A non parametric population approach for selecting biomarkers of a drug action

N. Terranova[1], F. Del Bene[2], F. Fiorentini[2], P. Magni[1], M. Germani[2]

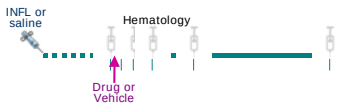
[1] Dipartimento di Informatica e Sistemistica, Università degli Studi di Pavia, Italy
[2] Accelera – Viale Pasteur 10, 20014 Nerviano, Milan - Italy

www.accelera.org

Intravenous treatment with a candidate drug administered at its optimal pharmacological dose was evaluated in healthy mice and in mice exposed to an inflammatory insult, with respect to a broad panel of inflammatory biomarkers. The objective of the study was to determine which biomarker was modulated by the compound under investigation.
Inflammatory biomarker concentrations were measured at different time points using a serial sacrifice design.
The concentration curves, both typical and individual ones, were modeled as stochastic processes, in which the only requirement was a certain degree of regularity of the time profiles. A Markov Chain Monte Carlo (MCMC) algorithm was applied to perform the Bayesian estimation of typical and individual Areas Under the concentration-time Curves (AUCs). A comparison with the Bailer and Bailer-Satterthwaite (B-S) methods was also performed considering real datasets.

METHODS

Three groups of animals were considered: two different groups were exposed to inflammatory insult (INFL) 3h before the intravenous treatment with the investigated compound or its vehicle, one additional group was exposed to saline (that does not cause inflammation) 3h before the treatment with the same compound. Inflammatory biomarker concentrations were measured at different time points using a destructive sampling design (6 mice for each time point for each group).



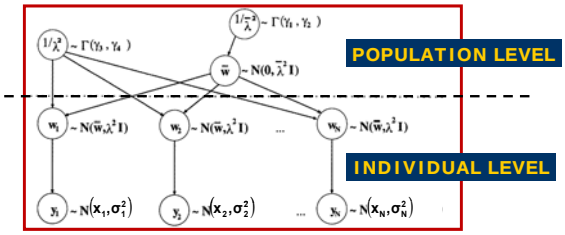
3 groups of animals:
(1) saline+Drug
(2) INFL+vehicle
(3) INFL+Drug

One sample per subject with 6 subjects sampled at 0 pre-dosing and 5, 15, 30, 60, 240 minutes post-dosing.

The individual and typical concentration curves are described in each group through a random walk population process (with the only requirement of a certain degree of regularity on the concentration profiles). They were estimated from data by numerically computing the posterior expectation through a MCMC algorithm.

Nonparametric AUC Estimation in Population Studies (NESPO) with Incomplete Sampling: a Bayesian Approach

P. Magni *et al.* 2003, JPP



Regularity of both typical and individual curves. Walks between two consecutive samples $\overline{w}_k=\overline{x}_k-\overline{x}_{k-1}$ and $w_{ik}=x_{ik}-x_{ik-1}$ are random variables, independent and normally distributed with 0 and $\overline{w}_k$ mean and variance $\overline{\lambda}^2$ and λ^2, respectively.

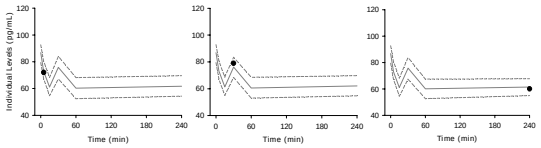
Each measurement is affected by an additive error: $y_{ik}=x_{ik}+v_{ik}$ with $v_{ik}\sim N(0,\sigma_i^2)$.

Prior distribution for the hyper-parameters $\overline{\lambda}^2$ and λ^2 specified through γ_1, γ_2, γ_3, γ_4.

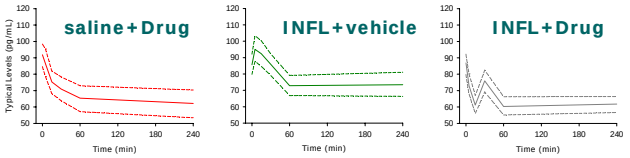
An estimation procedure based on MCMC method is defined to derive the posterior joint (and the marginals) probability distribution of the model parameters $\theta=\{\overline{\lambda}^2, \lambda^2, \overline{w}, w_1, w_2, \ldots, w_N\}$ given the data.

RESULTS

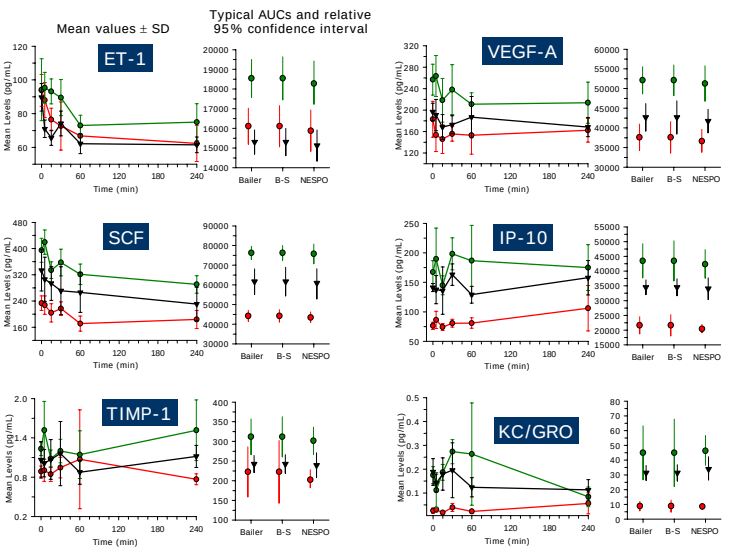
The presented approach was applied to a broad panel of inflammatory biomarkers.
Below, the observed concentrations of Endothelin-1 (ET-1) in 3 treated mice previously exposed to inflammatory insult (INFL+Drug) *vs.* the predicted individual mean profiles with their 95% confidence interval are shown as example.



The population model computed the typical subject mean profiles of ET-1 for the three groups of animals with the 95% confidence intervals.



After typical and individual profiles are estimated, the typical and individual AUCs were computed by numerical integration (i.e., trapezoidal rule) with the corresponding 95% confidence intervals.



	ET-1	VEGF-A	SCF	IP-10	TIMP-1	KC/GRO
Overlapping probability	3.32e-4	6.1e-3	7.8e-3	2.27e-2	2.9e-2	8.1e-2

Overlapping probability between the typical AUCs related to the INFL+vehicle (AUC_1) and INFL+Drug (AUC_2) groups computed on the sampling distribution obtained via MCMC.

CONCLUSIONS

The results of the study indicated that the NESPO approach was able to find those biomarkers that were differently expressed in the three groups of animals (minimal probability of overlapping between distribution) and to select suitable candidates of the compound action. ET-1, Vascular Endothelial Growth Factor A (VEGF-A), Stem Cell Factor (SCF), Interferon gamma Induced Protein 10 (IP-10), Tissue Inhibitor of Metalloproteinases 1 (TIMP-1) and the Growth-Regulated Alpha Protein (KC/GRO) were reported as examples. Obtained results were also confirmed by the Bailer and B-S methods.

Although the three statistical approaches yielded comparable results, the Bayesian nonparametric AUC estimation method:

- generates more reliable estimates of the mean and its variance taking into account the presence of possible outliers and uses the whole probability distribution to evaluate the difference among treatments.
- has wider applicability as it allows arbitrary sampling schedule (whilst Bailer and B-S are applicable only in case of destructive sampling data)