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Repeatability of the Data in Long-Term LC-MS-Based Serum Metabolomic Studies

Manshui Zhou

Center for Chemical Evolution, Georgia Institute of Technology, Atlanta, GA 30332, USA

Metabolites present in human serum and bodily tissues are the end products of cellular regulatory processes, and can be regarded as the ultimate response of biological systems to genetic or environmental changes [1]. As a "new" member of the OMICS family, the ability of metabolomics to explore the molecular complexity of life, especially in the areas of metabolic disorder and biomarker discovery [2-5] is now firmly established. Metabolomic studies comprise sample selection, collection and preparation, metabolite detection, data mining, pattern recognition using statistical analysis, biomarker identification and validation, and quantitative determination of biomarkers. These studies involve many disciplines and technologies, and organically integrate metabolite fingerprinting, biochemistry, and bioinformatics, resulting in challenges for the repeatability of the acquired data. However, statistical challenges resulting from data reproducibility in long-term serum metabolomic studies can be minimized if the metabolomic workflow strategy is carefully planned.

An untargeted serum metabolomic study to investigate the relationship of data repeatability versus sample size using a combination of UPLC-MS and chemometric methodologies has been reported [6]. The authors concluded that sample size determines the repeatability of the data, suggesting that fewer than 90 injections per column has been shown to provide adequate repeatability in a single block of 120 injections. Furthermore, a preventative maintenance between two blocks is mentioned but not clarified. A discussion regarding the preventative maintenance-related technical reproducibility, focusing on the interface between LC and MS, follows.

Although technical malfunctions in LC-MS systems are the main sources for the lack in repeatability in serum metabolomic data, some aspects are still easily ignored by the researchers. I totally agree with Zelena [6] that a QC sample should be analyzed in every four injections, as this can monitor the performance of the system. Most researchers suffer from the experience that the sensitivity of the mass spectrometer becomes worse with an increasing number of injections, the analysis of one batch of samples will create some artifacts and result in poor reproducibility of some features. For example, the coating materials on the ESI stainless steel capillary tube degrade over time. Additionally, the end tip of the stainless steel ESI tube experiences etching due to the acidic environment, which can lower the sensitivity as the number of injections is increased. In an effort to overcome these effects, a recommended method is to reverse the ESI capillary tube after the first month and replace it after the second month. Another factor is the position of the ESI tube, which is often ignored by researchers. Calibration and tuning are two important and necessary steps before the start of each batch. Tuning includes not only the ESI capillary tube and sample cone voltages, but also the position of the capillary tube. Automated runs save time and labor, but long and continuous runs can partially clog the instrument sample cone, greatly reducing the instrument sensitivity. Last but not least, another important factor is the gas stability and heater function. Some researchers often utilize the last volume of the nitrogen gas, but nitrogen gas pressure fluctuations provide inefficient electrospray and generate many artifacts in data analysis. Heater function is also an important source of variability, which should be regularly checked or replaced.

Metabolomics is emerging as a popular strategy to study biological systems. Regular preventative maintenance of LC-MS system can improve the reliability and repeatability of the data. It is our experience, having run hundreds of serum samples, that preventative maintenance can improve the quality of the data obtained from metabolomic studies.

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Corresponding author: Manshui Zhou, Center for Chemical Evolution, Georgia Institute of Technology, Atlanta, GA 30332, USA, Tel: 404-385-4427; E-mail: manshui.zhou@chemistry.gatech.edu

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