

THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

Accelerating Biological Research Using Automated High-throughput Two-dimensional Tandem Mass Spectrometry

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Mass spectrometry (MS) is becoming an increasingly popular technique to help answer biological questions. Advances in ionization and mass scanning methodologies have enabled scientists to collect exquisitely complex biological data sets to query the proteome, lipidome, and metabolome of biological systems, with goals such as disease modeling and drug discovery. The complexity of these data sets, however, comes at a cost of both sample run time and extensive data analysis. Conventional bio-MS methods are often coupled with chromatography and require several minutes to hours per sample, limiting sample throughput. Further, while MS is sensitive enough to detect subtle biological variabilities, it requires a high level of replication to confidently differentiate signal from noise. Additionally, manual analysis of even a handful of spectra quickly becomes unmanageable – computational approaches, specifically AI/ML based methods, are necessary to make sense of these data. However, AI algorithms are only as robust as the quality and wealth of data in the training set; thus, there is a need to collect greater volumes of phenomenon-specific data quickly.

To solve this problem, Teledyne FLIR is developing a mass spectrometry-based high-throughput screening (HITS) platform through DTRA's DOMANE program that can rapidly analyze hundreds of samples in an hour and captures complete biochemical profiles. Simultaneously, an AI analysis pipeline is being developed to correlate biologically observed trends with these biochemical profiles. The high-throughput nature of this platform is two-fold. First, biological samples are generated using an automated liquid handling robotic system. Second, the mass spectrometer in development combines two recently developed MS technologies amenable to high-throughput data analysis: a desorption electrospray ionization (DESI) source, and two-dimensional tandem mass spectrometry (2DMS). The DESI technique enables analysis of biological samples, including pathogens, with minimal sample preparation. The 2DMS scanning method is an unsupervised MS/MS technique which enables the acquisition of all precursor/product/neutral loss relationships in a single scan, producing 100x more MS information than convention MS/MS experiments in the same analysis time.

Our initial application of this technology is to understand a pathogen's lipidomic and metabolomic response to a medical countermeasure (MCM). Preliminary experiments with a panel of model organisms exposed to well-characterized MCMs have informed design strategies for the DESI-2DMS instrument. By leveraging Teledyne FLIR's 20+ year experience in producing portable MS instrumentation, the DESI-2DMS is designed with a relatively small form-factor while retaining the robust confidence of a conventional mass spectrometer. This is crucial for use in traditional biosafe environments (e.g. biosafety cabinets, BSL-3/4 clean rooms) where space is at a premium. This instrument, combined with an automated sample generation workflow, has the capability of screening orders of magnitude more MCMs than state of the art techniques; this will enable rapid MCM discovery against new and emerging threats.