Current Dilemmas and Future Perspectives for Breast Cancer Screening with a Focus on Optimization of Magnetic Resonance Spectroscopic Imaging by Advances in Signal Processing

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Abstract

Israel has a National Screening Program for early detection of breast cancer. The need to continue and even expand this program was recently stressed in light of the high risk in the population. However, the optimal modalities for breast cancer screening are controversial, especially for women at risk. Mammography, the established screening method, is critically examined, and molecular imaging techniques, such as magnetic resonance spectroscopy and spectroscopic imaging are explored, especially for primary breast cancer detection. MRS and MRSI are currently limited by their reliance on the conventional framework for data analysis in biomedical imaging, i.e., the fast Fourier transform. Recent mathematical advances in signal processing via the fast Padé transform can extract diagnostically important information, which until now has been unavailable with *in vivo* MRS. A clinical MRS signal illustrates the rapid and stable convergence provided by FPT, yielding accurate information about key metabolites and their concentrations at short acquisition times. We suggest that the next step would be to apply the FPT to *in vivo* MRS/MRSI signals from patients with breast cancer and to compare these to findings for normal breast tissue. The potential implications of such an optimized MRS/MRSI for breast cancer screening strategies are discussed, especially for younger women at high risk.

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Worldwide, breast cancer is the most commonly occurring cancer in women, and the leading cause of cancer-related deaths among women. In the year 2000, there were approximately 735,000 newly diagnosed cases of breast cancer [1]. The incidence of breast cancer is particularly high in Israel [2]. Ashkenazi women (East European origin) are known to be at elevated risk due to the high prevalence (approximately 2.5%) of founder mutations in the breast cancer susceptibility genes *BRCA1* and *BRCA2* [3], which confer an estimated 50–80% lifetime probability of breast cancer developing [4]. Moreover, a substantial percentage of Israeli women have been reported to take hormone replacement therapy during their postmenopausal years [5,6], and its use even for relatively short periods is associated with an increased risk of breast cancer, as recently confirmed by randomized clinical trials such the Women's Health Initiative [7]. (These findings were for combined HRT, estrogens and progestins.)

MRS = magnetic resonance spectroscopy
MRSI = magnetic resonance spectroscopic imaging
FPT = fast Padé transform
HRT = hormone replacement therapy

Israel has a National Screening Program aimed at early detection of breast cancer. The need to continue and even expand this program was recently stressed in light of the high risk of the population [2]. At present, however, some controversy exists regarding the optimal modalities for breast cancer screening, especially when applied to women at risk. In this review we critically examine the established screening method, i.e., mammography, and explore the possibilities offered by molecular imaging techniques, focusing upon magnetic resonance. We pay particular attention to the limitations of current applications of MRS and MRSI for primary breast cancer detection and demonstrate how recent mathematical advances in signal processing can extract diagnostically important information, which so far was unavailable with *in vivo* MRS/MRSI. On that basis, we suggest some further steps that are expected to lead to more effective strategies for early detection of breast cancer.

Regular screening with mammography reduces breast cancer mortality, but has limitations in diagnostic accuracy plus entailing exposure to ionizing radiation

Mammography for breast cancer screening

The currently recommended method for reducing breast cancer mortality is through a clinical breast examination and mammogram. Mammography is the only diagnostic modality currently approved specifically for breast cancer screening by the U.S. Food and Drug Administration. Regular screening with mammography has been consistently shown in randomized controlled trials to provide long-term reduction in breast cancer mortality [8]. It is estimated that in order to achieve a 30% reduction in breast cancer mortality, 80% of women aged 50 to 70 should comply with these guidelines. However, compliance with screening guidelines is often inadequate to achieve this goal [9]. In Israel, fewer than 50% of women were found to comply with mammography screening recommendations [10,11], despite the fact that all Israeli women aged 50–74 are entitled to free mammograms every 2 years [12].

One barrier to compliance with screening recommendations among women in Israel and elsewhere is concern over radiation from mammography [9,12,13]. This consideration is particularly germane for women under age 50, where "the balance between the number of breast cancer deaths prevented by screening compared with the number induced by radiation seems less favorable" [14]. The female breast is well recognized as a radio-sensitive organ. Follow-up of persons exposed to moderate to high levels of ionizing radiation consistently demonstrates a significantly increased risk of breast cancer, and the magnitude of risk is inversely related to age at exposure [1]. The very low energy X-rays used in screening mammography are considered to be more harmful, per unit dose, than high energy X-rays, such that the estimated radiation risk for younger women is regarded as sufficient to warrant starting routine screening 5–10 years later than currently recommended [15]. Moreover, mutations in the *BRCA* genes result in impaired DNA repair mechanisms and heightened sensitivity to radiation [16]. It is precisely among women with this hereditary risk that screening at an earlier age and at more frequent intervals has been suggested as a possible option [8]. According to Kuni et al. [17], among the "very radiosensitive subgroup: the women bearing a mutation of the gene *BRCA1* or *BRCA2*... repeated X-ray use must be definitely avoided."

Another barrier to compliance cited among women in Israel was perceiving mammography as inefficient in early detection [11]. This perception is not entirely unrealistic. The overall false negative rate is estimated to be about 10–15%, with some 10% of breast cancers not identified by mammography even when palpable [18]. This is clearly of great concern, since a false negative mammogram contributes to a delay in breast cancer diagnosis and results in poorer prognosis [19]. While highly sensitive for fatty breast tissue, mammographic detection of malignant lesions (unless calcified) is very difficult in dense breasts [20], which are commonly seen in younger women. Thus, earlier mammography screening for women at high risk could be problematic for a number of reasons. Further complicating the situation is that mammographically dense breasts are associated with use of combined HRT and are considered a marker for increased breast cancer risk among women after menopause [1,21]. Moreover, Tabár [22] points out that breast cancer is a heterogeneous disease, and the sensitivity of mammography varies in relation to the histopathologic subtype. While calcifications are relatively easy to see, these are present in only a minority of histologically verified breast cancers, with the rest being non-calcified stellate and circular masses that are often much harder to perceive.

The more commonly occurring problem for mammography is related to its poor specificity. Estimates of the positive predictive value of mammography have been as low as 15–30% [23]. The large numbers, up to 70–85%, of false positive mammograms lead to many biopsies of benign lesions; this is associated with considerable morbidity, not the least of which is anxiety. Among Russian immigrants to Israel, whose preoccupation was with immediate survival needs, this concern regarding screening mammography was poignantly expressed as: "I have no time for potential troubles" [12]. This implies that the fear engendered by a false positive mammogram could foster a fatalistic attitude, leading to decreased compliance with screening guidelines, which can result in later-stage diagnosis of breast cancer and increased mortality. Moreover, once a breast biopsy has been performed, subsequent mammographic evaluation in the region of the scarred tissue is rendered more difficult [19].

Currently, screen-film mammography is the gold standard for breast cancer screening. A number of promising innovations in mammography and other X-ray-based methods for diagnosing breast cancer are on the horizon. Full-field digital mammography was recently approved by the FDA for breast cancer screening, and has shown improved specificity, i.e., significantly lower recall rate and lower biopsy rate compared to SFM; however, FFDM has an insignificantly lower sensitivity than SFM [8]. It should also be recalled that all these mammography-based techniques would still entail exposure to ionizing radiation.

Molecular imaging in oncology: relevance for breast cancer screening

The U.S. National Cancer Institute has stressed that the dramatic advances in molecular imaging represent an extraordinary opportunity for early detection by identifying the key changes for the emergence and progression of cancer on the molecular and/or cellular level [24].

With a similar outlook, an entire special issue of the *European Journal of Cancer* was recently devoted to molecular imaging, termed "an explosion of new information" with tremendous implications for clinical oncology [25].

Functional imaging via positron emission tomography and scintimammography

PET has been the most commonly used molecular/functional imaging modality in oncology. The impact of fluorodeoxy-glucose PET scanning upon detection, staging and management of patients with cancer has been profound, and has become part of the routine diagnostic armamentarium for a large number of patients with suspected cancer. Since many tumor cells have a high metabolic rate mainly via the glycolytic pathway, FDG uptake has been used as a marker of malignancy. However, in tumors with low metabolic activity, FDG-PET has generally shown limited value.

Thus far, FDG-PET has been applied for diagnosing primary breast carcinoma when mammographic findings were ambiguous. A recent systematic review of the literature reveals an overall false negative rate of 12% for FDG-PET in the differential diagnosis of benign versus malignant lesions among patients with an abnormal mammogram of a palpable breast mass [26], with poorer sensitivity for carcinoma *in situ* and multifocal lesions. On the other hand, the positive predictive value of FDG accumulation is over 90% for breast cancer [18]. Single photon scintimammography using 99mTc sestamibi, which is taken up by mitochondria, has also been used

FDA = Food and Drug Administration
SFM = screen-film mammography
FFDM = full-field digital mammography
PET = positron emission tomography
FDG = fluorodeoxy-glucose

for diagnosis of primary breast cancer, with an overall sensitivity and specificity of 83% and 81%, respectively, but with much lower sensitivity for small tumors. In initial studies, dedicated SMM detectors have shown improved resolution, but also more visualization of benign lesions [23].

MRI and spectroscopy: early results in primary breast cancer diagnosis

- ***MRI***

As opposed to FDG-PET and mammography, magnetic resonance-based diagnostics entail no exposure to radionuclide or to ionizing radiation from X-rays. With recent advances, contrast-enhanced MRI has emerged as a method with sensitivity approaching 100% for detection of breast cancer [27]. MRI is particularly valuable for detecting malignant lesions in mammographically dense breasts [28]. Studies are currently underway to evaluate MRI as a possible screening method for women at high risk for breast cancer [8]. However, while contrast-enhanced MRI has high spatial resolution and is more sensitive than mammography, it has limited specificity, thus sharing with mammography the problem of a high false positive rate (approximately 50%) [29].

- ***MRS and MRSI***

Magnetic resonance can also be used to obtain information about a number of chemical constituents of tissues. This is achieved via MRS, which involves the *in vivo* application of traditional laboratory-based nuclear magnetic resonance techniques, and provides complementary biochemical and physiologic information in the form of spectra.

Proton MRS diagnostics based upon the presence or absence of a composite choline signal has been shown to increase the specificity of MRI for the diagnosis of breast cancer [29]. Choline is a component of phospholipid metabolism of cell membranes, and is a marker for membrane damage, cellular proliferation and density. It is generally used as a spectroscopic indicator of malignancy.

Katz-Brull and colleagues [29] recently reviewed the five published clinical studies using *in vivo* proton MRS, in which malignant and benign breast lesions were compared. They reported a sensitivity and specificity of 83% (95% confidence intervals 73–89%) and 85% (95% CI 71–93%) respectively, for identifying breast cancer in the 153 tumors examined, 53 of which were benign. Even better diagnostic accuracy was achieved among women aged 40 or younger, of whom 11 patients had breast carcinomas and 9 had benign breast lesions. These authors emphasized the potential of proton MRS for widespread application in breast cancer diagnostics, provided that the factors limiting its diagnostic accuracy are overcome.

Functional-anatomic imaging can be accomplished by combining MRS and MRI, yielding MRSI. Rather than selecting a single voxel from three orthogonal slices to encompass a specific volume, a spectrum is obtained at each point of selected grids that can be of various sizes. Thus, full volumetric coverage can potentially be achieved. As yet, however, the application of MRSI for breast cancer diagnostics has not been reported.

Current applications of in vivo proton MRS in breast cancer diagnostics: limitations related to reliance on the FFT

Until now, MRS has relied almost exclusively on the conventional theoretical framework for data analysis in biomedical imaging, i.e., the FFT, a mathematical procedure for converting the encoded/recorded time signal into a spectral representation. Several intrinsic limitations of the FFT that are specifically relevant to breast cancer diagnostics using MRS are discussed below.

- ***Low resolution and poor signal-to-noise ratio***

A major problem for MRI and MRS is the need for long imaging times with insufficient resolution [30]. This is due to performing data analysis based on the FFT, a low resolution spectral/image estimator. Using the FFT, a shape spectrum is obtained from pre-assigned frequencies whose minimal separation is determined by the acquisition time, T. In other words, the FFT spectrum is defined only on the Fourier grid points, k/T (k = 0,1,2...) [31].

The strategy used in attempts to improve resolution has been to increase the acquisition time and thereby decrease the distance $1/T$ between the grid points. However, this is not an adequate solution as clinical signals become heavily corrupted with background noise at longer acquisition times. Since MRS time signals decay exponentially, the larger signal intensities are observed early in the recording. It is therefore better to encode the time signal as rapidly as possible, i.e., to avoid long acquisition times at which mainly noise will be recorded. Thus, there are two mutually exclusive requirements, and as a result, within the FFT, attempts to improve resolution lead to a worsening of the S/N. This conundrum is graphically illustrated in Figure 1.

MRI and MRS are being examined as adjuncts or possibly even alternatives to mammography, especially for younger women at high risk

For breast cancer diagnostics using MRS, this is especially problematic due to the need for lipid suppression. The current strategy has been to increase the echo times, which diminishes the overlap with the lipid signal, but this is achieved by a diminution in signal intensity [29].

It should also be pointed out that since the FFT is a linear transform, it imports noise as intact from the measured time domain data to the frequency domain, further contributing to poor S/N. Overall, one of the major reasons for false negative findings

SMM = single photon scintimammography
CI = confidence interval

FFT = fast Fourier transform
S/N = signal-to-noise ratio

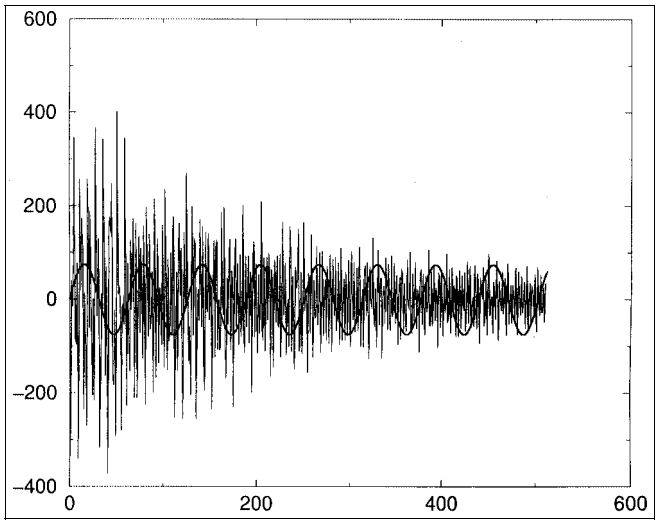

Figure 1. The relation between increase in acquisition time and signal-to-noise ratio (S/N) for a free induction decay (FID) digitized time signal with 512 points, as seen in a typical time signal from MRS on clinical scanners operating on 1.5T. The FID is represented by the dark, rapidly oscillating thin full line. Noise is represented here by a sine wave (thick full black line, of constant amplitude and periodic repetition). It can be seen that as time (the abscissa, in milliseconds) increases, the S/N dramatically worsens. The ordinate is the signal intensity in arbitrary units.
From Ref. 37, reprinted with permission from Cambridge International Science Publishing (http://www.cisp-publishing.com/jcmse.html)

using *in vivo* proton MRS to detect malignant breast lesions was poor S/N [29].

- ***Supplies only a shape spectrum and requires fitting***

The FFT is a non-parametric estimator, which supplies only the shape of spectral structures but not quantification. The peak parameters are extracted afterwards in a post-processing stage, by fitting the obtained structures to a sum of Gaussians or Lorentzians, or both. Thus, much information that is contained in the signal is not obtained in a unique manner, such as the actual position, width, height and phase of each metabolite [31]. Applications of *in vivo* MRS in breast cancer diagnostics have thus far mainly relied on a dichotomous variable, i.e., the presence or absence of a composite choline peak. This compromises diagnostic accuracy due to non-differential misclassification, especially because some choline may also be observed in benign breast lesions as well as in the normal breast during lactation. At the same time, due to the above-outlined problem of poor resolution and S/N, choline is often undetected in small tumors that are then misclassified as benign.

The use of fitting required by the FFT can lead both to spurious peaks (over-fitting) and to true metabolites being undetected (under-fitting). This is clearly unacceptable in the clinical setting; moreover, it renders inter-study comparisons tenuous, unless the same prior information is used to predetermine the number of metabolites. In other words, fitting is based upon prior knowledge/measurement, e.g., Linear Combination of Model Spectra (LCModel), before analysis of the actual *in vivo* spectrum. Although it has been claimed that fitting procedures can be automatic and objective, their major pitfalls and inherent subjectivity have been demonstrated [32]. Various fitting procedures can be applied, none of which are generated with certainty, especially for the number of metabolites and peak heights [32]. This problem is particularly important with respect to overlapping metabolites. As shown below, the peaks of most interest for breast cancer diagnostics are often closely overlapping.

- ***Small number of observable compounds***

Only a few compounds (low molecular weight, high concentration) are observable with the FFT on a clinical scanner, and these may not be the most critical for timely diagnosis of malignant processes. As discussed, basing the diagnosis of malignancy on the composite choline peak can be equivocal because benign breast lesions may also contain choline compounds, which is also the case for the normal breast during lactation. Moreover, use of longer TE to diminish overlap with the lipid signal diminishes the number of compounds that can be visualized [29].

In vitro MRS findings in breast cancer and in non-malignant breast tissue

In contrast to *in vivo* MRS breast examinations based mainly on one composite spectral entity (the total choline peak), the high resolution of *in vitro* MRS applied to extracted specimens provides a much greater insight into the metabolic activity of malignant breast tissue. Analysis of excised malignant breast tumors reveals that the composite choline peak contains a number of water-soluble metabolites such as phosphocholine, glycerophosphocholine, betaine, analogous compounds containing the ethanolamine head group, and taurine, as well as choline itself, whereas milk is comprised predominantly of choline compounds such as phosphatidylcholine as well as PC and free choline [29]. Katz-Brull et al. [33] applied *in vitro* analysis using tracer kinetics and ^{13}C and ^{31}P MRS to examine the biochemical pathways underlying the high levels of water-soluble choline metabolites seen in breast cancer. They identified two non-intersecting pathways: phosphorylation and oxidation of choline, to be augmented with malignant transformation of mammary cells, with increased synthesis of PC and betaine. They also found suppression of choline-derived ether lipids.

Advances in signal processing via the FPT should be applied to MRSI for breast cancer detection, and are expected to improve their diagnostic accuracy

Gribbestad et al. [34] performed an *in vitro* proton MRS study comparing 14 extracts of malignant breast tissue and one

TE = echo time
PC = phosphocholine

Table 1. Diagnostic accuracy of individual metabolite concentrations for identifying breast cancer

Breast cancer vs. normal breast tissue				Breast cancer vs. benign tumor (n=1) or normal breast			
	Predicted result				Predicted result		
Observed result	Normal breast	Breast cancer	% correct	Observed result	Normal breast	Breast cancer	% correct
Lactate (1.33 ppm*)							
Normal breast	12	0	100% (specificity)	Normal breast	13	0	100% (specificity)
Breast cancer	0	14	100% (sensitivity)	Breast cancer	0	14	100% (sensitivity)
Alanine (1.47 ppm)							
Normal breast	12	0	100% (specificity)	Normal breast	13	0	100% (specificity)
Breast cancer	1	13	92.9% (sensitivity)	Breast cancer	1	13	92.9% (sensitivity)
Choline (3.21 ppm)							
Normal breast	12	0	100% (specificity)	Normal breast	13	0	100% (specificity)
Breast cancer	0	14	100% (sensitivity)	Breast cancer	2	12	85.7% (sensitivity)
Phosphocholine (3.22 ppm)							
Normal breast	12	0	100% (specificity)	Normal breast	13	0	100% (specificity)
Breast cancer	1	13	92.9% (sensitivity)	Breast cancer	1	13	92.9% (sensitivity)
Glycerophosphocholine (3.23 ppm)							
Normal breast	11	1	91.7% (specificity)	Normal breast	12	1	92.3% (specificity)
Breast cancer	2	12	85.7% (sensitivity)	Breast cancer	2	12	85.7% (sensitivity)
Total choline (C + PC + GPC)							
Normal breast	11	1	91.7% (specificity)	Normal breast	13	0	100% (specificity)
Breast cancer	1	13	92.9% (sensitivity)	Breast cancer	1	13	92.9% (sensitivity)
Phosphoethanolamine (3.22 ppm)							
Normal breast	12	0	100% (specificity)	Normal breast	13	0	100% (specificity)
Breast cancer	1	3	92.9% (sensitivity)	Breast cancer	1	13	92.9% (sensitivity)
β-glucose (3.25 ppm)							
Normal breast	10	2	83.3% (specificity)	Normal breast	12	1	92.3% (specificity)
Breast cancer	5	1	16.7% (sensitivity)	Breast cancer	5	1	16.7% (sensitivity)
Taurine (3.27 ppm)							
Normal breast	12	0	100% (specificity)	Normal breast	13	0	100% (specificity)
Breast cancer	1	13	92.9% (sensitivity)	Breast cancer	1	13	92.9% (sensitivity)
Myoinositol (3.28 ppm)							
Normal breast	10	2	83.3% (specificity)	Normal breast	11	2	84.6% (specificity)
Breast cancer	3	6	66.7% (sensitivity)	Breast cancer	3	6	66.7% (sensitivity)

Assessed by Logistic Regression Analysis of *In Vitro* Proton MRS data from Ref. 34, and derived in part from Ref. 38.
* ppm denotes parts per million on the chemical shift axis.

fibroadenoma to non-involved breast from the same group of patients. We performed logistic regression analysis of their data to ascertain the sensitivity and specificity of individual metabolite concentrations for identifying breast cancer. Our results are shown in Table 1. Only lactate showed 100% diagnostic accuracy both with and without inclusion of the fibroadenoma. Choline had 100% sensitivity only when the fibroadenoma was excluded. With inclusion of the fibroadenoma, there were two false negatives based upon choline concentrations. Specificity, but not sensitivity, was 100% with and without inclusion of the fibroadenoma for alanine, choline, PC, phosphoethanolamine and taurine. While many of the metabolite concentrations in the malignant tissues were significantly correlated (Spearman ρ correlation, $P < 0.05$), alanine was not correlated with PE or with GPC, nor was choline concentration correlated with those of several other metabolites in the malignant tissues. Furthermore, Principle Components Analysis revealed that those metabolites with the strongest diagnostic accuracy did not consistently load with the others. We also performed paired analysis, which revealed a significant difference in all metabolite concentrations when comparing non-infiltrated and malignant breast tissue (always higher in the latter – *t*-test and non-parametric Wilcoxon, $P < 0.05$). However, GPC, PC, PE, total choline and lactate were also elevated in the fibroadenoma compared to the non-infiltrated tissue of that patient. Moreover, most of the calculated metabolite concentrations were at least one standard deviation greater than the mean for normal breast tissue in that sample. In contrast, the calculated concentration of myoinositol was nearly the same (0.465 and 0.448) for the fibroadenoma and for the non-infiltrated tissue, respectively, of the same patient, and showed the lowest difference from the mean for normal breast tissue (+ 0.52 SD).

On the basis of these data from a fairly small sample (with substantial missing data for a few metabolite concentrations in malignant tissues), definitive conclusions cannot be drawn about which metabolites are optimal for detecting the presence of breast cancer and distinguishing this from normal mammary tissue or benign lesions. Nevertheless, several metabolites (most notably

PE = phosphoethanolamine
GPC = glycerophosphocholine

lactate) showed particular promise with respect to diagnostic accuracy. On the other hand, total choline, upon which most *in vivo* proton MRS diagnoses are based, had marginally lower sensitivity and specificity than several other metabolites. Viewed together, these analyses corroborate this group of authors [34], that a very rich "window" of information is provided by *in vitro* ^{1}H MRS analysis of metabolite concentrations in malignant versus non-cancerous breast tissue. This should justify exploration of how *in vivo* proton MRS might tap into this rich source of information for improved primary breast cancer diagnostics.

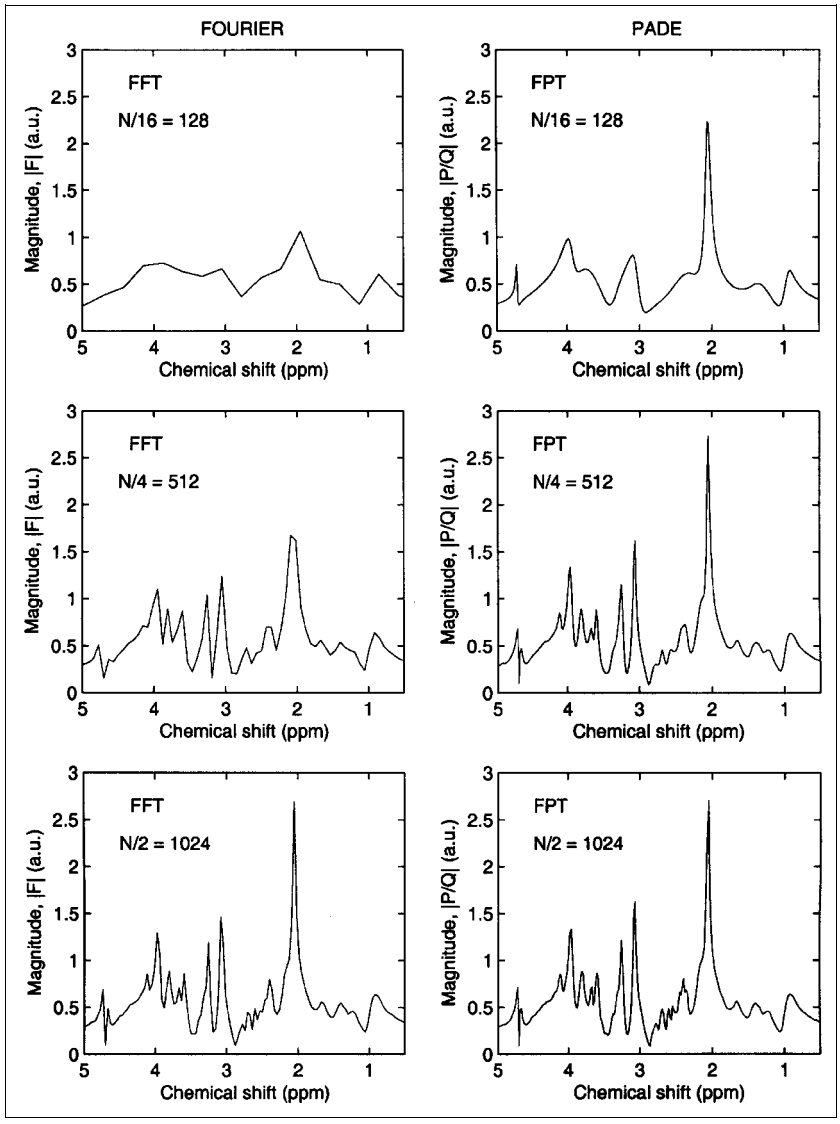

Figure 2. Fourier (FFT) and Padé (FPT) magnitude spectra for the truncated FID from Ref. 36. Here, a.u. denotes arbitrary units of the ordinate. The abscissa is the frequency spectrum labeled in dimensionless units of parts per million.

Potential relevance of the FPT for breast cancer diagnostics using MRS

A series of recent papers [30–32,35] conclusively demonstrated that the fast Padé transform, a non-linear, polynomial quotient as a rational function/approximation for the exact Taylor power series expansion of the raw time signal, can overcome many of the above-described limitations of the FFT. We now describe these improvements offered by the FPT, and their potential relevance for breast cancer diagnostics using MRS.

- ***Rapid, stable convergence with improved resolution and S/N***

A spectrum in the FPT does not use the fixed Fourier mesh in the frequency domain and can be computed at any frequency. Thus, resolution is not predetermined by the total acquisition time *T*. The conundrum between increasing acquisition time for improved resolution and increasing noise is thereby obviated by the FPT. This is especially important for detecting short-lived metabolites. One such is myoinositol, whose relaxation time is very short, so that it is discernable at a TE of 35 msec but not 144 msec or longer. As mentioned, *in vitro* data on this metabolite did provide some diagnostic insight. Namely, for all the available paired data comparing malignant breast extracts and non-infiltrated tissue, the myoinositol concentrations were elevated in the former, whereas in the fibroadenoma the concentrations were nearly identical to those of the surrounding tissue.

Furthermore, the FFT is limited by a sharp cutoff of the time signal at the end of the acquisition time, replacing any extension of the signal by zeros. In contrast, the FPT uses its polynomial quotient to extrapolate beyond the total acquisition time, and this also contributes to improved resolution [35].

A major reason for false negative findings using *in vivo* ^{1}H MRS to detect breast cancers is poor S/N [29]. As noted, the FFT has a poor S/N due not only to the need for long acquisition times but also because it is a linear mapping, since its transformation coefficients or weights are *independent* of the time signal points. By contrast, the FPT is a non-linear mapping, possessing coefficients that are *dependent* upon the time signal points. Unlike the FFT whose linearity preserves noise from the time signal, the non-linearity of the FPT allows for suppression of noise. The polynomial quotient from the FPT is recognized as the more familiar auto-regressive moving average process [31]. Furthermore, the FFT has a linear convergence ($1/N$) with increased signal length N, while the convergence of FPT is often quadratic ($\sim 1/N^2$) or better [31]. The rapid, stable convergence together with the enhanced resolution effectively result in markedly improved information content extracted by the FPT from the MRS signals at short acquisition times. This has been confirmed [32,35] by detailed comparisons of the FPT and FFT from high field clinical proton MRS data, and is illustrated in Figure 2.

- ***Determines exact number of metabolites, accurately estimating their parameters***

In contrast to the FFT, which is non-parametric supplying only a shape spectrum, the parametric FPT yields accurate estimates of all the relevant peak parameters (position, heights, widths, phases) of every true metabolite. The FPT provides precise numerical quantification without any free or adjustable parameters, i.e., without fitting, because it computes the spectra through the unique ratio of two frequency-dependent polynomials [31]. This feature could help improve the diagnostic accuracy of MRS. Rather than relying on the presence or absence of a given metabolite or composite peak (such as total choline), the actual peak height and the full width at half-maximum could be used to specify the normal concentration range versus values seen in malignancy. As shown above, this quantitative approach is vital for accurately identifying malignant breast lesions.

A key advantage of the FPT is its unequivocal specification of the exact number of metabolites from the encoded data, the free induction decay, without fitting. As mentioned, the FPT is a rational approximation of the exact power series expansion (Taylor or Laurent) of the raw time signal, or equivalently, the FID. This ratio is extracted directly from the FID. By computing the spectra through the unique quotient of two frequency-dependent polynomials, the FPT is superior to a single polynomial representation which is provided by the FFT. The parametric version of the FPT first unambiguously determines the number of metabolites, and thereafter accurately quantifies all the relevant parameters of each individual resonance, even those that are overlapped and corrupted with noise [35]. The FPT can identify spurious resonances by analytical methods; this is followed by a well-defined procedure for regularization, with preservation of the magnitude or power spectra and no loss of information. Overlapping or hidden metabolites, including those that may be disguised in noise, are retrieved with fidelity [31].

These features have potential clinical importance. With these new advances, the above-discussed constraints based upon fitting could be relaxed, and an exploratory and more comprehensive approach could be undertaken. In other words, instead of *a priori* defining that the composite choline peak is the key parameter of interest for breast cancer detection, the actual constituents of that and other peaks not observed when relying upon FFT could be systematically assessed for their diagnostic accuracy using *in vivo* proton MRS. This could be done in a similar fashion to the analysis performed above for the 10 metabolite concentrations obtained from *in vitro* MRS of breast tissue extracts. It should also be recalled that several of the most informative metabolites found on *in vitro* MRS were very closely clustered, i.e., within a range of about 0.1 parts per million.

In summary then, the fast Padé transform fulfills the most stringent requirements for tumor diagnostics: a) it markedly enhances resolution and S/N compared to the FFT; b) as a parametric method it provides precise numerical data for all peak parameters (position, height, width and phase) for every true metabolite; c) it specifies the exact number of metabolites from the encoded time data (FID) and can identify unambiguously overlapping metabolites as well as metabolites present in low concentrations, d) it computes metabolite concentrations most accurately due to the established one-to-one correspondence between frequencies and amplitudes that are obtained analytically; and e) it provides a strikingly robust and stable convergence for varying fractions of the full signal length, yielding reasonable concentrations of the main metabolites even for severely truncated time signals.

Illustration of the performance of the FPT for a clinical MRS signal

We now present an illustration of the performance of the FPT for a clinical MRS signal. For reference, the corresponding spectra from the FFT will also be given. We use measured time domain data acquired at 4 Tesla magnetic field strength from the brain of a healthy volunteer. These data of full signal length N = 2,048 encoded by the group at the Center for Magnetic Resonance Research, University of Minnesota, MN, USA [36] were kindly made available to us. In Figure 2, we present the FFT (left column) and FPT (right column) magnitude spectra at three signal lengths ($N/16$ = 128, $N/4$ = 512, $N/2$ = 1,024).

At the top of Figure 2 the most dramatic difference between the FFT and FPT spectra is seen at the shortest signal length ($N/16$ = 128). Here, practically no metabolite can be discerned using the FFT. In contrast, the FPT clearly detects several metabolites, and predicts over 80% of the true concentration of the leading resonance N-acetyl aspartate, located near 2 ppm. Even at a quarter of the full signal length ($N/4$ = 512), as seen in the left middle panel of Figure 2, the concentration of NAA predicted by the FFT barely attains 50% of the fully converged result at N = 2,048. This should be compared to the FPT, which at the same fraction ($N/4$ = 512) achieves approximately 100% of the correct NAA concentration [Figure 2, right middle panel]. Moreover, at this quarter signal length, the FPT yields nearly 100% of the true concentrations of two of the other main metabolites (creatine and choline, at approximately 3.0 ppm and 3.3 ppm, respectively), whereas the FFT clearly underestimates these two metabolite concentrations.

On the lower panel of Figure 2, the spectra computed by the FFT and FPT are depicted at $N/2$. Up to differences on the level of random noise, the FPT gives practically the same spectra for the half ($N/2$ = 1,024) and full (N = 2,048) signal length (the latter not shown to avoid clutter). On the other hand, the FFT must exhaust the entire signal length to resolve all the metabolites, such as the triplet of glutamine/glutamate at 2.3 ppm. For the FFT at $N/2$ the creatine peak is still substantially underestimated. Overall, it is seen at the bottom of Figure 2: that at half signal length the FPT can resolve with fidelity more than 20 metabolites, in which all peak parameters are accurately extracted including the overlapping resonances.

Most importantly, the FPT does not produce spurious metabolites or other spectral artifacts in the process of

FID = free induction decay

NAA = N-acetyl aspartate

converging in a strikingly steady fashion as a function of the increased signal length. This is in sharp contrast to most other existing parametric estimators that are unstable as a function of *N*, typically undergoing wide oscillations with unacceptable results before they eventually saturate, i.e., converge [35]. In fact, besides the computational efficiency of automatic software, the main reason for which the FFT gained popularity among users is that it presents no surprises, steadily converging with increasing signal length [37]. The FPT shares this advantageous property of the FFT, but in addition provides a much faster rate of convergence of the FPT, as clearly demonstrated in this and other [35] illustrations.

Conclusions and future perspectives

As shown by our analysis of *in vitro* MRS findings of extracted tissue from patients with breast cancer, much more spectroscopic information is potentially available for identifying malignant breast lesions than is currently obtained when *in vivo* clinical proton MRS signals are processed by the FFT. It has been clearly demonstrated that the FPT offers greater possibilities to extract the information from MRS signals.

As we recently suggested [38], the next step would be to apply the FPT to *in vivo* MRS signals from patients with breast cancer and to compare these to findings for normal breast tissue. Insofar as the FPT indeed proves to provide the predicted improvement in diagnostic accuracy of clinical MRS for breast cancer detection, MRS could then be used more widely in this domain. Since functional imaging is often of greatest value for oncology when combined with anatomic information, MRS plus MRI could be particularly promising for breast cancer screening of women at high risk. As pointed out by Katz-Brull et al. [29], the technical aspects of adding MRS to MRI can be feasibly handled in the clinical setting. Of vital importance would be the implementation of MRSI for breast cancer diagnostics in order to achieve full volumetric coverage, rather than relying on single voxel techniques.

It has been emphasized that a comprehensive breast cancer screening program should include risk assessment, and that screening strategies be tailored to individual risk [39]. However, reliance upon even the well-recognized risk factor of family history can sometimes be precarious, as for example in the case of adopted children. Denial, grief and fear can also hamper disclosure of the full extent of family risk [4]. Moreover, the heterogeneity of *BRCA* gene mutations is very great and their mode of inheritance not entirely clear, such that history in first- or second-degree relatives cannot be fully relied upon as a genetic risk indicator [39,40]. As reported by Hodgson et al. [40] in their study from the UK of *BRCA1* and *BRCA2* founder mutations among self-referred Ashkenazi women with breast or ovarian cancer, "33% of carriers had no family history of breast or ovarian cancer in first or second degree relatives. Conversely, 12% of non-mutation carriers had strong family histories, with both a first and a second degree relative diagnosed with breast or ovarian cancer." Furthermore, as pointed out by Cardenas and Frisch [39], due to difficulties in molecular testing of these large genes upon which mutations can occur at nearly any position, "unless a family already has a known mutation, genetic testing should be offered only as part of an approved research protocol to patients at high risk for breast cancer." In other words, widespread genetic testing for *BRCA1* and *2* susceptibility genes is not currently an option for surveillance purposes.

The question really is: how can breast cancer screening programs become truly comprehensive, i.e., population-based. It is well known that fear of cancer acts as a major barrier to adherence with screening guidelines [9,12]. Many women at high risk may therefore be the most reluctant to undergo regular mammographic screening, especially in light of its pitfalls, and most especially as these apply to younger women at high risk. It is our hope that the directions suggested in this paper might offer one way to help tackle these current conundrums, by providing a more diagnostically accurate method for early detection of breast cancer among women at any age, without exposure to ionizing radiation.

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References

1. Adami H-O, Hunter D, Trichopoulos D. Textbook of Cancer Epidemiology. New York: Oxford University Press, 2002.
2. Allweis TM, Nissan A, Spira RM, Sklair-Levy M, Fruend HR, Peretz T. Screening mammography for early diagnosis of breast cancer: facts, controversies, and the implementation in Israel. *Harefuah* 2003;142:281–6, 317 (Hebrew).
3. Dagan E, Gershoni-Baruch R. Hereditary breast/ovarian cancer – pitfalls in genetic counselling. *Clin Genet* 2001;60:310–13.
4. Surbone A. Ethical implications of genetic testing for breast cancer susceptibility. *Crit Rev Oncol Hematol* 2001;40:149–57.
5. Nir-Caein R, Nahum R, Yogev Y, Rosenfeld J, Fisher M, Kaplan B. Ethnicity and attitude toward menopause and hormone replacement therapy in northern Israel. *Clin Exp Obstet Gynecol* 2002;29:91–4.
6. Merom D, Ifrah A, Cohen-Manheim I, Chinich A, Green MS. Factors predicting current use of hormone replacement therapy among menopausal Jewish women in Israel. The National Women's Health Interview Survey, 1998. *IMAJ* 2002;4:671–6.
7. Chlebowski RT, Hendrix SL, Langer RD, et al., for the WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy post-menopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243–53.
8. Smith RA, Saslow D, Sawyer KA, et al. American Cancer Society guidelines for breast cancer screening: update 2003. *CA Cancer J Clin* 2003;53:141–69.
9. Terán L. Compliance with Mammography Screening Guidelines among Latinas: An Exploratory Study. PhD thesis. University of Southern California School of Medicine, Department of Preventive Medicine, 2004.
10. Lubish L, Greenberg S, Friger M, Shvartzman P. Breast cancer screening in two multicultural family practice teaching clinics. *IMAJ* 2001;3:579–83.
11. Ore L, Hagoel L, Shifroni G, Rennert G. Compliance with mammography screening in Israeli women: the impact of a pre-scheduled appointment and of the letter-style. *Isr J Med Sci* 1997;33:103–11.
12. Remennick L. "I have no time for potential troubles": Russian immigrant women and breast cancer screening in Israel. *J Immigr Health* 2003;5:153–63.
13. Bastani R, Marcus AC, Maxwell AE, Das IP, Yan KX. Evaluation of an intervention to increase mammography screening in Los Angeles. *Prev Med* 1994;23:83–90.

14. Beemsterboer PM, Warmerdam PG, Boer R, de Koning HJ. Radiation risk of mammography related to benefit in screening programmes: a favorable balance? *J Med Screen* 1998;5:81–7.
15. Brenner DJ, Sawant SG, Hande MP, et al. Routine screening mammography: how important is the radiation-risk side of the benefit-risk equation? *Int J Radiat Biol* 2002;78:1065–7.
16. De Vita VT, Hellman S, Rosenberg S, eds. Cancer: Principles and Practice of Oncology. 6th edn. Philadelphia: Lippincott Williams & Wilkins, 2001.
17. Kuni H, Schmitz-Feuerhake I, Dieckmann H. Mammography screening – neglected aspects of radiation risks. *Gesundheitswesen* 2003;65:443–6.
18. Rosé C, Dose J, Avril N. Positron emission tomography for the diagnosis of breast cancer. *Nucl Med Commun* 2002;23:613–18.
19. Prats E. Symposium of breast imaging. *Nucl Med Commun* 2002;23:607–8.
20. Kopans DB. Breast Imaging. 2nd edn. Philadelphia: Lippincott-Raven Publishers, 1998.
21. Greendale GA, Reboussin BA, Slone S, Wasilauskas C, Pike MC, Ursin G. Postmenopausal hormone therapy and change in mammographic density. *J Natl Cancer Inst* 2003;95:30–7.
22. Tabár L. Challenges in mammography from a clinical perspective [Abstract]. In: Imaging 2003: International Conference on Imaging Techniques in Subatomic Physics, Astrophysics, Medicine, Biology and Industry, 2003 June, Stockholm, Sweden.
23. Khalkhali I, Itti E. Functional breast imaging using the single photon technique. *Nucl Med Commun* 2002;23:609–11.
24. National Cancer Institute, Development of Novel Imaging Technologies (Phased Innovation Award), 2000 (http://www.health.gov/healthypeople/).
25. Jones T. The spectrum of medical imaging. *Eur J Cancer* 2002;38:2067–9.
26. Samson DJ, Flamm CR, Pisano ED, Aronson N. Should FDG PET be used to decide whether a patient with an abnormal mammogram or breast finding at physical examination should undergo biopsy? *Acad Radiol* 2002;9:773–83.
27. Orel SG, Schnall MD. MR imaging of the breast for the detection, diagnosis, and staging of breast cancer. *Radiology* 2001;220:13–30.
28. Wiberg MK. Magnetic resonance imaging in breast diagnosis. PhD thesis. Karolinska Institute, Center for Surgical Sciences, Division of Radiology, 2002.
29. Katz-Brull R, Lavin PT, Lenkinski RE. Clinical utility of proton magnetic resonance spectroscopy in characterizing breast lesions. *J Natl Cancer Inst* 2002;94:1197–203.
30. Belkić Dz. Fast Padé transform for magnetic resonance imaging and computerized tomography. *Nucl Instr Meth Phys Res A* 2001;471:165–9.
31. Belkić Dz. Exact analytical expressions for any Lorentzian spectrum in the fast Padé transform (FPT). *J Comp Meth Sci Engin* 2003;3:109–86.
32. Belkić Dz. Strikingly stable convergence of the Fast Padé Transform (FPT) for high-resolution parametric and non-parametric signal processing of Lorentzian and non-Lorentzian spectra *Nucl Instr Meth Phys Res A* 2004;525:366–71.
33. Katz-Brull R, Seger D, Rivenson-Segal D, Rushkin E, Degani H. Metabolic markers of breast cancer. *Cancer Res* 2002;62:1966–970.
34. Gribbestad IS, Sitter B, Lundgren S, Krane J, Axelson D. Metabolite composition in breast tumors examined by proton nuclear magnetic resonance spectroscopy. *Anticancer Res* 1999;19:1737–46.
35. Belkić Dz. Strikingly stable convergence of the fast Padé transform: applications to magnetic resonance spectroscopy (MRS). *J Comp Meth Sci Engin* 2003;3:299–382.
36. Tkáč I, Andersen P, Adriany G, Merkle H, Ugurbil K, Gruetter R. In vivo 1H NMR spectroscopy of the human brain at 7 T. *Magn Res Med* 2001;46: 451–6.
37. Belkić K. The need for quantitative biomedical spectroscopic imaging through magnetic resonance in oncology beyond the conventional Fourier-based signal processing. *J Comp Meth Sci Engin* 2003; 3:535–61.
38. Belkić K. Magnetic resonance spectroscopic imaging in breast cancer detection: possibilities beyond the conventional theoretical framework for data analysis. *Nucl Instr Meth Phys Res A* 2004;525:313–21.
39. Cardenas K, Frisch K. Comprehensive breast cancer screening. Programs now include individual risk assessment. *Postgrad Med* 2003;113:34–46.
40. Hodgson SV, Heap E, Cameron J, et al. Risk factors for detecting germline BRCA1 and BRCA2 founder mutations in Ashkenazi Jewish women with breast or ovarian cancer. *J Med Genet* 1999;36:369–73.

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Stocks have reached a permanently high plateau

Irving Fisher, Professor of Economics at Yale University, in 1929, on the eve of the stock market crash

Capsule

Treatment outcomes after highly active antiretroviral therapy

Enanoria et al. conducted a systematic review summarizing the evidence for treatment efficacy and tolerability of highly active antiretroviral therapies containing two nucleoside reverse transcriptase inhibitors (NRTI) with a protease inhibitor (PI), compared with two NRTIs alone for the treatment of HIV-1 infection in randomized controlled trials. Sixteen randomized controlled trials met the inclusion criteria and were included in the analysis from 328 articles screened. The pooled analysis indicated that treatment with two NRTIs with a PI is more effective in achieving viral suppression than two NRTIs alone (relative risk 3.44, 95% confidence interval 2.43–4.87). However, the RR for discontinuation of treatment due to adverse events of treatment with two NRTIs with a PI compared with two NRTIs alone was 181 (95% CI 1.17–2.79). The benefits of treatment with two NRTIs and a PI are substantial among those who can tolerate the regimen in comparison with treatment with two NRTIs alone.

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