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Leveraging spectral sparsity to realize enhanced separation of gas-phase ion populations

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ABSTRACT

When coupled with mass spectrometry, gas-phase ion mobility can enable the separation of isomers provided sufficient resolution. However, traditional limits on drift tube ion mobility resolution have been imposed by thermal diffusion and the duration of the initial ion gate pulse width. We demonstrate the first application of a post processing technique, specifically basis pursuit denoising (BPDN), for multiplexed IMS–MS experiments that not only minimizes data acquisition times, but realizes resolutions that exceed traditional predicted values. The multiplexing waveform used was based upon linear frequency modulation of the ion gate producing an ion gate pulsing sequence with a 50% duty cycle. This pulsing sequence further maximizes ion transmission and improved ion statistics in the m/z domain. Traditional, single pulse (signal averaged) and multiplexing IMS acquisitions demonstrate lowered resolution at extended ion gate pulse widths and minimizing this parameter results in decreased sensitivity from gate depletion effects and lowered ion gate duty cycle. Signal processing techniques involving BPDN was demonstrated on experimentally acquired IMS–MS data using the diastereoisomer ractopamine which exhibits two distinct gas-phase conformations with K_0 values differing by 0.022 $cm^2\ V^{-1}\ s^{-1}$. Systematically adjusting the experimental parameters related to effective ion gate pulse width, we illustrate the capacity of this method to yield peak resolutions >1.0 for ion gate pulse widths that routinely yield unresolved arrival time distributions utilizing standard deconvolution procedures or equivalent gate pulse widths that utilize traditional signal averaged IMS datasets. When viewed from the perspective of a single peak, BPDN can increase the observed resolving power by more than a factor of 2. Because resolution and ion throughput are simultaneously maximized, the application of this optimization method represents a fundamentally different approach to multiplexed IMS signal processing.

1. Introduction

Ion mobility spectrometry (IMS) is a rapid gas-phase separation technique with applications in threat detection and wide acceptance across many scientific disciplines. IMS separates ion populations based on a multitude of gas-phase ion properties that include ion-neutral collision cross section, number of charges, charge location, and propensity for gas-phase clustering. Coupling an IMS to a mass spectrometer (IMS–MS) provides improved peak detection capability to resolve ions in both the drift time and m/z domain. For the reason that IMS systems can provide a complementary dimension beyond m/z [1–5], many commercial mass spectrometers have now incorporated ion mobility measurements prior to m/z analysis. In select cases and operating parameters, IMS is capable of providing near or baseline separation of isomers [6–8]. While the range of m/z available to modern mass spectrometry ranges across multiple orders of magnitude, the range of drift times typically measured (related to reduced mobility and ion-neutral collision cross-sections) are comparatively compressed. Furthermore, while IMS–MS systems have demonstrated a unique capability for separating different classes of compounds (e.g. carbohydrates, peptides, and lipids), separations of isomers or isobars from compounds of similar classes is often more challenging while of greater interest [9–11].

A common observation for the analysis of acquired IMS–MS data for unknown mixtures, is the presence of multiple drift time peaks at a provided m/z. In these situations, identifications of drift time peaks may be particularly challenging because often the total number of peaks present and the peak profiles (e.g. intensity, peak shape, and peak width) are unknown. To distinguish the features of two closely separated conformers in the mobility domain, a range of operating conditions (i.e. temperature, pressure, drift gas, voltage)

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can be favorably altered on an IMS system to improve resolution required for peak identification. For an IMS system that utilizes a Bradbury Nielsen ion gate (BN), improvement in resolution can often be achieved by simply minimizing the contributions to peak width attributed to the gate pulse width duration. Operating at lower gate pulse widths routinely diminishes the ion population permitted into the drift cell resulting in decreased sensitivity at the detector. Therefore, longer data acquisition times are often necessary for confident identification of mobility separated peaks at lowered gate pulse widths. Unfortunately, longer data acquisitions may not be suitable when dealing with limited sample concentrations or when an IMS–MS system is coupled to an additional chromatographic technique (i.e. LC or GC).

Altering the gate pulse width duration represents just one of a range of methods widely utilized to improve the separating power of dispersive or drift tube IMS systems. Other methods include using non-traditional gating techniques [12–14], post-signal processing approaches [15–18], physical modifications to the gate [19–21], and identifying optimal instrument operating parameters [22,23]. Recent efforts to modify the gating region of the IMS to minimize the ion gate pulse width, but maximize the ion packet density using atmospheric pressure IMS drift cells, have yielded impressive results and continued pursuit of these approaches may even prove compatible with multiplexing techniques to enhance experimental duty cycle [19–21]. Additional approaches to enhancing resolution in the mobility domain include extended separation paths [24] and the concept of the ion compressor to theoretically indefinitely extend the drift path length [25]. Scanning approaches such as trapped ion mobility spectrometry have also demonstrated elevated levels of separation capacity while maintaining the ability to calculate ion-neutral collision cross sections following calibration procedures [26–28].

When viewed as a collective set of methods and techniques, many of the described efforts to improve sensitivity while maximizing resolution have focused heavily on instrumental efforts. Alternatively, post-processing techniques that are compatible with data containing relatively sparse signals (e.g. the predominance of the data bins are zeros) demonstrate the capacity to accurately reconstruct the target spectrum without sacrificing spectral resolution [29]. Though leveraged extensively in the fields of computer vision [30], medical imaging [31], and radar applications [32], these sparse spectral reconstruction approaches, specifically convex optimization techniques, have yet to be fully explored for IMS and IMS–MS data acquisition. The first known effort to incorporate ℓ_1 minimization techniques in association with a stand alone ion mobility was the report by Pomareda et al. where the least absolute shrinkage and selection operator (LASSO) technique was used as part of a Gaussian decomposition strategy to identify spectral features [15]. Their work demonstrated a marked improvement in IMS signal to noise ratio (SNR) but focused solely on signal single pulse, signal averaged modes of data collection an did not fully explore the impact of LASSO on resolving power as it relates to gate pulse width. Furthermore, the m/z separation afforded using a mass spectrometer provides inherently sparser IMS spectra which are maximally exploited using convex optimization approaches, often referred to as ℓ_1 minimization techniques [29].

Previously, our laboratory demonstrated a range of multiplexing approaches for drift tube ion mobility systems that enhance signal throughput without impacting separation capacity [6,14,33]. Significant improvement in ion statistics remain a primary motive for their use, however, these multiplexing techniques are not always free of defects. More specifically, the fidelity of the reconstructed signal is dependent upon correlating the applied ion gate pulsing waveform with the recorded signals. For the reason that the distribution of ion packets is not a static quantity (i.e. dependent upon multiple factors including, time, temperature, and ion reactivity), deviations between the applied waveforms and observed peaks can contribute to spectral errors. Nevertheless, the multiplexed nature of the IMS experiment produces data sets that are highly sparse and directly compatible with contemporary optimization techniques.

Using a diastereoisomer that exhibits two well-defined arrival time distributions as a test case, we demonstrate the benefits of applying convex optimization techniques for multiplexed IMS–MS measurements to realize significant gains in resolution at higher gate pulse width measurements. Because convex optimization allows IMS resolution to be maintained even for comparatively large effective gate pulse widths, this approach holds promise to minimize data acquisition time and has direct implications for coupling ion mobility and mass spectrometry systems with additional chromatography techniques.

2. Basis pursuit reconstruction of ion mobility spectra

2.1. Factors influencing ion packet distributions

For an idealized ion packet under IMS low-field normal operating conditions (reduced electric field strength $E/N \leq 2$), the *major* contributions to peak width observed after the ions have traversed the drift cell (measured at the detector), include the inherent diffusion of an ion and the duration of the admitting ion gate pulse width [22]. At low-field conditions, temporal diffusion of the thermalized ion packet is largely dependent upon the temperature of the neutral drift gas as described by Eq. (1), where k_B is the Boltzmann constant, T is defined by the temperature of the drift cell, q is the charge of the ion, and V is the voltage applied from the gate to detector under a constant uniform electric field, and t_d is the drift time of the ion measured from the center of the applied initial gate pulse:

$$t_{\text{diffusion}} = \left[\frac{16 \ln 2 k_B T}{qV}\right]^{1/2} t_d \tag{1}$$

The separation capacity of a dispersive IMS instrument is routinely quantified with the unitless resolving power (R_p) as shown in Eq. (2), where the peak width (FWHM) is measured at the full width at half-maximum:

$$R_p = \frac{t_d}{\text{FWHM}} \tag{2}$$

Under the pretense that the arrival time distribution of the arriving ion population is Gaussian (commonly observed under low gate pulse widths), we can apply Eq. (3) which relates the gate pulse duration (t_{gpw}) and the diffusion ($t_{\text{diffusion}}$) to the temporal spread (FWHM) measured after the initial packet of ions has reached the end of the drift cell [22]:

$$\text{FWHM} = \sqrt{t_{gpw}^2 + t_{\text{diffusion}}^2} \tag{3}$$

While R_p is commonly used to assess instrument performance, this parameter does not provide an explicit measurement of the difference between two peaks necessary for quantifying levels of separation desired for complex mixtures. A more standard approach is the quantitative measurement of resolution (R_s) which is widely used in chromatographic disciplines to describe the separation between two peaks [34]. In Eq. (4), t_{d1} and t_{d2} are the respective drift times of two adjacent peaks and W_{B1} and W_{B2} their associated peak widths measured at baseline (4σ). We will exclusively use Eq. (4) in the context of our discussion and measurement of resolution:

$$R_s = \frac{2 \cdot (t_{d2} - t_{d1})}{(W_{B1} + W_{B2})} \tag{4}$$

Operating conditions such as temperature, voltage, and pressure can be optimized in order to improve resolution and resolving

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