# Individual Reference Intervals for Personalized Interpretation of Clinical and Physiological Measurements

Murih Pusparum[1,2], Gökhan Ertaylan[2], Olivier Thas[1,3,4]

[1]Data Science Institute, Hasselt University, Hasselt 3500, Belgium
[2]Flemish Institute for Technological Research (VITO), Mol 2400, Belgium
[3]Department of Data Analysis and Mathematical Modelling, Ghent University, Ghent 9000, Belgium
[4]National Institute for Applied Statistics Research Australia (NIASRA), Wollongong 2500, NSW, Australia

E-mail for correspondence: murih.pusparum@uhasselt.be

**Abstract:** A reference interval (RI) of a clinical or physiological outcome refers to the range of outcomes that is expected in a healthy population. This interval is widely used in daily clinical practice for interpreting laboratory tests: when the outcome falls outside the RI, the physician will consider further examination. Whereas the conventional RI refers to a single population of healthy subjects, we argue that each individual may have different biological traits and therefore, may have its own Individual Reference Interval (IRI). We have developed methods for the estimation of IRIs when time series data on multiple subjects are available. In a first approach we used linear quantile mixed models (LQMM) to separately estimate the lower and the upper bounds of the IRIs. We have extended this method for simultaneously estimating the two bounds by constructing a joint LQMM for the lower and upper quantile. Parameter estimation is based on the asymmetric Laplace distribution for a likelihood function construction, and a Monte-Carlo Expectation-Maximization (EM) algorithm. The methods' performance is evaluated in a simulation study. Finally, we demonstrate the validity of the proposed methods on real life data including several clinical and physiological measurements collected within the VITO IAM Frontier study.

**Key words:** Reference interval; Linear quantile mixed models; EM algorithm; Personalized health