Coded Apertures in Mass Spectrometry

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Abstract

The use of coded apertures in mass spectrometry can break the trade-off between throughput and resolution that has historically plagued conventional instruments. Despite their very early stage of development, coded apertures have been shown to increase throughput by more than one order of magnitude, with no loss in resolution in a simple 90-degree magnetic sector. This enhanced throughput can increase the signal level with respect to the underlying noise, thereby significantly improving sensitivity to low concentrations of analyte. Simultaneous resolution can be maintained, preventing any decrease in selectivity. Both one- and two-dimensional (2D) codes have been demonstrated. A 2D code can provide increased measurement diversity and therefore improved numerical conditioning of the mass spectrum that is reconstructed from the coded signal. This review discusses the state of development, the applications where coding is expected to provide added value, and the various instrument modifications necessary to implement coded apertures in mass spectrometers.

Keywords
sector mass spectrometry, coded apertures, computational sensing, cycloidal mass analyzer, Mattauch-Herzog, miniaturization
1. INTRODUCTION

Advances in the performance of computing hardware have transformed the field of sensors and analytical instrumentation design. Semiconductor processing [i.e., Moore’s Law (1, 2)] and materials chemistry innovations (3, 4) have permitted dramatic increases in transistor speed. The resulting increases in computing power have enabled a paradigm shift in how sensors and analytical instruments are designed and operated. This new approach is referred to as computational sensing and integrates hardware and software design to optimize application-specific sensor performance. This is in direct contrast to the more familiar historical approach to sensing that attempts to adapt existing technology from a traditional application to a new area (e.g., adapting mass spectrometers in analytical chemistry labs to allow trace explosive detection in the field). Computational sensing includes a “front-end” rethinking of sensor design utilizing a mathematical representation of the sensing process as well as “back-end” signal processing that more efficiently achieves desired performance from limited data. As such, computational sensing includes enhancements to a broad array of sensing modalities, technologies, and environments. For example, compressive sensing theory (5–9, 10) is the realization that natural signals contain correlations that render full sampling redundant and allow signal recovery from undersampled measurement; adaptive sensing theory (11–15) is the concept that the optimal approach to measurement is adjusting the physical measurement being made as the instrument learns about the sample. Numerous instantiations of these and related techniques and tools have been demonstrated, including the single-pixel camera (16), the coded aperture snapshot spectral imager (17, 18), the coded aperture compressive temporal imager (19), compressive magnetic resonance imaging (20), compressive holoography (21, 22), compressive X-ray tomography (23, 24), ion trap multiresonant frequency excitation (25), pseudorandom mass spectrometers or monochromators (26), and coded aperture mass spectrometry (MS) (27–30); the last technique is the topic of this review.

This review focuses on recent progress in the theory and experimental demonstration of spatial coding (i.e., coded apertures) in MS. To provide the most timely and informative review, we do not attempt to cover temporal coding in MS and instead refer the reader to several relevant publications (25, 31–33). This limitation in scope further implies that the review focuses on sector-based mass spectrometers, as such instruments are the most appropriate for the implementation of spatial coding. We begin with a general introduction of aperture coding, discuss where coding is useful, and provide some historical context. We then discuss the mathematical basis for spatial coding and the reconstruction of spectra from the coded signals. Next, recent simulations and experimental results in three geometries are reviewed: a simple 90-degree magnetic sector, a Mattauch-Herzog mass spectrometer, and a cycloidal mass analyzer. The review also examines the subsystem requirements when coding is utilized, and in particular, the geometric constraints that coding places on the system. Finally, we discuss the conditions under which spatial coding can be expected to significantly improve mass spectrometer performance, and thus, by implication, this also covers the limitations of coding.

1.1. What Is Aperture Coding?

Conventional instruments, such as optical spectrometers and mass spectrometers, essentially act as sorters. Inputs such as ions or photons are sorted spatially, temporally, or both via a system architecture that uses relevant physics. Examples of spatially sorting system architectures include diffraction gratings in optics and sector and distance-of-flight mass analyzers in MS. Examples of temporally sorting system architectures include time-of-flight and ion trap mass analyzers. Figure 1 compares three different system architectures that, using relevant physics, implement no sorting (Figure 1a), near-perfect sorting (Figure 1b), and coded sorting (Figure 1c). In the
absence of sorting, the system throughput is large. However, no information can be inferred about
the system input (Figure 1d). In perfect sorting, the system architecture is designed using relevant
physics to implement near-perfect sorting. The spectrum can be directly inferred through a simple
calibration of the sorting parameter (Figure 1e). However, the architecture choices necessary to
achieve near-perfect sorting limit the system performance because the majority of the system input
is lost in the sorting process. In the coded sorting case, the system architecture still sorts but under
the realization that near-perfect sorting is not necessary. There is a vast continuum between no
sorting and near-perfect sorting. With appropriately structured sorting, the ability to infer the
spectrum is maintained through a computational inference but without the performance-crippling
architectural choices required for near-perfect sorting (Figure 1f).

Figure 1g–i show examples of a simple magnetic sector mass analyzer with a multichannel
position-sensitive imaging array detector with architecture choices to implement various degrees
of sorting. In the sector with no sorting, the ions are introduced into a region of uniform magnetic
field and travel along curved trajectories to the detector. However, their position at the detector
plane is random and unsorted (Figure 1g). As such, it is not possible to extract a spectrum from the
detector response. In the sector implementing near-perfect sorting, a narrow slit is used to localize
where the ions enter the magnetic field region, and an acceleration grid constrains the energy of
the ions. The position on the detector now depends primarily on the mass-to-charge ratio (m/z),
and a spectrum can be directly inferred from the spatial distribution of the detector response
(Figure 1b). The resolution is inversely proportional to the slit size, whereas the throughput
is directly proportional to the slit size, thereby introducing a performance-limiting throughput
versus resolution trade-off. In the coded sector, the slit is replaced with an array of slits of different
sizes called a coded aperture. The position in the detector plane now jointly depends on the m/z and
the specific pattern of slits (Figure 1i). The spectrum can be computationally inferred from the
spatial distribution of the detector response. The resolution depends on the smallest feature size,
and the throughput depends on the open area, thus breaking the throughput versus resolution
trade-off and enhancing performance. In this example, the throughput increases threefold, as
shown by three times as many circles of each color in the coded sorting (for the same acquisition
time) leading to a threefold increase in signal intensity and associated signal-to-background ratio
(SBR) after spectral reconstruction.

1.2. How Does Coding Improve Performance?

Several potential gains can accrue from coded aperture MS, arising primarily from two factors:
the Jacquinot (or open area) advantage (34) and the Fellgett (or multiplex) advantage (35). The
Jacquinot advantage occurs because coding allows for maximizing spectrometer throughput with-
out sacrificing spectral resolution. The potential benefit to the system designer depends on
the specific application but can include the following: system size reduction without a concomitant
performance decrease, system performance increase without concomitant system size increase,
relaxed ion-source design complexity, and operation in situations with extremely limited analyte
quantity. The Fellgett advantage occurs because coded instruments combine multiple signal ele-
ments together upon transduction. For the case of additive noise, this increases the signal level
with respect to the underlying noise (i.e., increases the signal-to-noise ratio, SNR) and therefore
reduces the error of the estimated spectrum.

If the system is shot-noise limited, however, the situation is more complicated. Speaking gen-
erally, multiplexing has no impact on the mean error level of the estimated spectrum. However,
there is an interesting interplay with the concept of transform noise discussed below. When the
signal of interest is sparse (it occupies only a small fraction of the total spectral channels) and also
stronger than the background, then multiplexing concentrates error in the channels outside the channels of interest. As the mean level of error is unchanged, this implies that the error in the channels of interest must necessarily have subshot-noise–level error.

1.3. History and Progress

The first efforts in coded aperture spectroscopy arose in infrared spectroscopy, specifically in the work of Golay in the 1950s (36, 37), and it developed rapidly (38). Eventually, the mathematical benefits of Hadamard matrix (39)-based codings were understood, and most coded aperture spectroscopy became based upon these methods (40–44), with development continuing over the years (45–48). Many of the early approaches had only a single detector element [or limited one-dimensional (1D) arrays of detectors], and as such, required coding apertures on the input and output planes to operate (they frequently required physical motion of one or both apertures). An
additional impact of this limitation was that most of the systems only achieved either the Jacquinot or Fellgett advantage but not both. Roughly a decade ago, the availability of large detector arrays led to the development of a fully static, single-mask aperture coding approach that achieved both the Jacquinot and Fellgett advantages (49).

These developments did not go unobserved in the MS community (50), but the need for dynamic actuation of the aperture codes reduced interest and limited the application of coding ideas to time-of-flight spectroscopy (31, 51, 52) until recently (27–30). These recent demonstrations of spatial coding covered in this review are based on the static coding described in the paper by Gehm et al. (49).

2. THE MATHEMATICS OF CODING IN MASS SPECTROMETRY

The mathematical treatment of aperture coding in MS involves the development of a matrix equation that relates the vector of acquired measurements, \( \mathbf{g} \), to the vector representing the input mass spectrum, \( \mathbf{S} \):

\[
\mathbf{g} = \mathbf{H}\mathbf{S} + \mathbf{n}. \tag{1}
\]

Here, \( \mathbf{H} \) is the system matrix or measurement matrix that incorporates a forward model of the physics and architecture of the measurement system (including the coded aperture), and \( \mathbf{n} \) is a vector representing any additive noise acquired during the measurement process. Reconstruction or inversion is then the process of recovering an estimate, \( \hat{\mathbf{S}} \), of the input spectrum, \( \mathbf{S} \), given a set of acquired measurements, \( \mathbf{g} \) (the recovery will not generally be exact due to the presence of noise). A schematic of the general situation is shown in Figure 2, and the various aspects are expanded upon in the subsections below.

2.1. Measurement Matrix and Forward Model

For any specific architecture, determining the measurement matrix \( \mathbf{H} \) begins by developing a forward model that describes the specific architectural and physical details of the system. These details are captured in the propagator \( b(x, y, x', y', m/z) \) that maps an ion \( m/z \) at a location \((x', y')\) to a detector location.

Figure 1

The aperture coding concept. System input with system architecture that, given the relevant physics, (a) does not sort, (b) implements near-perfect sorting, and (c) implements coded sorting. (d) Spectral information cannot be inferred from a system architecture with no sorting. (e) Spectral information can be directly inferred via simple calibration of the sorting parameter from a system architecture designed for near-perfect sorting. (f) Spectral information can be obtained via a computational inference between the sorting parameter and system architecture for coded sorting. The signal to background is increased, while the resolution remains the same. (g) An example of a magnetic sector physics architecture with no sorting capability. Ions pass into a region of uniform magnetic field (gray) directed out of the page. No information can be obtained from the signal at the detector. (h) An example of a magnetic sector designed to implement perfect sorting. An acceleration grid is added to localize the ion energy, and a narrow slit aperture is added to constrain the ion position before entering the region of magnetic field. Spectral information can be directly inferred via calibration of the position on the array detector. (i) An example of a magnetic sector designed for coded sorting. The acceleration grid constrains the ion energy, while the slit in (b) is replaced with a coded aperture of multiple slits of various widths. In this example, the coded aperture has two slits, one of which is twice the width of the other separated by the width of the smaller slit. The spectral information can be computationally inferred from the spatial distribution of the signal at the detector. The resulting spectrum has the same resolution due to the same minimum slit size but higher intensity due to the increased throughput.
Figure 2

Schematic of the spectral reconstruction process. The input mass spectrum, S, interacts with the physical architecture of the system and is corrupted by noise, n (both shot and additive), to yield a set of measurements, g. Knowledge of the system architecture, including the aperture code t, yields a system-forward model (measurement matrix), H, that describes the measurement process. A reconstruction algorithm then takes the acquired measurements, g, and the system-forward model, H, and calculates \( \hat{S} \), an estimate of the input mass spectrum.

In the input plane of the system to a location \((x, y)\) in the detector plane of the system (this treatment assumes that all ions have encountered an acceleration potential and, as a result, all velocity-dependent effects can be written in terms of the ion \(m/z\)). The details of the propagator, of course, depend on the system specifics. For a system with an input aperture function, \(t(x', y')\), the ion distribution, \(f(x, y)\), in the detector plane is then

\[
f(x, y) = \int \int \int dx' dy' d(m/z) t(x', y') b(x, x', y, y', m/z) S(x', y', m/z),
\]

with \(S(x', y', m/z)\) being the input mass spectral density. In a conventional instrument, \(t(x, y)\) describes the open area of the input slit, but in a coded system it describes the structured pattern of openings in the coded aperture.

The ion distribution is then transduced into a set of digital measurements via a 1D or two-dimensional (2D) array of detector elements. We let \(p_i(x, y)\) represent the pixel function of the \(i\)-th detector element in the array. The pixel function is defined to take a value of 1 within the spatial extent of the ion-sensitive region of the detector element and 0 outside. With this definition, the measurement on the \(i\)-th detector element is then given by

\[
g_i = \int \int dx dy p_i(x, y) \int \int dx' dy' d(m/z) t(x', y') b(x, x', y, y', m/z) S(x', y', m/z) + n_i,
\]

with \(n_i\) the additive noise contribution at the \(i\)-th detector element. If we assume that the input mass spectral density is spatially uniform (treating the nonuniform case leads to a theory of coded aperture mass spectral imaging), and we discretize the spectrum such that \(S_j\) is the \(j\)-th \(m/z\) bin, then we can write this as \(g_i = \sum_j H_{i,j} S_j + n_i\). We then interpret the indexed quantities as vectors and matrices to yield \(g = HS + n\), as previously mentioned. Note that for a conventional, slit-based instrument, \(H\) takes the form of an identity matrix—there is a one-to-one correspondence between ion \(m/z\) and a specific detector element. In a coded system, \(H\) has a complicated, off-diagonal structure representative of multiplexing. For a broad class of scenarios, \(H\) takes the form...
of a discrete convolution of the discretized input spectrum \( S \) and discretized aperture code, \( t \). Practically, the aperture code \( t \) is then chosen to maximize the invertibility of \( H \) given a desired open aperture.

### 2.2. Reconstruction Algorithm

Reconstruction is then the process of generating an estimate \( \hat{S} \) of the input spectrum \( S \), given the measurements, \( g \). Conceptually, we can view this as forming \( \hat{S} = H^{-1}g = H^{-1}(HS + n) = S + H^{-1}n \), which clarifies why the presence of noise precludes perfect reconstruction. Practically, numerical issues generally restrict reconstruction via direct application of the inverse matrix, \( H^{-1} \). Various techniques, including ordinary least squares (53), non-negative least squares (54), Richardson-Lucy deconvolution (55), or more advanced inverse solver with regularization (56), are used in practice depending on the specific details of the problem.

### 2.3. Potential Issues with Reconstruction

There are a number of important caveats regarding reconstruction, the first being the numerical sensitivity of inversion and wide array of potential methods mentioned above. More importantly, successful inversion depends crucially on the accuracy of the forward model. Mismatch can occur either because specific physical or architectural details have been omitted in the development of the physical model (e.g., for analytic simplicity) or because the as-built system does not perfectly represent the intended design. In either case, some form of calibration is generally required to refine the forward model to the point where high-quality reconstructions are possible. The final caveat regarding reconstruction is the issue of transform noise. When forming the reconstruction, noise on a given \( m/z \) channel will be distributed across many channels upon inversion, potentially adding noise even in channels where there is no signal. In the case of additive noise, as described above, this has little effect, as nominally every channel has a similar noise level; for shot-noise–limited situations, however, channels associated with strong spectral lines contain greater amounts of noise than the others. In this case, transform noise can appear as weak spectral features (or occlude actual weak spectral features that are present). This is an unavoidable issue with shot noise in a multiplexed measurement, and care must be taken to understand the intended system application and whether the transform noise issue will be problematic.

### 3. PROOF-OF-CONCEPT DEMONSTRATIONS

In this section, we describe several proof-of-concept demonstrations showing how aperture coding as applied to sector mass spectrometers can increase the throughput and SBR without adversely affecting the instrument resolution. We begin with the initial demonstrations of 1D and 2D aperture coding using a simple 90-degree magnetic sector instrument and then show how aperture coding is compatible with two other sector mass analyzers, the Mattauch-Herzog and cycloidal mass analyzers.

Although a signal multiplexing technique similar to a coded aperture approach was mentioned in a paper by C.J. Eckhardt and Michael L. Gross in 1970 (50), the first demonstrations of aperture coding using 1D and 2D codes in sector MS was accomplished using a simple 90-degree magnetic sector instrument and then show how aperture coding is compatible with two other sector mass analyzers, the Mattauch-Herzog and cycloidal mass analyzers.

Figure 3a shows a diagram of the experimental apparatus. The apparatus comprises an electron ionization source built from Kimball Physics eV parts, two \( 25 \times 25 \times 100 \text{-mm} \) bar magnets connected via a stainless steel yoke producing a field of 0.45 T, and a 40-mm diameter 10-\( \mu \text{m} \) pitch multichannel plate (MCP) detector with a phosphor screen and camera (camera not
Figure 3
One-dimensional coding proof of concept. (a) Schematic of the 90-degree magnetic sector mass analyzer used in the proof-of-concept experiments. (b) Diagram of the cyclic S matrix-coded apertures used. (c) Image of the phosphor screen for ethanol using a slit and order S-23-coded aperture. (d) Comparison of reconstructed spectra using slit and cyclic S-23-coded apertures. The inset shows the full width at half maximum for both the slit and reconstructed cyclic S-23 spectrum, indicating that the resolution remains the same. (e) Comparison of reconstructed spectra of slit and coded apertures for a small quantity of analyte. The coded aperture allows detection of peaks buried in the noise in the slit spectrum. Panels b–e adapted with permission from Reference 28 and Springer. Copyright 2015, American Society for Mass Spectrometry.

shown in figure). The electron ionization source was designed to have minimal dispersion in the ion energy and angle, as this apparatus lacked double-focusing properties. Further details on the apparatus and ion source design can be found in the supplementary information of Chen et al. (28). A forward model for this apparatus was developed and calibrated using argon and then tested using coded apertures based on cyclic S matrices (+4) up to order S-23 using 1D codes (Figure 3b) and up to order S-15 using 2D codes (see Figure 4a and Section 3.2) with a minimum feature size of 125 µm. Acetone and ethanol were utilized as the test analytes.
As described in Section 2.1, developing a forward model requires deriving the propagator of the system that maps a point on the aperture plane to a point on the detector plane. For this 90-degree system, using the Lorentz force law and the radius of curvature of the ion path, the propagator for the 90-degree system is

\[
b(x, x', y, y', m/z) = \delta \left[ x - x', y - \sqrt{\frac{8U (m/z)(u/e)}{B}} y' - y'^2 \right].
\]

Where the primed coordinates are measured in the aperture plane, the unprimed coordinates are measured on the detector plane, \( y \) is the mass dispersive direction, \( m/z \) represents the mass-to-charge ratio, \( B \) is the magnetic field, \( U \) is the ion energy, \( \delta \) is the Dirac delta function, and \( u/e \) is the ratio of an amu to the elementary charge in the desired set of units. A full derivation of Equation 4 can be found in the supplementary material of Chen et al. (28). Upon calibrating the forward model with singly and doubly charged argon, the forward model was modified to include a path
length–dependent magnification in the nonmass dispersive direction due to the angular spread of the ion source:

\[
b(x, x', y, y', m/z) = \delta \left\{ x - \left[ 1 + M_x(m/z)^{1/4} \right] x' \right\}
\]

This continuous propagator is then converted into a discretized forward model by the action of the finite detector pixels [see supplementary material in Chen et al. (28)]. To finalize calibration, we take an ion energy of 2 keV and adjust the parameters \( B, M_x, \) and \( \delta \) (pixel size) to achieve the best fit with the experimentally observed measurements of singly and doubly charged argon.

### 3.1. One-Dimensional Coding in a 90-Degree Magnetic Sector

Figure 3c shows images of the MCP phosphor screen of the slit and S-23–coded aperture with ethanol as the analyte. The images on the MCP for both the slit and coded aperture were recorded using the same exposure time. Figure 3d shows reconstructed mass spectra from the images in Figure 3c. The reconstructed spectrum using the S-23 aperture shows a greater than tenfold increase in throughput over the spectrum using the slit. In addition, as shown in the inset to Figure 3d, the full width at half maximum of the peaks in the slit and S-23 reconstructed spectra are the same, indicating that the coded aperture increases throughput without degrading the resolution.

Figure 3e demonstrates one key advantage of coding. The top shows a spectrum of ethanol measured at 1.0 \( \mu \)torr using a slit, whereas the bottom shows a spectrum of ethanol at the same pressure but with an S-23–coded aperture. In the spectrum reconstructed from the S-23–coded aperture, the SBR is significantly higher, enabling detection of peaks due to ethanol fragments that are lower intensity than the noise in the spectrum acquired using the slit.

### 3.2. Two-Dimensional Coding in a 90-Degree Magnetic Sector

In the optical domain, 2D spatially coded patterns are preferred over 1D codes. The 2D codes provide increased measurement diversity and therefore improved numerical conditioning of the reconstruction. Using the same 90-degree sector instrument described above with the same forward model, the 1D slits were replaced with 2D S-matrix codes (Figure 4a) (29). For better comparison, the length of the slit was allowed to vary to match the overall linear dimension of the coded aperture. Figure 4b–g show the image on the detector for the slit and corresponding coded aperture using ethanol as the analyte. Figure 4b shows the reconstructed spectra from the images in Figure 4b–g. Similar to the 1D-coded apertures, the 2D apertures show an increasing throughput with aperture order. However, due to the necessity of incorporating support structures into the fabricated apertures, the enabled throughput gain is actually less than with a 2D aperture of the same order. Furthermore, a slight loss in resolution was observed in the reconstructed spectra using the coded aperture. This is likely a result of the relatively poor imaging properties (such as nonfocusing in the z-direction) of this 90-degree sector when compared to optical spectrometers using similar codes that do not exhibit a loss in resolution.

### 3.3. Double-Focusing Sector Instruments

The simple 90-degree magnetic sector mass spectrometer is used to demonstrate the ability of aperture coding to increase instrument SBR without adversely affecting resolution or changing the...
measurement time required to achieve a given level of performance. However, it has limited mass range and resolution due to the inability to correct for the dispersion in the ion source. In contrast, double-focusing mass analyzers, such as the Mattauch-Herzog (57), Bainbridge-Jordan (58), and Hinterberger-Konig (59), offer a first-order correction to the energy and angular dispersion of the ions emerging from the ion source. The cycloidal mass analyzer developed by Bleakney & Hipple (60) produces perfect focusing for sufficiently uniform fields. The following sections describe work proving the compatibility of aperture coding with the Mattauch-Herzog and cycloidal mass analyzers.

### 3.3.1. One-dimensional coding in a double-focusing Mattauch-Herzog mass analyzer

To evaluate the compatibility of aperture coding with the Mattauch-Herzog mass analyzer, Russell et al. (27) compared simulated results using a first-order transfer matrix formalism, a finite element field solver, and a particle tracing algorithm; they compared the simulated results with those obtained by replacing the slit in an OI Analytical miniature Mattauch-Herzog instrument with an S-7–coded aperture. Figure 5a shows some characteristic particle trajectories emanating from the central optic axis and ±1,150 µm from it for different masses that were calculated using the finite element field solver and particle tracing algorithm.

Using the transfer matrix formalism for the Mattauch-Herzog geometry described in detail in Burgoyne et al. (61), the simulated image of the S-7 aperture pattern at the detector was compressed but well preserved (Figure 5c). As the transfer matrix formalism does not allow for fringing fields and incorporates the paraxial approximation that is valid only for distributions of ions close to the optic axis, the compatibility of the Mattauch-Herzog mass analyzer was investigated using finite element field solvers for the electric and magnetic fields. A custom particle tracing program based on the velocity Verlet algorithm and bilinear field interpolation was used to determine the simulated image quality of an S-7–coded aperture on the detector plane (Figure 5d). Similar to the transfer matrix calculation, the aperture pattern was also compressed but well preserved. Unlike
the transfer matrix, the finite element simulations showed a nonuniform intensity distribution that is likely a result of fringing fields near the entrance and exit of the electric sector.

To verify the compatibility of aperture coding with the Mattauch-Herzog mass analyzer, the slit in an OI Analytical/Xylem IonCam transportable mass spectrometer (http://www.oico.com/documentlibrary/3390spec.pdf) was replaced with an S-7–coded aperture. Higher-order apertures were not possible due to the width of the electric sector gap. The experimental results showed a similar compression of the coded aperture with poorer than expected resolution of the aperture and an intensity falloff at the edges of the pattern (Figure 5e). These effects are likely a result of the nonuniform illumination of the aperture by the ion source, fringing fields from the narrow electric sector gap, and nonuniform attenuation of the pattern by the circular Herzog shunts at the entrance and exit of the electric sector. Results showed that the Mattauch-Herzog is compatible with aperture coding, but modifications are needed to optimize the compatibility. Work is underway to develop electric sectors capable of imaging higher-order codes with the Mattauch-Herzog mass analyzer.

3.3.2. One-dimensional coding in a cycloidal mass analyzer. Whereas most double-focusing mass analyzers correct for energy and angular dispersion to first order, the cycloidal mass analyzer described by Bleakney & Hipple (60) is unique among sector mass analyzers in that it exhibits double focusing to all orders. Using perpendicularly oriented uniform magnetic and electric fields, ions emanating from the ion source travel cycloidal trajectories. The position \(a\) measured from the ion source at which an ion crosses the detector plane after traversing a 360-degree cycloidal path is described by the following equation,

\[
a = \frac{m}{Z} \frac{2\pi B^2}{E} + d, \tag{6}
\]

where \(m/z\) is the ion mass to charge, \(B\) is the magnitude of the magnetic field, \(E\) is the magnitude of the electric field, and \(d\) represents the distance between where the ion was generated and the origin of the coordinate system at the center of the ion source. The position does not depend on the energy or angle of ion emission from the ion source. From this equation it is also evident that the cycloidal mass analyzer will be inherently compatible with aperture coding, provided that the electric and magnetic fields are of sufficient uniformity. A prototype instrument is currently under development to verify this hypothesis.

4. FUTURE DIRECTIONS

4.1. System Requirements

As discussed in Section 3.3, some technical challenges are associated with adapting traditional mass analyzer geometries such as the Mattauch-Herzog and cycloid instruments with aperture coding. Both the cycloid and Mattauch-Herzog mass analyzers require ion sources that can produce ions over an extended region along the axis of the coded aperture. In addition, both require use of a focal-plane ion array detector. In recent years, a number of ion array detectors have been developed that can meet this requirement, including one based on a charge transimpedance amplifier array (62, 63) and charge-coupled device (CCD) technology called the IonCCD (64). The Mattauch-Herzog instrument, which is used in a variety of applications ranging from miniature systems (65–67) to inductively coupled plasma mass spectrometers for elemental analysis (68) and secondary ion mass spectrometers (69), was shown to be compatible with coding via simulation and experiment. However, fringing fields at the entrance and exit of the electric sector limit the ability to resolve
complex codes. Novel electric sector geometries are needed that limit the effects of fringing fields to fully realize the throughput enhancement enabled by aperture coding in the Mattauch-Herzog mass analyzer. The cycloid mass analyzer is inherently compatible with aperture coding and is particularly well suited to miniaturization for environmental applications (70–73) due to the overlapping nature of the electric and magnetic sectors. However, the imaging quality of the cycloid instrument depends on the uniformity of the electric and magnetic field. It is relatively easy to produce a uniform electric field using an array of regularly spaced electrodes. However, novel permanent magnet geometries that are lightweight and provide high field uniformity analogous to the Halbach (74) and Stelter (75) arrays are necessary to fully realize the potential of a miniature cycloidal mass analyzer coupled with aperture coding.

4.2. Applications

Coded aperture techniques should find wide application in areas that are highly sample constrained or that require simultaneous detection or miniaturization. Instruments that collect spectra in series, such as ion traps or quadrupoles, are not good candidates for coded aperture technique, but temporal coding is applicable (25). Instruments that detect ions in parallel will benefit from these techniques, as described in three examples. First, secondary ion mass spectrometry (SIMS) uses a beam of ions to ionize solid surfaces (76). In sector-based SIMS, these ions are detected using an array of detectors, which are frequently electron multipliers. Increasing throughput would allow a lower concentration limit to be detected or more samples to be processed. This is a limiting factor in the widespread adoption of SIMS-based diagnostic techniques (77). Second, isotope ratio mass spectrometry is frequently performed with magnetic sector-based instruments, as it requires high-precision and high-quality peak shapes (78). Increasing sensitivity and improving sample utilization through coding would allow smaller samples to be processed. Finally, miniature magnetic sector instruments would benefit from the throughput increase while maintaining resolution that aperture coding provides. The smaller size of the instrument limits the SNR because of both a reduction in the total number of ions generated and the reduced capability of smaller pumps, requiring the efficient use of samples.

4.3. Direct Detection

A promising research avenue for future consideration is direct detection. Here, the aperture code is chosen not to maximize the invertibility of $\mathbf{H}$, but rather to produce a set of distinct, distinguishable signatures that individually correspond to any one of a finite set of compounds or mixtures of interest. In this model, spectral estimation is not required, and direct detection of the compounds of interest is determined by the presence of the corresponding signature(s). The primary advantage of direct detection is system resource efficiency; such an approach would typically require fewer detector elements than a corresponding general instrument designed for full spectral estimation. A further enhancement would be to consider methods for adaptively adjusting the aperture code in response to prior measurements to maximize discrimination between compounds of interest that may be present. A version of this approach was recently demonstrated in optical spectroscopy by one of the authors (35).

**DISCLOSURE STATEMENT**

S.T.D. and Z.E.R. are establishing a new venture based on technology covered in this review. The following patents related to the technology discussed here have been filed: US 7399957 B2

ACKNOWLEDGMENTS


LITERATURE CITED

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New From Annual Reviews:

**Annual Review of Cancer Biology**
cancerbio.annualreviews.org • Volume 1 • March 2017

Co-Editors: **Tyler Jacks**, Massachusetts Institute of Technology
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The *Annual Review of Cancer Biology* reviews a range of subjects representing important and emerging areas in the field of cancer research. The *Annual Review of Cancer Biology* includes three broad themes: Cancer Cell Biology, Tumorigenesis and Cancer Progression, and Translational Cancer Science.

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