Quantifying bone structure, microarchitecture and pathophysiology with magnetic resonance.

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I. Introduction

Diseases affecting bone are the second most common cause of disability and are predicted to increase in prevalence in an aging population[1]. Imaging plays an increasingly important role in diagnosis, assessment of treatment response and follow up of diseases affecting bone, and provides a valuable alternative to invasive biopsy. Modern 'physiological' imaging techniques provide not only anatomical but also functional information, giving us valuable insights into the bone

microenvironment in both health and disease. As imaging delves deeper into tissue physiology, it is increasingly important that radiologists are aware of the effect of tissue pathology on the images they interpret. MRI has the versatility to image these aspects of bone pathology and lends itself to quantitative analysis. Furthermore it can image bone in detail or give an overview of skeletal involvement in disease.

Although in clinical practice most images are analysed qualitatively by radiologists, there has been a trend towards using quantitative imaging methods which provide objective physical measurements from tissue such as diffusivity, perfusion or tracer uptake. To quantify is to measure, and quantification within the science of magnetic resonance arose from the ability to measure the NMR properties of biological tissue. This led to attempts to characterise the nature of the tissue using these parameters [2]. Quantitative MRI therefore uses measurable MR parameters to describe tissue, rather than forming an image from non-quantitative values.

For a parameter to be clinically useful, it has to reflect a biologically significant process, such as change in a meaningful manner with the exacerbation or resolution of a disease process. There are a number of advantages to truly quantifying MR measurements. It is easier to test for reproducibility, sensitivity and specificity of the measurement. The data are easier to model and assess mathematically, and have the potential for machine learning and population studies. There is also the potential for automation of assessment in a manner not amenable to qualitative data.

In this work, we provide a brief overview of bone physiology and pathophysiology, before considering how magnetic resonance (MR) techniques can be used to ‘probe’ these physiological and pathophysiological processes.

II. Bone Physiology and Pathology

1. What is Bone?

Although the skeleton is sometimes viewed as a simple structural support for the body, it is increasingly clear that bone is in fact an active, dynamic organ, which plays a central role in the coordination of metabolic, endocrine and haematological processes. Bone is integral to the homeostasis of minerals such as calcium and phosphate, serves as a reservoir of growth factors and is the cradle of haematopoiesis[3].

The skeleton is composed of around 80% cortical bone and 20% trabecular bone [4]. Cortical bone is dense and composed of a branching network of cylindrical osteons called Haversian systems. Trabecular bone consists of osteons called packets arranged in a honeycomb pattern. The non-mineralised component of bone is called bone marrow and consists of adipocytes (yellow marrow) and haematopoietic cells (red marrow). The outer cortical surface of bone is covered in periosteum, except at joints, and the inner surface is covered by endosteum. Periosteum is a fibrous connective tissue whereas the endosteum is a membranous structure; both contain blood vessels, osteoblasts and osteoclasts.

The major cellular constituents of bone are osteoclasts, osteoblasts and osteocytes, which are surrounded by mineralised extracellular matrix. Osteoblasts synthesise bone matrix and regulate mineralisation by releasing vesicles that contain calcium and phosphate. The mineralised matrix of bone consists of collagenous proteins (mainly type I collagen) and bone mineral, which is mainly hydroxyapatite (4). Osteoblasts, which are surrounded by and buried within this matrix, then differentiate into osteocytes. A biochemical network forms connecting bone surface lining cells and osteocytes. Their main function is to transduce mechanical stress into a biological response by signally to the network of osteocytes and osteoblasts. Osteoclasts play a central role in bone remodelling and are the only cell capable of resorbing bone.

Bone is a dynamic structure, which undergoes growth, modelling and remodelling during life under influences from mechanical forces, metabolic factors and hormonal action. Bone remodelling is a continuous process where units of old bone are removed and replaced by new proteinaceous matrix, which is then mineralised. [4]. Regulation of osteoclast mediated bone resorption is under the influence of parathyroid hormone, vitamin D and calcitonin. Mineralisation of the matrix is regulated by osteoblasts and this modulates serum levels of calcium and phosphate under the influence of vitamin D. After a cycle of remodelling, 50 to 70% of osteoblasts undergo apoptosis and the others become osteocytes and bone lining cells[4]. Abnormal modelling can be activated in disease states such as multiple myeloma where osteoclasts are activated by bone lining cells expressing tartrate-resistant acid phosphatase due to an abnormal microenvironment created by plasma cell infiltration [4].

One of the most important functions of bone is haematopoiesis. The haematopoietic system is responsible for producing more than 100 billion mature blood cells a day [3]. Haematopoietic stem cells reside in the endosteum termed 'the haematopoietic niche' and have a rich vascular supply. The interactions between bone microenvironment and haematopoiesis are complex but its understanding is increasing rapidly. In particular, the bone microenvironment has been shown to play an important role in the pathogenesis of many diseases. For instance in leukaemia, bone marrow infiltration can suppress and stimulate osteoblasts [5]. Metastatic cancer cells have been shown to compete with haematopoietic cells for resources [5]. Hormones also influence the haematopoietic microenvironment. Both parathyroid hormone and oestrogen have been shown to have a role in modulation of the haematopoietic stem cells [3].

2. Bone Pathology

A useful way of classifying bone pathology is by micro-architectural changes, which radiologists can infer from imaging. New imaging techniques can detect abnormalities in density, quality, porosity, cellularity, the presence of fibrosis and fat content.

i. Change in cellularity

Bone cellularity is increased in pathological processes such as malignancy, infection and inflammation. These pathological processes can be further classified by which compartment they affect. For instance, primary and secondary bone tumour, infection and inflammation cause a change in cellular density and alter the size of the extracellular space. On the other hand, abnormal mineralisation or fibrosis in the extracellular space can cause increased packing of cells. The microenvironment of bone changes early and rapidly in aggressive processes. Rapid increases in bone cellularity cause a loss of fat, destruction of bone trabeculae and formation of new blood vessels, which can be quantified by MR techniques.

ii. Change of Vascularity

Bone is highly vascular and changes in vascularity can be a useful indicator of disease. Perfusion of bone is increased in inflammation and neoplasia. Reduced perfusion is seen in patients with peripheral vascular disease and with red cell abnormalities such as sickle cell anaemia.

The effect of reduced perfusion of bone can be seen as fairly characteristic lesions on MR. The earliest imaging sign of bone infarction is bone oedema, which represents cytotoxic oedema. In the chronic phase, fibrosis of the marrow and sclerosis of bone is seen.

Increased perfusion to bone can occur in various pathological states. Perfusion of tissues is complex and involves various compartments. One of the simplest models explaining tissue perfusion uses two compartments: blood plasma and the interstitial space[6]. For a given cardiac output, increased

tissue perfusion can be due to increased permeability of existing vessels or an increase in the number of blood vessels supplying tissue. Both increased permeability and neo-angiogenesis exist in inflammation and neoplasia; and can be detected by MR techniques.

iii. Change of bone remodelling

Many disease processes affecting bone lead to bone fragility characterised by a decrease in bone mass and quality. Bone quality depends on several factors such as bone mineralisation, remodelling rate, number of micro-fractures and microarchitecture [7]. Bone loss takes place due to remodelling imbalances in the activity of osteoclasts and osteoblasts. Several factors can perturb this balance from changes in hormone concentration in osteoporosis to inflammatory cytokines in rheumatoid disease[8].

When this balance is tipped in the favour of bone loss in osteoporosis, there is a reduction in bone mass with thinning of trabeculae and increased porosity of cortical bone. Although the thinning of the trabecular network is well recognised, cortical porosity has been less well studied due to the challenges in its imaging. Traditional approaches have measured cortical bone thickness, which does not fully characterise its quality. In fact the degree of porosity is considered the main microstructural feature of the cortex [9]. Porosity may seem like a property that leads to an inherent mechanical weakness of bone but it serves an important purpose. The vascular channels are required to sustain and nourish the syncytium of interconnected osteocytes, whereas the nanopores play an important role in mechanosensation [10]. Although the mechanical cost of porosity is small in healthy bone, in pathological states, such as chronic kidney disease, disuse and parathyroid treatment, increased porosity leads to bone fragility [9]. Geographical increases in porosity due to inefficient redistribution of bone mass is associated with increase rates of fracture in patients with diabetic patients [11].

III. Imaging Methods

i. Diffusion weighted imaging

Diffusion weighted imaging assesses the Brownian motion of water in its microscopic environment. The signal detected reflects the movement of water at a micrometre scale beyond the usual millimetre resolution of MRI. The diffusion-weighted image however is affected by other parameters other than diffusion such as tissue perfusion and T1 and T2 relaxation times. The DWI image is constructed by applying diffusion sensitising gradients to a T2 weighted image. The degree of diffusion sensitisation is defined by the 'b value'; with lower b values providing perfusion weighting and higher b values providing diffusion weighting [12]. However as T1 and T2 relaxation times of tissue vary under different physiological and pathological conditions, diffusion weighted imaging can be difficult to interpret. Apparent diffusion coefficient calculations can quantify the diffusion effect by using two or more acquisitions at different b values[13]. The ADC value is only truly accurate if water diffusion behaves freely but in tissue it remains useful as it gives a summary of the diffusion characteristics at a voxel level. Diffusion is restricted when molecules encounter boundaries which prevent free movement and in human tissue the main boundaries are cell membranes [14]. The variation of ADC in physiological or pathological conditions is thought to be due to the effect of processes largely affecting the extracellular space. The contraction of the extracellular space from cell proliferation or swelling causes restricted diffusion as indicated by a decrease in ADC. With improving technology, higher b values can be achieved and, with more complex analyses, may reveal intracellular space and membrane interactions [15].

ADC values of bone correlate with bone marrow cellularity and micro vessel density in the extracellular space and this has been shown to be useful in neoplastic conditions. For instance, ADC can increase in osteosarcoma following chemotherapy, indicating tumour response even when no reduction in tumour size has occurred [Figure 1] [16]. In multiple myeloma, whole body DWI has been shown to be a highly sensitive technique for quantifying disease burden [17] and can detect

early treatment response, relapse and progression even when not captured by serum and urine analysis [Figure 2] [18]. With successful treatment, the volume of cell infiltration decreases and there is less restriction to free water movement, leading to an increase in ADC values [19]. The use of several b-values allows differentiation between perfusion and diffusion effects on signal in bone marrow. Both rapid micro perfusion, which causes a fast initial decay due to abnormal blood vessel proliferation, and slower signal decay related to diffusion in the interstitial space can be evaluated by the intra-voxel incoherent motion model in myeloma [20]. The ability to measure difference in metrics allows for a quantitative assessment of disease burden, which can be monitored on follow up studies.

DWI is effective in early diagnosis of sacroiliitis and monitoring treatment response in patients with seronegative sponyloarthropathies [21,22]. ADC values are significantly higher in patients even in the early stages of ankylosing spondylitis compared to normal controls [23]. In enthesitis related arthritis DWI measurements reflect the response to anti-THF therapies and are more objective than visual scoring [22]. Computation tools have been developed to quantify bone ADC values which are comparable to conventional STIR sequences [21]. DWI has been shown to be useful in the assessment of hip ischaemia in patients with Legg-Calve-Perthes disease [24], and in particular, median ADC ratios have reported as a reproducible means of assessing hip ischaemia.

ii. Dynamic Contrast Enhancement

DCE-MRI is based on rapid acquisition of images after contrast injection allowing quantification of tissue perfusion and kinetics. The basis of DCE MRI is the rapid acquisition of a series of T1-weighted images before and after infusion of a T1-shortening, diffusible contrast medium [6].These can provide a detailed time-intensity curve which can then be used to estimate the concentration of contrast medium in the region of interest [25].

DCE-MRI is useful in assessing microcirculation of bone marrow infiltrated by tumour. Tumour angiogenesis in myeloma leads to increased uptake of contrast and this subsequently decreases with

effective therapy [26]. In myeloma, DCE-MRI has been shown to be useful in distinguishing hyper-cellular haematopoietic marrow from neoplastic marrow. Perfusion changes can occur early in treatment response as has been shown in osteosarcoma correlating with histological necrosis [27].

DCE MRI lends itself to quantitative analysis. Semi-quantitative analysis is based on the time to intensity graph, which can be used to calculate various metrics such as time to peak and area under the curve. The early phase of enhancement reflects tissue micro-vascularisation and the later phases of washout reflect capillary permeability and interstitial space enhancement [28]. Quantitative perfusion analysis uses pharmacokinetic models to explain contrast exchange between the intravascular and extravascular space. There are three principle parameters: the transfer constant K_{trans}, the extravascular extracellular space fractional volume (V_c) and K_{cp} (backflow transfer constant) [26]. In highly permeable scenarios, the transfer constant is equal to blood plasma flow per unit volume of tissue and in low permeability it depends on the permeability between blood plasma and the extravascular extracellular space. Characteristic perfusion patterns can aid the diagnosis of osteoid osteomas, osteoblastomas, and giant cell tumours of bone [29].

iii. Chemical Shift-Encoded Imaging

Chemical shift-encoded imaging (CSI) was first described by WT Dixon, using a simple modification of a spin echo sequence to acquire 'fat-water in phase' and 'fat-water opposed phase' images, facilitating the generation of water-only and fat-only images [30]. Although there were a number of technical limitations with the original technique, this technology has now developed to the point where fast, accurate and quantitative CSI is relatively easy to implement on most clinical scanners.

Modern CSI typically uses multi-echo spoiled gradient echo (SPGR) sequences, with data acquisition at multiple echo times (usually between 3 and 8). There are a variety of analytic tools available that can generate fat fraction maps, for example 'Iterative Decomposition with Echo Asymmetry and

Least squares (IDEAL)' [31]. Each pixel has a value of between 0 (pure water), and 1 (pure fat). In normal bone marrow, most pixels have a value around 0.5, indicating approximately equal signal contributions from water and fat.

CSI is particularly useful for disorders, which affect the bone marrow, where pathological processes tend to cause either an increase or a decrease in fat content. For example, a number of authors have demonstrated a reciprocal relationship between marrow fat and bone mineral density in patients with osteoporosis, leading to investigation of FF as a biomarker in osteoporosis [32–35]. Similarly, in obese patients, marrow fat has an adverse effect on bone microarchitecture [36]. Interestingly, patients with anorexia nervosa undergo an increase in marrow fat content despite losses in overall body fat, possibly because marrow adipose tissue undergoes a homeostatic change designed to increase appetite and insulin sensitivity [37,38].

In patients with metastatic cancer, tumour cells infiltrating the marrow effectively 'displace' the normal fatty marrow and therefore cause a reduction in FF. For example, symptomatic multiple myeloma patients have significantly lower FF measurements than those with symptomatic disease [39]; FF measurements can potentially also be used to stratify patients according to their depth of response to treatment [Figure 3] [40].

An interesting recent development is the use of CSI to quantify inflammation in patients with spondyloarthritis. Areas of 'active' juxta-articular inflammation (bone marrow oedema) cause a reduction in FF, whereas chronically inflamed sites (fat metaplasia) undergo an increase in FF [Figure 4] [41]. FF measurements could therefore be useful as a marker of inflammatory disease severity and activity. A key advantage of CSI in this setting is that disease severity can be assessed directly from the image, removing the need for subjective interpretation by a radiologist.

iv. Ultra short TE and Zero-TE

The MR signal intensity of a voxel containing tissue is dependent on many factors including the mean transverse relaxation time (T2 and T2*) of the tissue being examined in a particular voxel. Tissues are heterogeneous and are composed of a spectrum of transverse relaxation times. Bone, especially cortical bone, contains a high fraction of components with ultrashort transverse relaxation times, which are in the order of 0.39-0.5 msec. However ultrashort time to echo (UTE) sequences including zero TE using short minimum echo times below 1 msec are now able to interrogate the microarchitecture of bone. One of the main challenges in cortical bone imaging is the contamination of signal from muscle and fat, which is being addressed by novel subtraction techniques [42] These techniques have produced promising quantitative cortical bone maps [Figure 5]. Zero-TE sequences differ from other ultrashort TE sequences because the readout gradient is applied prior to excitation. It has some advantages over other UTE sequences including reduced eddy current effects and minimal acoustic noise due to the elimination of rapidly switching gradients in between TRs.

UTE sequences have been used to study cortical porosity by characterising bound water versus free water. Porosity is an important determinant of bone quality and strength[43]. A study has shown that indirect measurements of porosity and T2 relaxation times of cortical bone may be correlated with its material property; for instance short T2 relaxation times have been shown to correlated with failure strain in cadaveric femoral bone [44]. Zero TE sequences have been used to study in vivo trabecular bone architecture [45].

3. Imaging at the Extremes of Scale: From Single Voxel Spectroscopy to Whole Body Imaging

i. MR Spectroscopy

MR Spectroscopy (MRS) provides information on the molecular composition of tissue and has been used in the brain to characterise lesions but it also shows promise for bone lesions and bone marrow imaging. MRS spectra can be acquired from nuclei, which have non-zero spin such as protons, carbon-13 (^{13}C), sodium (^{23}Na) and phosphorus-31 (^{31}P). In musculoskeletal imaging, proton MRS has been studied the most in the context of tumour and fat characterisation. ^{31}P spectroscopy requires specialised hardware and provide lower spatial resolution [46] but has been used to investigate energy metabolism in normal and diseased states. Sodium MRI images the sodium nuclei of tissues but in musculoskeletal imaging, it remains a research tool primarily in early osteoarthritis looking at hyaline cartilage proteoglycan losses [47].

The most common methods of fat characterisation by proton MRS are single voxel methods such as stimulated echo acquisition mode (STEAM). Single voxel methods are simpler, faster and suffer less from magnetic field inhomogeneity compared to multivoxel techniques [46]. Aggressive bone lesions demonstrate high cell membrane turnover and studies have shown that the metabolite choline, which encompasses free choline, phosphocholine and glycerophosphocholine, is increased in malignant lesions [43]. Early studies on MR spectroscopy of bone lesions used a qualitative assessment of choline content but more recent studies have calculated absolute choline concentrations [48]. There are limitations to this method but there is a movement towards quantitative assessments of the tumour metabolic signature in the literature [43]. MRS therefore shows promise in increasing sensitivity and specificity of MR in detecting malignancy and therefore obviating invasive biopsies.

1H-MRS has also been used to study the triglyceride chemical composition of bone marrow in vivo [49] and elevated marrow lipid content has been found in patients with osteoporosis and osteopenia

[50]. Since lipid peaks in marrow are usually incompletely resolved on 1H-MRS, the application of prior knowledge in spectral analysis can enable the reliable assessment of overlapping lipid peaks [51]. Provided that signal contributions from individual lipid peaks can be identified and measured, 1H-MRS can also assess changes in lipid composition that occur in osteoporosis.

ii. Micro-MRI

Micro-MRI provides high resolution imaging of bone allowing the evaluation of both cortical and trabecular properties at a scale of 100-200 micrometres (in plane resolution)[52]. It rivals and performs similarly to high-resolution peripheral quantitative computed tomography (HR-pQCT) without using ionising radiation. Micro-MRI use sequences such as spoiled gradient echo, balanced steady state free precession (b-SSFP) and fast large spin echo (FALSE) to provide exquisite detail of bone [53][54]. Metrics such as bone volume fraction, topology and orientation can be quantified which correlate well with equivalent CT measurements [55].

Micro-finite-element analysis can be applied to high resolution data sets to analyse the examined 3D trabecular network and estimate mechanical properties such as stiffness and elastic modulus [56].. Furthermore 3D voxel models can be fed into a micro-finite-element stimulator, which can model the change in parameters in response to intervention and predict the mechanical implications of hormonal treatments such as in osteoporosis [20].

iii. Whole Body MRI

From detailed imaging of the microarchitecture of bone, WBMRI images abnormalities throughout the skeleton. This approach is useful for systemic conditions affecting bone such as haematological malignancies, bone metastases and rheumatological disorders. Studies comparing WB-MRI and PET-CT on a lesion by lesion basis have shown higher overall diagnostic accuracy for WB-MRI [57]. Furthermore whole body data sets using functional sequences such as DWI and DCE can be used to create quantitative maps of disease burden and activity [58]. DWI lends itself to easy delineation of

bone lesions with semi-automated segmentation software. This has been used to quantify burden of disease which correlates with established prognostic biomarkers [59]. Furthermore ADC changes in individual lesions and globally in the whole body can be used to determine treatment response in patients with metastatic bone disease and myeloma [60,61].

WBMRI has become the gold standard for assessment of multiple myeloma as it is more sensitive for marrow infiltration by plasma cells compared to conventional radiography and CT [Figure 2] [62]. MR imaging patterns of bone marrow involvement have been shown to have prognostic value (diffuse disease has a better outcome than focal lesions) and correlate with 5 year survival rate in patients treated with autologous bone marrow transplantation[63]. WB-MRI outperforms bone scintigraphy in the detecting metastatic bone disease from solid cancers as shown in meta-analyses[64].

In the setting of ankylosing spondylitis, WBMRI allows the global assessment of both acute and chronic involvement of the axial and peripheral skeleton. Detecting pre-structural changes are important in diagnosing the condition early allowing for early aggressive treatment and improving patient outcome [65].

The main obstacles to the widespread adoption of WB-MRI are related to access to scanners, and lack of radiological expertise. Scans can be long but with careful planning and the use of fast imaging sequences (such as Dixon scans), whole body scans with both morphological and functional imaging can be achieved in as little as 30 minutes [66].

WB-MRI data sets represent a daunting amount of information for radiologists to read. However with standardisation in MRI acquisition and validated biomarkers, automatic segmentation will help radiologists analyse image sets rapidly and understand disease phenotypes at a population level. There are a number of techniques which are being refined but the most promising are based on machine learning [67].

IV. Conclusion

Bone imaging is changing. MRI can provide anatomical and functional information and multiparametric and quantitative techniques offer a new insight into bone disease. These techniques have the potential for improvement of disease diagnosis, assessment of disease activity and treatment response, and for prognostication. Using computational methods it may be possible to create a comprehensive anatomical map of disease with quantitative metrics on disease activity and bone quality. These data have the potential for early treatment stratification and therapeutic escalation where necessary.

The challenge for radiologists is identifying which parameters add clinical value. Currently there are a number of techniques, which provide interesting data about disease processes but there is a lack of evidence comparing these techniques in a quantitative way to determine the quality of diagnostic information. Furthermore, there is a lack of economic analyses comparing different techniques and on the evaluation of the impact on patient outcome. Further research is necessary to assess the true impact of quantitative bone measurements on disease management and outcome.

Figures

Figure 1

MRI images of the lower limb of a 26-year-old male with osteosarcoma before and after two cycles of chemotherapy: Coronal T2W showing a metaphyseal lesion (a1, arrow), which has not changed in

size post treatment (a2). Axial m-Dixon fat only image (b1) shows no appreciable difference post treatment (b2). Axial DWI b1000 image (c1) showing a penumbra of high signal in the lateral aspect of the lesion before treatment which is of lower signal post treatment (c2). Axial ADC map (d1) shows corresponding low ADC in the periphery suggestive of cellular tumour, which increases post treatment suggestive of response to treatment (d2) (Images courtesy of Dr. Harbir Sidhu, University College London Hospital).

Figure 2

Representative MR images showing a bone lesion in the right pelvis of a patient with Multiple Myeloma before and 8 weeks after treatment. Focal lesion (arrow) demonstrated on (A) coronal pre-contrast fat-only mDixon, (B) pre-contrast water-only mDixon, (C) post-contrast water only mDixon and (D) b1000 diffusion weighted imaging at baseline (A1–D1) and 8 weeks (A2–D2) in a patient who achieved very good partial response after induction chemotherapy (images courtesy of Dr. Dr Arash Latifoltojar, University College London Hospital).

Figure 3

Whole body chemical shift-encoded MR (CSE-MR) images from a patient with multiple myeloma. Fat only (A), water only (B) images, and fat fraction maps (C), are shown from left to right. A diffuse pattern of cellular infiltration of the vertebral bodies and iliac wings is demonstrated bilaterally in contrast to the normal fatty composition of the femoral and tibial bone marrow (images courtesy of Dr. Arash Latifoltojar, University College London Hospital).

Figure 4

Quantifying disease in Spondyloarthritis by Fat fraction mapping (PDFF – proton density fat fraction). Coronal images of the sacroiliac joints show areas of periarticular bone marrow oedema (a,b). Arrowed regions show high signal on the STIR image (a) and a reduction in fat fraction (b).

Conversely, areas of fat metaplasia (c,d), which arise in areas of previous inflammation, show high signal on the T1-weighted image (c), and increased fat fraction (d).

Figure 5

Cortical bone maps generated from phase sensitive dual inversion recovery subtraction using Ultrashort Echo time (UTE) MRI. Axial image of the tibia and fibula showing high signal in the cortical bone and no signal from surrounding fat or muscle (images courtesy of Professor Graeme Bydder, UCSD).

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