Abstract

Statistical Methods for the Standardization of Diagnostic Assays

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Diagnostic assays are measurement systems, measuring the concentration of analytes in human body liquids. To ensure the stability of the measured values over time, each diagnostic assays should be standardized against a so-called master sample. This is a sample with known concentration, which is measured by a very specific and precise measurement method. From this master copies are made subsequently, such that at the end of the chain a patient sample is measured on the standardized system.
A main problem for standardization systems of diagnostic assays is the definition of a master, which is stable, as analyte may be lost over time. Manufacturers of diagnostics assays as well as international organizations, especially the IFCC[1] have recognized the need for standardization systems of diagnostic assays that ensure stability.
Networks of laboratories are formed, which measure master samples with a reference measurement method and the averaged value of these measurements becomes the value of the master, the so-called assigned value. This value assignment is repeated after a certain time span for the next master sample, such that if the network is stable the continuity of master samples will be guaranteed.

In the context of such laboratory networks several statistical questions arise, which are discussed and answered throughout this thesis.

First it must be clear how the assigned value of the respective master and the uncertainty associated with this value is derived. The first part of the thesis examines a routine process of standardization within a laboratory network. The main sources of uncertainty within this process are revealed and how these sources have to be combined to obtain the uncertainty of the assigned value is shown. Especially the question how the uncertainty of the master is transferred to the uncertainty of the copies is discussed. A Bayesian model is presented which enables the inclusion of the uncertainty of the master within the calibration process. Based on a simulation study it is shown that this model leads to much better results for the estimation of a measured value as well as its uncertainty, than the conventional calibration models. Further it is shown how so derived measured values should be combined to obtain the assigned value and its uncertainty.

The second part is dedicated to the identification of outliers in data of standardization networks. This is important for two reasons: one reason is that new laboratories may want to join

[1] International Federation of Clinical Chemistry

a standardization network. As the network should ensure the stability of the master, the new laboratory must fit to the network. The other reason is that failures of measurements of the members of the network need to be detected before the assigned value is calculated. For both questions rules have to be defined which are valid for multiple value assignments.
The outlier identification for both tasks is based on robust estimation methods for linear mixed models. First it is shown how outlier identification rules for general linear mixed models can be defined. Afterwards two special cases, the one-way random effects model and the random coefficients model are regarded. Both are useful for the analysis of data from laboratory networks, the first one if only one sample within the network is regarded, the second if multiple samples are of interest. Finally an interpretation of the impact of these rules for allowable measurement deviations within a laboratory network is given.

The third part of the thesis deals with repeated method comparison studies which are necessary, if a standardization system is replaced by a new one. This might happen if global standardization system replace existing national systems, or if a more specific measurement method is established. In these cases, assigned values might change and recalculation formulas are needed for the transformation of new values into old ones and vice versa. Concepts are presented for the comparison of repeated method comparison studies.
Further the combination of these studies via hierarchical Bayesian models, to obtain a recalculation formula, is presented. The focus lies especially on the impact of the prior distributions on the results and the definition of appropriate prior distributions based on posterior predictive checks.

The presented statistical methods are applied to data of the IFCC network for standardization of HbA1c.