Mass Spectrometry Analysis of Proteomic Mixtures: The Quest for Personalized Medicine

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Abstract: Tremendous progress in biotechnology has not translated into the dramatic improvements in patient care that were initially anticipated. Personalized medicine—the delivery of optimal therapy based upon an individual’s molecular fingerprint—has been realized only partially. The publication of the human genome sequence was the first milestone: microarray analysis of gene expression has provided some insights into treating disease. We expect the next milestone will be routine analysis of a patient’s proteome from a drop of blood. The proteome—the ensemble of proteins encoded by the genome—offers a more direct, complete, and dynamic view of physiology than the genome.

Mass spectrometry is the technique of choice for detection, identification, and quantification of the proteome. Fourier-transform mass spectrometers (FTMS) can measure mass to part-per-million (ppm) accuracy, allowing highly parallel identification of many proteins in a complex mixture. Current FTMS mass accuracy represents an inflection point: a unit increase in mass accuracy yields critically large gains in the number of identified proteins.

To improve mass accuracy and protein identification, we have followed a paradigm common to many projects at ESSRL: replacing ad hoc, curve-fitting based methods with maximum-likelihood estimation. In particular, we achieved a four-fold improvement in mass accuracy by estimating the physical parameters describing an FTMS experiment rather than fitting detected peaks with parabolas, the standard practice. We anticipate that improved analysis of mass spectra will help to make personalized medicine a reality.

Monday, September 25, 2006
4:00 PM
Bryan 305

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