RESEARCH ARTICLE

IonCCD™ for Direct Position-Sensitive Charged-Particle Detection: from Electrons and keV Ions to Hyperthermal Biomolecular Ions

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Abstract

A novel, low-cost, pixel-based detector array (described elsewhere Sinha and Wadsworth (76(2), 1) is examined using different charged particles, from electrons to hyperthermal (<100 eV) large biomolecular positive and negative ions, including keV small atomic and molecular ions. With this in mind, it is used in instrumentation design (beam profiling), mass spectrometry, and electron spectroscopy. The array detector is a modified light-sensitive charge-coupled device (CCD) that was engineered for direct charged-particle detection by replacing the semiconductor part of the CCD pixel with a conductor Sinha and Wadsworth (76(2), 1). The device is referred to as the IonCCD. For the first time, we show the direct detection of 250-eV electrons, providing linearity response of the IonCCD to the electron beam current. We demonstrate that the IonCCD detection efficiency is virtually independent from the particle energy (250 eV, 1250 eV), impact angle (45°, 90°) and flux. By combining the IonCCD with a double-focusing sector field mass spectrometer (MS) of Mattauch-Herzog geometry (MH-MS), we demonstrate fast data acquisition. Detection of hyperthermal biomolecular ions produced using an electrospray ionization source (ESI) is also presented. In addition, the IonCCD was used as a beam profiler to characterize the beam shape and intensity of 15 eV protonated and deprotonated biomolecular ions at the exit of an rf-only collisional quadrupole. This demonstrates an ion-beam profiling application for instrument design. Finally, we present simultaneous detection of 140 eV doubly protonated biomolecular ions when the IonCCD is combined with the MH-MS. This demonstrates the possibility of simultaneous separation and micro-array deposition of biological material using a miniature MH-MS.

Key words: IonCCD, Pixelated detector, Charged particle detection, Beam profiling, Non-scanning mass spectrometry, Double-focusing sector field, Hyper-thermal ions, Simultaneous mixture separation, Micro-array deposition

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Introduction

Charge-coupled devices (CCDs), like complementary metal oxide semiconductor (CMOS) devices, are not just limited to light detection and their use extends to particle

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detection. In the field of nuclear and particle physics, CMOS technology gave birth to pixel-based detectors for vertexing and tracking applications such as the CMOS active pixel sensor (CMOS-APS) [2] and monolithic active pixel sensor (MAPS) [3]. At low energies (sub keV), and particularly for mass spectrometry purposes, CCD technology allowed the development of a modified device (IonCCD), which is the subject of this work. The early version of the IonCCD was used in a miniature sector-field MS instrument as a focal plane detector for direct positive keV ion detection generating scan-free mass spectra [1]. In fact, being an array detector, the IonCCD can be used for any dispersive technique, such as Auger electron spectroscopy, ion-surface scattering experiments, or as a beam profiler when directly facing a beam of charged particles. This latter application is very useful for instrumentation design and diagnostics.

Combining the IonCCD with a miniature double focusing sector field type mass analyzer of Mattauch-Herzog geometry (MH-MS) [4, 5] provides a powerful analytical tool in mass spectrometry. The analyzer, briefly, uses a combination of a radial electric field and a homogeneous magnetic field to obtain both velocity and direction focusing over the entire focal plane simultaneously for all masses. The spatial focusing on the focal plane is proportional to the width of the opening slit (S) located at the analyzer entrance and to the ratio R_m/R_e (magnetic and electric radius described by the ion). Several types of detectors have been used with the MH-MS, such as: photographic plate [6], ion collectors coupled to electrometers [7], electro-optical imaging detector (EIOD) [8, 9], Spiraltron matrix coupled to a resistive anode [10], collector cups for linear mixture separation and material deposition (soft-landing) using a nonhomogeneous magnetic field [11, 12], delta-doped CCD, [13] faraday-strip array detector [14–23], CMOS based pixilated array detector [24], and of course the modified CCD array detector (IonCCD) in early work [1]. Using an ESI source, we present results for the IonCCD coupled with a miniature MH-MS showing simultaneous biological mixture separation for potential micro-array ion deposition applications [25].

In this work, we characterized the IonCCD using several types of charged particles at different energies, incidence angles, and beam fluxes. The reader should note that this IonCCD version was engineered and specially designed for detection of positive ions. However, despite this fact, we demonstrated, for the first time, that the IonCCD is capable of detecting negative ions and electrons, albeit with more limited dynamic range than for positive ions. The mechanism of negative particle detection is not yet fully understood and will be the subject of further studies. The negative particle detection capability makes the IonCCD a good candidate as a position-sensitive detector (PSD) for most instruments requiring electron detection.

Low energy ion detection in the hyperthermal regime is presented as well. Those energies are typically used to gently deposit ions onto surfaces, thereby preserving their molecular weight, initial charge state, structure, and biological information. This process is referred to as soft-landing and has been

reviewed in the literature [26–30]. We also demonstrate the beam profiling capability of the IonCCD by characterizing a 15-eV ion beam exiting an rf only collisional quadrupole.

Detector Description

The IonCCD operates in virtually the same fashion as common photo-sensitive CCDs [31], in which the semiconductor oxide part responsible for the hole-pair formation upon photon bombardment is replaced by a conductor electrode (TiN) for charge collection through ion neutralization upon impact. The IonCCD is shown in Figure 1 (Supplemental Information); Figure 1a shows the photographic image illustrating the whole length of the chip wire-bonded to a circuit board with a $46 \times 69 \text{ mm}^2$ footprint where most of the length is occupied by the array detector (densely packed 2126 active pixels). All data presented in this work were produced with a non-cooled IonCCD (36 °C as measured on its cold foot). Using atomic force microscope imaging (AFM), nano-scale topography of the upper detector surface is revealed. Figure 1b (Supplemental Information) is an AFM image obtained in contact mode of a representative portion of the array, which repeats in both directions. The manufacturer topography specifications are clearly confirmed with the following dimension values: 21- μm pixel width, 1.5-mm pixel length, 3- μm pixel-to-pixel gap, and 500-nm gap depth. The electrode pixel consists of a 200-nm thick TiN layer vapor deposited on top of a 300-nm thick Al layer. The TiN is used for its inert chemical properties and its robustness. Note in Figure 1b the clear pixel surface curvature artifact of the manufacturing process. Line profile data of the AFM image reveals pixel floor curvature of about 0.3- μm elevation per 10.5- μm pixel half width, well understood through the chip manufacturing process. Such densely packed structure extends for 51 mm comprising 2126 active pixels with a 24- μm pitch providing a pixel area ratio (PAR) of 87.5%, 88.0%, 88.6%, and 89.4% for 90°, 75°, 60°, and 45° incidence angle, respectively.

Virtually every charged particle discharges on the floating pixel electrode upon impact. The pixel accumulates a total charge, proportional to the integration time and charged particle beam flux. The collected charge from each pixel may be gathered for measurement by simultaneously draining the charge of each pixel into its readout well creating a pixel specific charge packet. By cycling, or clocking, the voltages on the array of electrodes in a “bucket brigade” method, each packet of charge is moved down the detector line to arrive finally at the gate electrode of a readout amplifier. The output of the amplifier is a voltage proportional to the charge on its gate. Every pixel output voltage is then amplified through a two-value gain pre-amplifier ($G=1$ or 2). The clocking and voltage measurements are controlled by a field programmable gate array (FPGA). The FPGA also determines the order of the measurements, so that each signal voltage can be matched up with its corresponding pixel, to reconstruct a profile or a spectrum. After the signal for each pixel is recorded, the collection electrode resets the entire CCD so that a new

observation can commence. The “fill and spill” method of clocking the potentials for charge collection and transfer as used in our detector is described elsewhere [1].

The IonCCD operation is summarized in the diagram in Figure 2 (Supplemental Information). Briefly, the continuous charged particle flux is detected through a discharge of the ions on the individual pixel electrodes. The continuous ion discharge is integrated (integration time T ranges from 83 μ s to 5 s) in all active pixels in a parallel fashion. The result is a total of 2142 analog total charges (Q_i), and hence, an analog voltage (V_i), output of the individual 2142 pixels, is produced by the capacitive nature of the pixel. The capacitance value of the pixel defines the limit of detection (LOD) of the IonCCD. Lower values would increase the sensitivity but also the noise level and vice versa as shown in Eq. 1:

$$V_i = \frac{Q_i}{C} = \frac{1}{C} \int_0^T \left(\frac{dq}{dt_i} + I_d \right) dt \quad (1)$$

where, $C=80$ fF pixel capacitance, $(dq/dt)_i$ = current deposited/discharged on pixel number i , and I_d = dark current (contribution of the chip thermal noise and electronics noise).

From a total of 2142 pixels, 16 pixels (the first seven and the last nine pixels of the array), though readout, do not contribute to charged particle detection and are only used for chip troubleshooting. The pixel well is designed to hold up to 1×10^6 electrons producing a maximum voltage of 2 V (see Eq. 1) yielding 2 μ V/ e^- . Those figures are very important as they define the linear dynamic range of the IonCCD. During the integration time, the ongoing discharge of the ion flux reduces the electrode gate barrier with the voltage difference being the final signal. It is this drop of voltage that is used as the analog voltage (V_i). In addition to the generated charge by an incoming charged particle, there is charge collected that is due to various forms of non-ideal leakage and thermal activation that will be present at the same average level whether the IonCCD is exposed to an ion beam or not; collectively these effects are called the dark current (I_d). Usually, the dark current increases linearly with integration time and can provide the ultimate limit to the IonCCD sensitivity. There is also a time-independent voltage component, which is added to the baseline due to the overall circuitry of the camera (V_c). Note that the IonCCD response can depart from precise linearity with small signals and with signals approaching the full capacity of the charge well, and it is often necessary to measure these departures in order to ensure operation in the linear dynamic range.

All voltages (a total of 2142) are read in a parallel fashion (20.4 μ s of parallel read out time) and are then read serially in a shift register fashion at a rate of 1.2 μ s per pixel (2.7 ms of serial read out time). The output voltage for each pixel is converted by an analog-to-digital converter (ADC) to a digital integer (“ADC unit,” or ADU) that is proportional to voltage. We use 16-bit (0 to 65535), 0- to -4-V ADC producing 61- μ V signal increments. The result is a series of

discrete or digital numbers (dN) as function of pixel number (i) as shown in Eq. 2:

$$dN_i = G \times \frac{V_i + V_c}{\frac{4}{2^{16}}}, \quad (i = 1, 2, \dots, 2142) \quad (2)$$

Finally, the raw digitized data are displayed as a function of pixel number to illustrate either a spectrum (when coupled to a dispersive instrument) or a beam profile (for direct beam detection). Eq. 2 shows that the IonCCD response is linear to the charged particles flux as well as to the ion charge state. The response of the IonCCD to 1 keV ions is studied over three orders of magnitude of beam current (see Figure 3 in the Supplemental Information). For this experiment the IonCCD is operated at 15 ms integration time and 5.4 ms readout time to profile a well-defined ion beam width (~ 290 μ m). Plotted is the peak area of the IonCCD signal profile as function of the beam current measured when replacing the IonCCD with an electrode plate (p.3). The IonCCD signal is shown to be linear throughout the whole range considering the error bars in ion-beam current readings (horizontal error bars). The total noise level of the detector (chip and electronics contributions), as shown in the top insert of Figure 3 (Supplemental Information) is about 9 dN per pixel (± 9 dN error bars in top insert) at room temperature with no averaging. This value is the standard deviation of the pixel signal defined with consecutive 200 frames. The vertical error bars in the data are given by the sum of standard deviations of the pixels under the peak. When using frame averaging, a linear dynamic range of 10^4 is obtained, a direct consequence of noise-floor drop to 0.9 dN. The dynamic range can easily be extended to 10^{5-6} when using different integration times. Using Eqs. 1 and 2 (30 e^- /dN), the noise corresponds to about 270 and 27 electrons in non-averaging mode and averaging mode, respectively. The data in Figure 3 (Supplemental Information) are well within the measured detection efficiencies discussed in the next sections. To guide the eyes, the green and blue lines are added in Figure 3 representing the 63 and 100 particle/dN detection efficiency values respectively. Note that the ion peak shape is maintained between the two extreme beam currents, 250 fA (top insert) and 250 pA (bottom insert), which is about 12 pixels wide. The acquisition rate (spectrum/frame per second) is defined by the combined integration and total read out times, resulting in a maximum frame rate of 360 Hz (83 μ s integration time). This frame rate is limited by the signal-processing rate of the standard camera electronics system used to drive the chip. In fact, the chip is designed to run at 2 kHz.

Experiments

To perform the IonCCD characterization we used five different experiments as shown in Figure 1 with the respective experimental parameters shown in Table 1.

Figure 1. Schematics of the five experimental configurations used to characterize the IonCCD: I) Detection of electrons using accelerated thermionic electrons from a hot filament; II) Direct Ar^+ detection using an EI ion source; III) EI source coupled to a sector-field instrument for simultaneous m/z separation and detection; IV) Detection of low-energy ions from an ESI source using a sector-field for simultaneous m/z separation and detection; and V) Beam profile of low-energy ion beam exiting the CQ (dotted line area)

Direct Electron-Beam Detection

The IonCCD was mounted in front of an in-house built electron gun. The latter, as shown in Figure 1-I, consisted of a hot Rhenium filament for thermionic electron generation, a repeller plate to push the electrons forward, an extraction lens, and finally, a set of two 100- μm wide slit plates (20 mm apart) to define the electron beam on the IonCCD array axis. Two mask plates, one right behind the other, were located in front of the IonCCD where the current was monitored at m.p.1 while m.p.2 was biased to suppress losses from secondary electron emission from the IonCCD surface. In this configuration, electron detection efficiency was studied at 250 eV and 90° incidence angle using different electron beam currents. To achieve such measurements, the IonCCD is replaced by an electrode plate p.3.

Direct ion Beam Detection

The IonCCD was mounted in front of an electron impact (EI) ion source. A non-heated, 20-cm long capillary (50 μm i.d.) was used as the Ar sample inlet. As shown in Figure 1-II, the IonCCD was mounted onto a rotatable platform to study the influence of the ion impact angle on the IonCCD detection efficiency. Four discrete impact angles of 45°, 60°, 75°, and 90° were probed. For every incidence angle, the ion energy was varied from 250 to 1250 eV with 200-eV steps. The EI filament power was run at two settings, 2.73 W and 3.19 W, resulting in two ion beam currents on the IonCCD with a factor of eight between them. In the same fashion as in experiment I, the IonCCD was replaced by an electrode plate p.3 to provide detection efficiency measurements.

Table 1. Parameters used in various experimental configurations

	I	II	III	IV	V
	Electron gun	EI source	EI with MH-MS	ESI with MH-MS	ESI source
Particle	Electrons	Ar	Air and breath constituents	SP and GS peptides	KA_4 and P1 peptide
Incidence angle (°)	90	45, 60, 75, 90	45	45	90
Impact energy (eV)	250	[250, 1250]	800	140	15
Charge state (a.u.)	-1	+1, +2	+1, +2	+2	-1, +1

MH-MS Coupled to an EI Source

The EI source was coupled to a miniature MH-MS using air and breath samples for mass analysis as shown in Figure 1-III. The different ionic compounds were detected by the IonCCD located at the analyzer focal plane at 1000 eV impact energy and 45° incidence angle.

MH-MS Coupled to an ESI Source

The biomolecular ions were produced by an electrospray ion source (ESI), transferred through the heated capillary and an electro-dynamic ion funnel and finally thermalized and collimated to less than 0.5 mm diameter beam by a collisional quadrupole as shown in Figure 1-IV. The experimental setup is described in detail elsewhere [32]. The ions were then injected into a miniature MH-MS with a 200 μm wide slit plate (object slit). The analyzer was positioned 1 mm away from a 1 mm internal diameter conductance limit. We used a mixed solution containing two different peptides, a neuro-peptide Substance P (SP) and an antibiotic peptide cyclic Gramicidin S (GS) with respective masses of 1347.63 and 1140.71 u. Due to the high masses, both peptides were detected in their doubly protonated states at $m/z=571.5$ for GS and 675 for SP.

Hyperthermal Ion Beam Profiling

In this last experiment as shown in Figure 1-V (dashed area), the MH-MS was removed and the IonCCD was mounted directly behind the collisional quadrupole with a 1-mm internal diameter conductance limit in between. This configuration was chosen first to probe the beam quality of the thermalized ions using the novel IonCCD and second to quantify the detection efficiency of the array detector. For the latter purpose, a special plate mount (p.3) was built to measure the ion beam current detected by the IonCCD maintaining the detection geometry for more accurate detection efficiency measurements. In this configuration the peptide beam current was first measured using the electrode plate; the instrument was then vented to replace the electrode plate with the IonCCD. The beam profile was recorded at 3 different integration times (5, 10, and 15 ms) using the same instrument optics settings. Two peptides, KA₄ and AYSSGAPPMPPF (labeled as P1) with nominal masses of 431 u and 1221.56 u, respectively, were used in these experiments. The above peptides were chosen for comparison of detection efficiency of positive and negative hyperthermal ions because they produce predominantly singly protonated and singly deprotonated species in the positive and negative ESI, respectively.

In the experiments where detection efficiencies were extracted, the charged particle current measurements were provided by Keithley digital electrometers and picoamp-meters providing readings within 5 % accuracy. Within the

scope of this paper such accuracy, together with the instrumentation errors presented in the next section are adequate for the premier presentation of the IonCCD detection efficiency.

Results and Discussion

Electron Detection

Figure 2 shows the IonCCD response to a 250-eV electron beam at normal incidence angle. The linearity of the detector was studied across most of the integration time window (83 μs , 5 s). Figure 2a shows the linearity of the detected electron beam signal at short integration time (83 μs , 2 ms). In this run, an electron beam current of 38 nA, monitored at the first mask plate (m.p.1) was used when applying 2.5 W across the filament. Figure 2b shows the same experiment at long integration time (20 ms, 1 s), where in this case, because of the much longer integration time, a lower electron current of 100 pA (1.4 W across the filament) was used to avoid IonCCD signal saturation. Note that in both graphs, linearity of the IonCCD signal as a function of the integration time is confirmed. The fitted slopes in (a) and (b) are a factor apart of 260 (−8585 dN/ms versus −33 dN/ms). This factor is directly related to the different electron beam currents irradiating the IonCCD, which are proportional to the current monitored at m.p.1 (38 nA versus 100 pA), which accounts for a factor of 380. The comparable values suggest that the IonCCD response to the electron beam is independent of the electron fluence on the pixels as well as to the integration time. The detection efficiency study of the IonCCD response versus the electron beam fluence is better shown in Figure 2c when plotting the incoming particle number per IonCCD signal unit (particle/dN) as function of the electron beam current (pA) collected when the IonCCD is replaced with an electrode plate. To achieve those measurements, the electron gun output was scanned from low to high currents while measuring it first with the IonCCD and then with an electrode plate. This forced the vacuum chamber to be vented in between measurements to replace the IonCCD with an electrode plate. To avoid large intrinsic errors between runs due to different electron gun outputs, both data sets were normalized to their respective monitored electron beam currents at m.p.1. As shown in Figure 2c, detection efficiency of about 3000 particle/dN with 21% relative standard deviation (RSTD) was obtained throughout the whole electron beam current range.

Ion Detection

Similar to the previous experiments, linearity and detection efficiency studies of the IonCCD were performed using a positive ion beam. The EI ion source replaced the electron gun to produce a positive ion (Ar^+) beam. In the same fashion as in the previous experiment, the Ar^+ beam was defined with a set of two plates with 100- μm slit openings. The IonCCD in this case was mounted on a rotatable

Figure 2. IonCCD response to 250-eV electron beam at normal incidence angle: (a) and (b) IonCCD total signal as function of integration time; (c) Normalized IonCCD response to electrons as a function of electron beam current

platform allowing for ion detection at different incidence angles. An electrode plate was used, replacing the IonCCD, to measure the ion currents and determine detection efficiency values. Figure 3 shows the IonCCD detection efficiency (particle/dN) plotted as function of the incident ion energy (250 and 1250 eV) at different incidence angles. The error bars in the figure are produced when averaging the values taken at three integration times (10, 20, and 30 ms). The inset is a polar plot showing the detection efficiency (particle/dN) as the radius as a function of the incidence angle for 1250 eV impact energy. The error bars reflect averaging over the IonCCD integration time. Using the combined values of detection efficiencies in Figure 3, an average value of 125 particle/dN with 16% RSTD is measured. The angular dependence, as shown in Figure 3, was measured to be negligible within the errors (13% RSTD); however, a slight improvement ($-0.3 \text{ particle/dN/degree}$) was evident from 90° to 45° , which can be rationalized by the shadowing effect increase of the elevated pixel regions (see Supplemental Information). Increasing the ion beam current 8-fold did not seem to affect the detection efficiency within 13% RSTD. Furthermore, the incidence angle experiments allowed us to demonstrate that the full width at half maximum (FWHM) of the Ar^+ beam follows exactly a cosine behavior with incidence angle (see Figure 4 in Supplemental Information). This result shows that the IonCCD provides accurate measurements of the

ion beam shape, allowing a realistic measurement of the spatial ion-beam profile. The lack of dependence of the IonCCD detection efficiency on the ion-beam parameters is important for imaging of product ions produced in scattering experi-

Figure 3. Normalized IonCCD response to positive ions (Ar^+) as a function of the incidence energy and angle and IonCCD integration time. The inset is a polar plot showing the angular dependence at 1250 eV impact energy with the radius describing the detection efficiency

ments. In fact, the 51-mm array, when properly mounted, could easily be used to detect secondary charged particles from surfaces and correlate the yields as a function of the scattering angle (differential scattering cross sections).

Air Monitoring

When mounted on the focal plane of a MH-MS, the IonCCD records mass spectra as shown in Figure 4. Figure 4a is a single mass spectrum at $t=0$ s; it shows the simultaneous detection of several ionic compounds which are constituents of the sampled air. Electron impact (EI) ionization, the ion source used for this work, is known to be a relatively violent ionization process (70 eV electrons). We can measure clearly the respective fragments of the major air constituents as well as the doubly charged rare gas Ar. Figure 4b shows a 3D color code contour of successive frames, recorded with no averaging at a frame rate of 200 Hz. This was achieved with a 2.3-ms integration time and 2.7-ms readout time, which equates to a 46% duty cycle. The IonCCD response, expressed in dN (color z-axis), is plotted as a function of the respective ion detection coordinates on the IonCCD given by the pixel number (x-axis) and spectrum/frame acquisition time in seconds (y-axis). The color-coded signal range in Figure 4b is truncated to 2500 dN to better illustrate the variations of the low-signal compounds. The total acquisition time illustrated is 5 s, which contains 1000 spectra or frames

(5 ms per frame). Note that except for water and carbon dioxide, all compounds show no variation with a steady signal height. To better follow the signal change of specific compounds, one could plot either the associated peak area or peak height as a function of time. Figure 4c illustrates peak height of the relatively low-signal compounds for the first 2.5 s. The fast rise and drop in CO_2 and H_2O levels are the results of a speech modulated sampled gas when the operator talks in front of the sample inlet; in other words, in vivo fast breath analysis. As shown in Figure 4c, the Ar level is not affected by the analyzed breath as it originates solely from the ambient air. Note at the end of the Figure 6c spectrum the double structure burst in CO_2 and its respective delayed (~ 70 ms) H_2O signal. This is probably due to their eluting time difference in the non-heated sample inlet capillary (20-cm long and 50- μm inner diameter) where non-polar molecules elute faster than polar molecules. The 55-ms spaced double structure in CO_2 is quite evident at a 200-Hz frame rate. Such an acquisition speed is key for fast gas chromatography (GC) coupled to MS detection; especially for two-dimensional GC with MS detection where peak widths in the 2D total ion chromatogram (TIC) spectra are usually well below the 100-ms mark. The advantage of simultaneous detection of air constituents makes compound quantification fairly straightforward. For example, using the averaged signal ratio $\text{Ar}^+/\text{CO}_2^+$ (~ 14) within the first 500 ms of Figure 4c and the known electron-impact total cross sections of Ar ($\sigma_{n=1}=2.66 \text{ \AA}^2$) [33] and CO_2 ($\sigma_{n=1}=3.15 \text{ \AA}^2$)

Figure 4. Air and breath analysis. (a) Mass spectrum of the simultaneously detected air constituents (logarithmic scale); (b) 3D color-coded plot of the IonCCD response (Z-axis) as function of pixel number (X-axis) and time (Y-axis); (c) Peak height of relatively low-signal compounds versus time showing signal modulation in CO_2 and its delayed H_2O counterpart

[34] as well as the Ar atmospheric value in air (9300 ppm), one can deduce the indoor CO₂ level of about 500 ppm. This value is very satisfactory considering the low signals involved (indoor carbon dioxide levels are usually greater than outdoor levels which are about 300 to 400 ppm).

Though it is not possible to measure the dependence of the detection efficiency of the IonCCD on the ion charge state using the experiment in Figure 1-I and II, it is possible to have an idea of the dependence using the experiment in Figure 1-III. Data from Ar and Kr gas samples were separately used to produce a clean mass spectrum consisting of singly and doubly charged species using the EI source at 70-eV electron energy. Using the measured ionization cross section ratios of Ar and Kr at 70 eV electron energy,[35] the respective transmissions in the sector field using the full 3D SIMION model and, finally, the IonCCD peak area signal of both species one can roughly measure the detection efficiency (d.e.) ratio. A value of 2.7 and 1.9 for Ar and Kr, respectively, were extracted, though deviating from the expected factor of 2, which is due to errors in the cross sections and MH-MS transmission values, they suggest that the IonCCD response, just like the image charge detectors in FT-ICR and Orbitrap instruments, is linear with respect to the particle charge state.

Hyperthermal Ion Detection

The IonCCD was used to detect low-energy biomolecular ions (15, 120) eV. This hyperthermal energy regime allows the detected ions to be gently deposited or “soft-landed” on the TiN surface of the IonCCD. First, we present the results of the beam profiling experiments (Figure 1-V) where the

IonCCD was directly facing the thermalized biomolecular ions exiting the rf only collisional quadrupole (CQ). Figure 5 shows the beam profile of the thermalized and collimated protonated peptides $[KA_4+H]^+$ and $[P1+H]^+$ (top panel) and deprotonated peptides $[KA_4-H]^-$ and $[P1-H]^-$ (bottom panel). The four beams were profiled at energy of 15 eV (CQ biased at ± 20 V) with three different IonCCD integration times: 5 ms (in blue), 10 ms (in red), and 15 ms (in green). The “hairy” structure present at the top of the peaks for $P1^+$ and $P1^-$ at 15 ms integration time results from the presence of highly charged solvent droplets in the ion beam. Indeed, these droplets were observed in much greater intensity when the IonCCD was positioned directly behind the electrodynamic ion funnel and there was less time for desolvation. Figure 5 also indicates a loss of sensitivity for negative ions at longer integration times. This is due to detector saturation at -1000 counts (dN) for negative ions as compared with $+30,000$ counts (dN) for positive ions. Not shown in Figure 5, when the ion optics are tuned for optimum beam focus, the IonCCD records beam profiles with FWHM as sharp as 300 μm . This experimental result, shows for the first time, the strong focusing and collimating capabilities of the collisional quadrupole, as the measured ion beam dimensions are about three times smaller than the conductance limit opening (1.5 mm). However, the profiles in Figure 5 were generated using the settings that provided maximum beam intensity after the conductance limit as measured on the electrode plate: $I(KA_4^+) = 430$ pA, $I(P1^+) = 620$ pA, $I(KA_4^-) = 78$ pA, $I(P1^-) = 109$ pA. Clearly, maximum transmission results in relatively poor beams focus (FWHM = 1 to 2 mm). Since the produced beams are clearly larger than the IonCCD pixel length

Figure 5. IonCCD signal output showing the beam profile of four peptide species at hyperthermal energies. Illustrated on the left is KA_4 at 431 u and on the right is P1 at 1221.56 u with both peptides produced in protonated and deprotonated states. Three integration times are used for IonCCD detection efficiency quantification purposes

(1.5 mm), a part of the beam current is lost. The design of the electrode plate takes care of that loss as it is mounted right behind a mask with a horizontal slit of 1.5 mm width allowing a one-to-one comparison between the registered beam currents reported above and the peak area obtained in Figure 5. For every ionic species used and for every integration time, a respective IonCCD detection efficiency is extracted (see Figure 5). A mean detection efficiency of 87 ion/dN with 29% RSTD was obtained from the data shown in Figure 5. When comparing the effect of the peptide size on the IonCCD detection efficiency in the positive mode, we observe a slightly better efficiency for KA_4 (66 ion/dN @ 1% RSTD) versus P1 (107 ion/dN @ 26% RSTD). The comparison, in the negative mode, leads to the opposite conclusion with better efficiency for P1 (71 ion/dN @ 8% RSTD) versus KA_4 (105 ion/dN @ 24% RSTD). Considering the scope of this paper, it is safe to state that the detection efficiency of the IonCCD for hyperthermal peptides (positive/negative and small/large ions) is identical to the KeV and sub-keV Ar^+ within their respective errors and is about 100 particles/dN. The electron beam experiment does not fit the general trend of the IonCCD response to ionic species.

Due to the fact that we do not understand yet the true mechanism involved in detection of negatively charged particles, as the IonCCD by design is supposed to detect positively charged particles; it is hard to present a solid argument explaining the large discrepancy in electron detection efficiency compared to negative ions (30-fold). The electron detection experiment was conducted carefully to avoid major artifacts. With experimental errors being on the order of 10 % of percent, the 30-fold deviation cannot be rationalized by the experimental error. However the electron detection experiment is valuable as it first confirms the

electron detection capability of the IonCCD and second will motivate the chip designer to explain the mechanism of negatively charged particle detection in general and the reason of seemingly poor electron detection efficiency in particular.

Figure 6 shows the time-dependence of the IonCCD maximum signal in the beam profile when monitoring the singly protonated peptide $(KA_4+H)^+$ beam exiting the collisional quadrupole. In this case the beam was tuned for maximum focus with FWHM of about $340\text{ }\mu\text{m}$ as measured by the IonCCD. After about 3 h, the IonCCD recorded strong beam instability. Increasing slightly the syringe pump flow helped stabilizing the signal even better than in the first 3 h. In fact, the relatively low scatter in the obtained signal reveals an oscillatory pattern with peak-to-peak amplitude of about 10% of the mean signal and an oscillation period of about 30 min. This can either be due to the electrospray behavior or to the material build up on the detector surface affecting the charge transport to the electrodes in a cyclical fashion. However, further studies need to be performed to confirm the existence of those oscillations and their origin. After 9 h of continuous beam profiling and at the end of the syringe solution injection, the signal drops to the baseline level with some short-lasting remaining bursts. The bottom insert in Figure 6 is a photograph of the IonCCD pixel array region showing clearly the actual deposited spot on the IonCCD after 9 h of continuous beam profiling. The visible spot size is about $500\text{ }\mu\text{m}$ centered on the pixel. This dimension fits perfectly with the beam profile acquired by the IonCCD. Due to the hyperthermal energy of the detected ions and the inert nature of the detector surface (TiN), the discoloration was easily removed by wiping off the surface with a methanol wet cotton swab (top insert in Figure 6).

Figure 6. Nine h of singly protonated peptide $(KA_4+H)^+$ soft-landing monitored by the IonCCD located after a collisional quadrupole

This experiment clearly shows that the IonCCD can successfully be used as a beam profiler under the conditions tested. In fact, if one would consider 100% soft-landing efficiency on the detector surface with a tight packing of KA_4 peptides ($\sigma \sim 300 \text{ \AA}^2$) in a $340\text{-}\mu\text{m}$ spot diameter ($S \sim 9 \times 10^4 \mu\text{m}^2$), a value of deposited mono-layers can be estimated ($\text{ML} \sim \sigma^*(9 \text{ h} \times 200 \text{ pA/q})/S \sim 1000$). Although this value is the upper limit, one should include the contribution of neutrals since the IonCCD is in line of sight of the electrospray. This is very encouraging as we showed that beam profiling can be achieved for a reasonably long time in such a harsh environment.

This section is dedicated to simultaneous mass-over-charge (m/z) separation of an electrosprayed peptide mixture solution using a miniaturized MH-MS. Coupling an electrospray source to a sector-field instrument was performed in the 90 s [36–41] using a special array detector [42] as an alternative mass spectrometric method for analysis of large biomolecules. The simultaneous m/z separation of electrosprayed peptides in this work (Figure 1–VI), was motivated by another research effort [11, 12]. In those experiments, a nonhomogeneous magnetic-sector field was used for a linear separation to achieve deposition of the different peptides on a 16-channel collector with disassembled bins. In our case, we used the IonCCD pixels as collectors while monitoring the separation and deposition of two peptides, an antibiotic peptide Gramicidin S and a neuro peptide Substance P. As shown in Figure 7, baseline separation of the two peptides was achieved despite the use of a wide $200\text{-}\mu\text{m}$ object slit in the analyzer (twice the standard width). The excessive 40 pixels FWHM broadening of the doubly protonated ion peaks is partly due to the large object slit used in the analyzer degrading the resolution of the system. At this low resolution, the large fragments originating from peptide loss of water (-18 u) and ammonia (-17 u) with half mass

separation due to the doubly charged nature of the ions are convoluted with the parent ions, resulting in a broad tail at the lower mass side. The somewhat bimodal nature of the ion energy exiting the collisional quadrupole [32] can also affect the mass resolution as the low energy component would contribute to a signal tail at low mass side. Note that the peak separation in Figure 7 can be used to determine the doubly protonated ion energy, which is calculated back to be about $2 \times 70 \text{ V} = 140 \text{ V}$. This value is in accordance with the voltage bias of the CQ (120 V) with the most ion energy contribution coming from the region between the latter voltage and the conductance limit biased at 20 V .

Conclusions

Extensive work on the relatively new array detector (IonCCD) is presented. Its design allows for charged-particle detection from atmospheric pressure to high vacuum. The direct detection of charged particles is demonstrated using electrons, keV light ions, and hyperthermal biomolecular ions. The electron detection efficiency is measured to be around 3000 particle/dN, about an order of magnitude lower than the 100 particle/dN value obtained for keV-sub keV Ar^+ and hyperthermal biomolecular ions. In fact the ion detection efficiency value is measured with relative good accuracy despite the use of two different IonCCDs in two different laboratories across the country. The IonCCD detection efficiency shows no dependence, within the relatively low experimental errors, on the ion energy, flux, incidence angle, and ionization state (cations, protonated ions, and deprotonated ions). The detection efficiency of the IonCCD shows a direct dependence on the charge state of the detected particle, which is in agreement with the operation principle of the IonCCD. The 100-particle/dN value suggests chip quantum efficiency (QE) of 0.25 to 0.33; in other words, as few as 4–3 incoming particles produce one chip-electron. With no frame averaging (noise floor of 9 dN or 270 electrons) and at room temperature, a value of 0.5 fA/pixel/s is measured for the IonCCD LOD with a signal-to-noise ratio of 3. We are currently investigating off-chip electronic noise sources to reduce the above value, hence improving both dynamic range and sensitivity of the IonCCD.

However, the lower value of the IonCCD detection efficiency for electrons necessitates further attention. From the solid-state physics point of view, it is necessary to explain the large discrepancy in the data obtained with the various ionic species as well as the mechanism involved in detecting negatively charged particles. This capability of the IonCCD is very important if one uses the detector in any experiment relying on electron detection.

The detector response signal shows linearity over three orders of magnitude with respect to both beam current and integration time with a systematic 10^4 value when frame averaging is applied. This value can easily be extended to 10^{5-6} when using different integration times. At $100\text{-}\mu\text{s}$

Figure 7. Micro-array deposition and separation of two doubly charged peptides, Gramicidin S (571.5 u), and Substance P (675 u) monitored by the IonCCD coupled to a double-focusing sector field instrument of MH geometry

integration time, the detector produces up to 360 spectra (frames) per s to be limited only by the standard camera electronics given that the chip is designed to run at up to about 2-kHz frame rates. The combination of the high-speed capability of the detector together with an MH-MS would be ideal for coupling to fast GC, GC×GC, and ion mobility as those front end systems produce sharp chromatogram peaks (100 ms down to 1 ms).

The demonstrated electron detection capability would make the IonCCD a potential candidate for low cost and compact scan-free electron-energy analyzers, as the IonCCD by itself is a low cost compact detector. This would also open new opportunities to use the IonCCD as a 1D or even a 2D pixilated anode to read out the amplified signal from an MCP (MCP-IonCCD preliminary results already obtained). This would eliminate the phosphor screen step needed by photosensitive CCDs as well as the line of sight condition (view ports) needed by a CCD outside the vacuum chamber. Though not mentioned in this paper, the IonCCD can easily be floated to ± 3 kV adding an extra dimension to imaging. Such flexibility allows the detector to be coupled to numerous instrumentation and locations on the potential diagram allowing mesh free imaging.

We demonstrate for the first time the operation of the IonCCD in the proximity of rf fields when used as a beam profiler. This allowed us to examine the focusing capabilities of the collisional quadrupole of an ESI source; in this case, beam profiles were measured to be about 500 μm FWHM or less despite the large conductance limit used (1.5 mm diameter). The inert nature of the IonCCD surface makes it easy to rinse off the deposited materials when hyperthermal energy ions are used. The IonCCD was successfully used with a miniaturized MH-MS at low ion energy (140 eV) to simultaneously separate an electro-sprayed peptide mixture solution. In fact, one could couple the magnetic sector to an electro-static quadrupole; the IonCCD would be mounted on one of the three exits and could be used as a diagnostic tool for the dispersed biomolecular ion species prior to simultaneous micro-array depositions through either two remaining quadrupole exits.

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