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Finding the REAL differences among biochemical and chemical noise in Metabolomics profiling experiments

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Introduction: Metabolomics is used within the pharmaceutical industry to investigate biochemical changes resulting from pharmacological responses to potential drug candidates. The ability to identify markers of toxicity/efficacy can significantly accelerate drug discovery and helps define the appropriate clinical plan. Data from LC-MS metabolomic profiling experiments contains large amounts of chemical background which often confounds biomarker discovery. New mass spectrometer technology and data processing software were utilized here to reduce chemical background; animal experiments were designed to investigate the influence of animal age and nutrition in relation to drug-induced changes.

Methods: Blood samples were taken from groups of male rats (fully satiated, acute and chronic fasting, different ages). LC-MS analyses were performed in positive and negative modes using a hybrid Orbitrap mass spectrometer capable of fast scanning at ultra high resolution (>50K), and a 12-minute UHPLC separation. Study data was analyzed using new component detection algorithms in SIEVE 2.0 software to determine metabolic effects of food deprivation and aging rats.

Results: In a typical LC-MS metabolomics data set, much of the data is redundant (multiple ions per component), and much of the data is irrelevant (chemical noise). In addition, external factors that influence metabolic profiles such as animal age and level of nutrition increase the level of biological noise. Hence, it is tremendously challenging to discover reliable markers for drug efficacy and/or toxicity. As the majority of chemical entities observed are unknown, it is especially important to filter out false positives before valuable resources are spent on extensive structure elucidation studies.

Instruments capable of ultra high resolution (>50K) at an acquisition speed compatible with UHPLC addresses the issues of chemical noise and redundancy by providing the appropriate resolution that is required in a complex biological matrix to distinguish the different components. Such data allows sophisticated data reduction and processing software to more reliably recognize related signals. This approach not only leads to a massive reduction in data size which in turn removes noise from statistical analyses used to ascertain differences between treatments, but it also provides higher fidelity quantitation for targeted analysis as analytes are distinct from other chemical interferences.

On the biological side, other factors such as nutrition and animal age have a profound impact on metabolic profiles. Most metabolic changes are modest in extent, but can exacerbate or obscure drug induced metabolic effects and are therefore a significant variable in model design. Understanding and cataloging these changes in normal rat helps to minimize “biological noise” and provides more confidence in assigning drug related metabolic changes.

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