix (FIM) is derived from first-order approximation for random effect parameters (nd) of a population model [2]. The FIM for a sparse data (FIMSP) is derived as the inverse of the second derivative of log-likelihood (Q0). Hereafter, sparse data which consists of nd observations with additive residual error for an individual i, y_i = (dose, time_i, n_i, d_i, O_i)., is used as an example for explanation. The FIMSP is described in equation (1) and (2). The θ and ω are represented a vector of fixed effect parameters and a variance for random effect parameter, respectively. The ϕ below is a variance-covariance matrix of the 1st order Taylor series approximation of the model for random effects η at zero [2]. The tr(X) is a sum of diagonal elements of matrix X.

\[
FIMSP = \left[ \frac{\partial^2 Q}{\partial \theta^2} \right]^{-1} = \frac{\partial^2 Q}{\partial \theta^2}^{-1}
\]

The Fisher information matrix for analysis with priors is introduced below. When a prior is conducted with PRIOR in NONMEM, prior distributions for θ and Ω are normal and inverse-Wishart distributions, respectively. Therefore, log-likelihood for the analysis with priors (O_{SP}) can be described as follows (Gilesgog et al [1]).

\[
O_{SP} = Q - \log(S0) - \frac{1}{2} \sum_{i=1}^{nd}(y_i - \hat{y}_i)^2 - \frac{1}{2} \sum_{j=1}^{n_i}(d_i - \hat{d}_j)^2 - \frac{1}{2} \sum_{k=1}^{d_i}(O_k - \hat{O}_k)^2
\]

The proposed information of a prior related to the sparse data is as follows.

\[
Nb = FIMSP + FIMSP_0 - 1 = \frac{\partial^2 Q}{\partial \theta^2} = \frac{1}{2} \sum_{i=1}^{nd}(y_i - \hat{y}_i)^2 - \frac{1}{2} \sum_{j=1}^{n_i}(d_i - \hat{d}_j)^2 - \frac{1}{2} \sum_{k=1}^{d_i}(O_k - \hat{O}_k)^2
\]

In practice, the FIMSP in equations (1) and (2) are obtained by PFIM of R software tool [2]. Hence, the FIMSP is obtained by adding minus second derivative matrix of log of prior distributions (first term of each equation (3) and (4)) to the FIM from PFIM as below. The A and B represent second derivative of log of prior distribution with respect to θ and Ω, respectively. Minus second derivative of log of prior distributions (elements without priors are zero). The Fisher information matrix for analysis with priors (O_{SP}) can be described as follows (Gilesgog et al [1]).

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\]