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Signal Processing

Less is More: How Compressed Sensing is Transforming Metrology in Chemistry

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Mathematics has had a profound impact on science, providing a means to understand the world around us in unprecedented ways. With the advent of the digital age, the subject of information theory has grown hugely in importance. In particular, over the last two decades significant advances in our understanding of sampling and function reconstruction have culminated in the development of an idea known as compressed sensing. What seems like an abstract idea is now having a profound impact throughout the scientific world—from enabling high-resolution imaging of pediatric patients in clinical medicine through to advancing 3D electron tomography images of nanoparticle catalysts and NMR spectroscopy studies of proteins. In this Minireview, we summarize these applications and provide an outlook on how the principles of compressed sensing are leading to entirely new approaches to measurement throughout the physical and life sciences.

1. Introduction

Developments in signal processing will always be integral to the advancement of metrology. One technique in particular, compressed sensing, is increasingly being shown to enable the study of systems hitherto inaccessible because of, for example, their sensitivity to radiation beam damage or their transient nature. We are all familiar with the concept of "compression" in signal processing in this age where we routinely store digital images in cameras and mobile phones or music in personal music devices. Compression enables us to accurately reproduce a "signal", be it an image, a song, or a chemical spectrum from significantly less information than would otherwise be required. Compressed sensing extends the concepts of data compression to the acquisition of signals. The logic behind compressed sensing is straightforward—if it is possible to compress an image, say, into a dataset comprising far fewer data points, then why acquire the "redundant" data points in the first instance? Simply from the perspective of data acquisition times, we see immediately that this makes it possible to acquire data at a faster rate given that fewer data points are required for each image frame. Equivalently, it is possible to acquire measurements at a higher spatial resolution in a given acquisition time. In some fields, such as astronomy, where concepts in signal processing are well established, compressed sensing is now a commonly used tool. However, in the chemical and biological sciences the impact of compressed sensing is only just being seen and there exist exciting opportunities for making entirely new measurements by exploiting this approach to data acquisition and image reconstruction.

Most phenomena that we study are described by a continuous function or "signal". However, the signal characterizing any given system can only be probed experimentally by making (or "sampling") discrete measurements of that system. Sampling theory[1,2] established many years ago that if we have a band-limited signal, and we sample at twice the frequency of the highest frequency component, then our discrete measurements perfectly describe the continuous signal that we are trying to measure. It has also long been known that in many cases it is possible to accurately reconstruct a signal with fewer samples than are required by sampling theory.[3–8] The very significant contribution made by compressed sensing is that it provides a mathematical framework that quantifies how accurately a signal can be reconstructed when fewer samples are acquired than traditional

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sampling theory requires.[9,10] This rigorous theoretical framework provides the confidence to extend these techniques to new applications, and to identify entirely new sensing strategies and devices that exploit these ideas. The explosion of interest in this field from both the theoretical and applied sciences means that it is not possible to present a comprehensive review of the entire field. Instead we present an introduction to this exciting field of information theory and signal processing, and in particular how it might impact everyday laboratory spectroscopic and imaging methods.

2. What is Compressed Sensing?

Compressed sensing is an information sampling theorem that defines the number of measurements required to faithfully reconstruct a signal, as well as providing guidance as to how these measurements should be obtained. The key premise to compressed sensing is that the signal of interest contains only a small amount of "information". In a mathematical sense, "information" characterizes how much data is required to reproduce a signal accurately. Therefore, the information content of a signal can be described by the number of non-zero elements required to describe the signal. Somewhat counter-intuitively, this definition characterizes a totally random signal, such as the white noise seen on a television that is not tuned, as having very high "information" content; by contrast the series of pictures comprising a television show contain a relatively small amount of information. The key reason for this is that signals that are of interest typically contain a lot of structure—for example, pixels in an image will correlate strongly with other nearby pixels. The idea of signal compression is to use the structure of the signal to reduce the number of data points required to describe the original signal. This idea is what underpins common image compression algorithms such as jpeg. In these compression schemes, an image is fully sampled and then transformed into some new basis. The large coefficients of the new basis are stored, while the small coefficients are discarded. There may be many more small coefficients than large coefficients, and thus when the small coefficients are discarded, the amount of information representing the image is reduced or "compressed". Compressed sensing goes even further, as it exploits the ideas behind compression to reduce the number of data points required to measure the signal in the first place. In essence, compressed sensing seeks to acquire the signal directly in compressed form.

The mathematics of compressed sensing is well established and has been discussed previously with reference to specific examples.[9–13] In the following we highlight only a few of the most salient findings.

Formally, we wish to obtain a signal $\mathbf{x}$ (written as a column vector with n entries or values) using a set of measurements $\mathbf{y}$ (written as a column vector with m entries or values) and a linear measurement system described by a matrix $\mathbf{A}$. In other words, we want to solve the set of linear equations given by:

$$\mathbf{y} = \mathbf{A}\mathbf{x} + \boldsymbol{\sigma}, \quad (1)$$

where $\boldsymbol{\sigma}$ is the vector characterizing the noise in the measurements. Ignoring noise for now, conventional sampling theory dictates that $m = n$ measurements are required to recover $\mathbf{x}$. However, for many situations we want to recover $\mathbf{x}$ from $m \ll n$, and hence there are infinitely many solutions that satisfy Equation (1). Compressed sensing theory tells us that it is possible to recover $\mathbf{x}$, even when $m \ll n$. Furthermore, compressed sensing theory provides guidelines on 1) the number of measurements, 2) the characteristics of $\mathbf{A}$, and 3) the types of algorithm to use to stably recover $\mathbf{x}$.

In compressed sensing theory, it is the degree to which a signal can be compressed that determines the number of measurements required. A signal $\mathbf{x}$ is compressible if it can be well described using $s \ll n$ non-zero coefficients (a signal is said to be "sparse" if this approximation is exact). The "information" content of the signal is described by the location and magnitude of the s non-zero coefficients. Many signals of interest are directly compressible. For example, in spectroscopy the useful information in the signal is the magnitude and location of the peaks in the spectrum. However, the number of peaks will often be orders of magnitude less than the total number of possible locations for these peaks, hence the spectrum is readily compressible. Given that a signal can be represented by only s non-zero coefficients, then compressed sensing theory states that $\mathbf{x}$ can be recovered from only m measurements, where m is given by:

$$m \propto s \log(n/s) \ll n. \quad (2)$$

This powerful result means that recovering a signal at higher resolution (i.e. greater n) does not require a linear increase in

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the number of measurements, but instead is determined primarily by the information content (number of non-zero elements s) of the signal.

Compressed sensing theory only holds if the measurements and compressible basis are "incoherent". Incoherence is an unusual concept but essentially ensures that the information from many coefficients of $\mathbf{x}$ is contained in each measurement, and that the encoding of the coefficients of $\mathbf{x}$ is different for each measurement. Another way of interpreting the incoherence condition is that in an incoherent sampling regime, artefacts arising from undersampling add as noise-like interference. This allows the true signal coefficients to be recovered as they stand-out above the interference. Since it can almost guarantee very high incoherence, randomized sampling has played an important role in the development of compressed sensing. However, empirical studies have shown that completely random sampling is unlikely to be optimal,[14–17] whilst nature provides evidence to suggest that random sampling using a Poisson-gap distribution is preferable.[18] In practice, most compressed sensing work has used a weighted sampling distribution with the weighting being chosen based on the application. In fact, recent theoretical advances have shown that such semi-random sampling strategies may indeed be optimal.[19]

Lastly, to recover the signal $\mathbf{x}$ from the underdetermined system of equations described by Eq. (1), it is necessary to introduce some prior knowledge about the signal. In the context of compressed sensing, this prior knowledge is that the true solution is compressible, or in other words we seek to find the solution with the fewest non-zero elements that is consistent with the measured data. The number of non-zero elements is commonly called the l_0-pseudo norm and is denoted $\|\mathbf{x}\|_0$. Therefore, we seek the solution with minimum l_0-norm. Unfortunately, finding this solution directly is intractable (it falls in the class of NP-hard problems). One of the key findings of compressed sensing theory is that this solution can be well approximated by the minimum l_1-norm, which is defined as:

$$\|\mathbf{x}\|_1 = \sum |x_i|. \tag{3}$$

This astonishing finding can be understood relatively simply by considering the solution described by an l_p-ball—that is the set of values that have a constant l_p-norm, as illustrated in Figure 1 for a simple signal described by two coefficients, x_1 and x_2. The minimum l_0 solution will always correspond to the point at which only one of the two possible variables is non-zero. By contrast, the established approach of least squares minimization, or using the l_2-norm (defined by $\|\mathbf{x}\|_2 = (\sum_i |x_i|^2)^{0.5}$) on the regularizing term, penalizes large coefficients, and thus will generally find a smooth solution with both variables non-zero. l_1-norm minimization results in a sparse solution because the "pointiness" of the l_1-ball means that with high probability the minimum-l_1 solution will lie on one of the axes; the small coefficients are then suppressed while the important larger coefficients carrying information about the signal in the sparse domain are preserved. Thus, the minimum l_1-norm solution will, with very high probability, yield the same solution as the minimum l_0-norm. The equivalence of the l_0- and l_1-minima is powerful as the intractable l_0-minimum solution can therefore be readily found by solving the l_1-minimization problem:

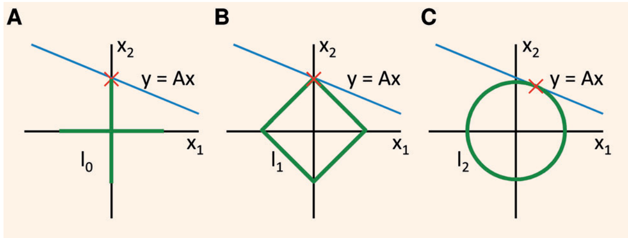

Figure 1. All of the solutions that satisfy the equation $\mathbf{y}=\mathbf{Ax}$ are illustrated by the blue line. If the underlying solution is known to be sparse, then the minimum l_0-norm solution will yield the true solution. The "l_0-ball" of solutions with equivalent l_0-norm is given by the green lines in (A). A minimum l_0 solution is indicated by the red cross. However, this solution is intractable to find for problems with realistic numbers of dimensions. In many cases, the pointiness of the l_1-ball provides an equivalent solution, as illustrated in (B). Finding the minimum of the l_1-norm is a simple convex optimization problem and therefore readily solved. By contrast the more conventional l_2-minimum (least squares solution) will almost always yield a non-sparse solution, as illustrated in (C). This example is a slight oversimplification as x is only a two-dimensional vector. In this case, the minimum l_0-norm does not yield a unique solution. For realistic problems and where sufficient measurements are taken (i.e. $m > s\log(n/s)$), the l_0-norm yields a unique solution and the l_1-norm will yield an equivalent solution. Adapted from Ref. [13].

$$\text{minimize } \left\|\hat{\mathbf{x}}\right\|_1 \quad \text{subject to } \left\|\mathbf{A}\hat{\mathbf{x}} - \mathbf{y}\right\|_2 \leq \varepsilon \tag{4}$$

where $\hat{\mathbf{x}}$ is the reconstruction of the true signal $\mathbf{x}$ from the measured data $\mathbf{y}$, and ε is characterized by the standard deviation of the noise in the data. Equation (4) describes a convex optimization problem, and therefore is simple to solve with a variety of standard algorithms (e.g. see Ref. [20]). Furthermore, it can be shown that the solution to Equation (4) will yield an estimate of the true solution $\mathbf{x}$, even in the presence of noise in the measured data, with an accuracy bounded by:

$$\left\|\mathbf{x} - \hat{\mathbf{x}}\right\|_2 \leq C_1 s^{-1/2}\|\mathbf{x} - \mathbf{x}_s\|_1 + C_2\varepsilon, \tag{5}$$

where $\mathbf{x}_s$ is the best s-sparse approximation of $\mathbf{x}$ and C_1 and C_2 are small positive constants.[21] Equation (5) means that the solution to Equation (4) will yield an estimate of $\mathbf{x}$ that is almost as accurate as the best s-sparse approximation of $\mathbf{x}$. There are two major implications of this result: firstly, if $\mathbf{x}$ is s-sparse (i.e. $\mathbf{x} = \mathbf{x}_s$), then in the absence of noise the recovery will be exact, secondly, even in the presence of noise, any error in the reconstruction is not dramatically amplified.

Where compressed sensing can be implemented, the undersampling that becomes possible represents a substantial reduction in data acquisition time over the conventional "bandwidth" limited approach identified by Shannon and Nyquist[1,2] whereby the signal must be acquired with sufficient resolution to distinguish spectral peaks across the whole bandwidth. As an example, consider a spectrum with five peaks covering a bandwidth of 1000 Hz but with any two peaks separated by only 1 Hz. The "bandwidth" limited approach would require 2000 data points to determine the intensity of the spectrum at each frequency location over the entire bandwidth. By contrast, the compressed sensing framework would require perhaps 30 data points to identify the intensity and location of the five non-zero peaks. Many choices are available for the basis used to define the compressed representation, and so compressed sensing theory is very powerful. Examples of sparse bases include the discrete cosine transform, discrete wavelet transform, and spatial finite differences (optimization using this latter transform is often referred to as total variation). Recent work has extended these concepts even further to include signals that have a concise representation or are structured-sparse,[22,23] for example most spectroscopy data.[24]

We illustrate the concept of compressed sensing in Figure 2 using one of the classic images from image compression theory—the cameraman. If we have a device that takes samples of the cameraman image in the Fourier domain, then conventionally we would require one data point for each pixel in the final image, and we could obtain the image using a simple Fourier transform. If we acquire fewer measurements but still reconstruct using a Fourier transform, then the missing information manifests as blurring, interference or noise-like artifacts in the reconstructed image. However, compressed sensing theory tells us that if we can represent our image sparsely, it should be possible to reconstruct the image from these incomplete data. The cameraman image can be represented sparsely using a wavelet transform, and hence is well reconstructed from only a subset of the measurements conventional sampling theory requires. The most obvious advantage of employing a compressed sensing methodology is that by decreasing the number of data points that are required to obtain the desired information, datasets—be they spectra or images—can be acquired much faster than is currently achievable. Although the mathematics of compressed sensing has only been presented recently, the ideas date back to image processing of radio interferometry measurements in the 1970s. Therefore, we briefly review these early contributions but also consider how compressed sensing is still contributing to developments in astronomy.

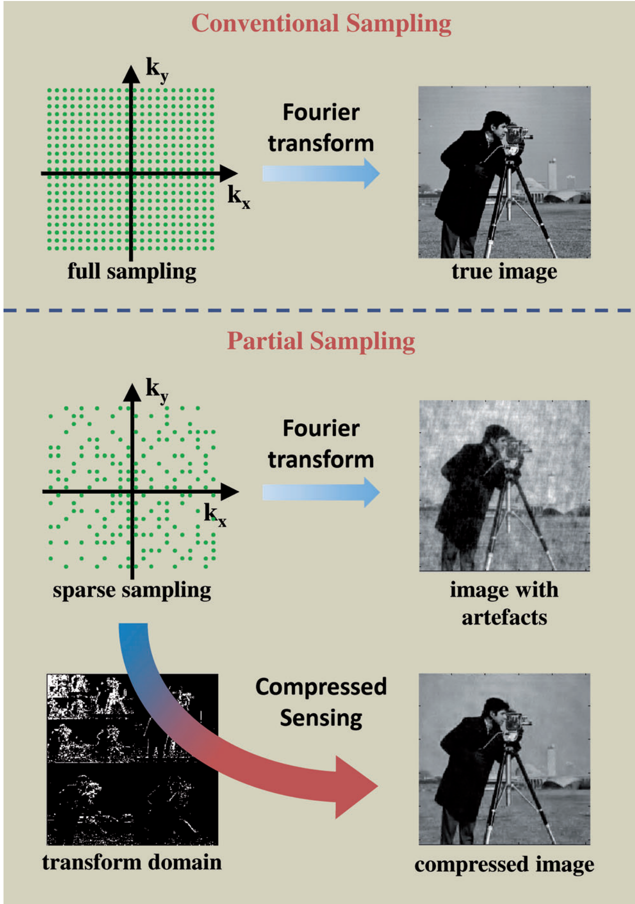

Figure 2. Conventional sampling requires measurement of one data point for every pixel in an image. Sparse sampling approaches result in artefacts if reconstructed using conventional techniques, such as the Fourier transform. However, by enforcing sparsity in a transform domain, Compressed sensing overcomes these limitations and recovers the original image with a high degree of accuracy. In this case, the transform used here was a two-dimensional separable Coiflet transform.[25] In the transform domain large coefficients appear white, whilst small or zero coefficients appear black; few coefficients in the transform domain are white (< 10%) indicating that the image is represented sparsely.

3. Astronomy and Radio Astronomy

Astronomical data (especially resulting from surveys) are often naturally sparse in the image domain and, as a result, sparse image reconstruction ideas are well-established. In the field of radio astronomy the idea of reconstructing sparse images has an even longer heritage. A radio interferometer (such as the Jansky Very Large Array, JVLA) measures components of the sky-brightness distribution in the Fourier domain with each pair of antennae measuring a single Fourier component. Current arrays consist of tens of antennae and therefore contain far fewer measurements than pixels in the reconstructed image. The development of the CLEAN algorithm in 1974 provided a powerful tool to reconstruct such synthetic aperture interferometry data in radio astronomy, as illustrated in Figure 3.[3] CLEAN has proved extremely successful in radio astronomy[26] and some version of the CLEAN algorithm is routinely used in the processing schemes for all modern synthesis arrays. However, it was not until the development of compressed sensing that a theory was developed that fully described the conditions that are required to apply CLEAN. The mathematical framework provided by compressed sensing will likely lead to more automated image reconstruction algorithms as well as improved sensitivity and resolution.[27]

One particularly interesting application of compressed sensing in astronomy has been to optimize the transmission of images from space satellites, such as the European Space Agency's Herschel satellite. The sheer quantity of data produced by instruments such as the Herschel satellite (4 Gbps) overwhelm data transfer rates (120 kbps) and therefore necessitate the use of image compression tech-

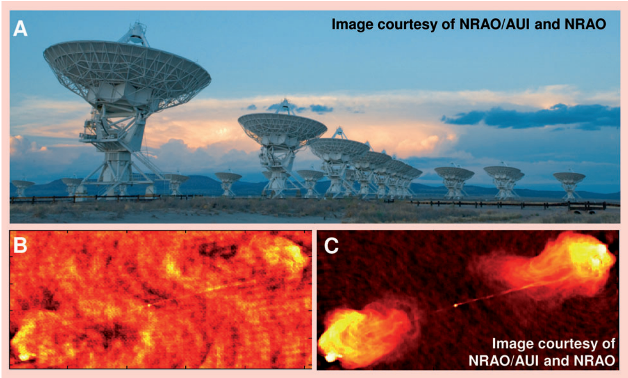

Figure 3. Radio interferometers, such as the Jansky Very Large Array (JVLA), have limited observation time available and a fixed geometry of the antennae (A). These restrictions lead to poor resolution images using direct Fourier reconstruction (B). By contrast CLEAN, an algorithm based on sparse-sampling concepts and closely related to compressed sensing, can be used to recover the image accurately, as shown in (C).

niques prior to transmission of the data. Furthermore, CPU time on the satellite is severely limited, preventing the use of complex image compression algorithms. The original proposal by the European Space Agency relies on averaging multiple frames to reduce the data transfer load.[28] However, this has the effect of reducing the spatial resolution. A compressed sensing approach would provide a 30% enhancement in spatial resolution relative to averaging, with no reduction in sensitivity and an equivalent computational load during encoding.[29]

In many ways it is remarkable that compressed sensing is having such a significant impact in a field in which signals are routinely reconstructed from incomplete data. Indeed, this observation serves to demonstrate the potential impact that compressed sensing can make in other areas of biology, chemistry, physics, and medicine in which these concepts are relatively new. By way of example, three areas of particular interest are now taken as case studies. First, we consider magnetic resonance imaging (MRI) which is increasingly engaging with these ideas. Second, we examine how compressed sensing provides a means of limiting exposure to ionizing radiation in computerized tomography (CT) and how this opens opportunities for studying nanoscale systems using electron tomography. Finally, we move away from imaging methods to consider how compressed sensing will have impact in the use of multi-dimensional spectroscopic techniques—we take as the example nuclear magnetic resonance (NMR) spectroscopy.

4. Magnetic Resonance Imaging

MRI is now the premier diagnostic tool in medicine and is widely used to characterize a variety of soft-tissue injuries, detect cancer, vascular disease, and spinal injuries and study the structure and function of the brain. In all these applications the imaging time is often lengthy—in many cases several minutes—which can lead to patient movement during image acquisition and patient discomfort. It is therefore not surprising that medical MRI saw one of the first practical applications of compressed sensing outside of astrophysics.[11] The first demonstrations of compressed sensing with MRI were in magnetic resonance angiography and fast imaging of the brain. The amount of data sampled was reduced by a factor of 2 to 10, without significant degradation in image quality. In this example, a standard imaging protocol was used and the reduction in data required provides a corresponding reduction in imaging time of a factor of 2 to 10. However, the real strength of compressed sensing is that it can be combined with other more complex MRI techniques to enable "single-shot" imaging, which can reduce the acquisition time to the extent where 3D images of the brain can now be obtained in as little as 32 ms.[30] A few of the other examples where compressed sensing has been applied include time-resolved cardiac imaging,[31] spectroscopic MRI,[32] and functional MRI (fMRI).[30,33] Despite its recent introduction, compressed sensing is already impacting clinical practice in paediatric medicine[34] where it is reducing artifacts arising from patient movement (see Figure 4). This impact will likely be further enhanced in the coming years with the anticipated incorporation of compressed sensing algorithms into commercial software.[35]

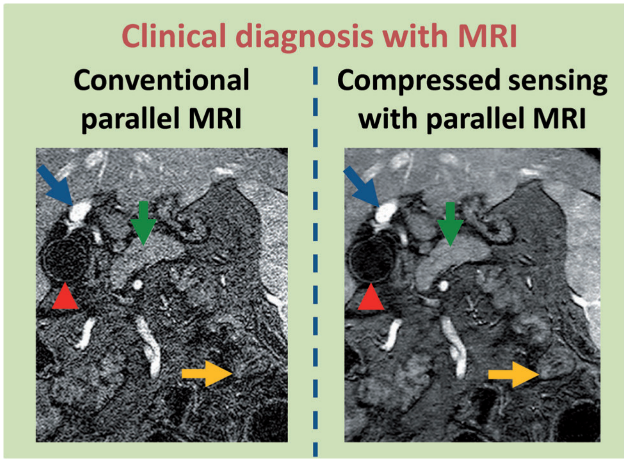

Figure 4. Clinical paedeatric imaging is challenging as patients are rarely able to stay still long enough to acquire high-resolution images. Compressed sensing is leading to better clinical diagnosis in paedeatrics by reducing acquisition times and hence improving spatial resolution of images. Compressed sensing techniques show improved delineation of the pancreatic duct (green arrow), bowel (orange arrow), and gallbladder wall (red arrowhead), and equivalent definition of portal vein (blue arrow), relative to conventional parallel MRI. Adapted from Ref. [34].

Compressed sensing is also having increasing impact in non-medical MRI, where images may be very sparse, such as transport in microchannel flows and microfluidic arrays[36–38] or chemical reactors.[39] Microfluidics is a fascinating area of research that has the potential to revolutionize chemical synthesis, analytical chemistry, and biological analysis.[40] However, the major appeal of such technology, its small size, also makes it challenging to study.[38] Bajaj et al. have demonstrated that compressed sensing, in combination with remote detection, is well suited to studying microfluidic devices as they are inherently simple (sparse) structures.[37] Another application in which compressed sensing techniques appear particularly promising is in the characterization of multiphase flows.[41] Multiphase flows are ubiquitous in both the natural and industrial worlds, ranging from the granular dynamics at work in the Sahara desert, through to the production of next generation fuels from biomass, and the sequestration of carbon to reduce global warming. However, these systems are optically opaque, hence there are few tomographic methods—particularly those offering chemical specificity—that can study such systems. The combination of MRI and compressed sensing provides a means for non-invasively studying opaque systems rapidly enough to provide insight into the fundamental physics governing these complex multiphase flows. Indeed, it is now possible to obtain high-resolution velocity images typical of multiphase flows in as little as 5 ms at a spatial resolution of 300 μm; these techniques can therefore now be applied on time scales over which the hydrodynamics of the phenomenon under investigation do not change significantly. For example, liquid velocity fields have been measured around a rising bubble demonstrating a link between sideways-moving vortices beneath the bubble and the side-to-side "jittering" that bubbles make as they rise.[41] These measurements are not possible using other measurement techniques, and would not be possible with MRI without the use of compressed sensing.

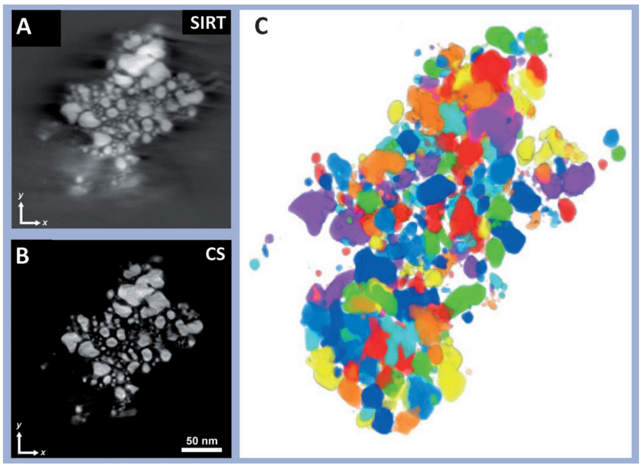

Figure 5. Electron tomography reconstructions of GaPd nanocatalysts. A) Conventional SIRT reconstruction shows significant artefacts resulting from the limited tilt angle and number of projections that can be acquired. B) Compressed sensing reconstruction significantly improves the clarity of the tomogram. The clear demarcation between the individual grains of the nanoparticle permits simple segmentation of the image. Individual grains can then be readily identified and analyzed quantitatively. Segmentation of the image in (B) is illustrated in (C) where each nanoparticle or agglomerate of nanoparticles is shown with a colour that differs from those of its nearest neighbors. Adapted from Ref. [47].

5. Computerized Tomography

CT is perhaps the most common technique for studying optically opaque systems, with applications ranging from medical imaging, to engineering, physics and biology. Compressed sensing has been demonstrated to provide accurate reconstructions from a small number of projections in a variety of CT applications, including micro-X-ray CT of small animals[42] and medical CT.[43] However, of most interest to chemistry and materials science is the application of compressed sensing to exotic modalities such as electron tomography.[44–50] Electron tomography uses accelerated electrons to permit imaging with sub-Angstrom accuracy.[51,52] The high spatial resolution achievable using electron tomography makes it appealing for the characterization of catalysts, viruses, and nano-plasmonics. However, electron tomography is challenging to apply as the ion beam focusing restricts the range of tilt angles that can be acquired and the beam is strongly ionizing which limits the number of projections that can be acquired. Compressed sensing is helping to overcome these limitations to improve the spatial resolution and quantitative structural analysis that can be achieved.

Figure 5 illustrates the benefits of compressed sensing in characterizing the structure of GaPd catalyst particles.[47] GaPd has been identified as a promising alternative to AgPd for highly selective hydrogenations involving conversion of sp-bonded to sp^2-bonded carbons.[53–55] Such reactions are critical in many pharmaceutical and agrochemical reactions, as well as in removing impurities from monomer olefinic reactants that are to be polymerized. However, it is becoming increasingly evident that the nanoscale structure of catalysts is critical to determining the selectivity and conversion. Electron tomography provides a tool that can be used to identify these structures. Conventional reconstruction techniques such as simultaneous iterative reconstruction technique (SIRT) produce significant artefacts and blurred tomograms, which makes quantitative analysis of nanoscale structure very challenging (see Figure 5 A).[56] Compressed sensing provides clearer tomograms with much better demarcation between the nanoparticles and the background (see Figure 5B). The cleaner image provided by compressed sensing makes identification and quantification of the structure of individual grains in the nanocluster clear and simple (Figure 5C).[47]

One of the major benefits of compressed sensing in electron tomography is that as well as identifying the location of the species, the intensity of the signal can also be recovered quantitatively. Electron tomography is sensitive to the chemical composition as the intensity of a projection image scales with the atomic number Z. Therefore, it is possible to identify different atomic species through changes in the intensity. Recently, such an approach has been used to provide a method for elemental mapping of the structure of bimetallic core–shell nanoparticles.[57] Bimetallic nanostructures provide greater stability and potentially enhanced catalytic activity compared with monometallic structures.[58,59] However, to be able to design such nanoparticles, a detailed understanding of the chemical composition of the nanoparticles at an atomic scale is required. Compressed sensing electron tomography measurements were used to define the changes in structure that occur at the interface between gold and silver in a core–shell nanoparticle.[57] These measurements will lead to a greater understanding of how the atomic structure determines, e.g., the catalytic performance of bimetallic nanoparticles and hence provide a method for optimizing their design in the future.

As mentioned, a major challenge in electron tomography is that the electron beam is strongly ionizing thus limiting the number of projections (or data) that can be acquired. A similar problem is encountered in almost all CT-based imaging techniques and therefore there is considerable interest in reducing the total dose of ionizing radiation to which samples are exposed, be they patients in clinical medicine, nanocatalysts or virus particles. However, this issue is of most concern when studying biological material where the total exposure restricts the signal-to-noise ratio and number of projection measurements that can be performed. In the extreme case of electron tomography studies of biological tissue, 1000 projections might be acquired in order to achieve high spatial resolution (ca. 2 nm), but this limits the signal-to-noise ratio of each measurement to ca. 1! In the compressed sensing framework, the expected error in a reconstructed image actually grows with the number of measurements, if the dose is fixed.[60] Therefore, a better approach may be to perform a relatively small number of measurements, each with a higher signal-to-noise ratio. Preliminary work has demonstrated that compressed sensing can produce higher quality electron tomography reconstructions than conventional state-of-the-art algorithms from as few as 9 projections.[44] Compressed sensing has also suggested alternative acquisition protocols in electron tomography to further reduce the exposure of beam-sensitive samples.[61–63] These developments could revolutionize electron tomography of beam-sensitive nanoscale samples including biological structures, e.g., virus particles[64] and the exciting areas of time-resolved (4D),[65] spectrally-resolved, and atomic resolution electron tomography.[49,57] For example, compressed sensing was recently combined with an electron tomography technique known as electron energy loss spectroscopy (EELS) to enable mapping of the surface plasmon resonance around a silver nanocube 100 nm in size.[48] In this case, only five spectrally resolved tilt images could be acquired before the sample was degraded by the electron beam. However, these images were sufficient to permit a direct visualization of the edge, face and corner modes of surface plasmon resonance that occur in this system.

6. NMR Spectroscopy

Turning now to NMR spectroscopy, we find that compressed sensing has not yet been widely employed by this community yet there is potential for significant benefits—particularly concerning speed of data acquisition. For example, the 3-dimensional (3D) spectroscopy experiments required for protein structure characterization, take up to 4 weeks to acquire using conventional techniques.[66] The long acquisition time of multi-dimensional NMR has meant that NMR data have long been reconstructed from fewer measurements than Nyquist sampling would suggest is necessary;[6–8] in this field such approaches are typically referred to as non-uniform sampling or NUS. Of course such NUS data cannot be reconstructed using conventional Fourier transformation, instead a variety of new data processing methods, including linear prediction, maximum entropy, and projection reconstruction NMR have been developed.[67] In each case, the goal is to increase the speed, sensitivity (in a given time) and resolution of NMR.[68,69] The results of these techniques are often impressive; however they have not been widely adopted because of a lack of a robust implementation.[70] Compressed sensing provides a mathematical framework to unify signal reconstruction techniques across a variety of disciplines and hence will enable algorithms that have been established as robust in applications such as astronomy to be readily implemented in, e.g., NMR spectroscopy. We can therefore expect sparse sampling techniques to become commonplace in all areas of spectroscopy research, indeed compressed sensing has recently been demonstrated for 2D Fourier transform infrared spectroscopy.[71]

The first demonstrations of compressed sensing with multidimensional NMR have recently been reported for applications in characterization of biomolecules[72–74] (see Figure 6 for an example). These techniques are now being extended to even more challenging biomolecular applications, such as nuclear Overhauser effect spectroscopy (NOESY) which provides information on the 3D conformation of proteins.[74–76] An advantage of compressed sensing for use with multidimensional NMR is that it permits very high spectral resolution in realistic acquisition times. The high spectral resolution has been shown to permit characterizations of subtle differences in spectra, for example, in near-symmetric cyclodextrins.[77] A conventional 2D HSQC spectrum of these cyclodextrins would require 20 h of experiment time, but this was reduced to 1 h using compressed sensing. A full assignment requires three different experiments, thus compressed sensing permits a full assignment to be completed from a set of overnight experiments.

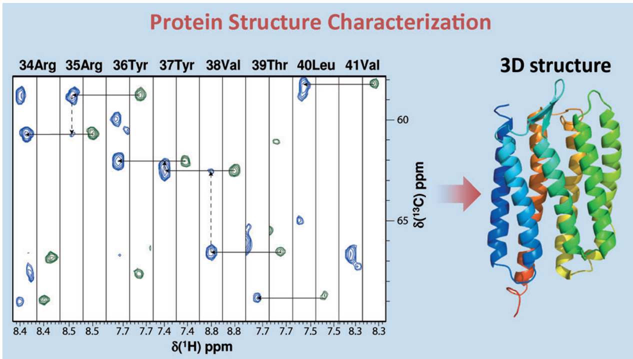

Figure 6. NMR spectra for sensory rhodopsin II obtained using compressed sensing. The spectrum shows strips from the 3D HNCA (blue) and HN(CO)CA (green) spectra that are used to perform backbone assignment of the protein. These data were reconstructed from only 16% of the fully sampled data set, and yet were of sufficient quality to permit sequential protein backbone assignment. These data can be used to help determine the 3D structure of proteins in solution, as illustrated by the ribbon diagram shown. Adapted from Ref. [72].

One exciting development of multidimensional NMR is the so called "ultrafast" or single shot multidimensional NMR technique.[78] Ultrafast NMR uses imaging gradients to permit the acquisition of a multidimensional spectrum in a single excitation. Whilst very powerful, ultrafast NMR requires strong gradients and a high signal-to-noise ratio, limiting the systems to which it can be applied. Shrot et al.[73] recently demonstrated that using a compressed sensing approach permits a reduction in the gradient strength by a factor of 5. A weaker gradient means that the spectral bandwidth can be reduced and the signal-to-noise ratio improved proportionately. These advances will further increase the range of systems that can be studied using ultrafast NMR, including higher dimensional experiments.

Perhaps the most significant opportunities arising from the implementation of compressed sensing are in the high-dimensional measurements that are essential for characterizing ever larger protein structures.[79] Compressed sensing theory states that the number of measurements required to recover a signal is dependent primarily on the number of non-zeros in the signal and is dependent only weakly on the number of points in the final spectrum, as described by Equation (2). This means that the dimensionality of the experiment can be increased with only a slight increase in the number of measurements. For example, to add a third dimension to a 2D experiment containing n_2 points in the first indirect dimension and n_3 points in the second indirect dimension, would conventionally require a factor of n_3 additional measurements; in the compressed sensing framework only a factor of $[1+\log(n_3)/\log(n_2)]$ additional measurements are required. Assuming say 32 points in each dimension, this would represent a time saving of up to 16 times; for higher resolution spectra the saving would be even greater. Such theoretical analysis is also supported by empirical studies which suggest that 2D NMR spectra require 20% sampling, 3D spectra require 4% sampling and 4D spectra require only 0.8% of the Nyquist sampling requirement.[70] With a conventional acquisition of higher dimensional spectra, it is typical to accept significant spectral aliasing in order to minimize the additional data acquisition time. However, by employing compressed sensing, data can be acquired in the additional dimension at the time cost of only a few additional measurements and without incurring any aliasing artefact, hence significantly increasing the effective spectral resolution. The additional resolution provided by compressed sensing with multi-dimensional NMR experiments has been shown to be of particular benefit in NOESY type experiments where nearby peaks are likely to overlap.[74–76]

It is important to consider the implications of a compressed sensing approach on the apparent sensitivity of an NMR experiment. There is often significant confusion surrounding the analysis of sensitivity in NMR. Sensitivity is sometimes defined as the signal-to-noise ratio, or sometimes as the signal intensity itself. However, perhaps the most appropriate definition is the ability to detect a signal. This latter approach was recently used to demonstrate that compressed sensing significantly increases the sensitivity of NMR experiments, especially when multiple indirect dimensions are acquired.[68] It has also been shown that compressed sensing is able to recover the intensity of the peaks quantitatively.[75] Quantitative recovery and enhanced sensitivity are especially important for studies of biological macromolecules, where often the weak peaks are most significant for accurate structure determination. Figure 7

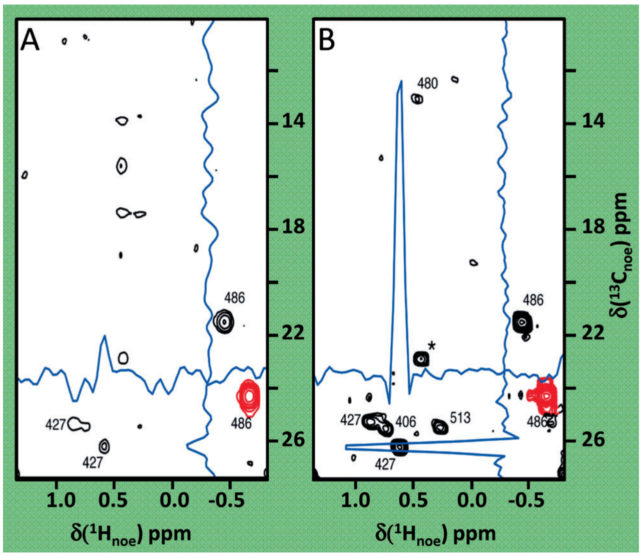

Figure 7. Excerpts from 4D NOESY NMR spectra for the MED25 component of the human Mediator complex with the transactivation domain of the *Herpes simplex* transcriptional activator VP16. The methyl groups of the isoleucine, leucine and valine residues were selectively labeled. The spectra were reconstructed from the same experimental data but using either A) the discrete Fourier transform or B) a compressed sensing algorithm, in this case the Harvard Medical School implementation of Iterative Soft Thresholding. The blue lines are 1D traces through the 486/427 cross peak. In these experiments, it is the low-intensity cross peaks that provide the most useful structural information. Artefacts arising from undersampling of the data in the indirect dimensions obscure the cross-peaks in (A). These artefacts are eliminated in the compressed sensing reconstruction in (B), permitting accurate, quantitative determination of the intensity of the cross peaks. Adapted from Ref. [76]; the original figure also contains a comparison with the Forward Maximum Entropy algorithm.

shows a comparison of non-uniformly sampled data reconstructed using a conventional Fourier transform and compressed sensing.[76] The conventional Fourier transform approach results in very small peaks that are difficult to distinguish from the noise. By contrast, the compressed sensing reconstruction produces much sharper and stronger peaks that are distinguished from the noise easily. The compressed sensing approach therefore enables the characterization of three peaks in this plane that were obscured in the conventionally processed spectrum.

A recent review of compressed sensing applications in multidimensional NMR highlights the potential of this technique, but also provides guidelines for the practical implementation of compressed sensing.[70] Such work indicates that compressed sensing techniques will shortly be accessible to the broader NMR community and will no longer be restricted to those laboratories with specialists in signal processing. Already, compressed sensing techniques are being used in many fundamental studies of protein structure,[80–84] including some examples that exploit four- and higher-dimensional NMR experiments.[76,85,86] New, more accessible implementations of compressed sensing will ensure it is even more widely available in the future. Thus, the higher dimensional experiments permitted by compressed sensing will facilitate the characterization of larger, more complex proteins than ever before, such as the important family of mammalian G protein-coupled receptors (GPCRs) that are the target of approximately 25% of all modern medicinal drugs[87] or intrinsically disordered proteins which play a major role in many signal transduction pathways.[88]

7. Limitations of Compressed Sensing

Whilst providing astonishing results in many situations, compressed sensing is not universally applicable and there are several limitations that must be considered. The essential aspect is that for compressed sensing theory to hold, it is necessary that the measurement meet the criteria outlined in Section 2. The most challenging of these criteria are the requirements for incoherence of the sensing matrix and the identification of a basis in which the signal is compressible. Many measurement systems provide direct point source data regarding the system studied, and therefore compressed sensing cannot be applied directly in these cases. For example, a conventional digital camera has a detector for every pixel that is captured of a scene and hence there is no incoherence between the detector array and the image captured. However, even for these situations, compressed sensing may be able to provide a benefit when there are restrictions in terms of power or data transmission.

It is also interesting to consider how compressed sensing theory behaves in the context of repeated noisy measurements. In this case, two approaches could be considered: 1) m independent noisy measurements could be obtained, but with each measurement repeated such that it has a high signal-to-noise ratio and n observations are acquired in total or 2) n independent measurements are obtained, but each with a low signal-to-noise ratio. These two cases correspond to the same total number of measurements, but do not necessarily yield equivalent results. Intuitively, one might assume that a noisy signal is best reconstructed from n independent measurements. However, empirical evidence suggests that this is not always true.[39,68] The reason for this discrepancy is presumably linked to the energy distribution of the signal and theoretical explanations for these findings are ongoing.[19] A particularly interesting result in this respect is the work of Willet et al. who show that when the noise is Poisson distributed, fewer measurements each with higher signal-to-noise ratio will lead to a significant increase in quality of the final image.[60]

8. Summary and Outlook

Compressed sensing was born out of a desire to bypass the seemingly unnecessary steps of acquiring a fully sampled image and then compressing it for storage. The question therefore arises as to whether it succeeds in this regard. In certain situations, such as in the example of the Herschel satellite in astronomy, the ability to simultaneously measure and compress your result is hugely powerful. However, in many cases it is unlikely that compressed sensing will actually replace conventional compression of fully sampled data. Compressed sensing is only likely to replace conventional compression when the measurements, or the transmission of the measurements, are costly. Instead what compressed sensing provides is the ability to measure systems that are unstable (e.g. when studying proteins by NMR spectroscopy)[72] or sensitive to the measurement (e.g. when using ionizing radiation).[43] Furthermore, compressed sensing provides a new framework in which to construct a measurement system. This is perhaps the area in which the most exciting developments are now occurring.

The most famous example of a new sensing protocol is the development of the "single-pixel camera."[12] Here, instead of recording a photograph of a scene by using an array of sensors (e.g. in a CCD), the single-pixel camera has just a single sensor; the scene is recovered by recording multiple measurements with this single sensor, with spatial encoding achieved using a micro-mirror array, as illustrated in Figure 8. Compressed sensing is then used to recover the image from these measurements and knowledge of the orientations of the mirrors in the array. Similarly, a coded aperture can be used to project incoherent samples of a scene onto a low-resolution sensor, and hence capture the entire image in a single shot.[89] Both these approaches have the effect of transferring the

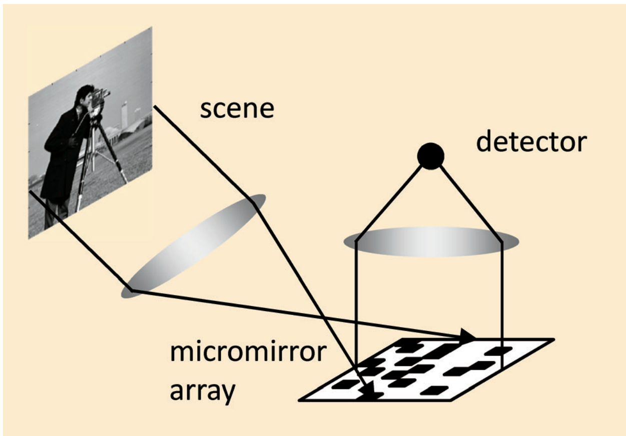

Figure 8. Illustration of the single pixel camera idea. In this system the scene of interest is projected onto a micromirror array which obscures parts of the scene. All of the light from the scene is then focused onto a single pixel detector. The micromirror array then changes such that different aspects of the scene are illuminated. After several measurements the complete scene can be reconstructed, even though each individual measurement was recorded using only a single pixel detector. Adapted from Ref. [13].

complexity of the image capture from the hardware (acquisition) to the software (reconstruction). Compressed sensing therefore provides a means to image systems rapidly where an array sensor is expensive or not yet available at the frequency of interest; for example, at terahertz frequencies.[90] Further, by integrating the image compression with the data acquisition, compressed sensing significantly reduces the demands on the imaging sensor making high-resolution imaging cheaper and more energy efficient—which will have significant impact in the development of the next generation of sensors for everyday devices, such as mobile phones.

The concepts of compressed sensing have also been demonstrated to enable ultrafast optical imaging at sub-wavelength resolution.[91,92] The resolution of optical imaging is typically limited to half the wavelength of light. A reconstruction inspired by compressed sensing has recently been reported to enable ultra-fast sub-wavelength coherent diffraction imaging (CDI). In this case, a 532 nm laser was used to measure objects with better than 100 nm resolution.[92] The motivation for this work was to extend the imaging resolution of CDI to characterize the structure of molecules that cannot be crystallized. Even higher resolution measurements have been reported by exploiting the concept known as stochastic optical reconstruction microscopy (STORM).[92] Here researchers were able to track microtubules in a living Drosophila S2 cell with 42 nm spatial resolution and second-scale time resolution. These results demonstrate that optical imaging techniques can now be used to monitor nanometer scale phenomena in living tissue in real time.

Interestingly, compressed sensing, itself born out of information theory, is now recognized as potentially providing a means of increasing the bandwidth of information transmission.[93] In the case of radio-frequency analogue-to-digital converters (ADCs), in many applications the bandwidth required is beyond the capabilities of current ADC technology, where sampling is performed at the Nyquist rate. In particular, sampling at such a high rate would overload hard drives and data transfer systems. For example, a 1 GHz signal, even sampled with a resolution of 16 bits, would produce data at a rate of 4 $GB\,s^{-1}$, which would fill modern hard drives in a matter of minutes. Using compressed sensing the resulting signal can be sampled at a much lower rate and, further, it should be possible to tailor the accuracy of the ADC in light of the size, weight and power requirements of the application. Such advances will make fully digital sampling possible across a broad range of applications in spectroscopy.

The concept of reconstructing a signal that is known to be sparse has existed since the 1960s. However, for much of this time applications were restricted to a few specialized areas of science. Compressed sensing has now provided a unique framework that has enabled the complex concepts of sparsity and information theory to make the transition from the specific mathematical discipline of information theory through to real world problems. As a result, only one third of the articles citing the seminal publications on compressed sensing are in the fields of mathematics and computer science, with the remainder including acoustics, astronomy, biology, chemistry, geophysics, medicine, and oceanography, with new disciplines being added to that list daily.

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