Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

K984167

JAN 12 1999

SUMMARY OF SAFETY AND EFFECTIVENESS

- This 510(k) summary of safety and effectiveness information is submitted in accordance with the requirements of 21 CFR Part 807.87(h).

- Identification of Submitter
  Larry A. Kroger, Ph.D., 414-544-3894, November 19, 1998

- Identification of the Product
  SAGE 7 Spectroscopy Analysis Option

  Manufactured by: GE Medical Systems
  3200 N. Grandview Blvd.
  Waukesha, WI 53188

- Marketed Devices

  The SAGE 7 Spectroscopy Analysis option is an enhancement to the currently marketed SA/GE Analysis option in distribution since the reclassification of Magnetic Resoncance Diagnostic devices (ref. 53 FR 5078, Feb. 1, 1989).

- Device Description

  The GE SAGE 7 Spectroscopy Analysis Software is designed to operate on GE Signa Horizon Systems and GE Advantage Windows workstations. It provides a toolkit of software applications to handle a wide variety of tasks associated with spectroscopy data management. The SAGE (**S**pectroscopy **A**nalysis **GE**) package provides the capability for the trained clinical spectroscopist to reconstruct, analyze, and display spectra and spectroscopic images to provide information to support a diagnosis. SAGE 7 provides a tool for the spectroscopist to process raw spectroscopy data into spectra or spectroscopic images, view them, and optionally perform numerical analyses to obtain spectroscopic parameters (ex. peak positions, widths, heights, areas, etc.).

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

SUMMARY OF SAFETY AND EFFECTIVENESS

- Indications for Use

SAGE 7 is a package of software tools for MR spectroscopic data processing and display. SAGE 7 is indicated for use for a wide variety of MR spectroscopic data management tasks, including file handling, display, processing/modeling, analysis, storage and hard copy output. The resultant spectroscopic presentations, when interpreted by a trained physician, can provide physiological / chemical information that can be useful in determining a diagnosis.

- Comparison with Predicate

The SAGE 7 Spectroscopy Analysis option is an enhancement to the SA/GE Analysis option. The basic operations (ex. Fourier transform, phasing, peak-picking, integration, fitting, etc.) have not significantly changed, and are provided in both SAGE 7 and the SA/GE Analysis option. What has changed is the sophistication of the user interface. In addition, the increased computational capability of modern workstations have made possible as routine operations some sophisticated curve-fitting algorithms that were impractical on older computer hardware.

- Summary of Studies

The SAGE 7 Spectroscopy Analysis option was evaluated to International medical equipment safety standard IEC 601-2-33 titled Particular requirements for the safety of magnetic resonance equipment for medical diagnosis. The SAGE 7 Spectroscopy Analysis option is comparable to the SA/GE Spectroscopy option.

- Conclusions

It is the opinion of GE that the SAGE 7 Spectroscopy Analysis option is substantially equivalent to the SA/GE Spectroscopy option. SAGE 7 does not include any new indications for use, nor does use of this device result in any new potential hazards.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 08/30/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JAN 12 1999

Larry A. Kroger, Ph.D.
Senior Regulatory Programs Manager
GE Medical Systems
P.O. Box 414 , W-709
Milwaukee, WI 53201

Re: K984167
SAGE 7 Spectroscopy
Dated: November 19, 1998
Received: November 20, 1998
Regulatory class: II
21 CFR 892.1000/Procode: 90 LNI

Dear Dr. Kroger:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4613. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Capt. Daniel G. Schultz, M.D.
Acting Director, Division of Reproductive,
Abdominal, Ear, Nose and Throat,
and Radiological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

510(k) Number (if known): K984167

Device Name: SAGE 7 Spectroscopy

Indications For Use:

SAGE 7 is a package of software tools for MR spectroscopic data processing and display. SAGE 7 is indicated for use for a wide variety of MR spectroscopic data management tasks, including file handling, display, processing/modeling, analysis, storage and hard copy output. The resultant spectroscopic presentations, when interpreted by a trained physician, can provide physiological / chemical information that can be useful in determining a diagnosis.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

David G. Legnon

(Division Sign-Off)
Division of Reproductive, Abdominal, ENT, and Radiological Devices
510(k) Number K984167

Prescription Use X OR Over-The-Counter Use_____
(Per 21 CFR 801.109)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JAN 12 1999

Larry A. Kroger, Ph.D.
Senior Regulatory Programs Manager
GE Medical Systems
P.O. Box 414 , W-709
Milwaukee, WI 53201

Re: K984167
SAGE 7 Spectroscopy
Dated: November 19, 1998
Received: November 20, 1998
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21 CFR 892.1000/Procode: 90 LNI

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Sincerely yours,

Capt. Daniel G. Schultz, M.D.
Acting Director, Division of Reproductive,
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Enclosure

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Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

510(k) Number (if known): K984167

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(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

David A. Lagomarsino

(Division Sign-Off)
Division of Reproductive, Abdominal, ENT, and Radiological Devices
510(k) Number K984167

Prescription Use X OR Over-The-Counter Use_____
(Per 21 CFR 801.109)

2

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food And Drug Administration

1/7/99

m: Reviewer(s) - Name(s) R. J. Boyle

Memorandum

ject: 510(k) Number K984167

The Record - It is my recommendation that the subject 510(k) Notification:

- ☐ Refused to accept.
- ☐ Requires additional information (other than refuse to accept).
- ☑ Accepted for review 1/4/99.
- ☑ Is substantially equivalent to marketed devices.
- ☐ NOT substantially equivalent to marketed devices.
  - De Novo Classification Candidate? ☐ YES ☐ NO N/A
- ☐ Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Is this device subject to Postmarket Surveillance?	☐ YES	☑ NO
Is this device subject to the Tracking Regulation?	☐ YES	☑ NO
Was clinical data necessary to support the review of this 510(k)?	☐ YES	☑ NO
Is a prescription device?	☑ YES	☐ NO
Was this 510(k) reviewed by a Third Party?	☐ YES	☑ NO
Special 510(k)?	☐ YES	☑ NO
Abbreviated 510(k)?	☐ YES	☑ NO

This 510(k) contains:

Truthful and Accurate Statement ☐ Requested ☑ Enclosed
(required for originals received 3-14-95 and after)

☑ A 510(k) summary OR ☐ A 510(k) statement

☐ The required certification and summary for class III devices

☐ The indication for use form (required for originals received 1-1-96 and after)

terial of Biological Origin ☐ YES ☑ NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

Confidentiality ☐ Confidentiality for 90 days ☑ Continued Confidentiality exceeding 90 days

Predicate Product Code with class: Additional Product Code(s) with panel (optional):

90 LNI II 892.1000

Branch Chief: R. A. Phillips (Branch Code) RADS (Date) 1/8/99

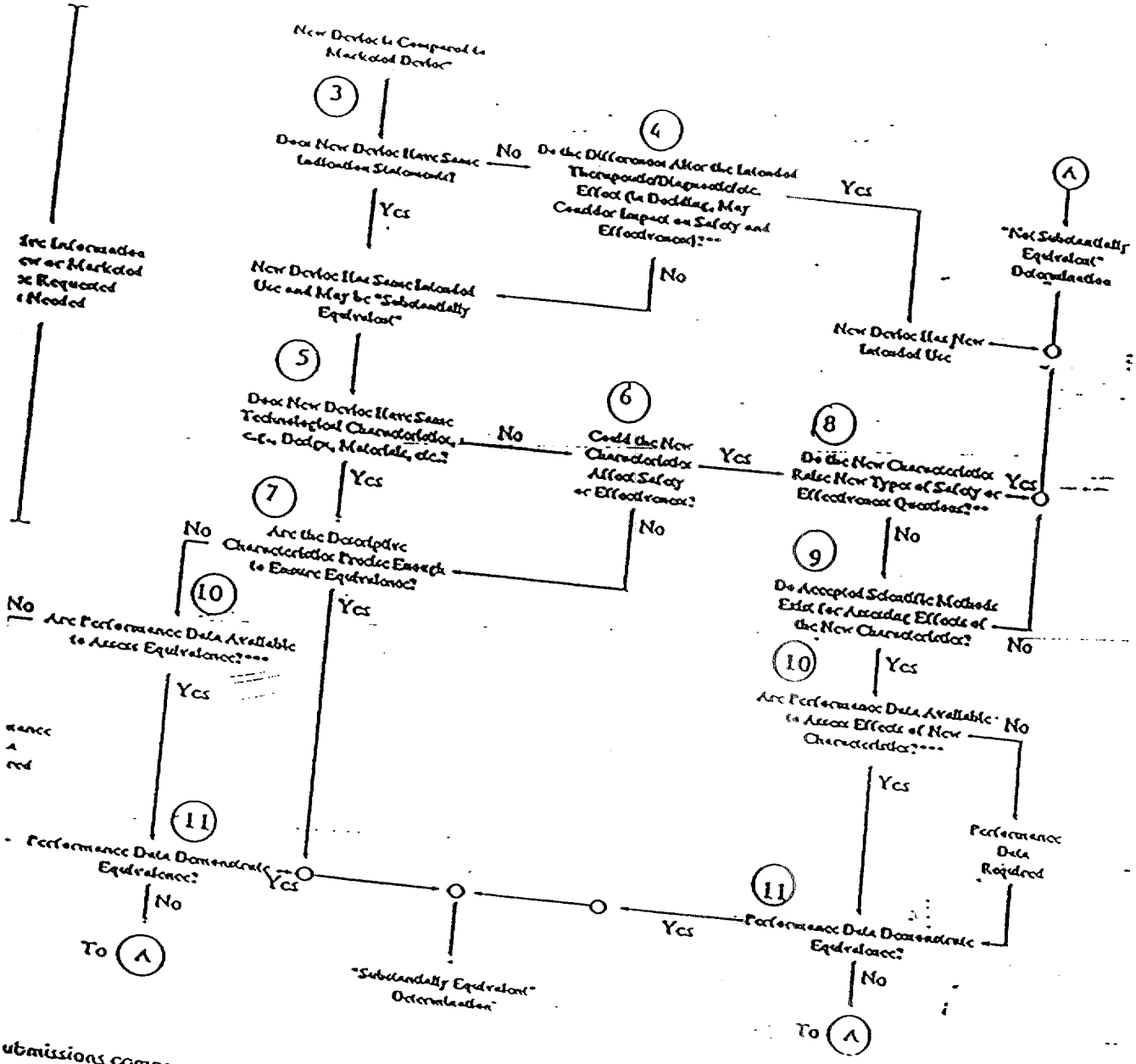
3

iew: (Division Director) 1/12

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS (DETAILED)



ubmissions compare new devices to marketed devices. FDA requests additional information if the relationship marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

ision is normally based on descriptive information alone, but limited testing information is sometimes required.

r be in the 510(k), other 510(k)s, the Center's classification files, or the literature.

4

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

K 984167 "SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

REVIEWER: RXL DIVISION/BRANCH: DMAERO/CIDB

TRADE NAME: SAGE 7 COMMON NAME: MR SPECTROSCOPY ANALYSIS OPTION

PRODUCT TO WHICH COMPARED: 892.1000
(510(k) NUMBER IF KNOWN)

	YES	NO	
1. IS PRODUCT A DEVICE?	✓		- IF NO STOP
2. DEVICE SUBJECT TO 510(k)?	✓		- IF NO STOP
3. SAME INDICATION STATEMENT?	✓		- IF YES GO TO 5
4. DO DIFFERENCES ALTER THE EFFECT OR RAISE NEW ISSUES OF SAFETY OR EFFECTIVENESS?			- IF YES STOP - NE
5. SAME TECHNOLOGICAL CHARACTERISTICS?		✓	- IF YES GO TO 7
6. COULD THE NEW CHARACTERISTICS AFFECT SAFETY OR EFFECTIVENESS?		✓	- IF YES GO TO 8
7. DESCRIPTIVE CHARACTERISTICS PRECISE ENOUGH?	✓		- IF NO GO TO 10 - IF YES STOP - SE
8. NEW TYPES OF SAFETY OR EFFECTIVENESS QUESTIONS?			- IF YES STOP - NE
9. ACCEPTED SCIENTIFIC METHODS EXIST?			- IF NO STOP - NE
10. PERFORMANCE DATA AVAILABLE?			- IF NO REQUEST DATA
11. DATA DEMONSTRATE EQUIVALENCE?			

NOTE: IN ADDITION TO COMPLETING PAGE TWO, "YES" RESPONSES TO QUESTIONS 4, 6, 8, AND 11, AND EVERY "NO" RESPONSE REQUIRES AN EXPLANATION ON PAGE THREE AND/OR FOUR

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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NARRATIVE DEVICE DESCRIPTION

1. INTENDED USE: For MR spectroscopic data processing and display.

2. DEVICE DESCRIPTION: Provide a statement of how the device is either similar to and/or different from other marketed devices, plus data (if necessary) to support the statement. The following should be considered when preparing the summary of the statement. Is the device life-supporting or life sustaining? Is the device implanted (short-term or long-term)? Does the device design use software? Is the device sterile? Is the device for single use? Is the device for home use or prescription use? Does the device contain drug or biological product as a component? Is this device a kit? Provide a summary about the devices design, materials, physical properties and toxicology profile if important.

SUMMARY:

(see attached review)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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EXPLANATIONS TO "YES" AND "NO" ANSWERS TO QUESTIONS ON PAGE 1 AS NEEDED

1. EXPLAIN WHY NOT A DEVICE: _____

2. EXPLAIN WHY NOT SUBJECT TO 510(k): _____

3. HOW DOES THE NEW INDICATION DIFFER FROM THE PREDICATE DEVICE'S INDICATION: _____

4. EXPLAIN WHY THERE IS OR IS NOT A NEW EFFECT OR SAFETY OR EFFECTIVENESS ISSUE: _____

5. DESCRIBE THE NEW TECHNOLOGICAL CHARACTERISTICS: The addition of a GUI and curve fitting algorithm that enhance the user interface.

6. EXPLAIN HOW NEW CHARACTERISTICS COULD OR COULD NOT AFFECT SAFETY OR EFFECTIVENESS: These changes will not have any deleterious effect on safety or effectiveness. Effectiveness will be enhanced.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

510(k) Review

K984167

GENERAL INFORMATION

Company Name: GE Medical Systems

Address: P.O. Box 414, W-709
Milwaukee, WI 53201-0414

Dated: 11/19/98
Received: 11/20/98

Contact: Larry A. Kroger, Ph.D.
Regulatory Program Manager
414 544 3894

Manufacturing Address: GE Medical Systems
3200 N. Grandview Blvd.
Waukesha, WI 53188

Tradename: SAGE 7

Common Name: MR Spectroscopy Analysis Option

Product Code: 90 LNI Class: II

FR Classification No.: 892.1000

Intended Use: For MR spectroscopic data processing and display.

Device to which Equivalence is Claimed and Manufacturer:

Manufacturer: GE Medical Systems

Tradename: PROBE

Document Control: K930265

Previous Submissions: None

8

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Applicable Guidance: Software Contained in Medical Devices, 5/29/98

Standard Questions:

Normal, Simplified, Tier I Review? **Normal**

Is the device subject to postmarket surveillance? **No**

Is a summary or certification of safety and effectiveness included? **Summary included**

Is the device life-supporting or life-sustaining? **No**

Is the device implanted (short-term or long-term)? **No**

Does the device contact tissue or skin? **No**

Does the device design use software? **Yes**

Is the device disposable? **No**

Is the device sterile? **No**

Is the device for single, home or prescription use? **Yes**

Does the device contain drug or biological products? **No**

Is the device subject to the Radiation Control Act? **No**

Other standards? **IEC 60601-2-33**

DETAIL REVIEW

Device Description:

Indications -

The device is indicated for a wide variety of MR spectroscopic data management tasks, including file handling, display, processing/modeling, analysis, storage and hard-copy output.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

Technical Characteristics -

(b)(4)

The processing operations made available are:

- Convolution filter
- Spectral Apodize
- Spatial Apodize

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

- Unchop (chopped data to unchopped format)
- Zerofill
- Fourier Transform
- Baseline Correct
- Phase (correction)
- Spectral Offset/Peak Registration
- Flip, Shift & Transpose
- Integrate (spectral dimension)
- Math. (adds, subtracts, etc. with ref. data)
- Replicate
- Extract Display Channel
- Extract Zoom Region
- Average Lines
- Manual FID Generate
- Peak Table FID Generate
- HSVD FID Generate

Laboratory and Clinical Data:

Laboratory Tests - see "Clinical Studies" below

Clinical Studies -

Attachment 8 of the submission provides an example of the clinical use of the device for data analysis.

(b)(4)

Seven full page illustrations show:

1. FID representation of the raw data
2. Non-phase corrected spectral reconstruction
3. Phase corrected portion of calculation
4. Demonstration of zoom capability
5. Analysis of peak region with quantitative results in a dialog box
6. Analysis of noise
7. Demonstration of the capability to superimpose a grid of spectra on a proton anatomical image. Also shown is a magnified single voxel spectrum.

11

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

Labeling:

Promotional Material -

A 3 page draft product data sheet for the device is included. It describes the functions of the device in detail and explains its key features. The information in the data sheet is consistent with that in the balance of the submission.

Operator's Manuals -

An 37 page illustrated draft Operator Manual is included. The manual covers:

- Safety
- Quick Start: Getting Started with SAGE
- The Data Model
- File Operations
- Display Operations
- Processing Operations
- Analysis Operations
- Recon Operations
- Macro Operations: Customizing and Extending SAGE
- Frequency Domain Fitting
- Tips and Hints

The term "Recon" is used for panels that combine the most common processing options on one panel for a given data set. Six Recons are available:

- ◊ Spectrum
- ◊ Image
- ◊ CSI
- ◊ PROBE
- ◊ PROBE-Q
- ◊ PROBE Quant.

The information appears adequate to support the safe and effective use of this device.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Software:

Hazard Analysis -

(b)(4)

Development Methodology -

Attachment #7 of the submission describes Software Development, Verification, Validation and Testing. The major elements in the process employed are:

* Functional requirements & system specifications
* Software design & development techniques
* Verification & Validation
    - Module level
    - Module integration
    - Quality Control of full package
    - Field trials
    - Initial installation monitoring
* Test results and analysis

From the included information outlined above, it appears that the applicant has in place a development and test methodology that will ensure the software functions as required.

Certification -

A dated and signed certification is included.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Substantial Equivalence:

Tabular Comparison -

A chart is included in Attachment #6 that compares the six main features of the device to those of the predicate. The chart shows that the submitted device contains essentially the same functions as the predicate, however, with additional capabilities and user options.

Predicate Promotional Literature -

Attachment #5 contains the Predicate Device Literature which consists of the device: 1) Characteristics, 2) Safety Parameters, 3) Imaging Performance, and 4) Spectroscopy Performance.

Important Similarities and Differences -

The submitted device performs the same basic MR spectroscopy analysis functions as the predicate. The major difference is in the capabilities of the GUI that has additional capabilities including pull down menus, dialog boxes, and multiple window displays made possible with state-of-the-art computers. It also allows SI data to be overlaid on anatomical or spectroscopic images.

Conclusion:

The submitted device is essentially equivalent to the identified predicate device.

Recommendation:

I believe that this device is equivalent to: 90 LNI

Classification should be based on: 892.1000

Class: II

Robert J. Doyle
January 6, 1999

14

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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Internal Administrative Form

	YES	NO
1. Did the firm request expedited review? 2. Did we grant expedited review?		✓
3. Have you verified that the Document is labeled Class III for GMP purposes? 4. If, not, has POS been notified?		
5. Is the product a device? 6. Is the device exempt from 510(k) by regulation or policy? 7. Is the device subject to review by CDRH?	✓ ✓	 ✓
8. Are you aware that this device has been the subject of a previous NSE decision? 9. If yes, does this new 510(k) address the NSE issue(s), (e.g., performance data)?		✓
10. Are you aware of the submitter being the subject of an integrity investigation?		✓
11. If, yes, consult the ODE Integrity Officer.		
12. Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N0332, September 10, 1991.		

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

Screening Checklist
For all Premarket Notification 510(k) Submissions

Device Name: SAGE 7 | K984167

Submitter (Company): GE MEDICAL SYSTEMS

Items which should be included (circle missing & needed information)	SPECIAL YES	SPECIAL NO	ABBREVIATED YES	ABBREVIATED NO	TRADITIONAL YES	TRADITIONAL NO	✓ IF ITEM IS NEEDED AND IS MISSING
1. Cover Letter clearly identifies Submission as: a) "Special 510(k): Device Modification" b) "Abbreviated 510(k)" c) Traditional 510(k)	GO TO # 2,4		GO TO # 3,4,5		GO TO # 4,5		
2. "SPECIALS" - ONLY FOR MODIFICATIONS TO MANUFACTURER'S OWN CLASS II, III OR RESERVED CLASS I DEVICE							
a) Name & 510(k) number of legally marketed (unmodified) predicate device							
b) *STATEMENT - INTENDED USE AND INDICATIONS FOR USE OF MODIFIED DEVICE AS DESCRIBED IN ITS LABELING HAVE NOT CHANGED**			*If no - STOP not a special				
c) *STATEMENT - FUNDAMENTAL SCIENTIFIC TECHNOLOGY OF THE MODIFIED DEVICE HAS NOT CHANGED**			*If no - STOP not a special				
d) Design Control Activities Summary							
i) Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis							
ii) Based on the Risk Analysis, an identification of the verification and/or validation activities required, including methods or tests used and acceptance criteria to be applied							
iii) A declaration of conformity with design controls. The declaration of conformity should include:							
1) A statement signed by the individual responsible, that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results demonstrated that the predetermined acceptance criteria were met							
2) A statement signed by the individual responsible, that manufacturing facility is in conformance with design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review.							16

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

→ → → CONTINUE TO SECTION 4 ← ← ←

	SPECIALS		ABBREVIATED		TRADITIONAL		✓ IF ITEM IS NEEDED AND IS MISSING
	YES	NO	YES	NO	YES	NO	
3. ABBREVIATED 510(K): SPECIAL CONTROLS/CONFORMANCE TO RECOGNIZED STANDARDS							
a) For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type							
b) If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.							
c) For a submission, which relies on a recognized standard, a declaration of conformity to the standard. The declaration should include the following:							
i) An identification of the applicable recognized consensus standards that were met							
ii) A specification, for each consensus standard, that all requirements were met, except for inapplicable requirements or deviations noted below							
iii) An identification, for each consensus standard, of any way(s) in which the standard may have been adapted for application to the device under review, e.g., an identification of an alternative series of tests that were performed							
iv) An identification, for each consensus standard, of any requirements that were not applicable to the device							
v) A specification of any deviations from each applicable standard that were applied							
vi) A specification of the differences that may exist, if any, between the tested device and the device to be marketed and a justification of the test results in these areas of difference							
vii) Name/address of test laboratory/certification body involved in determining the conformance of the device with applicable consensus standards and a reference to any accreditations for those organizations							
d) Data/information to address issues not covered by guidance documents, special controls, and/or recognized standards							

→ → → CONTINUE TO SECTION 4 ← ← ←

17

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

4. GENERAL INFORMATION: REQUIRED IN ALL 510(K) SUBMISSIONS	SPECIALS		ABBREVIATED		TRADITIONAL		✓ IF ITEM IS NEEDED AND IS MISSING
	YES	NO	YES	NO	YES	NO	
a) trade name, classification name, establishment registration number, address of manufacturer. device class					✓		
b) OR a statement that the device is not yet classified	FDA - may be a classification request; see coordinator						
c) identification of legally marketed equivalent device	NA				✓		
d) compliance with Section 514 - performance standards	NA						
e) address of manufacturer					✓		
f) Truthful and Accurate Statement					✓		
g) Indications for Use enclosure					✓		
h) SMDA Summary or Statement *(FOR ALL DEVICE CLASSES)*					✓		
i) Class III Certification & Summary *(FOR ALL CLASS III DEVICES)*							
j) Description of device (or modification) including diagrams, engineering drawings, photographs, service manuals					✓		
k) Proposed Labeling:							
i) package labeling (user info)					✓		
ii) statement of intended use					✓		
iii) advertisements or promotional materials					✓		
i) MRI compatibility (if claimed)					N/A		
m) Comparison Information (similarities and differences) to named legally marketed equivalent device (table preferred) should include:							
i) labeling					✓		
ii) intended use					✓		
iii) physical characteristics					✓		
iv) anatomical sites of use					✓		ATTCH 2
v) performance (bench, animal, clinical) testing	NA				✓		
vi) safety characteristics	NA				✓		
n) If kit, kit certification					N/A		
5. Additional Considerations: (may be covered by Design Controls)							
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:							
i) component & material							
ii) identify patient-contacting materials							
iii) biocompatibility of final sterilized product							
b) Sterilization and expiration dating information:							
i) sterilization method							
ii) SAL							
iii) packaging							
iv) specify pyrogen free							
v) ETO residues							
vi) radiation dose							
c) Software validation & verification:							
i) hazard analysis					✓		
ii) level of concern					✓		
iii) development documentation					✓		
iv) certification					✓		

Items shaded under "NO" are necessary for that type of submission. Circled items and items with checks in the "Needed & Missing" column must be submitted before acceptance of the document.

Passed Screening ✓ **Yes** ____ **No**
Date: 1/4/99

Reviewer: [signature]
Concurrence by Review Branch: ____

18

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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DIVISION OF REPRODUCTIVE, ABDOMINAL, EAR, NOSE AND THROAT
AND RADIOLOGICAL DEVICES

MEMORANDUM OF TELEPHONE CONVERSATION

BETWEEN: R. J. Doyle Date: 12/15/98

AND: Larry A. Kroger, Ph.D.

TITLE: Senior Regulatory Programs Manager

COMPANY: GE Medical Systems

PHONE NUMBER: 414 544 3894

FAX NUMBER:
(if applicable)

DOCUMENT NUMBER: K984167
(if applicable)

SUMMARY: I called to indicate that screening of the submission was completed and that the following material was not found: 1) The safety parameters referred to in Section 5.B, and 2) The hazard analysis for the software contained in this device.

He indicated he would check with the individual who prepared this submission and get back to me in a day or two.

Signed: /S/

Original to: K984167
Copy to: R. A. Phillips

SLJ/RRG 11/20/92 Rev. 3/30/94

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

K984167/A1

GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

December 23, 1998

RECEIVED
28 DEC 98 10 59
FDA/CDRH/ODE/DMC

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

Attention: Mr. Robert Doyle

Subject: **510(k) Notification -**
SAGE 7 Spectroscopy Analysis Option

Reference: **K984167**

Dear Mr. Doyle;

We are writing in response to our telephone conversation of December 15, 1998 regarding the referenced subject.

(1) The safety parameters for the SAGE 7 option are the same as for the presently marketed MR System (K980114) in that the SAGE 7 option is essentially a post processing device. Enclosed is the Device Characteristic Chart from the MR System, K980114, with the safety parameters stated on page 3.

(2) The SAGE 7 option is a post processing function a failure of which would not likely result in a patient injury. Thus, the level of concern is considered minor. The Hazard Analysis is enclosed.

We trust that we have addressed your concerns, but please contact us if further questions arise concerning the information in this submission. You may reach me by telephone at (414) 544-3894 or by Fax at (414) 544-3863.

Sincerely,

Thomas A. Denke, Ph.D.
for
Larry A. Kroger Ph.D.
Senior Regulatory Programs Manager

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

SP 22

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GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

Signa CVMR System

DEVICE CHARACTERISTICS

Type of Magnet	Superconducting, self-shielded		
Static Field Strength	1.5T		
Type of RF Coils	Cylindrical head coil	quadrature	transmit/receive
	Cylindrical body coil	quadrature	transmit/receive
Data Acquisition Modes	2D single-slice and multi-slice, including contiguous slices 3D volume imaging		
Pulse Sequences	2D Inversion Recovery (IR) 2D Spin Echo (SE) 2D and 3D Gradient Echo Acquisition 3D Steady State Free Prescession 2D Time of Flight (TOF) including Gated TOF 3D TOF 2D Multi-Planar Gradient Recalled (MPGR) 2D and 3D Spoiled Gradient Recalled (SPGR) Fast Spin Echo (FSE) including Single and Multishot 2d FSE, Fast Flair, and Multislab 3D FSE Magnetization Transfer Spin Echo Fast Card PC Cine and Cine SPGR 2D and 3D Vascular Inversion Recovery EPI Fast CINE Gated Multishot EPI		

Imaging Options The following enhancements are compatible with various pulse sequences:

Flow Compensation
Respiratory Compensation
ECG triggered Cardiac Gating
Peripheral Pulse triggered cardiac gating
Respiratory Triggering
Graphic Prescription
SAT (Spatial and Spectral Presaturation)
Fat/Water Suppression
Phase Offset, Multi Planar (POMP)
Spectral PreSaturation
Image Intensity Correction
Extended Dynamic Range
Phase & Frequency Offset
Square & Rectangular Pixel
Magnetization Transfer Contrast
Ramped Pulse Direction
AutoScan
Assymmetric FOV
Variable Bandwidth
No Phase Wrap
Rectangular FOV
Blood Suppression
Tagging
CMON

Confidential to GE Medical Systems
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

Signa CVMR System

Reconstruction Techniques	Fermi filters, Fourier transforms, zero filling, phase corrected Hermitian conjugate techniques for fractional NEX or echo
Type of installation:	Fixed
Slice Selection Method	Gradient-mediated frequency and phase encoding using selective excitation, saturation, and physical localization
Display Matrix	512 x 512
Acquisition Matrix	Phase and frequency encoding from 128 to 512 in steps of 32
Image Acquisition Time	By selecting the number of excitations (NEX), repetition time (TR), and number of phase encoding steps (matrix size), the operator defines the scan time and the desired number of signal averages to be performed to archive optimum signal-to-noise ratio. 2D Multislice — TR x (Acquisition Matrix) x NEX 2D Gradient Echo — TR x (Acquisition Matrix) x NEX x #acquisitions 3D — TR x (Acquisition Matrix) x NEX x #slices/#slabs
Pre and Post Processing	Analog to digital conversion Anti-alias low pass filtering to reduce artifacts Signal averaging for multi-NEX acquisitions Fermi filtering to reduce quantization noise Baseline correction and scaling and clipping pixel values for renormalization Fourier transformation Pixel interpolation for display purposes Phase corrected Hermitian conjugate techniques for fractional NEX or fractional echo Image filtering
Number of slices, ranges and Increments	2D - 1.8 to 20 mm slice thickness in 0.1 mm increments. Operator variable interslice spacing in increments as small as 0.1 mm, as large as 200 mm. Interleave option for multi-slice imaging. Up to 256 slice locations 3D - 4 to 128 variable slab contiguous slice volume imaging. Slice thickness of 0.5 mm to 5.0 mm in 0.1 mm increments.
Slice Orientation	Direct transverse. sagittal, coronal, oblique, and double-oblique plane imaging, as well as Multi-Slice, Multi-Angle and Radial imaging.

Confidential to GE Medical Systems
Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

Signa CVMR System

SAFETY PARAMETERS

Maximum static field	1.5T
dB/dt	35.6 (1 + (132/^{1})) T/s where ^{1} is ramp time in µs.
RF Power Deposition (SAR)	< 2 W/kg whole-body average < 8 W/kg peak
Acoustic Noise level	< 110 dBa

IMAGING PERFORMANCE

Specification Volume	Head Coil	168 mm diameter sphere	
	Body Coil	266 mm diameter sphere	
Signal-to-Noise Ratio	Head Coil	75 < SNR < 95	
	Body Coil	50 < SNR < 60	
Geometric Distortion	@ center		± 1.5%
	@ ± 15 cm		± 3.0%
	superior to inferior coil symmetry		± 3.0%
Slice Profile	Shinnar-LeRoux		
Slice Thickness	Spin Echo @ 3 mm	3 mm ± 0.3 mm	
	Spin Echo @ 5 mm	5 mm ± 0.4 mm	
	Spin Echo @ 10 mm	10 mm ± 0.6 mm	
Interslice Spacing	Variable from 0 to 200 mm ± 5%		

INTENDED USES

Anatomical Region	Whole Body
Nuclei Excited	Proton imaging (H-1)
Diagnostic Uses	2D and 3D imaging

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

Safety/Regulatory Hazard Analysis for SAGE 7

Potential Hazard	Minimum Requirements	Planned Control	Verification of Control	Status

(b)(4)

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

Safety/Regulatory Hazard Analysis for SAGE 7

Potential Hazard	Minimum Requirements	Planned Control	Verification of Control	Status

(b)(4)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

Safety/Regulatory Hazard Analysis for SAGE 7

Potential Hazard	Minimum Requirements	Planned Control	Verification of Control	Status
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(b)(4)

Confidential and Proprietary to GE Medical Systems

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

November 20, 1998

GENERAL ELECTRIC MEDICAL SYSTEM
3200 N. GRANDVIEW BLVD.
WAUKESHA, WI 53188
ATTN: LARRY A. KROGER

510(k) Number: K984167
Received: 20-NOV-1998
Product: SAGE 7

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

On January 1, 1996, FDA began requiring that all 510(k) submitters provide on a separate page and clearly marked "Indication For Use" the indication for use of their device. If you have not included this information on a separate page in your submission, please complete the attached and amend your 510(k) as soon as possible. Also if you have not included your 510(k) Summary or 510(k) Statement, or your Truthful and Accurate Statement, please do so as soon as possible. There may be other regulations or requirements affecting your device such as Postmarket Surveillance (Section 522(a)(1) of the Act) and the Device Tracking regulation (21 CFR Part 821). Please contact the Division of Small Manufacturers Assistance (DSMA) at the telephone or web site below for more information.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (HFZ-401) at the above letterhead address. Correspondence sent to any address other than the Document Mail Center will not be considered as part of your official premarket notification submission. Because of equipment and personnel limitations, we cannot accept telefaxed material as part of your official premarket notification submission, unless specifically requested of you by an FDA official. Any telefaxed material must be followed by a hard copy to the Document Mail Center (HFZ-401).

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMA. If you have other procedural or policy questions, or want information on how to check on the status of your submission (after 90 days from the receipt date), please contact DSMA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsmamain.html or me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Staff
Office of Device Evaluation
Center for Devices and Radiological Health

27

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

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K984167

GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

November 19, 1998

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20 Nov 98 10 37
FDA/CDRH/OCE/DMC

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

Subject: **510(k) Notification - SAGE 7 Spectroscopy Analysis Option**

To Whom it May Concern:

GE Medical Systems intends to begin marketing the SAGE 7 Spectroscopy Analysis option to GE's Signa Magnetic Resonance Systems. This option is an enhancement to the currently marketed SA/GE Spectroscopy Analysis option. The difference is the user interface. The increased computational capability of workstations have made possible as routine operations some sophisticated curve-fitting algorithms that were impractical on older computer hardware.

The following information is in accordance with 21 CFR 807.87 and is set forth in the same order.

1. DEVICE NAME

Device Name:	SAGE 7
Common Name:	Spectroscopy Analysis Option

2. FDA CLASSIFICATIONS

Device Classification Number:	892.1000
Classification Panel:	Radiology Devices Panel
Device Product Code:	LNI
Device Class:	II

3. ESTABLISHMENT REGISTRATION NUMBER

Registration Number:	2183553
Manufacturer Address:	GE Medical Systems 3200 N. Grandview Blvd. Waukesha, WI 53188

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

4. APPLICABLE PERFORMANCE STANDARDS

No applicable Performance Standards have been issued under Section 514 of the Food, Drug and Cosmetic Act. The SAGE 7 Spectroscopy Option was evaluated using the voluntary standard:

IEC 601-2-33 International Standard for Medical Electrical Equipment Part 2: Particular requirements for the safety of magnetic resonance equipment for medical diagnosis

5. PROPOSED LABELS, LABELING AND ADVERTISEMENTS

A. Device Characteristics - Attachment #2.

B. Safety Parameters - Attachment #2

C. Imaging Performance Parameters - not applicable

D. Spectroscopy - Attachment #8

E. Software version - The software evaluation process is in Attachment #7. The SAGE 7 Spectroscopy software option is in the process of being verified such that no date related hazards will exist at the year 2000.

F. Intended Uses: - Attachment #2

G. Proposed Labeling:

1) User Manual - Attachment #4 is the User manual which is an addendum to the presently marketed Signa Horizon System (K962061). This manual only addresses the new software. There are no new safety warnings.

2) Product Data Sheet (draft copy) - Attachment #~~5~~ 4 is a product data sheet.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

6. EQUIVALENCY INFORMATION

In the opinion of GE Medical Systems the SAGE 7 Spectroscopy Analysis software option is substantially equivalent to the spectroscopic data analysis capabilities of the GE Hydrogen Spectroscopy Option - PROBE (510(k) K930265) and its predecessor the GE SA/GE spectroscopy option in commercial distribution following reclassification of magnetic resonance diagnostic devices (ref. 53 FR 5078, Feb. 1, 1989) from Class III to Class II. The diagnostic effectiveness, safety, and intended use of the SAGE 7 option is substantially equivalent to the predicate devices as described in the referenced 510(k) and the GE reclassification petition (87P-0214) for a Magnetic Resonance Diagnostic Device. This opinion is supported by a comparison of features as noted in Attachment #6 as well as the following information:

A. Summary of information respecting safety and effectiveness - see Attachment #1
B. Product specifications (predicate devices) - see Attachment #5
C. Description of software, verification, validation and testing - see Attachment #7

7. MODIFIED DEVICE - As stated above, the SAGE 7 option updates SA/GE with state of the art computer technology.

8. PERFORMANCE TESTING FOR MR DIAGNOSTIC DEVICES

A. Performance Parameters for a MR Imaging Device - not applicable

B. Performance Parameter Test Documentation for a MRID - Attachment #8

C. Performance Testing for a Spectroscopy Device - Attachment #8

D. Testing for Safety of MR Diagnostic Devices - not applicable - this is a post processing option

E. Sample Clinical Output for a MR Diagnostic Device - Attachment #8

I believe, to the best of my knowledge, that all data and information submitted in this premarket notification are truthful and accurate and that no material fact has been omitted. If you have any questions concerning the information in this submission, you may reach me by telephone at (414) 544-3894 or by Fax at (414) 544-3863.

Sincerely,

Larry A. Kroger

Larry A. Kroger Ph.D.
Senior Regulatory Programs Manager

Enclosures: 2 copies

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8130

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GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

November 19, 1998

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20 NOV 98 10 37
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Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

Subject: **510(k) Notification - SAGE 7 Spectroscopy Analysis Option**

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Registration Number:	2183553
Manufacturer Address:	GE Medical Systems 3200 N. Grandview Blvd. Waukesha, WI 53188

31

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

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B. **Safety Parameters** - Attachment #2

C. **Imaging Performance Parameters** - not applicable

D. **Spectroscopy** - Attachment #8

E. **Software version** - The software evaluation process is in Attachment #7. The SAGE 7 Spectroscopy software option is in the process of being verified such that no date related hazards will exist at the year 2000.

F. **Intended Uses:** - Attachment #2

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Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

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Sincerely,

Larry A. Kroger

Larry A. Kroger Ph.D.
Senior Regulatory Programs Manager

Enclosures: 2 copies

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8313

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

PREMARKET NOTIFICATION

TRUTHFUL AND ACCURATE STATEMENT

(As Required by 21 CFR 807.87(j))

I certify that, in my capacity as a Program Manager of MR for GE Medical Systems, I believe to the best of my knowledge, that all data and information submitted in the premarket notification for SAGE 7 Spectroscopy Analysis software are truthful and accurate and that no material fact has been omitted.

Mark Jaster

GE Medical Systems Date: 9/23/98

(Premarket Notification 510(k) Number)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

510(k) Number (if known):_____

Device Name: SAGE 7 Spectroscopy

Indications For Use:

SAGE 7 is a package of software tools for MR spectroscopic data processing and display. SAGE 7 is indicated for use for a wide variety of MR spectroscopic data management tasks, including file handling, display, processing/modeling, analysis, storage and hard copy output. The resultant spectroscopic presentations, when interpreted by a trained physician, can provide physiological / chemical information that can be useful in determining a diagnosis.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use_____ OR Over-The-Counter Use_____
(Per 21 CFR 801.109)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

SAGE 7 Spectroscopy Analysis Option

TABLE OF CONTENTS — ATTACHMENT

Device Summary

Summary of Information Respecting Safety and Effectiveness..... 1

Labels, Labeling and Advertisements

Device Characteristics Chart 2

Operator Manual (draft copy) 3

Product Data Sheet (draft copy) 4

Predicate Device Literature 5

Comparison Chart 6

Software Development Verification, Validation and Testing 7

Performance Testing for MR Diagnostic Devices

Sample Clinical Output for a MR Diagnostic Device 8

Literature 9

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

ATTACHMENT #1

Summary of Information Respecting Safety and Effectiveness

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

Records Processed under FOIA Request 2015-5936; Released by CDRH on 09/30/2015

GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

SUMMARY OF SAFETY AND EFFECTIVENESS

- This 510(k) summary of safety and effectiveness information is submitted in accordance with the requirements of 21 CFR Part 807.87(h).

- Identification of Submitter
  Larry A. Kroger, Ph.D., 414-544-3894, November 19, 1998

- Identification of the Product
  SAGE 7 Spectroscopy Analysis Option

  Manufactured by: GE Medical Systems
  3200 N. Grandview Blvd.
  Waukesha, WI 53188

- Marketed Devices

  The SAGE 7 Spectroscopy Analysis option is an enhancement to the currently marketed SA/GE Analysis option in distribution since the reclassification of Magnetic Resoncance Diagnostic devices (ref. 53 FR 5078, Feb. 1, 1989).

- Device Description

  The GE SAGE 7 Spectroscopy Analysis Software is designed to operate on GE Signa Horizon Systems and GE Advantage Windows workstations. It provides a toolkit of software applications to handle a wide variety of tasks associated with spectroscopy data management. The SAGE (**S**pectroscopy **A**nalysis **GE**) package provides the capability for the trained clinical spectroscopist to reconstruct, analyze, and display spectra and spectroscopic images to provide information to support a diagnosis. SAGE 7 provides a tool for the spectroscopist to process raw spectroscopy data into spectra or spectroscopic images, view them, and optionally perform numerical analyses to obtain spectroscopic parameters (ex. peak positions, widths, heights, areas, etc.).

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GE Medical Systems

P.O. Box 414, W-709
Milwaukee, WI 53201
USA

SUMMARY OF SAFETY AND EFFECTIVENESS

- Indications for Use

SAGE 7 is a package of software tools for MR spectroscopic data processing and display. SAGE 7 is indicated for use for a wide variety of MR spectroscopic data management tasks, including file handling, display, processing/modeling, analysis, storage and hard copy output. The resultant spectroscopic presentations, when interpreted by a trained physician, can provide physiological / chemical information that can be useful in determining a diagnosis.

- Comparison with Predicate

The SAGE 7 Spectroscopy Analysis option is an enhancement to the SA/GE Analysis option. The basic operations (ex. Fourier transform, phasing, peak-picking, integration, fitting, etc.) have not significantly changed, and are provided in both SAGE 7 and the SA/GE Analysis option. What has changed is the sophistication of the user interface. In addition, the increased computational capability of modern workstations have made possible as routine operations some sophisticated curve-fitting algorithms that were impractical on older computer hardware.

- Summary of Studies

The SAGE 7 Spectroscopy Analysis option was evaluated to International medical equipment safety standard IEC 601-2-33 titled Particular requirements for the safety of magnetic resonance equipment for medical diagnosis. The SAGE 7 Spectroscopy Analysis option is comparable to the SA/GE Spectroscopy option.

- Conclusions

It is the opinion of GE that the SAGE 7 Spectroscopy Analysis option is substantially equivalent to the SA/GE Spectroscopy option. SAGE 7 does not include any new indications for use, nor does use of this device result in any new potential hazards.

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ATTACHMENT #2

Device Characteristics Chart

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SAGE 7 Spectroscopy Analysis Option

(from Draft 6/19/98 for MR Premarket Notification Guidance Document)

DEVICE CHARACTERISTICS

(i)	Resonance nuclei	(b)(4)
(j)	Compounds of Interest:	
	Tissues of Interest:	brain, liver, muscle.
(k)	Description of specialized spectroscopic hardware	SAGE 7 requires no specialized spectroscopic hardware for its operation.
(l)	Description of specialized spectroscopic software	Refer to the SAGE 7 Operator Manual and the SAGE 7 Product Data sheet for description of postprocessing. Localization is accomplished by the Signa MR System during data acquisition.
(m)	Shimming Techniques	Voxelated autoshim (3 plane phase map solved over volume of interest) is performed by the Signa MR System.
(n)	Solvent suppression methods	Water suppression is accomplished on the MR System.
(o)	Peak Assignment Methods	SAGE 7 does not assign label peaks in spectra.
(p)	Signal enhancement techniques	None
(q)	Acquisition times	2 to 30 minutes as set up on the Signa MR System at acquisition time.

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ATTACHMENT #3

Draft Copy of Operator Manual

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SAGE
LX User's Guide

Version: 1.0
Date: May 15, 1998

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1 Introduction **1**
1.1 Safety 1

2 Quick Start: Getting Started with SAGE **2**
2.1 The "sage" Startup Command 2
2.2 Data File Handling 2
2.3 Loading Data Files into SAGE 3
2.4 Internal Data versus Data Files 3
2.5 The Recon Panels 3
2.6 Online Help 3

3 The Data Model **4**
3.1 Domains and Dimensions 4
3.2 Active, Reference and Multiple Data Sets 4

4 File Operations **5**
4.1 Load and Save Files 5
4.2 Hardcopy 7

5 Display Operations **8**
5.1 General Display Rules 8
5.2 Data Display Modes 8
5.3 Point by point vs Summing Displays 9
5.4 Spectrum Display 10
5.5 Image Display 12
5.6 Stack Plot Display 14
5.7 Spectral Grid 15
5.8 Data Description 16
5.9 Composite Displays 16
5.10 Scaling of Displays 17
5.10.1 User Scaling Values 17
5.10.2 Setting the User Scaling Values 17
5.11 Zooming and Graphical Manipulations 18
5.11.1 Graphically Selecting a Zoom Region 18
5.11.2 Typing in a Zoom Region 18
5.11.3 Moving to a New Slice 19
5.11.4 Copying Zoom Values 19
5.11.5 Using Two Zoom Regions 19
5.12 Other Graphical Manipulations 19
5.13 The SAGE Colormap 19

6 Processing Operations **20**

7 Analysis Operations **22**

8 Recon Operations **24**

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9 Macro Operations: Customizing and Extending SAGE 25
9.1 Parameter Files 25
9.2 Quick Macros 25
9.2.1 Recording a Quick Macro from the GUI 26
9.2.2 Running a Quick Macro 26

10 Frequency Domain Fitting 27
10.1 Introduction 27
10.2 Background 27
10.2.1 The Fit Metric 27
10.2.2 The Fitting Algorithms 27
10.2.3 The Model Functions 28
10.2.4 The Spectrum 29
10.2.5 Collating Parameters, and Calculating the Spectrum 30
10.2.6 Modifications to the Spectrum 31
10.3 Changing a Parameter 32
10.4 For Further Information 32
10.5 Fit Control File Example 32

11 Tips and Hints 37

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1 Introduction

This document describes the SAGE spectroscopic processing and display software package. "SAGE" is an acronym for Spectroscopy Analysis by General Electric. SAGE provides file handling, display, hardcopy, processing, and analysis capability and is driven by a graphical user interface (GUI).

The following figure is the SAGE main panel. This main panel appears after starting the SAGE program. Note that the title bar of the main panel shows the SAGE version number.

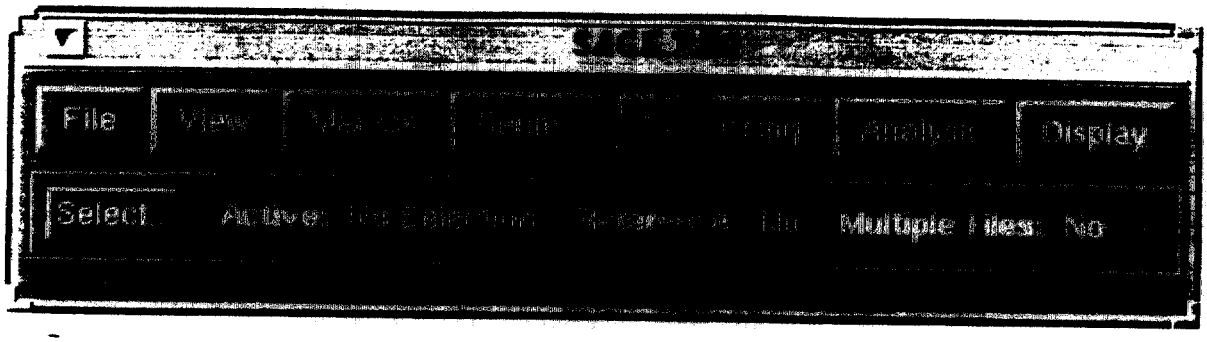

Figure 1. SAGE Main Panel

1.1 Safety

All operators shall be thoroughly familiar with the Signa system operator manuals and the potential hazards associated with MRI. Refer to the "Safety" section of your Signa operator manual.

1.2 User Training

This system should only be operated by medical professionals specifically trained in spectroscopy.

46

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2 Quick Start: Getting Started with SAGE

After installation, the user is ready to run the SAGE software. This section gives a brief overview of SAGE startup and execution. The following chapters fill in the details.

2.1 The "sage" Startup Command

This Section assumes the user is sitting at a workstation terminal upon which SAGE is installed. When running SAGE remotely, see the next section.

First one must start a window that accepts UNIX commands. In the following, "RMB" refers to the Right Mouse Button:

Signa LX (SGI):

Generally the user will want to move to the Tools Desktop (icon picture includes a hammer) or the Applications Desktop ("GE" icon) because there is usually more space in which to work. Then with the cursor on the display background/desktop press and hold the RMB to get the Root Menu. From the Root Menu, choose "Service Tools–>Command Window".

Now one is ready to start SAGE by executing the **sage** command in the command window:

```
host% sage
```

SAGE continues to run until terminated by the user with "File–>Exit SAGE".

2.2 Data File Handling

One of the keys for understanding SAGE concerns how SAGE handles data files.

First of all, SAGE reads the Signa header of a data file and creates a custom header file with the extension ".shf". For example, given a data file with the name "P00512.7", SAGE will create a header file with the name "P00512.7.shf" that contains all of the information needed by SAGE to display and process the data.

When SAGE creates the custom ".shf" header file it also copies the data file and the ".shf" header file into its own data base. The SAGE data base is in a hierarchical format which is layed out per:

<SAGE_DATABASE>/Site/Patient_ID/Study/Series/<data_file>

The above SAGE_DATABASE is the location of the SAGE data base.

The basic concept is that a Scanner has its data files in certain locations and SAGE will only read or copy data from those locations; it specifically never writes anything to the Scanner data file locations. SAGE uses its own SAGE database area for working on the data files.

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2.3 Loading Data Files into SAGE

The technique used to load data into SAGE depends on the data location and data type per the following table, where "Local" refers to the Scanner running SAGE and "Remote" refers to a Scanner connected to the Scanner running SAGE via a local network:

Data Location & Type	Load via
Local SAGE data all types	"File–>Load–>SAGE Data..."
Local Raw "P" files	"File–>Load–>Raw Data..."
Local Spectrum "G" files	"File–>Load–>Raw Data..."
Remote Raw "P" files	"File–>Load–>Raw Data..."
Remote Spectrum "G" files	"File–>Load–>Raw Data..."
Local LX Recon–ed Images	Main SDC Browser using "SAGE Transfer" button to transfer to SAGE data base, then "File–>Load–>SAGE Data..."

Where:

SAGE data:	Refers to any data type where the data file is accompanied by a custom SAGE ".shf" header file.
Raw "P" files:	These data files are located on a Scanner at "/usr/g/mrraw".
Spectrum "G" files:	This type is only produced by Signa 5.x and earlier. It has been replaced by the Raw Spectro type in LX, a part of the Raw "P" file family. These data files are located on a Scanner at "/usr/g/mrspecraw".
LX Recon–ed Images:	The main LX/SDC Browser has a "SAGE Transfer" button that transfers chosen images to the SAGE data base and creates the custom ".shf" SAGE header files.

2.4 Internal Data versus Data Files

You can experiment, "play" and use trial and error with SAGE and yet you have practically no chance of corrupting your original data file. This is because none of the processing steps in SAGE are written to disk unless you execute "File–>Save–>Data...", and even then the default is to use a new data file name (default new name is the original name plus "_pro" extension).

2.5 The Recon Panels

Generally the best way to begin processing is by using the Recon panels. Use "Macros–>Recons" to choose the Spectrum, Image, CSI, PROBE or PROBE Recon recon panels.

After that, we suggest checking out the various menu items on the Main Panel via the "File", "Edit", "Macros", "Processing", "Analysis" and "Display" buttons to see what is available.

2.6 Online Help

Online help files are available via "File–>Help–>SAGE Help...". Choose the desired Topic and then the desired Subtopic. As an alternative, most panels have a "Help" button that will bring up the help file for that particular panel.

48

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3 The Data Model

3.1 Domains and Dimensions

SAGE models all data sets as 3–D Chemical Shift Imaging (CSI) data; that is, all data sets are assumed to be four dimensional, with the first dimension representing time or frequency, and the remaining dimensions representing space or spatial frequency. However, any of these dimensions can have length 1. Thus, a single voxel spectrum of 2048 points will be considered a 2048 x 1 x 1 x 1 data set; a conventional image will be considered a 1 x 256 x 256 x 1 data set.

The above assignments of domains to dimensions are not strictly enforced in any way, but are assumed to be true in innumerable places. Because it is impossible to anticipate the needs of every analysis protocol, SAGE does not attempt to restrict the application of analysis and processing options. It is the operator's responsibility to ensure that the appropriate processing and/or analysis operations are used. For example, the image display routines will display data from the second and third dimensions of the data set. An example of a place where the assignment of domains to dimensions can be ignored is when looking at a time series of spectra — the second dimension will represent time rather than space. Provided no spatial processing is requested (e.g. spatial apodization), no problems should arise.

3.2 Active, Reference and Multiple Data Sets

Up to 32 data sets can be loaded into SAGE at any one time. Only one data set at a time can be designated as the "Active" data set. Operations are performed on the Active data set and results are saved to the Active data set.

SAGE only refers to data sets stored as UNIX disk files during the Load Data operation. Once a data set is loaded into SAGE memory, the disk file is no longer used. Therefore one can do any number of operations on a data set loaded into SAGE and it will have no effect on the original disk file. In order to save processed data to a UNIX disk file, one must specifically do a Save Data operation.

A few operations use a second data set that is designated as the "Reference" data set. For example, SAGE has a Math panel that can add, subtract, multiply or divide the Active data set by the Reference data set. The result is placed into the Active data set.

When one wants to do the exact same operation or sequence of operations on more than one data set, SAGE allows one to choose any number of data sets as "Multiples". Every operation that is done to the Active data set is also done to each of the Multiple data sets.

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4 File Operations

4.1 Load and Save Files

SAGE provides the following file handling functions:

- Load Signa data files.
- Load flat (ie. no included header) data files.
- Load spectroscopy data sets from a remote Signa.
- Save processed data files.
- Load and save table files. Tables are used to store the results of Peak Find, Marquardt Fitting and HSVD Fitting (see Chapter 7 for information on these items).
- Load and save parameter files. Parameter files are mainly used with Macros (see Macro Chapter 9).
- Open as many as 32 data sets concurrently.

The following shows the Load/Save Panel as an example of File Handling panels.

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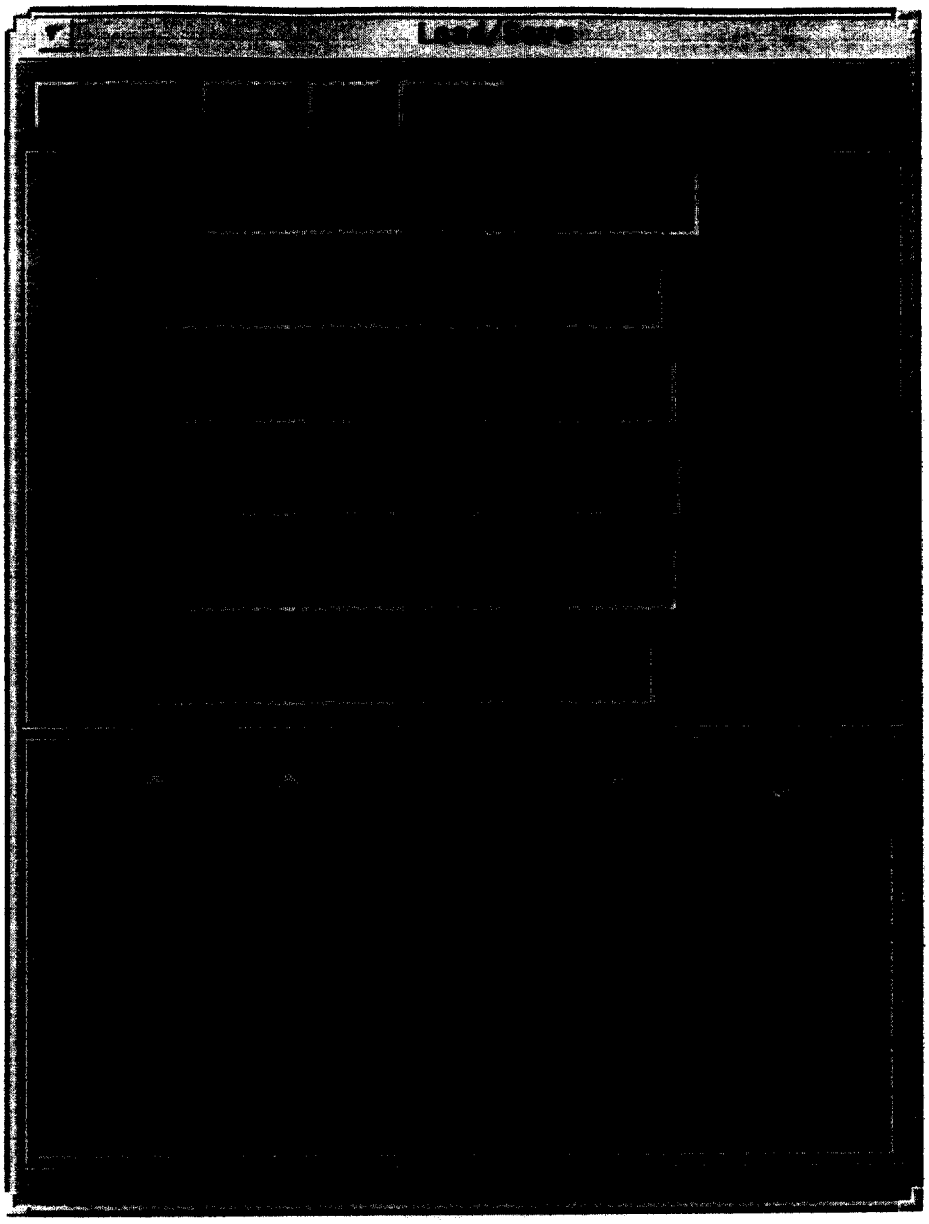

Figure 2. Load/Save Panel

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4.2 Hardcopy

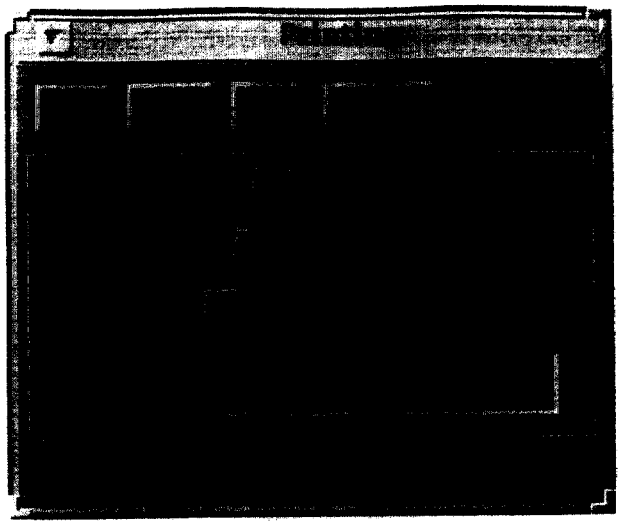

Figure 3. Print Panel

PostScript output is generated by the Print panel. All open displays of the Active data set will be printed, one to a page. Three options are available in generating PostScript:

1. Output to a printer.
2. Encapsulated PostScript file output, suitable for inclusion in other documents.

If direct output to a printer is selected, a one line annotation and timestamp is added to bottom of each page.

Files will appear in the directory from which you started SAGE.

Both Landscape and Portrait orientation are available.

Output plot sizes have been preselected. You can choose Small, Medium, or Large, or choose Screen to render a display to the same dimensions it is displayed on the screen.

The UNIX utility program **xpsview** can be used to preview PostScript output.

52

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5 Display Operations

We will first describe the overall display strategy — that is, the general rules for how to go from data set to displayed data. We then describe the specific rules used for each display.

5.1 General Display Rules

The following are the general rules used to take a data set and display it on the screen or on hardcopy:

- Multiple (up to 4) displays of a data set are allowed. Any mix of display types is allowed. Multiple displays allows some nice ways to watch one view of a data set while adjusting a parameter on another view.
- One channel (Real, Imaginary, Magnitude, Phase, or Power) is displayed. If multiple displays are present, all display the same channel (i.e. the channel is a property of the data set, not the display).
- The displays are all scaled by the same values. For Image displays, the scale and offset are used as a window and level. There are two scaling modes, one where the global range of the data is considered, and another where only the displayed zoom region is considered. In addition, user settable scale and offset can be applied.
- The current zoom values in the first three dimensions are applied to all displays. The only exception is when one display of a multiply displayed data set is being used to interactively set the zooms for that data set (the rules for this case are described in Section 5.11, Zooming).

  In the third spatial dimension (the slice dimension), the low zoom value is used. This is because not all displays are able to represent the third dimension, so to keep all views of the data consistent, all views will show the low zoom.

Note: All data points within the zoomed region are plotted using IDL's normal plotting algorithm. This is sometimes called "smush" mode to differentiate it from other plotting algorithms that select only every n–th data point.

5.2 Data Display Modes

Each data set can have the following display modes set:

- Channel — Real, Imaginary, Magnitude, Power, Phase and Phase Unwrapped.
- Scale and Offset, including Global or Local scaling (see Section 5.10) and Grayscale scaling for images.
- Time Units — seconds or points.
- Frequency Units — parts per million (ppm), Hertz or points.
- Spatial Units —millimeters or points.
- Zoom — various zoom options include: Zoom from units, Zoom from Spectrum, Zoom from Image, Zoom from Reference, Unzoom and Previous Zoom.

The following shows the Display Parameters Panel where many of the above display modes can be set.

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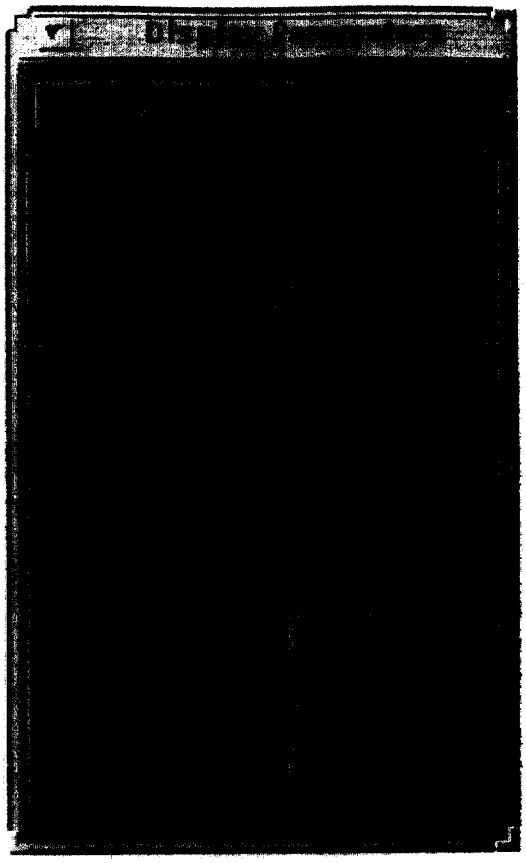

Figure 4. Display Parameters Panel

5.3 Point by point vs Summing Displays

Some displays (Stack, Grid) represent each point of the data set separately on the display. In other displays (Image, Spectrum) the point on the screen represents the sum of multiple data points.

When displaying a point by point display in Global mode, it should be scaled relative to the maximum and minimum values in the entire data set. When displaying a summing display in Global mode, it needs to be scaled relative to the maximum and minimum that would appear in the data if it were not zoomed.

Note: All points within the zoom region are plotted. This is sometimes called "smush" mode.

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5.4 Spectrum Display

The Spectrum display is used to present 1–D spectra, as well as the sum of spectral lines for CSI and other multi–frame data sets per the algorithm in the following paragraph.

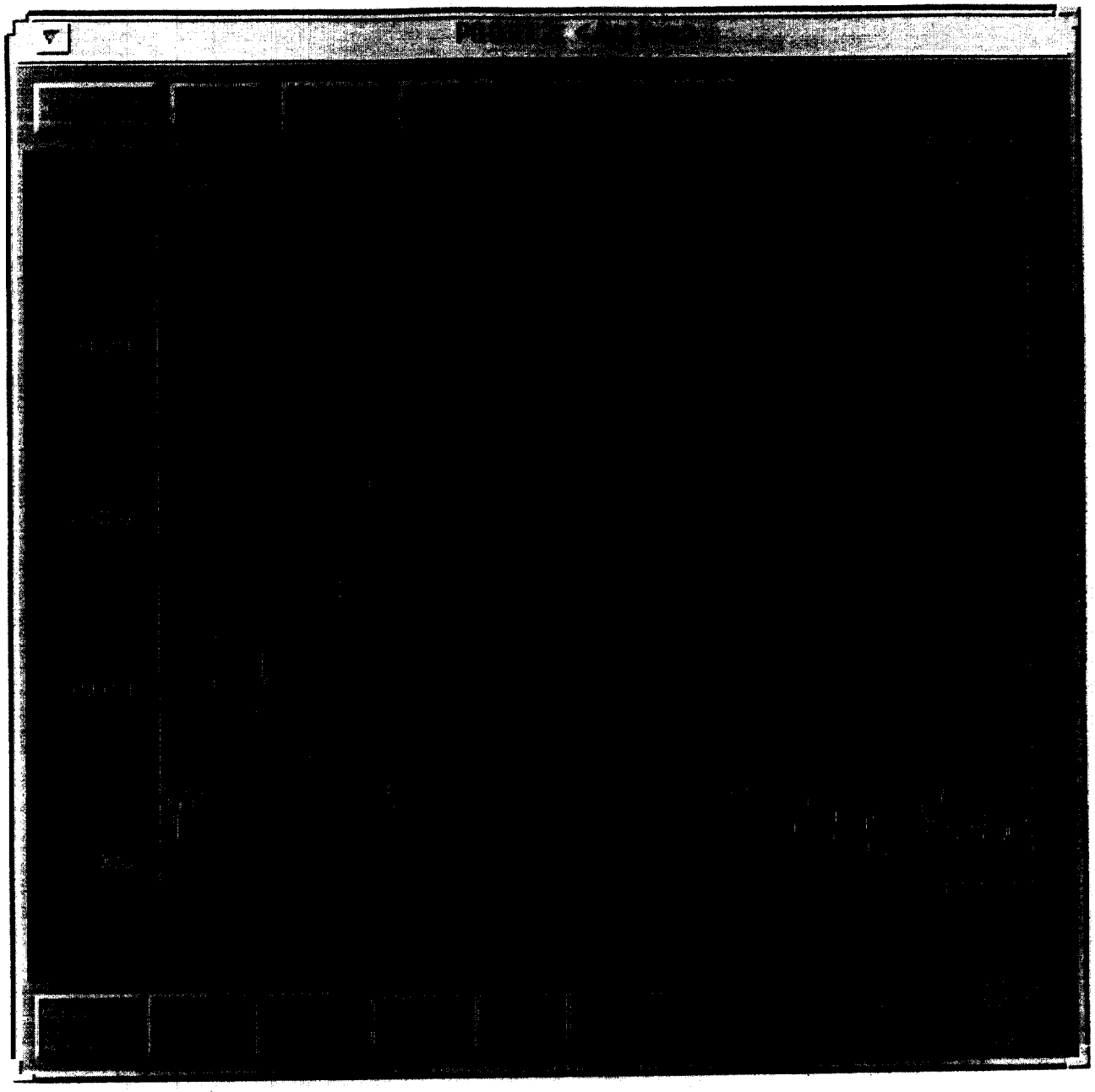

Figure 5. Spectrum Display

The Spectrum display will be used as the most basic type to present spectroscopic data.

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The algorithm to generate the Spectrum display for multi–frame data sets is:

- Extract the specified slice in the fourth dimension; the default is the lowest numbered slice. Extract the specified zoom region in the first three dimensions.
- Extract the channel to be displayed.
- Sum over the first two spatial dimensions (dimensions 2 and 3).
- Scale appropriately. Scale/offset are applied as window/level to Spectrum displays.
- Render the plot.

The order of channel extraction and summation is reversed for the phase channel.

The Spectrum window proportions are not constrained like the Image display — it will resize to any requested size.

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5.5 Image Display

The Image display is used to represent 2–D and 3–D images, and projections in the spectral direction of 2–D and 3–D CSIs.

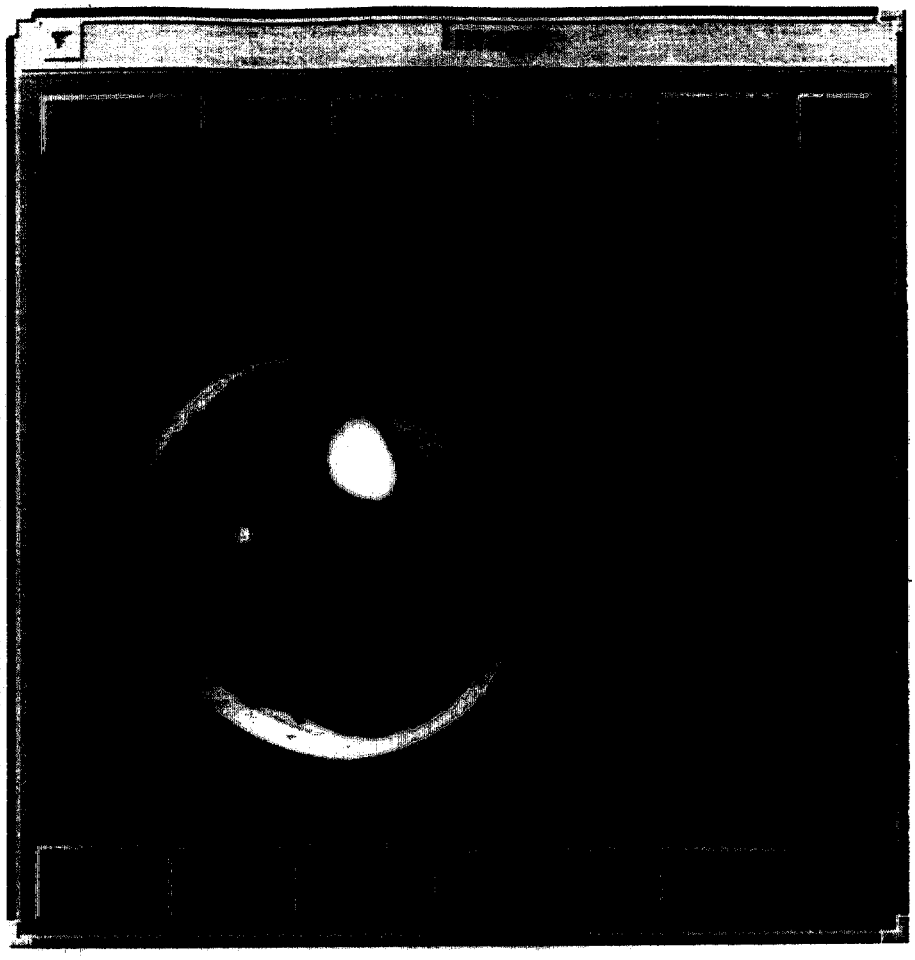

Figure 6. Image Display

The algorithm to generate the Image data is:

- Extract the specified slice in the fourth dimension. Extract the specified zoom region in the first three dimensions.
- Extract the channel to be displayed.
- Sum along the first dimension.
- Scale as appropriate (see Section 5.10, Scaling). Scale/offset are applied as window/level to Image displays.
- Magnify the data (see below), and render it.

It may not be possible to generate a display of a particular size, since the image proportions are constrained by the pixel proportions, the selected zoom region, and the requirement to use integer interpolation factors when magnifying the Image. SAGE creates a window for which the geometric mean of the *x* and *y* dimensions is as close as possible to the geometric mean of the requested size. If a window of the correct size already exists, it is used, otherwise the current display window is destroyed and a new one created. The size of the newly created window is then written into the requested size field in the header to prevent unnecessary window creations.

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The size of an Image can be changed by dragging on the resize corner of its display window. This updates the requested size, hence forcing a recalculation of the actual size. This will only work with the currently designated Active data set.

Magnification is done by pixel replication, bilinear interpolation, or Fourier interpolation. However, care is taken to zoom symmetrically about the center of a pixel — there can be an enormous difference between the location of the center of a pixel and the location of the edges.

The Image is annotated with the directions and FOV.

[illegible] values on the panel will be set to the [illegible] channel presents its parameters [illegible]

58

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5.6 Stack Plot Display

The Stack plot display is used to present CSI and accumulate mode data. Note that SAGE allows for independent zooming in all dimensions, so it is possible to display the signals from any rectangular subarray as a Stack plot.

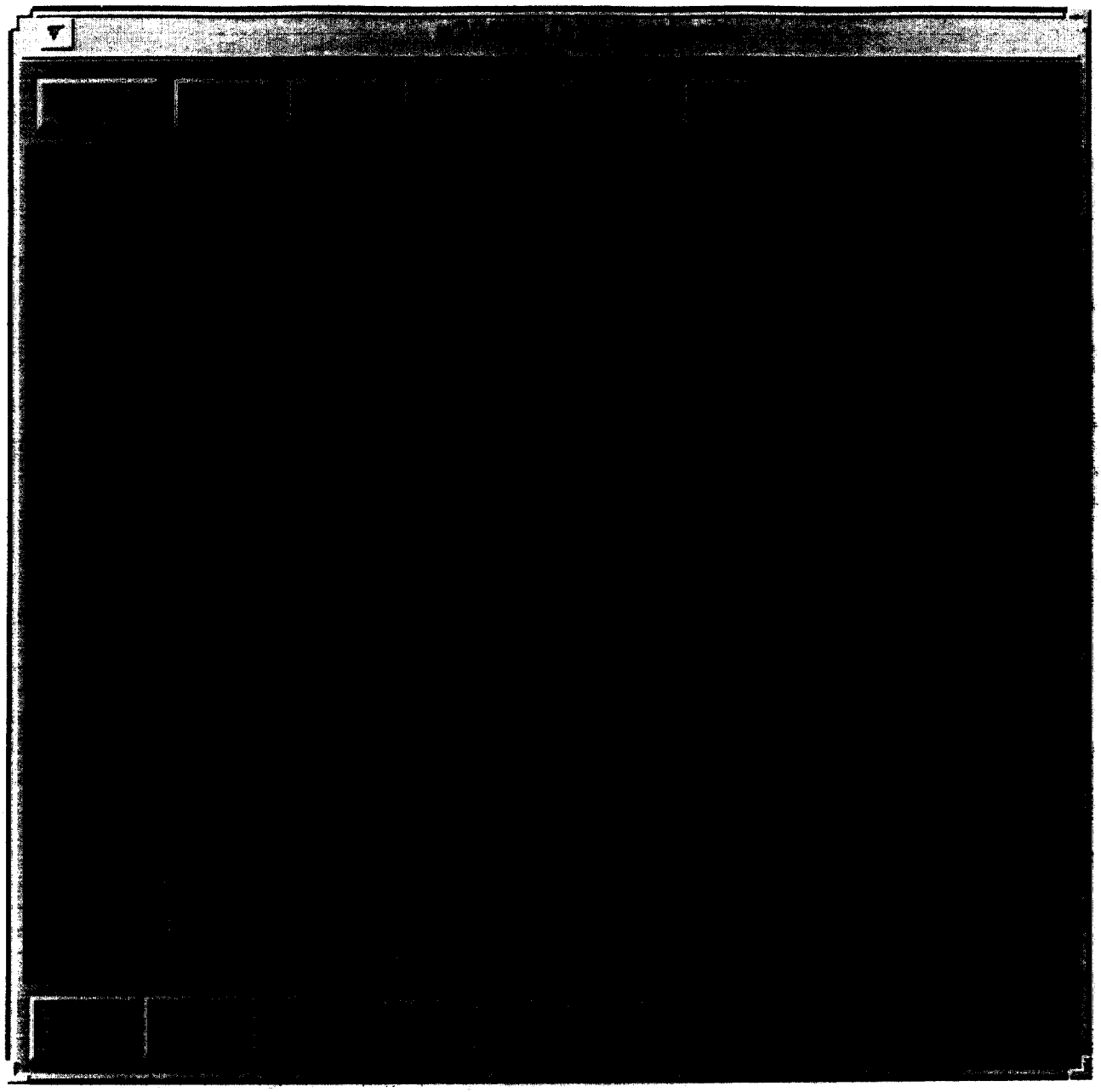

Figure 7. Stack Plot Display

The Stack plot lines form a parallelogram on the screen — the shape of this parallelogram can be manipulated to form the desired display. This is described in Section 5.11, Zooming. Also, each individual line can overlap with the lines above and below it (depending on the scale factors applied by the user). Whitewashing allows hidden line removal.

59

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The Stack has one horizontal axis drawn in (following the tilt of the parallelogram, not directly under the bottom plot).

To aid the user in figuring out which line is which, annotation is placed on each new *x* line.

5.7 Spectral Grid

The spectral Grid is used to present CSI data. It has the following features:

- A zoom region can be extracted in two dimensions, so you can display any rectangular subregion.
- The individual plots are shaped proportionally with the voxels that they represent, in the same manner as an Image display.

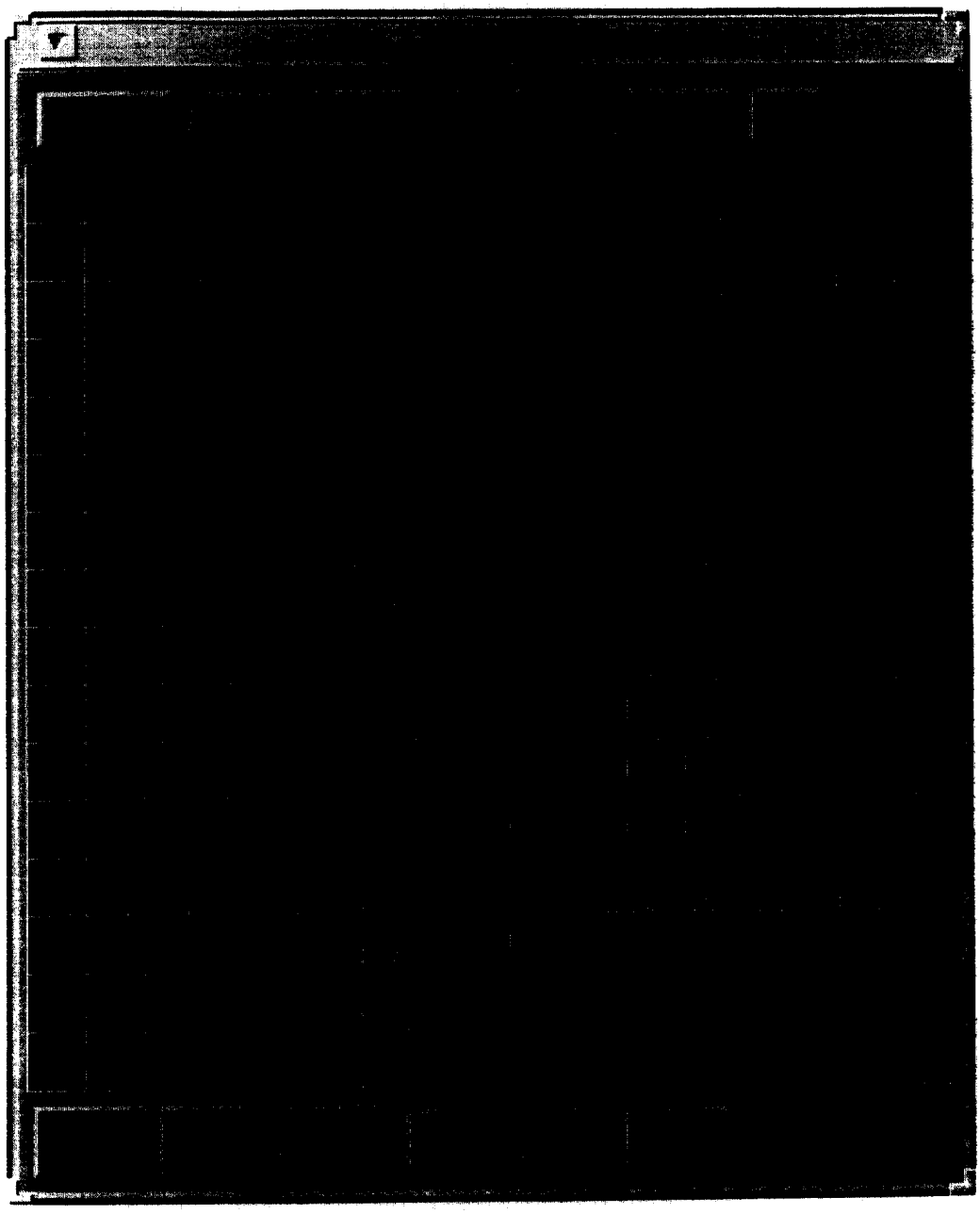

Figure 8. Spectral Grid Display

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5.8 Data Description

Rather than attempt to annotate all the multiple displays of a data set, a special "annotation only" display is used. By opening a Description display, the user can determine basic information about the data set that is being shown on the screen. This display will also print with the other displays.

5.9 Composite Displays

Three composite displays are available — these show two or more data sets simultaneously.

The first is Overlay Spectrum which pops up a panel where any other spectrum data can be overlayed on the Active data set spectrum. The Active data set spectrum display determines the X and Y scale values for the overlay window.

The second is known as a Spectrum+RefSpectrum display, and plots the spectrum of the Reference data set, then overlays the spectrum from the Active data set on top. The plot scaling is determined by the Reference spectrum.

The third composite display, the Grid+RefImage display, shows the image of the Reference data set with a grid of spectra from the Active data set superimposed. The spectra are spatially registered with the image.

Figure 9. Grid plus Reference Image Display
Example of Composite Display

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5.10 Scaling of Displays

Scaling refers to the vertical plot limits used for line plot displays, and the window/level settings applied to images. SAGE uses a single set of numbers for both purposes, to maintain the approach that all displays should be consistent.

SAGE scaling has a number of different operating modes, to support the following scenarios:

- You wish to display the current zoom range using the full dynamic range of the display. To do this, set scaling into Local mode.
- You wish to display the current zoom range relative to the range of the entire data set. To do this, set scaling into Global mode.
- You wish to magnify a section of a plot. Change the user scaling factors.
- You wish to set the plot limits to be the same as a Reference data set. Change the user scaling factors using the Set Relative to Reference method.

The choice between local and global scaling can be set on the Display Parameters panel. The user scaling factors are set on the Scale/Offset panel, and are particular to each data set.

5.10.1 User Scaling Values

To change the appearance of the SAGE displays, the user can enter two values, scale and offset. Scale and offset can be specified in many ways; the interpretation chosen for SAGE is that the plot range is scale times bigger than the data range, and the center of the plot vertical axis is offset times the data range above the horizontal axis. To plot the full dynamic range of the data requires scale=1.0, and offset=0.5. Increasing the displayed size of the data on the screen (for example, to expand small peaks) requires that scale be made smaller. Moving the data up on the screen requires that offset be made smaller.

5.10.2 Setting the User Scaling Values

Several methods are provided to set the scale and offset.

Firstly, graphical methods allow interactive setting of the scales:

- Window/Level widget. This widget provides a means of interactively varying the scale and offset while observing an image. For speed, the interactive operation is actually applied to the colormap, then applied to scale and offset when the operation is complete.
- Picking off a Spectrum display. Horizontal bars placed on a Spectrum are positioned at the desired minimum/maximum positions. The bars are moved using the same interaction methods that drive the vertical bars used for picking zoom regions (see Section 5.11, Zooming).
- Buttons to expand/contract a plot by a factor of two. The scale and offset are adjusted so that the minimum value on the axis remains constant.

Next, exact methods are provided to allow comparison of data sets:

- Type in values of scale and offset.
- Set scale and offset equal to a Reference set.
- Set scale and offset so that minimum and maximum are the same as a Reference data.

The final method strictly works only for point by point displays, since it does comparisons using the global range rather than the projected ranged required for Spectrum and Image displays. However, given the rules for summing displays, this method will also work for display of non–CSI Spectra and non–CSI Images, where the projections only sum a single point. This method will also fail if Local scaling is in use, since the data ranges of the Reference data set are known only for Global mode. In Local mode, no record is available of what the plot range for the Reference is.

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5.11 Zooming and Graphical Manipulations

Zooming refers to selection of a subregion in one or more dimensions of a data set. In SAGE, multiple displays of a single data set are possible, but the same zoom settings are used for all displays. Zoom values are retained for all dimensions.

Zooms are selected graphically by using the mouse on displays, or by explicitly typing in values. The interaction method is consistent for all the types of zooming.

5.11.1 Graphically Selecting a Zoom Region

Normally, a display of the the Active data is used to adjust the zoom values of that data set. However, if the Reference data set is in use, then the zoom cursor will appear on the Reference display instead. In the following section, keep in mind that the cursor may not appear directly on the display being zoomed.

Depending on the axis to be zoomed, the data must be be displayed in different ways. To adjust the spectral axis, a Spectrum plot is required. To adjust the first and second spatial axes, an Image is required. If the data is not correctly displayed, the zoom operation ends with an error.

Once a method is selected, the zoom cursor appears on the appropriate plot of the data (Active or Reference). The position of the zoom cursor will represent the current zoom values of the data set. The user can then move the range (by dragging middle), or select a new range (by dragging left). The form of the zoom cursor will depend on the axis which is to be zoomed. For a spectrum, a pair of vertical bars is used. For an image, a box is used.

The positions of the cursor on the display are constrained to legal positions corresponding to the data. For example, if the Reference image is a normal image, and the Active data is a CSI image with low resolution, then the corners of the box are only allowed to move so that the box wholly encloses pixels from the CSI image. This requires the zooming routine to calculate all the legal positions and pass them to the cursor drawing routine.

Once a cursor position is established (multiple moves or redraws are allowed), the right mouse button initiates the zoom action. A menu is displayed, allowing the user to choose "`Cancel`", i.e. ignore the just requested value; "`Zoom; Quit`", i.e. apply the requested values and continue operations; or "`Zoom; Zoom again`", i.e. apply the requested values then enter the zoom cycle over again.

If a Reference data set is being used, or if multiple displays of the Active data are present, then the display being used graphically to display the zoom region does not update until the user quits the zooming interactions. The Active data set can be displayed in any way desired, then regions interactively selected on a Reference. The final rule allows a data set to be used as its own Reference. By not updating the display being used graphically to display the zoom region, the region can be moved around easily.

5.11.2 Typing in a Zoom Region

The Zoom panel provides type–in access to the data set. The values on the panel will be set to the current Active data zoom limits when the Reset button is clicked. This panel presents its parameters in *scale* units.

43

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5.11.3 Moving to a New Slice

The zoom value in the third spatial dimension cannot be set graphically. Use the Next Slice, Previous Slice buttons on the Zoom menu.

5.11.4 Copying Zoom Values

The simplest way to copy zoom values from a Reference data set to the Active data set is to choose the appropriate graphical zooming method, then move the cursors to their limits on the display. If the Active data set currently has a larger zoom region set than the Reference, the cursors will begin at the edges, and you can simply use the right button menu to tell SAGE to apply the initially selected region.

The Zoom panel can also be used for this task as follows. The Zoom panel cannot be dismissed or closed in the middle of this operation, but must must be kept open:

- Choose the data set from which you wish to copy zooms and set it as the Active data set.
- Click Reset on the Zoom panel to set the current zoom values into the panel.
- Choose the new data set as the Active data set.
- Click the "Zoom" button on the Zoom panel.

5.11.5 Using Two Zoom Regions

Two zoom settings are recorded in the data header. The current and previous zoom values can be exchanged, allowing you to toggle between two views of the data.

5.12 Other Graphical Manipulations

The shape of the base parallelogram that supports a Stack plot can be altered graphically. A shaped cursor is used — you can grab any corner and drag it to a new position. All subsequent stacks will use the same support.

Various operations, such as baseline correction, allow you to graphically pick points off a display. A cross–hair cursor is used for this work. By clicking left, you can register its position. If a particular number of clicks is required, the cursor will disappear after they have all been performed, otherwise it can be dismissed by clicking right.

5.13 The SAGE Colormap

The default SAGE colormap is optimized for the display of greyscale images on 8–bit hardware. A total colormap of 192 entries is used, allocated as follows:

- 128 level greyscale.
- 16 level red, blue, and green scales for display of color images.
- 8 item rainbow for use as highlights and cursors. The colors in this rainbow are, in order, black, blue, green, cyan, red, violet, yellow, and white.
- 8 item greyscale for use as highlights and cursors.

The 128 element greyscale and the color scales window and level together. The greyscale is gamma corrected.

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6 Processing Operations

The following processing options are available:

- Convolution Filter. Applies a convolution filter to the data.
- Spectral Apodize. Multiplies the spectral dimension of a data set by an apodization function.
- Spatial Apodize. Multiplies the spatial dimension(s) of a data set by a Fermi window.
- Unchop. Converts OPNEX=1 or chopped data to an unchopped format.
- Zerofill. Places zeros before and/or after the data in any dimension of a data set.
- Fourier Transform. Transforms any dimensions of a data set to their conjugate domains, while simultaneously applying phase corrections to position and phase.
- Baseline Correct. Corrects baseline for offset and roll.
- Phase. Phase corrects a spectrum or a CSI data set by the application of zero and first order phase. Zero order phase can be done manually or calculated automatically. First order phase must be done manually.
- Spectral Offset/Peak Registration. Spectral Offset offsets the spectral dimension of a data set. Peak Registration independently peak aligns each voxel spectra in a CSI data set.
- Flip, Shift, Transpose. Flips a data set about any dimension, shifts a data set along any dimension, or swaps any two dimensions of a data set.
- Integrate. Integrates the spectral dimension of a data set.
- Math. Adds, subtracts, multiplies or divides the Active data set with the Reference data set and/or constants.
- Replicate. Replicates a data set any integer number of times along any axes.
- Extract Display Channel. Extracts the displayed channel (Real, Imaginary, Magnitude, Power, Phase or Unwrapped Phase) of the Active data set. A complex data set becomes real–only data consisting of the desired channel data.
- Extract Zoom Region. Extracts the data points in the zoom region and deletes the remaining data from the data set.
- Average Lines. Averages all lines in the spectral dimension of a data set over all the other dimensions. It is the sum of all spectral lines of the data set divided by the total number of spectral lines. The resulting data set is always 1D.
- Manual FID Generate. Creates signals consisting of a number of decaying sinusoids based on input by the user.
- Peak Table FID Generate. Creates signals consisting of a number of decaying sinusoids based on a peak table (see "Create Peak Table" in the following section).
- HSVD FID Generate. Creates signals consisting of a number of decaying sinusoids based on the table generated by HSVD Fit (see "HSVD Fit" in the following section).

The following figure shows the Spectral Apodization Panel as an example of Processing panels.

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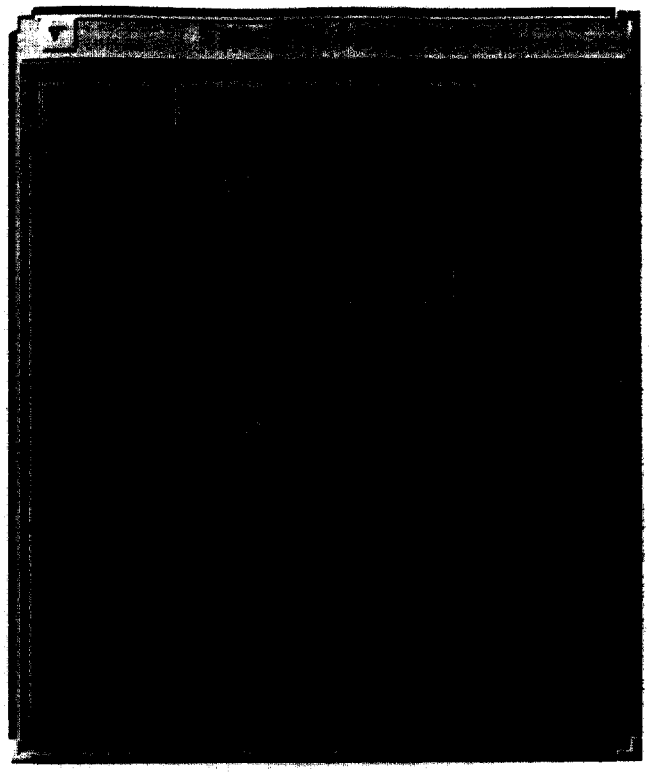

Figure 10. Spectral Apodization Panel
Example of Processing Panel

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7 Analysis Operations

The following analysis options are available:

- Create Peak Table. Determines and stores information about the peaks in a spectrum or CSI data set. Information provided is amplitude, frequency, width, phase and area of each peak.
- Analyze Spectrum. Provides simple information about an interactively selected region of a Spectrum plot. Information provided is the position of the two cursors, width between cursors, value of data at each cursor and the average, standard deviation and Integral of the data between the cursors.
- Analyze Image. Provides simple information about an interactively selected region of an Image plot. Information provided is the upper left and lower right positions of the selected region, and the area, average and standard deviation of the data within the region.
- Frequency Domain Fit. Performs a sequence of fitting algorithms with various parameters specified as either constrained or free. The fitting sequence is based on control statements in a user–created file that can be optimized for any particular need.
- Marquardt Fit. Performs a Marquardt–Levenberg non–linear least squares minimization algorithm on the information in a Peak Table.
- HSVD Fit. Performs a Hankel prediction with singular value decomposition on a time domain data set.

The following figure shows the Spectrum Analysis Panel as an example of Analysis panels. The spectrum that it is analyzing is shown in the figure after the panel.

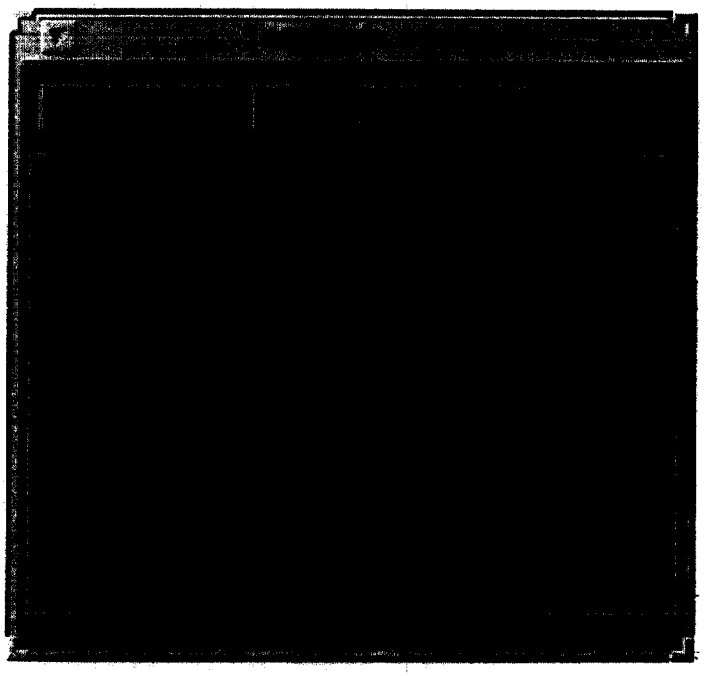

Figure 11. Spectrum Analysis Panel
Example of Analysis Panel
(The corresponding data display is Figure 12)

C7

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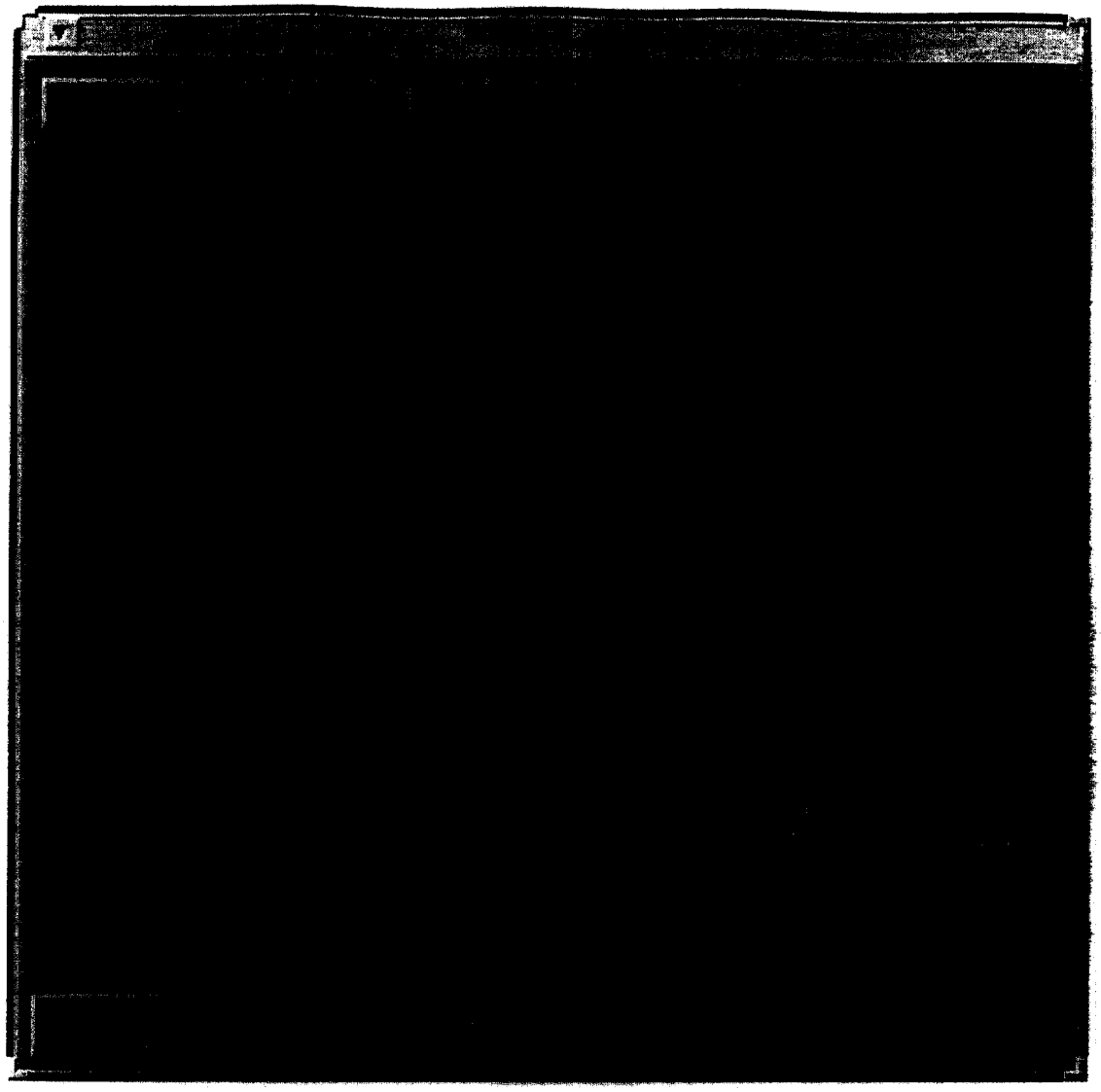

Figure 12. Spectrum Display showing Spectrum Analysis cursors
(Goes with Figure 11)

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8 Recon Operations

In SAGE, we use the term "Recon" for panels that combine the most common processing options on one panel for a particular data set type. The following Recons are available:

- Spectrum. Provides spectral apodization, fourier transform and zerofill operations.
- Image. Provides spatial apodization, fourier transform and zerofill operations.
- CSI. Provides unchop (if needed), spectral apodization, spatial apodization, zerofill, fourier transform, baseline correction, zero–order autophase, peak registration and orientation operations.
- PROBE. Provides internal water referencing, convolution filtering, spectral apodization, zerofilling and fourier transform operations on the average of the suppressed frames.
- PROBE–Q. Provides internal water referencing, spectral apodization, convolution filtering, zerofilling and fourier transform operations separately on each of the suppressed frames.
- PROBE Quant. Provides internal water referencing, water subtraction, fixed deapodization, baseline correction, noise estimation, Marquardt fitting, spectral apodization, convolution filtering, zerofilling and fourier transform operations on the average of the suppressed frames.

The following shows the PROBE Quant Panel as an example of Recon panels.

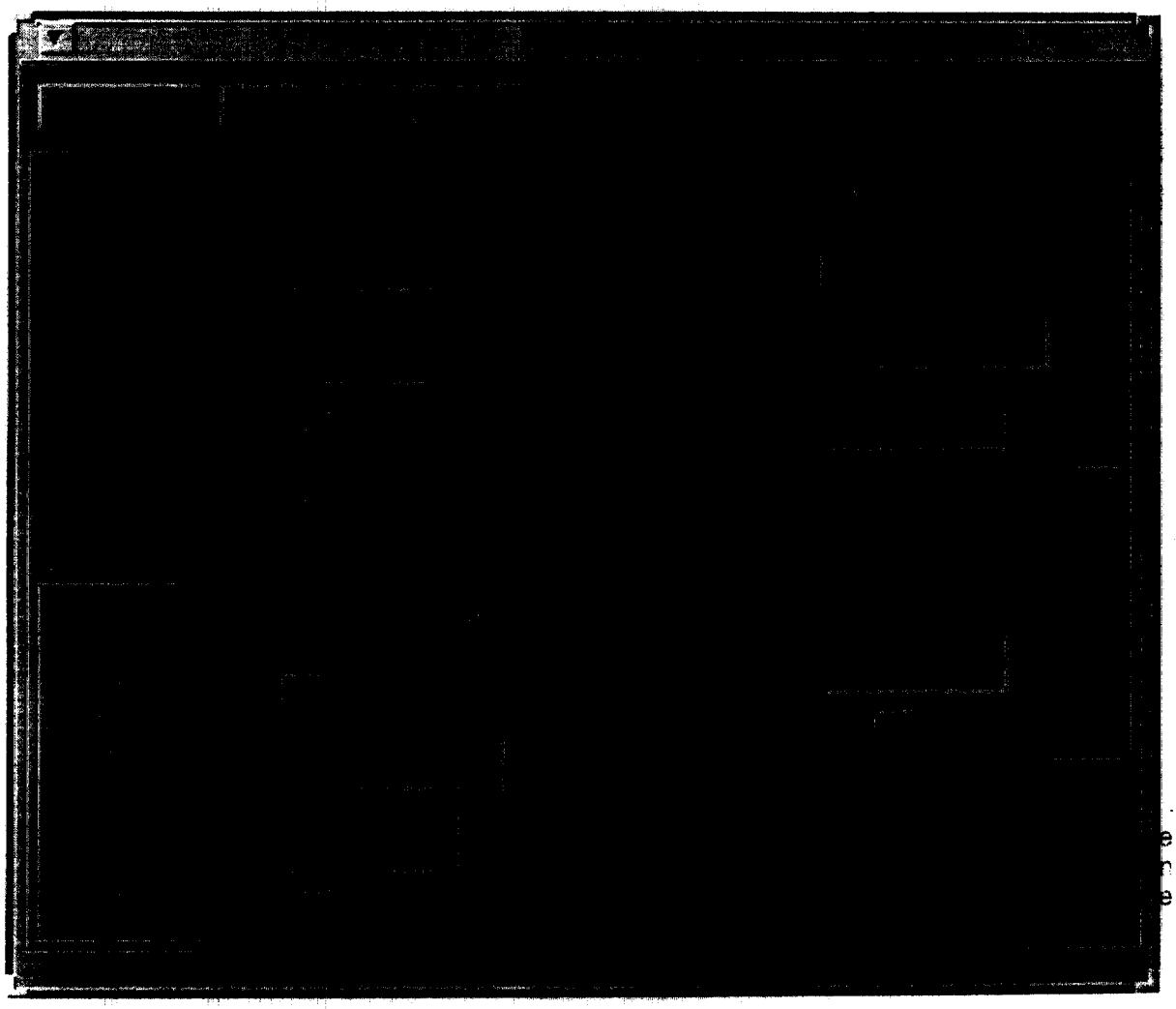

Figure 13. PROBE Quant Panel
Example of Recon Panel

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9 Macro Operations: Customizing and Extending SAGE

One of the major features of SAGE is the extensive customization abilities it gives the user. There are a number of mechanisms available for this work:

- Values for all static processing parameters can be saved and restored from files. Individual parameters can be set at startup or in macros.
- Quick Macros allow the recording of a set of GUI operations and later play back of them on a different data set.

9.1 Parameter Files

A parameter file is an IDL save format file that contains saved values of all processing parameters. By loading this file in an environment that declares all the parameter common blocks, the saved values can be restored.

9.2 Quick Macros

SAGE has a built in Macro Recorder/Player. The user can record a sequence of operations, store the sequence as a special macro file, and then play back the sequence.

Quick macros provide a mechanism for writing simple macros by operating the GUI widgets. These macros do not provide much flexibility, as you cannot access the full scripting capability of IDL.

Quick macros are a record of the *functions* called, but not of the *parameters* that those functions were called with. The parameters to the macro are provided at run time by using the current values of the static parameters, i.e. by grabbing values from the GUI panels. This allows you to repeatedly run a macro, altering arguments to functions by changing values on the appropriate GUI panels.

A quick macro can also be run using a saved parameter file. If this option is chosen, the saved parameters will be loaded for the duration of the macro run, thus ignoring the parameters currently on the GUI panels. You can automatically save a parameter file at the conclusion of a macro recording; the saved file will have the same root name as the macro file, and reside in the same directory.

The following shows the Quick Macros Panel which is the Macro recorder/player.

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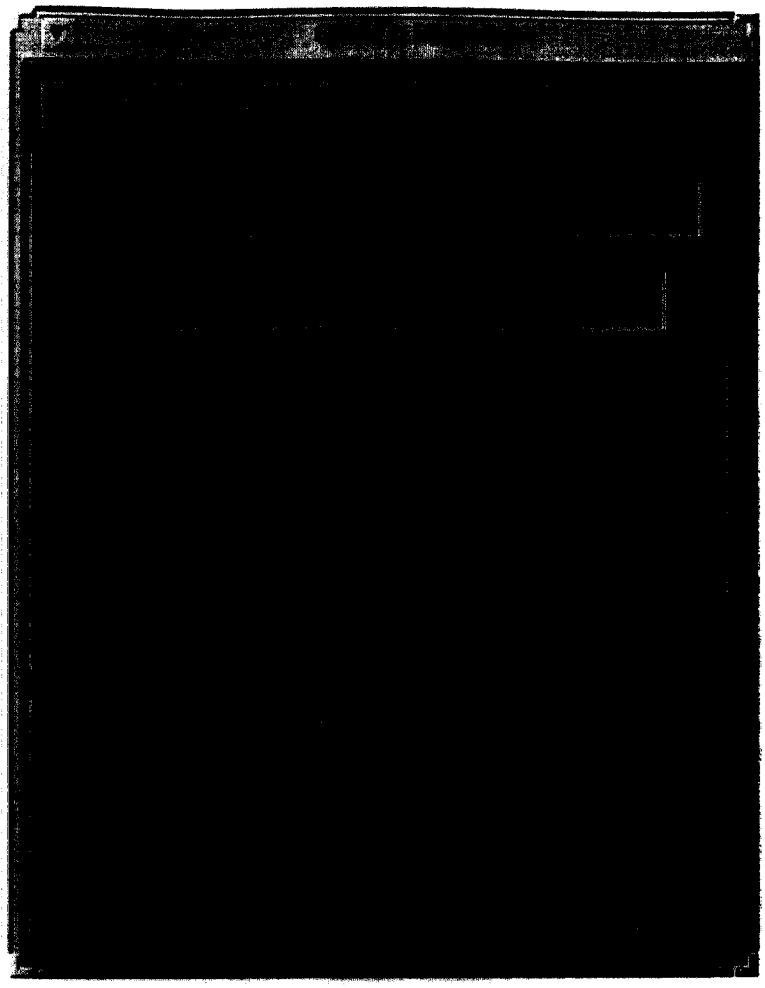

Figure 14. Quick Macros Panel

9.2.1 Recording a Quick Macro from the GUI

The GUI event handling functions are responsible for writing an appropriate line to the macro file whenever an event that should be included in a macro occurs. Typically, only the final action event (e.g. apodize, FFT, etc.) is recorded. Changes of parameters, etc., are not recorded. At the moment, events that launch interactive operations such as zooming are not recorded, nor are operations that load and save data, table, or parameter files.

9.2.2 Running a Quick Macro

SAGE reads and executes the macro file one line at a time. If the Use Saved Params option is set to Yes, SAGE will look for and load a parameter file with the same root file name as the macro. The current parameter values are saved in a temporary file, and restored after the macro has run.

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10 Frequency Domain Fitting

10.1 Introduction

This chapter describes the frequency domain fitting software developed for SAGE. First we describe the basic problem. Next, we set up a framework for gaining more control over the fitting process, to allow incorporation of *a priori* information. Then we describe in detail how all calculations are performed. Next, a suggestion for methods of user interaction is given. And finally we show an example of a Fit Control File.

10.2 Background

The frequency domain fitting of spectra involves the determination of the parameters of model functions that, in some sense, fit the Fourier transformed signal with the best accuracy. The fit metric, the model functions, and the method of determining parameters, are all choices the implementer must make. Other fitting methods exist, and nothing in this report is meant to imply that frequency domain methods are the answer to all problems. These include time–domain methods (fitting model functions to the FID, application of ARMA models, LP methods, etc.), model–spectrum fitting (using solution spectra rather than parametric models), and so on.

10.2.1 The Fit Metric

The simplest, and by far the most common, measurement of the goodness of fit is the X^2 statistic. Given a set of data $y_1,\ldots, y_N$, and a model function y with parameters $a_1,\ldots, a_k$, evaluated at test points $x_1,\ldots, x_N$, the goodness of fit is simply:

$$X^2 = \sum (y_i - y(x_i\ ;\ a))^2$$

assuming that the data points all have equal variance.

10.2.2 The Fitting Algorithms

To improve the fit, an algorithm is required to vary the parameters in an attempt to reduce X^2. Once again, there a semi–infinite number of choices for this task. The major problem is that X^2 is non–linear in many of the parameters, and so a direct least–squares solution is not possible.

Three algorithms will be employed in the iterative fitting process:

- For optimization of arbitrary sets of parameters, we will employ the industry standard non–linear parameter optimizer, the Marquardt–Levenberg algorithm. This technique takes steps in the parameter space in a direction indicated by the derivatives of X^2 with respect to the parameters. The length of the steps is determined by the second derivative, or Hessian, matrix. If a step succeeds, Marquardt–Levenberg assumes that the Hessian must be good, and increases its "trust" in that matrix. If a step fails, this indicates that the Hessian is probably wrong, and so it decreases its trust. As multiple steps fail, the method eventually falls back to steepest descent with a small step size. As multiple step succeed, the method becomes quadratic in its convergence.

  The main problem observed with Marquardt in practice is that it tends to get "over–enthusiastic" about perceived improvements in the fit, and take off in wild directions. This is particularly true when many parameters are available. To counter this tendency, we have reduced the "increase in trust" factor below that commonly used. We will also, by appropriate modeling, substantially reduce the number of free variables that Marquardt has to play with. Nonetheless, a case can certainly be made for more conservative descent strategies, such as the simplex methods.

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Marquardt also fails to take advantage of the ability to solve exactly for the linear parameters (in our case, the amplitudes and phases). This can be remedied by appropriate modification—let the non–linear parameters be optimized via the iterative method, but perform the exact linear solution at each step. More on this below.

- For optimization of the linear parameters, we employ complex singular value decomposition to solve the linear least–squares problem.
- For frequency optimization, we employ the discrete Convolution method.

10.2.3 The Model Functions

For this work, we will restrict the model functions to be either complex Lorentzian lines or real Gaussian lines. To lift the Gaussian phase restriction, we need analytic forms of both the real (absorption) and imaginary (dispersion) mode components — at present we do not have a closed form expression for the imaginary component of a Gaussian line.

The fitting algorithm will be able to consider the complex data, or the real or imaginary parts only, or the power or magnitude data.

Some preliminary math. The FT transform of a one–sided exponential decay is:

$$exp(-t)\ H(t) \Rightarrow \sum (1 - 2j\pi s)\ /\ (1 + (2\pi s)^2)$$

where $H(t)$ is a step function. For NMR spectroscopists, linewidth is measured as FWHM, and so a line of width w Hz, amplitude A, frequency f, and phase θ will be described by:

$$s(t) = A\ exp(j\theta)\ exp(j2\pi ft)\ exp(-\pi wt)\ H(t)$$

Applying the scaling and shift theorems, the exponential decay transforms to a peak

$$S(s) = (A/(\pi w))\ exp(j\theta)\ (1 - j2F)/(1 + 4F^2)$$

where

$$F = (s - f)\ /\ w$$

is the normalized frequency.

From this point on, we drop the πw term in the amplitude, and reintroduce it in the area calculation once the fit has been performed. That is, we will work with peaks of the form:

$$S(s) = A\ exp(j\theta)\ (1 - j2F)/(1 + 4F^2)$$

[illegible]

[illegible] amplitude and real [illegible] to baseline [illegible]

[illegible] free

73

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10.2.4 The Spectrum

A "Spectrum" is a collection of peaks, grouped into "Moieties". Each Moiety is a collection of "Lines", for example, the component peaks of a triplet. There are sets of parameters that apply to individual Lines, to Moieties, and to the Spectrum as a whole. By carefully selecting which components to vary, fitting algorithms can be made much more robust.

The parameters presented immediately below are further explained by proceeding equations.

The lowest level parameters, those that apply to each Line, are:

1. The Line frequency f_l in Hertz. If a Line is part of a multi–Line Moiety, this value serves as the frequency relative to the Moiety frequency.
2. The Line width w_l in Hertz. As for frequency, this value serves as relative width in a multi–Line Moiety. If all Lines are the same width, set this value to 0.
3. The Line amplitude ratio a_l. If a Line is part of a multi–Line Moiety, this value serves as the relative amplitude ratio to other lines in the Moiety.
4. The Line phase θ_l in degrees. This value will almost always be used for including known phase distortions due to mixing times, multiple quantum effects, etc., that affect just this Line relative to other Lines in the same Moiety. Other mechanisms, described below, allow inclusion of the effects of acquisition delays.

At the next level up, the Moiety parameters are:

1. The number of Lines in the Moiety.
2. The Moiety frequency f_m in Hertz, relative to the Spectrum center frequency, which is applied as an additive factor to the Line frequencies.
3. The Moiety width w_m in Hertz also applied as an additive factor.
4. The Moiety amplitude ratio a_m, an amplitude ratio relative to the other Moieties which is applied as a multiplicative factor to all Lines in the Moiety.
5. The Moiety phase θ_m in degrees, also applied as an additive factor.

A Moiety may have 0 lines, in which case the f_m, w_m, a_m, and θ_m are used directly to generate a single line. This reduces the number of parameters in such cases, since no line parameters are required.

Finally, the Global parameters are:

1. The number of Moieties in the Spectrum.
2. The Global frequency shift f_g in Hertz. This is applied as an additive frequency shift. If many Moieties are known to have fixed relative frequencies, then this single parameter may be used to optimize all peaks concurrently without having many free variables.
3. The Global width w_g in Hertz, applied as an additive factor.
4. The Global zero order phase $\theta_{g,0}$ in degrees. For a spin echo spectrum with no J–modulation, this is the only phase parameter required to be free.
5. The Global first order phase $\theta_{g,1}$ in degrees, due to delay in acquisition relative to the coherence point.
6. The currently applied zero and first order phase correction ϕ_0 and ϕ_1 in degrees. These parameters are intended to provide information to the lineshape generator about any correction that has been applied prior to fitting. As explained below, this phase correction is not the same as that provided by the two previous fields.
7. A constant offset. Such offsets arise from many sources, including use of certain digital filters. Failure to include them in a model can seriously distort the fitting algorithm.
8. The channel to fit. You can choose to work with the complex data directly, or to extract real, imaginary, magnitude, or power channels on which the fit should be carried out.

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Clearly, in many cases there are redundant parameters in this description of the spectrum. This results in some performance degradation of the fitting algorithms as they calculate many unnecessary derivatives. However, by carefully controlling which parameters are free to vary, the number of parameters in the fit can be drastically reduced over conventional fitting routines. For example, the a priori knowledge that the relative positions of the peaks are fixed allows the algorithm to optimize a single Global frequency shift, rather than separate frequency parameters for all peaks. On the other hand, if one peak has a variable position (e.g. Pi), then that individual parameter can be set free to vary, without automatically freeing all other frequency variables.

10.2.5 Collating Parameters, and Calculating the Spectrum

To manufacture each individual peak in the Spectrum, the parameters from the Line, Moiety, and Global levels must be collated to form a set of "Component" parameters. The signal for that Component, and its derivatives with respect to the parameters are calculated. The signal is added to the Spectrum, and the chain rule is used to calculate the derivatives of the spectrum with respect to the Line, Moiety, and Global parameters.

The Component frequency is the sum of the Global, Moiety, and Line frequencies,

$$f_c = f_g + f_m + f_l$$

the Component width is the sum of the Global, Moiety, and Line widths,

$$w_c = w_g + w_m + w_l$$

the Component amplitude is given by the product of the Line and Moiety amplitudes,

$$a_c = a_m a_l$$

and the Component phase the the sum of the Global, Moiety, and Line phases, plus an additional frequency dependent effect due to first order phase,

$$\theta_c = \theta_{g,0} + f_c\theta_{g,1} + \theta_m + \theta_l$$

As noted earlier, a Moiety may have 0 lines. In this special case, the line parameters are deleted from these equations.

For each Line in the spectrum, then, we can calculate the effect on the signal S and all its derivatives. The Component signal is simply added to the spectrum, as it accumulates Component by Component,

$$S = S + S_c$$

The derivatives of the signal with respect to the Line parameters are:

$$\partial S/\partial f_l = \partial S_c/\partial f_c + \theta_{g,1}(\partial S_c/\partial \theta_c)$$

$$\partial S/\partial w_l = \partial S_c/\partial w_c$$

$$\partial S/\partial a_l = a_m(\partial S_c/\partial a_c)$$

$$\partial S/\partial \theta_l = \partial S_c/\partial \theta_c$$

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The derivatives of the signal with respect to the Moiety parameters are:

$$\partial S/\partial f_m \ += \ \partial S_c/\partial f_c \ + \ \theta_{g,1}(\partial S_c/\partial \theta_c)$$

$$\partial S/\partial w_m \ += \ \partial S_c/\partial w_c$$

$$\partial S/\partial a_m \ += \ a_c(\partial S_c/\partial a_c)$$

$$\partial S/\partial \theta_m \ += \ \partial S_c/\partial \theta_c$$

where the notation "+ =" denotes a running sum over all the Lines in the Moiety.

Finally, the derivatives with respect to the Global parameters are:

$$\partial S/\partial f_g \ += \ \partial S_c/\partial f_c \ + \ \theta_{g,1}(\partial S_c/\partial \theta_c)$$

$$\partial S/\partial w_g \ += \ \partial S_c/\partial w_c$$

$$\partial S/\partial \theta_{g,0} \ += \ \partial S_c/\partial \theta_c$$

$$\partial S/\partial \theta_{g,1} \ += \ f_c(\partial S_c/\partial \theta_c)$$

10.2.6 Modifications to the Spectrum

A number of additional transformations may be performed on the spectrum before it is finally compared with the data. In this section, we track the changes that need to be made to the signal and the various derivatives as these changes are made.

1. Phase Correction

   If zero– and first–order phase correction has been applied to the data, the signal becomes

   $$T(s) \ = \ exp(\phi_0 - \phi_1) \ S(s)$$

   and the derivatives become

   $$\partial T/\partial a \ = \ exp(\phi_0 - \phi_1) \ \partial S/\partial a$$

2. Channel Extraction

   If the real or imaginary channel are specified, then that channel can be extracted from the signal and all derivatives.

   If magnitude is required, then take the magnitude of the signal,

   $$M(s) \ = \ \sqrt{\| S(s) \|^2}$$

   and calculate the new derivatives via

   $$\partial M/\partial a \ = \ (1/(2M)) \ (2 \ Re(S) \ Re(\partial S/\partial a) \ + \ 2 \ Im(S) \ Im(\partial S/\partial a))$$

   For a power spectrum, extract the power of the signal

74

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$$P(s) = \| S(s) \|^2$$

and calculate the new derivatives via

$$\partial P/\partial a = 2\ Re(S)\ Re(\partial S/\partial a) + 2\ Im(S)\ Im(\partial S/\partial a)$$

10.3 Changing a Parameter

The following sequence of steps is required to generate a new trial set of parameters:

1. At the current location, calculate the gradient and curvature matrices required by the Marquardt algorithm. For ease of coding, we will calculate all derivatives, and then extract the those corresponding to the free non–linear parameters.
2. Make a step in the non–linear parameters.
3. Calculate the least–squares solution for the free linear parameters at the new location.
4. Evaluate X^2 at the new location. If it is better, then accept this new location, and increase confidence in the curvature matrix. If it is worse, then reduce the confidence, and try again.

There are no linear parameters for the magnitude and power spectrum cases. For real or imaginary channel, the amplitudes of the Moieties are the linear variables.

For complex fitting, the complex amplitudes of the Moieties are the linear variables. However, we may wish to constrain the phase variation to be zero and first order, rather than on a peak by peak basis. This is accomplished via the following rules:

1. If the individual moiety phases are specified as linear variables, then the complex amplitude will be directly used to calculate the line phases.
2. If the global zero and first order phases are specified as linear variables, then:
   (a) Assume that any extra first order phase correction is small, less that 2π across the spectrum.
   (b) Find the component with the largest magnitude, use this peak to determine a zero order phase correction. Subtract this phase out from all the moiety phases.
   (c) Fit a linear function to the phases, to determine the zero and first order corrections required.

It may be best in the long run to treat the global variables as "linear" variables in this fashion for the early stages of optimization, then allow them to be non–linearly optimized in later stages.

10.4 For Further Information

See the help file under "**File->Help->SAGE Help**", topic "**Analysis**", subtopic "**Frequency Domain Fitting**" for detailed information about the Fit Control File keywords and parameters. Sample Fit Control Files are supplied with each SAGE release and reside in the subdirectory **$GE_SAGE_DIR/sage_user/fit_control**. Sample data for the preceding sample Fit Control Files are supplied at:

- **$SAGE_DATABASE/SampleData/TestSuite/FreqFit/1/naa.**
- **$SAGE_DATABASE/SampleData/TestSuite/FreqFit/1/p31brain.**

10.5 Fit Control File Example

The following is an example of a Fit Control File. This is the file that controls the specifics of Frequency Domain Fitting.

```
# @(#) p31brain.ssf     Version 1.4
# Copyright (c) 1993 by General Electric Company.  All rights reserved.
```


77

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```
#
# Frequency Domain Fit control file for P31 Brain spectrum
# -------------------------------------------------------

# Set parameters used by all passes
# ---------------------------------
# Moiety #0 is the background, or baseline, signal.

# global parameters
global
0,  0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0
0,    0,   0,   0,   0,   0,   0,   0,   0,   0

# background signal
add_moiety
0, -138.0, 100.0, 1.0, 0.0, 0.0
0,      0,     0,   1,   0,   0

fit_range
-1000.0, 1000.0

fit_method
Marquardt

# First Pass
# ----------
# Use Marquardt fitting for baseline amplitude.

channel
Magnitude

marq_terminate
10.0, 5.0, 5.0, 0.0001

end_update

# Second Pass
# -----------
# Fit baseline frequency, width and amplitude.

change_moiety_free
0
0, 1, 1, 1, 0, 0

end_update

# Third Pass
# ----------
# Add global amplitude and real channel only to baseline fit.

change_global_free
0,   0,   0,   1,   0,   0,   0,   0,   0,   0

channel
Real
```


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78

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```
end_update

# Fourth Pass
# -----------
# Add all other components.
# Fit amplitudes.

channel
Real

# ATP gamma (Moiety #1 with 2 Lines)
add_moiety
2, 0.0,  15.0, 1.0, 0.0, 0.0
0,   0,     0,   1,   0,   0
# line 1
-7.5, 0.0, 1.0, 0.0, 0.0
   0,   0,   0,   0,   0
# line 2
7.5, 0.0, 1.0, 0.0, 0.0
  0,   0,   0,   0,   0

# ATP alpha (Moiety #2 with 2 Lines)
add_moiety
2, 133.0,  15.0, 1.0, 0.0, 0.0
0,     0,    0,   1,   0,   0
# line 1
-7.5, 0.0, 1.0, 0.0, 0.0
   0,   0,   0,   0,   0
# line 2
7.5, 0.0, 1.0, 0.0, 0.0
  0,   0,   0,   0,   0

# ATP beta (Moiety #3 with 3 Lines)
add_moiety
3, 362.0,  15.0, 1.0, 0.0, 0.0
0,     0,     0,   1,   0,   0
# line 1
-7.5, 0.0, 1.0, 0.0, 0.0
   0,   0,   0,   0,   0
# line 2
0.0, 0.0, 2.0, 0.0, 0.0
  0,   0,   0,   0,   0
# line 3
7.5, 0.0, 1.0, 0.0, 0.0
  0,   0,   0,   0,   0

# PCr (Moiety #4 with 0 Lines)
add_moiety
0, -69.0, 20.0, 1.0, 0.0, 0.0
0,     0,    0,   1,   0,   0

# PME (Moiety #5 with 0 Lines)
add_moiety
0, -146.0, 50.0, 1.0, 0.0, 0.0
0,      0,    0,   1,   0,   0
```


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```
# PDE (Moiety #6 with 0 Lines)
add_moiety
0, -244.0, 25.0, 1.0, 0.0, 0.0
0,      0,    0,   1,   0,   0

# Pi (Moiety #7 with 0 Lines)
add_moiety
0, -197.0, 15.0, 1.0, 0.0, 0.0
0,      0,    0,   1,   0,   0

# change background to protect width
change_moiety_free
0
0, 0, 0, 1, 0, 0

marq_terminate
20.0, 5.0, 0.2, 0.00001

end_update

# Fifth Pass
# ----------
# Fit global amplitude and phase, and tweak up individual
# frequencies, widths and amplitudes.

# global parameters
change_global_free
0,    0,   0,   1,   0,   0,   0,   1,   1,   0

# background signal
change_moiety_free
0
0, 1, 1, 1, 0, 0

# ATP gamma
change_moiety_free
1
0, 1, 1, 1, 0, 0

# ATP alpha
change_moiety_free
2
0, 1, 1, 1, 0, 0

# ATP gamma
change_moiety_free
3
0, 1, 1, 1, 0, 0

# PCr
change_moiety_free
4
0, 1, 1, 1, 0, 0

# PME
change_moiety_free
```


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```
5
0, 1, 1, 1, 0, 0

# PDE
change_moiety_free
6
0, 1, 1, 1, 0, 0

# Pi
change_moiety_free
7
0, 1, 1, 1, 0, 0

fit_range
-500.0, 500.0

end_update
```


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11 Tips and Hints

The following is aimed at answering the main questions that we received with the previous version of SAGE:

1. If you prefer a "flat" data file area, in other words a single directory rather than the SAGE default directory tree of `$SAGE_DATABASE/Site/Patient_ID/Study/Series`, then leave the default blanks in the `Site`, `Patient_ID`, `Study`, and `Series` entries of the Load/Save panel, edit the `Database` entry to the desired directory, then push the `File` button and the list of data files in that directory will be listed.
2. To save intermediate results, use "`File->Copy Data`", or see Item 3.
3. Use the main panel `Select...` button to choose the Active and Reference data sets and to set the Save options of No Save, Backup and Duplicate. The Save Duplicate mode will make a duplicate data set anytime a new display occurs.
4. Matching zoom regions between 2 or more data sets is explained in Section 5.11.4.
5. Matching scale and offset between 2 or more data sets is first done by using the main panel `Select...` button to choose a Reference data set, then using the "`Display -> Scale/Offset`" panel to select "`Adjust Scale/Offset -> Set Relative to Ref`".
6. CSI Orientation, or Reconstruction of SI Data with RAS Orientation

   Following the Fourier transformation of the raw data, correct for chop in OPNEX=1 studies by shifting the data by half its resolution in X, and then proceed with the following transpose and flip operations: (Note: these operations can be found under the "Processing" pull down menu as "Flip/Shift/Transpose...")

   For HD coil with default phase and frequency and for Body or Other coil with swapped phase and frequency:

   A. Presscsi, echocsi, steamcsi and shortecho

   Transpose X & Y
   Flip X

   B. Fidcsi and spinecho

   Transpose X & Y
   Flip Y

   For Body coil with default phase and frequency and for HD coil with swapped phase and frequency:

   A. Presscsi, echocsi, steamcsi and shortecho

   Flip X
   Flip Y

   B. Fidcsi and spinecho

   These are correct as collected.

82

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ATTACHMENT #4

Product Data Sheet (draft copy)

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SAGE 7 Spectroscopy Analysis Software

Application

The GE SAGE™ 7 Spectroscopy Analysis Software is designed to operate on GE Signa™ Horizon™ LX systems, GE Advantage Windows™ workstations (Version 1.2+), and any commercial workstations running IRIX (Version 6.2+) or Solaris (Version ??+) operating systems. It is available for Signa Horizon LX systems as part of the ProSpector™ MultiNuclear Spectroscopy option and the Peak Performance™ Spectroscopy Suite; and is also offered separately.

SAGE 7 is the latest version of GE's spectroscopic processing and display software. It provides a powerful toolkit of software applications to handle a wide variety of tasks associated with spectroscopy data management: including file handling, display, processing, analysis, storage and hardcopy output.

Although SAGE 7 has a graphical user interface for enhanced ease of use, this product has been designed for experienced or "power" users who require maximum flexibility in spectroscopy data processing with minimal automation or guidance. Familiarity with basic UNIX command syntax and file structures is required.

Description

- SAGE 7 fully integrates into standard GUI for Signa Horizon LX and Advantage Windows workstations for easy access and intuitive operation. Program access is available from the Image Display (exam browser) and GE Applications desktops on the Signa Horizon LX operator console; and from the exam browser on Advantage Windows workstations (all versions).
- When used on a Signa Horizon LX, all SAGE 7 functions are available anytime during all non-service operating modes with uncompromised full system simultaneity.
- SAGE 7 models a variety of data sets from Signa systems: local and remote raw "P" files, local and remote spectrum "G" files, local LX reconstructed images, and local SAGE data files.
- SAGE 7 models all data sets as 3D chemical shift imaging (CSI) data; that is, all data sets are assumed to be four-dimensional, with the first dimension representing time or frequency, and the remaining dimensions representing space or spatial frequency.
- Up to 32 data sets can be loaded into SAGE 7 at any one time. Only one data set at a time can be designated as "active", with all operations performed on and saved to the active data set.
- SAGE 7 provides the following file handling functions:
  - Load Signa data files
  - Load flat (i.e. no included header) data files
  - Load spectroscopy data sets from a remote Signa
  - Save processed data files
  - Load and save table files. Tables are used to store the results of Peak Find, Marquardt Fitting and HSVD Fitting
  - Load and save parameter files. Parameter files are mainly used with macros
- Hardcopy output is available in PostScript format that may be output to a printer or as a file. Both landscape and portrait orientations are available.
- SAGE 7 can display up to 4 data sets simultaneously with a mix of data sets possible. One data channel (real, imaginary, magnitude, phase or power) may be displayed, with each display of a multiple display set to the same channel. Displays are scaled by the same values, with the current zoom values in the first three dimensions applied to all displays.
- Display modes include:
  - Channel: Real, imaginary, magnitude, power, phase and phase unwrapped
  - Scale and Offset: Includes global or local scaling and grayscale scaling for images
  - Time Units: Seconds or points
  - Frequency Units: Parts per million (ppm), Hertz or points
  - Spatial Units: Millimeters or points
  - Zoom: Zoom from units, spectrum, image or reference; unzoom and previous zoom
- Display types include point-by-point, image, spectrum, stack plot and spectral grid. Displays may be scaled through a variety of methods Window/level control is available for image displays.
- A default SAGE colormap is available and is optimized for the display of grayscale images on 8-bit hardware. A total colormap of 192 entries is used as follows:
  - 128 level grayscale
  - 16 level red, blue, green scales for display of color images
  - 8 item rainbow for use as highlights and cursors. The colors in this rainbow are, in order, black, blue, green, cyan, red, violet, yellow, and white
  - 128 element grayscale and the color scales window and level together. The grayscale is gamma-corrected
- Spectral data processing features include:
  - Convolution Filter: Applies a convolution filter to the data
  - Spectral Apodize: Multiplies the spectral dimension of a data set by an apodization function
  - Spatial Apodize: Multiplies the spatial dimension(s) of a data set by a Fermi window
  - Unchop: Converts OPNEX=1 or chopped data to an unchopped format
  - Zerofill: Places zeros before and/or after the data in any dimension of a data set
  - Fourier Transform: Transforms any dimensions of a data set to their conjugate domains.

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84

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Tokyo, Japan - Fax: 81-3-3223-8560
Singapore - Fax: 65-291-7006

simultaneously applying phase corrections to position and phase
- Baseline Correct: Corrects baseline for offset and roll
- Phase: Phase corrects a spectrum or a CSI data set by the application of zero and first order phase. Zero order phase can be done manually or calculated automatically. First order phase must be done manually
- Spectral Offset/Peak Registration: Spectral offset offsets the spectral dimension of a data set. Peak registration independently peak aligns each voxel spectra in a CSI data set
- Flip, Shift, Transpose: Flips a data set about any dimension, shifts a data set along any dimension, or swaps any two dimensions of a data set
- Integrate: Integrates the spectral dimension of a data set
- Math: Adds, subtracts, multiplies or divides the active data set with the reference data set and/or constants
- Replicate: Replicates a data set any integer number of times along any axes
- Extract Display Channel: Extracts the displayed channel (real, imaginary, magnitude, power, phase or unwrapped phase) of the active data set. A complex data set becomes real-only data consisting of the desired channel data
- Extract Zoom Region: Extracts the data points in the zoom region and deletes the remaining data from the data set
- Average Lines: Averages all lines in the spectral dimension of a data set over all the other dimensions. It is the sum of all spectral lines of the data set divided by the total number of spectral lines. The resulting data set is always 1D
- Manual FID Generate: Creates signals consisting of a number of decaying sinusoids based on input by the user
- Peak Table FID Generate: Creates signals consisting of a number of decaying sinusoids based on a peak table
- HSVD FID Generate: Creates signals consisting of a number of decaying sinusoids based on the table generated by HSDV fit

- Analysis options include:
  - Create Peak Table: Determines and stores information about the peaks in a spectrum or CSI data set. Information provided is amplitude, frequency, width, phase and area of each peak
  - Analyze Spectrum: Provides simple information about an interactively selected region of a spectrum plot. Information provided is the position of the two cursors, width between cursors, value of data at each cursor and the average, standard deviation and Integral of the data between the cursors
  - Analyze Image: Provides simple information about an interactively selected region of an Image plot. Information provided is the upper left and lower right positions of the selected region, and the area, average and standard deviation of the data within the region
  - Frequency Domain Fit: Performs a sequence of fitting algorithms with various parameters specified as either constrained or free. The fitting sequence is based on control statements in a user-created file that can be optimized for any particular need
  - Marquardt Fit: Performs a Marquardt-Levenberg non-linear least squares minimization algorithm on the information in a peak table
  - HSVD Fit: Performs a Hankel prediction with singular value decomposition on a time domain data set

- Recon operations include:
  - Spectrum: Provides spectral apodization, Fourier transform and zerofill operations
  - Image: Provides spatial apodization, Fourier transform and zerofill operations
  - CSI: Provides unchop (if needed), spectral apodization, spatial apodization, zerofill, Fourier transform, baseline correction, zero-order autophase, peak registration and orientation operations
  - PROBE: Provides internal water referencing, convolution filtering, spectral apodization, zerofilling and Fourier transform operations on the average of the suppressed frames
  - PROBE-Q: Provides internal water referencing, spectral apodization, convolution filtering, zerofilling and Fourier transform operations separately on each of the suppressed frames
  - PROBE Quant: Provides internal water referencing, water subtraction, fixed deapodization, baseline correction, noise estimation, Marquardt fitting, spectral apodization, convolution filtering, zerofilling and Fourier transform operations on the average of the suppressed frames

- One of the main features of SAGE 7 is the extensive automation capability. Values for all static processing

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85

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parameters can be saved and resto4re from tiles. Individual parameters can be set at startup or in a set of macros.

- SAGE 7 has a built-in Macro Recorder/Player that allows the user to record a sequence of GUI operations, store the sequence as a special macro file and then play back the sequence.

Warranty

The published Company warranty in effect on the date of shipment shall apply. The Company reserves the right to make changes.

Regulatory Compliance

SAGE 7 is a CE-compliant device which satisfies regulations regarding Electro-Magnetic Compatibility (EMC) and Electro-Magnetic Interference (EMI), pursuant to IEC-601.

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ATTACHMENT #5

Predicate Device Literature

(from the MR Reclassification Federal Register Vol. 53, No.46, March 9, 1988)

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SIGNA MAGNETIC RESONANCE DIAGNOSTIC SYSTEM
System Specification

Characteristics

Nuclei	Sodium-23	Hydrogen-1	Phosphorus-31
RF coils	1 cylindrical-head	3 cylindrical-head, body, local(limbs) 3 flat circular-3", 5.5" spine, 5.5" general purpose 1 rectangular-spine 2 flat coplanar 20 cm xmit-7.5, 13.5 cm receive	2 flat coplanar 20 cm xmit-7.5, 13.5 cm receive
Localization Methods	Gradient-mediated frequency and phase encoding using: selective excitation, saturation, and physical localization		
Sampling Technique	Phase and frequency encoding in rectilinear and spiral geometries		
Acquisition Modes	1D, 2D (multislice and sequential), 3D and 4D		
Pulse Sequences	Imaging & Spectroscopy Spin Echo (SE) Inversion Recovery (IR) Saturation Recovery (SR) Gradient Recalled Echo (GR) Stimulated Echo (STE)	Spectroscopy Free Induction Decay (FID) Polarization Transfer Multiple Quantum Coherence Driven Equilibrium	
Reconstruction Techniques	Apodized (filtered) Fourier Transforms (FT) Projection Reconstruction		
Acquisition Matrix	32x32, 64x64, 128x128, 64x256, 96x256, 128x256, 192x256, 256x256, 256x512, 512x512		
Display Image Matrix	256x256 & 512x512		----
Spectra	----	256 to 2048 points	
Motion-Synchronized Acquisitions	ECG-Triggered Cardiac Gating Peripheral Cardiac Gating Respiratory Compensation		
Data Processing Techniques	Analog to digital signal conversion Anti-alias low pass filtering to reduce artifacts Signal averaging for multi-NEX acquisitions Fermi filtering to reduce quantization noise Baseline correction and scaling and clipping pixel values for renormalization Fourier transformation Pixel interpolation for display purposes		

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Safety Parameters

Nuclei	Sodium-23	Hydrogen-1	Phosphorus-31
Static Field	1.5 T		
dB/dt	<20 T/sec		
SAR	≤4 W/kg whole-body average ≤8 W/kg peak		
Acoustic Level	65-90 dB		

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89

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Imaging Performance

Nuclei	Hydrogen-1	Sodium-23
Specification Vol. Head coil Body coil	168 mm diameter sphere 266 mm diameter sphere	
Signal-to-Noise Head coil Body coil	>65 >92	119 (154 mM NaCl) ----
Uniformity	<40 % variation	
Image Distortion	≤5 %	
Slice Thickness	3, 5, and 10 mm - ±1 mm 15 mm - ±2 mm 20 mm - ±3 mm	
Slice Spacing	Variable from 0 to 200 mm ±5 %	
# of Simultaneous Slices	1 to 60	
Slice Profile	See figures in Appendix I1.4	
Pixel Size	= FOV/(Acquisition Matrix) Usual range is 0.31 to 3.75 mm	
Image acquisition Time	2D Multislice -(TR) X (Acquisition Matrix) X NEX 2D Sequential -(TR) X (Acquisition Matrix) X NEX X #SLICES 3D -(TR) X (Acquisition Matrix) X #SLICES/#SLABS	
	TR range is 0.02 to 4 sec ± 1 % (ungated) Acquisition Matrix = 32, 64, 128, 256, or 512 NEX (# of Excitations) range from 1 to 98 #SLICES is 1 to 60 #SLABS is 1 to 16 FOV (Field-Of-View) range is 2 to 48 cm	

90

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Spectroscopy Performance

Nuclei	Hydrogen-1	Phorphorus-31
Localization	DRESS accuracy = ds SLIT DRESS accuracy = ds PRESS accuracy = $(ds_x^2+ds_y^2+ds_z^2)^{1/2}$ where ds = slice thickness accuracy (see image performance)	
Homogeneous volume	100 mm diameter sphere ($\leq$0.1 ppm)	
Peak Width and Separation	Sufficient to resolve spin-spin coupling of approx. 7Hz	Sufficient to resolve spin-spin coupling of approx. 15Hz
Signal-to-Noise 20 cm/T 7.5 cm/R 20 cm/T 13.5 cm/R Sensitivity with Metabolic Concentration	>1000 > 500 for H_2O peak under specified measurement conditions	20 (typical) 15 (typical) for 50 mM H_3PO_4 peak under specified measurement conditions
Frequency Calibration	Relative to water at 4.75 ppm	
Spectra Acquisition Time	= (TR) X (Acquisition Matrix) X NEX TR range is 64 to 2048 msec $\pm$ 1% (ungated) NEX (# of Excitations) range from 2 to 5000 Acquisition Matrix for 1D is 1 2D is K_y 3D is (K_y) X (K_x) 4D is (K_y) X (K_x) X (K_z) where K_x, K_y, K_z=2, 4, 8, 16, 32, 64, or 128	

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9

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ATTACHMENT #6

Comparison Chart

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Comparison Chart of SA/GE and PROBE vs. SAGE 7 Spectroscopy Analysis Option

	Predicate Devices		
Feature	**SA/GE** Reclassified	**PROBE SVQ** K930265	**SAGE 7**
User Interface	Provides user control of processing, display, and analysis functions via a command-line interface with spectra and images displayed on fixed video screen.	Automatic creation and analysis of spectrum after each acquisition.	Provides user control of processing, display, and analysis functions through familiar X-windows graphical user-interface (GUI) using a combination of a mouse and keyboard. Processing controlled through buttons, pull-down menus, dialog boxes, and other standard X-windows GUI elements. Allows multiple display windows.
Data Processing Functions	Provides common spectroscopic processing functions (ex. apodization, FFT's, phasing, baseline correction, etc.).	Performs apodization, auto-phase, FFT, and baseline correction of 1D spectra.	Provides common spectroscopic processing functions (ex. apodization, FFT's, phasing, baseline correction, etc.).
Display Functions	Allows display of spectra collected as 1D or spectroscopic images (SI), and conventional MR images.	Displays 1D spectra.	Allows display of spectra collected as 1D or spectroscopic images (SI), and conventional MR images. Allows the display of SI data in grid format, optionally overlaid on an anatomical or spectroscopic image.
Data Handling Functions	Allows the display and independent processing of multiple raw data-sets in one session. Display limited to one data-set at a time.	Processes each raw data-set automatically after each acquisition.	Allows the display and independent processing of multiple raw data-sets in one session. Multiple data-sets may be visible simultaneously.
Analysis Functions	Provides methods to obtain spectral parameters (ex. amplitude, linewidth, etc.) via non-linear regression analysis, peak-picking, and integration.	Performs non-linear regression to obtain spectral parameters for the ^{1}H spectra of common brain metabolites.	Provides methods to obtain spectral parameters (ex. amplitude, linewidth, etc.) via non-linear regression analysis, peak-picking, and integration. Provides multiple regression techniques (including the method used in the PROBE analysis).
System Platform	Uses proprietary, dedicated, and obsolete computer hardware, operating system, and display hardware.	Uses the SIGNA scanner hardware, operating system, and image-display functions.	Will run on multiple computer platforms, using the windows display system.

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ATTACHMENT #7

Software Development, Verification, Validation and Testing

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SOFTWARE DEVELOPMENT PROCESS

(b)(4)

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(b)(4)

(b) (6)

Software Engineering

Date

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ATTACHMENT #8

Sample Clinical Output for a MR Diagnostic Device

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Example of Data Processing using SAGE 7

The following example demonstrates the use for SAGE 7 for data analysis.

Data Collection

Data was collected on a ^{31}P Spherical Phantom using the scan protocol shown below.

Pulse Seq.	Spin Echo (MRS)
Plane	Axial
Mode	2D
Frequency	25.85MHz
Spectral width	2500 Hz
Number of points	1024
NEX	2
FOV	24 cm
Scan Thickness	20 mm
TR	4000 ms
Flip angle	60^0

The data obtained during the scan was transferred into the SAGE 7 (Spectroscopy Analysis by GE) database and processed with SAGE 7. The following paragraphs and figures describe the steps followed in this example.

Figure 1 shows the FID representation of the raw data. This figure also shows several of the SAGE 7 utility screens. In the upper left corner is the SAGE 7 Main Window. In the lower left is shown the database access window.

Figure 2 shows the non-phase corrected spectral reconstruction of the data. The lower left window is an example of one of many operation specific dialog windows.

Figure 3 shows the phase correction portion of the calculation.

Figure 4 demonstrates the zoom capability of SAGE 7. The area between the adjustable vertical cursors is zoomed, as shown in the next figure.

Figure 5 shows the analysis of the peak region of the spectrum. The peak is analyzed in the region marked by the vertical cursors and the results displayed in the Spectrum Analysis dialog box.

Figure 6 details the analysis of the noise level. Again, the area between the vertical cursors is analyzed and the results displayed in the Spectrum Analysis dialog.

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Figure 7 demonstrates the ability of SAGE 7 to superimpose a grid of spectra on a high resolution proton anatomical image. This demonstrates the spatial distribution of the spectral peaks. Also included in this figure is a single voxel spectrum, which was extracted for closer examination.

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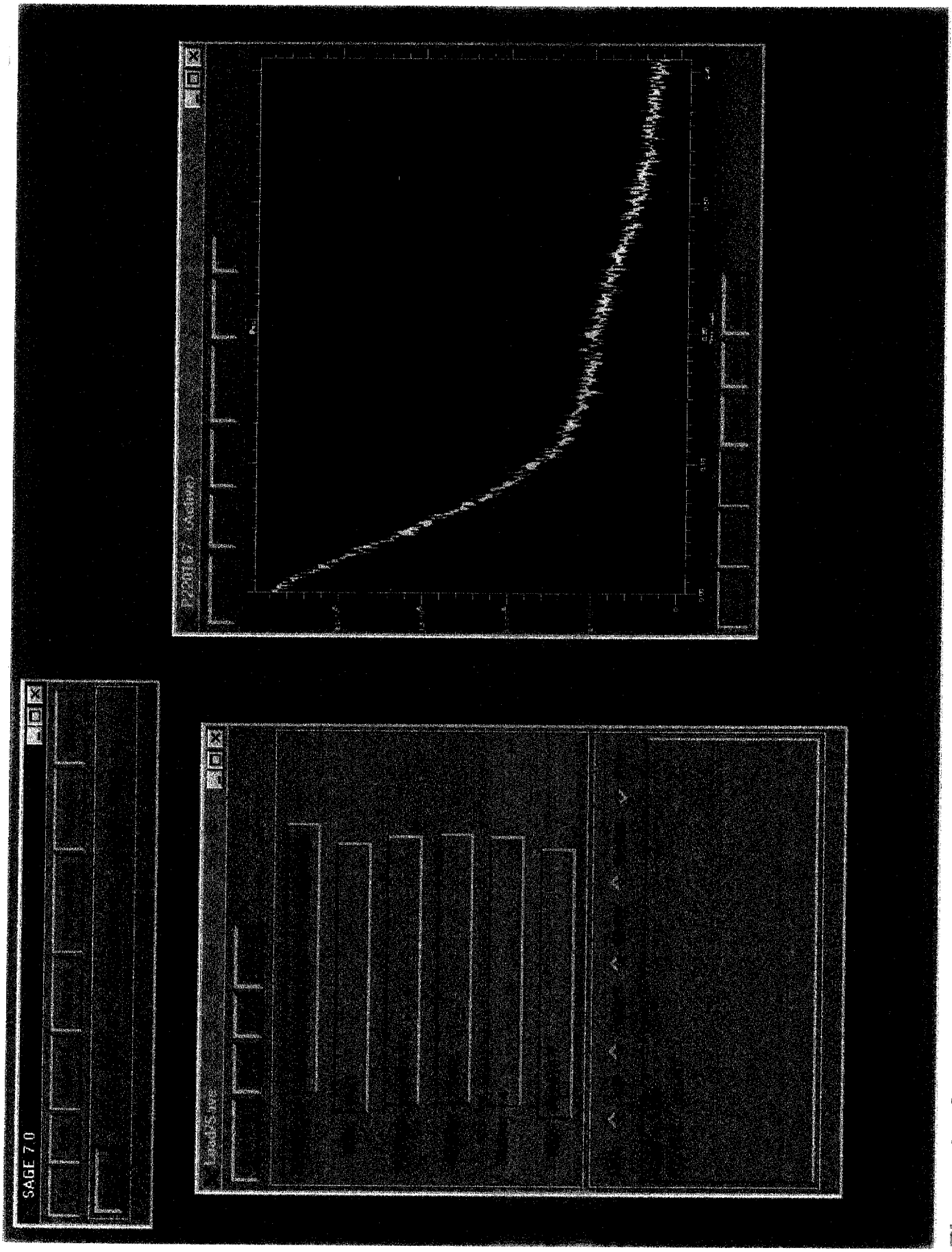

Figure 1 SAGE 7 Main Window, Database Window and FID Data Display

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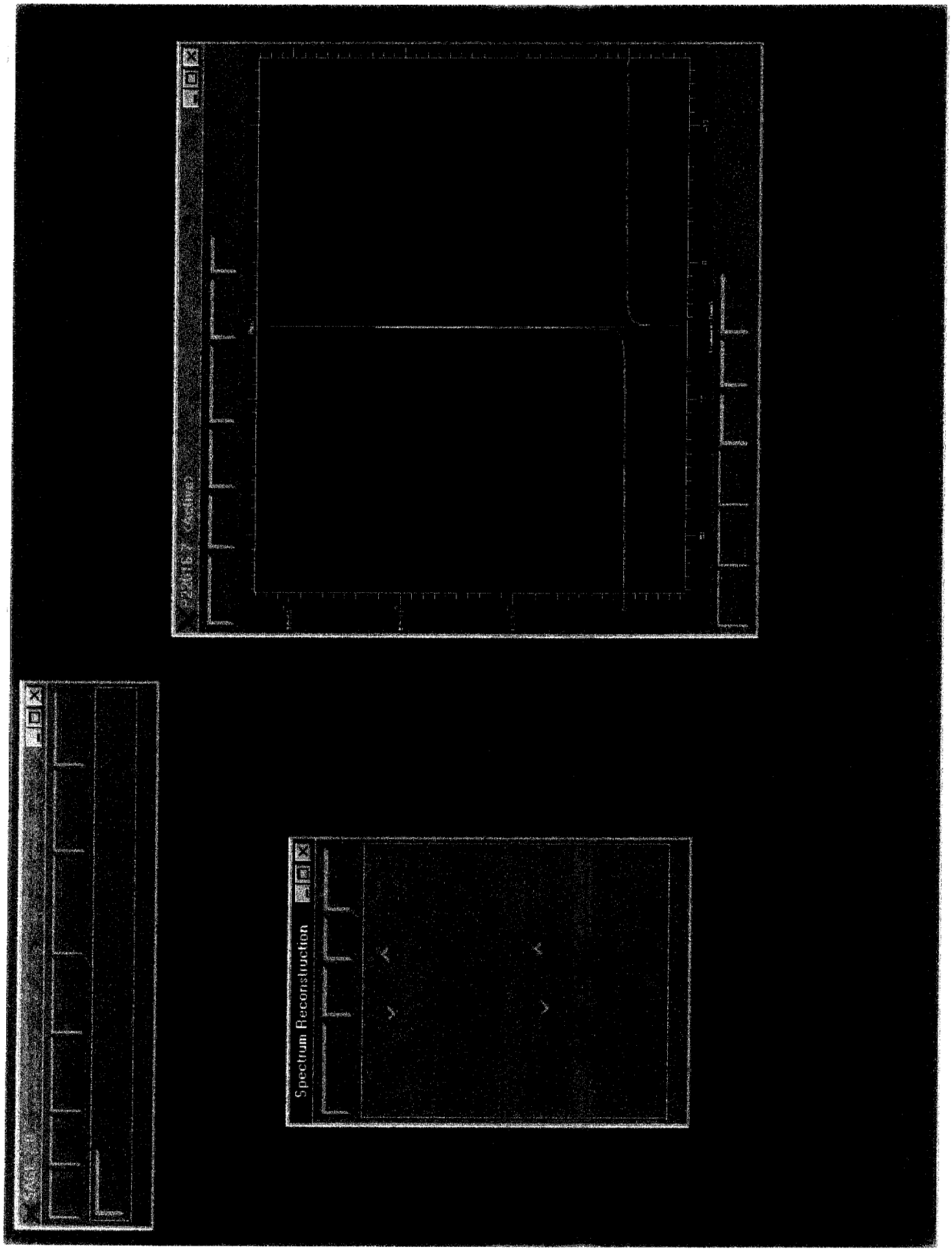

Figure 2 Spectral Reconstruction

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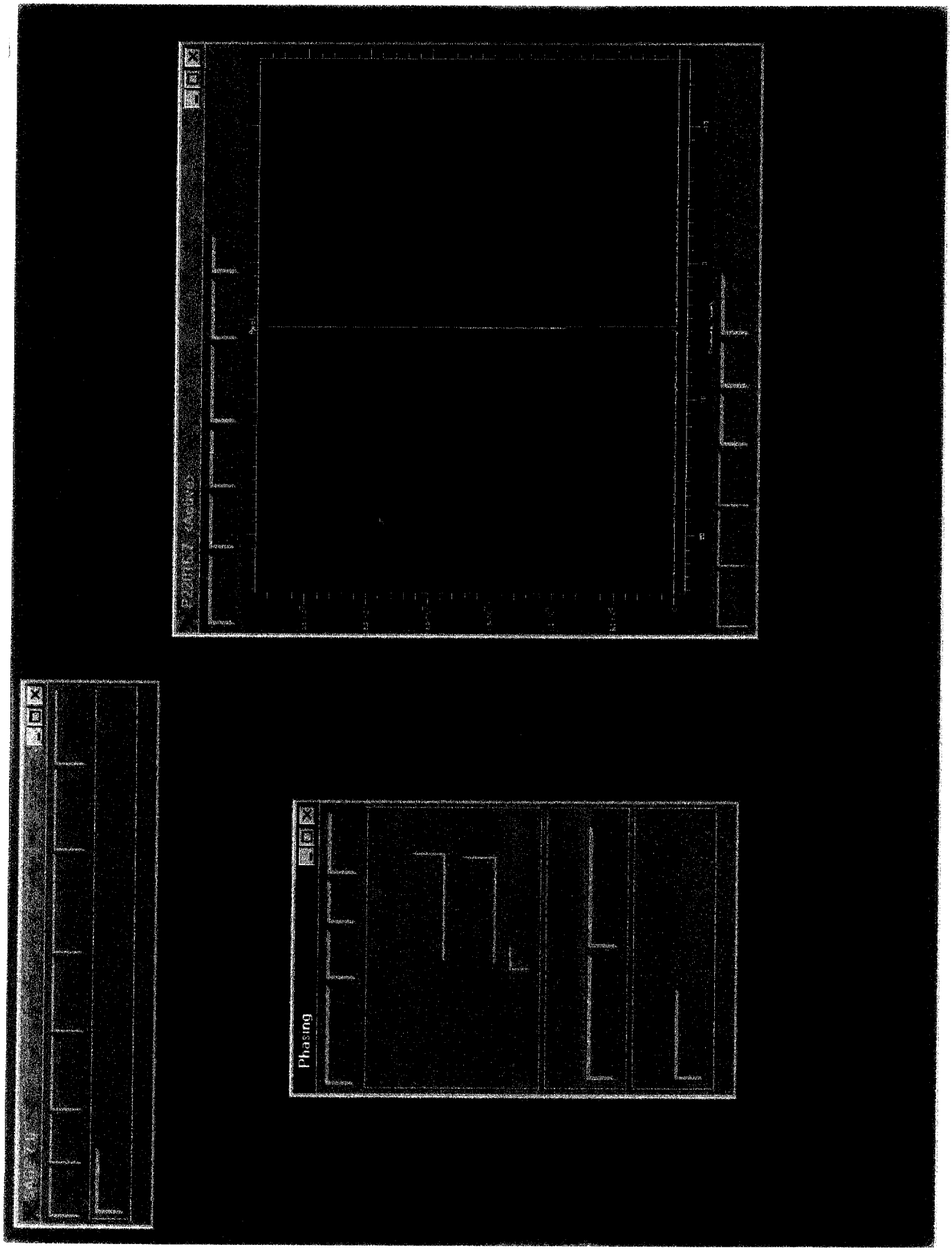

Figure 3 Phase Correction

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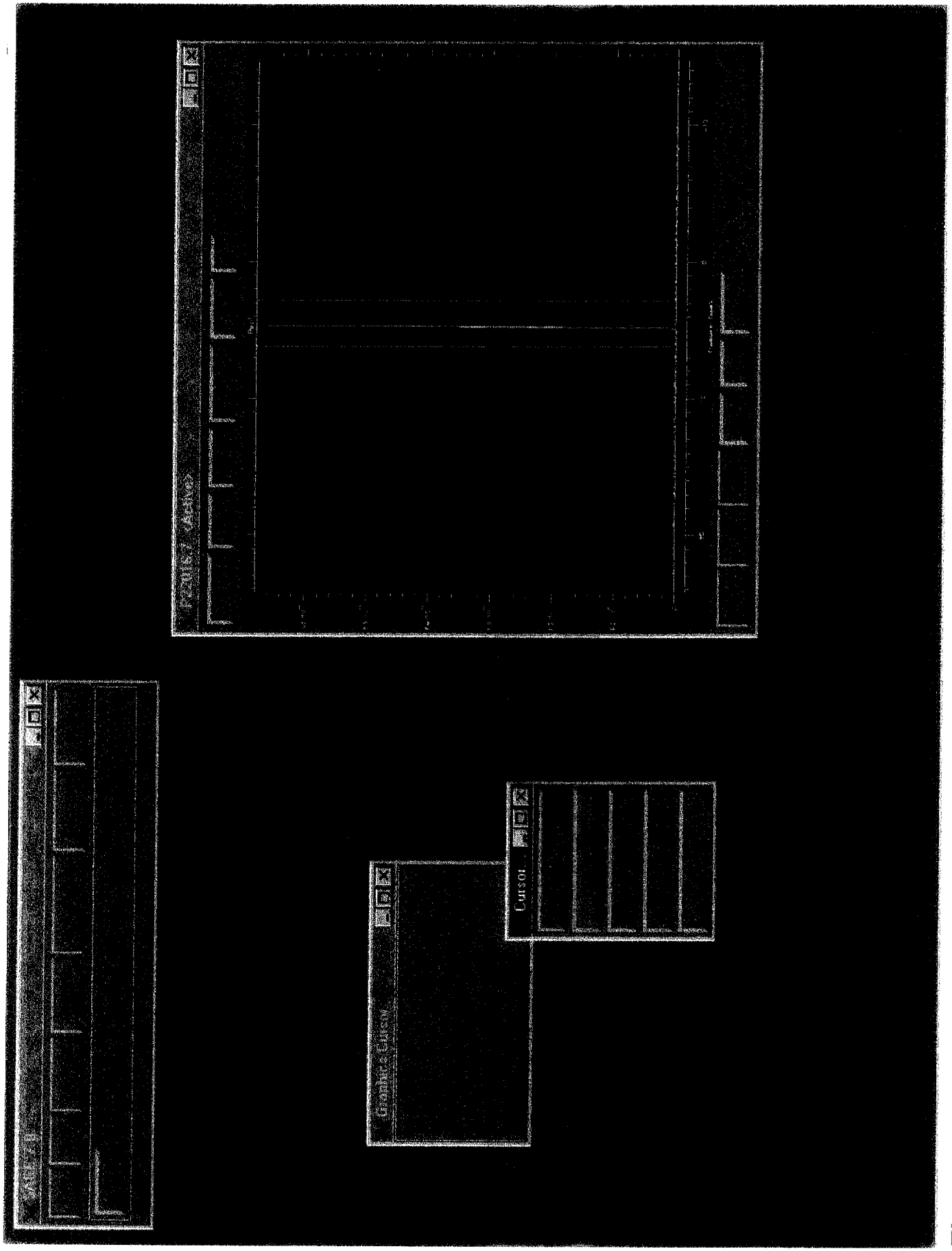

Figure 4 Setting up for Zoom operation

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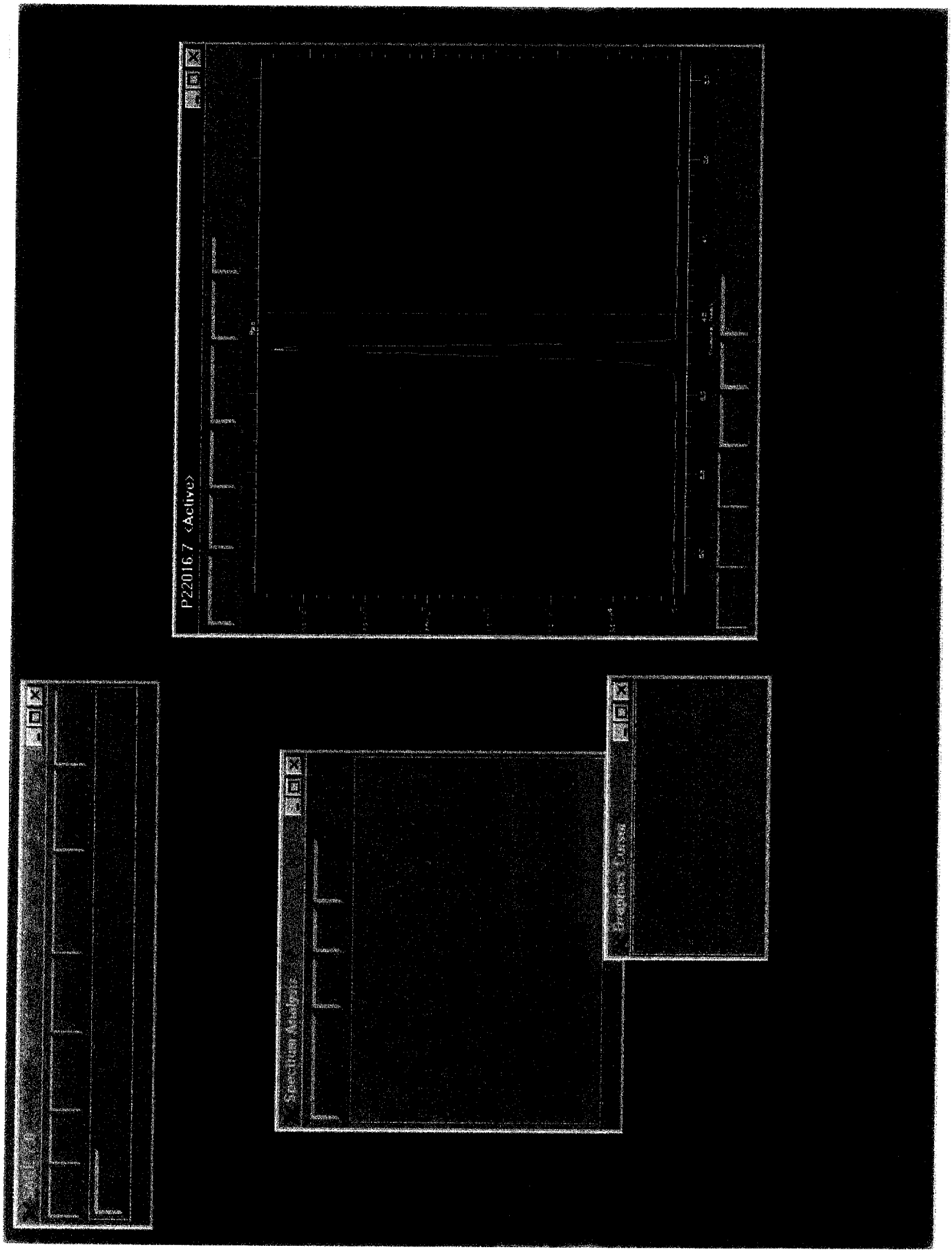

Figure 5 Analysis of peak region

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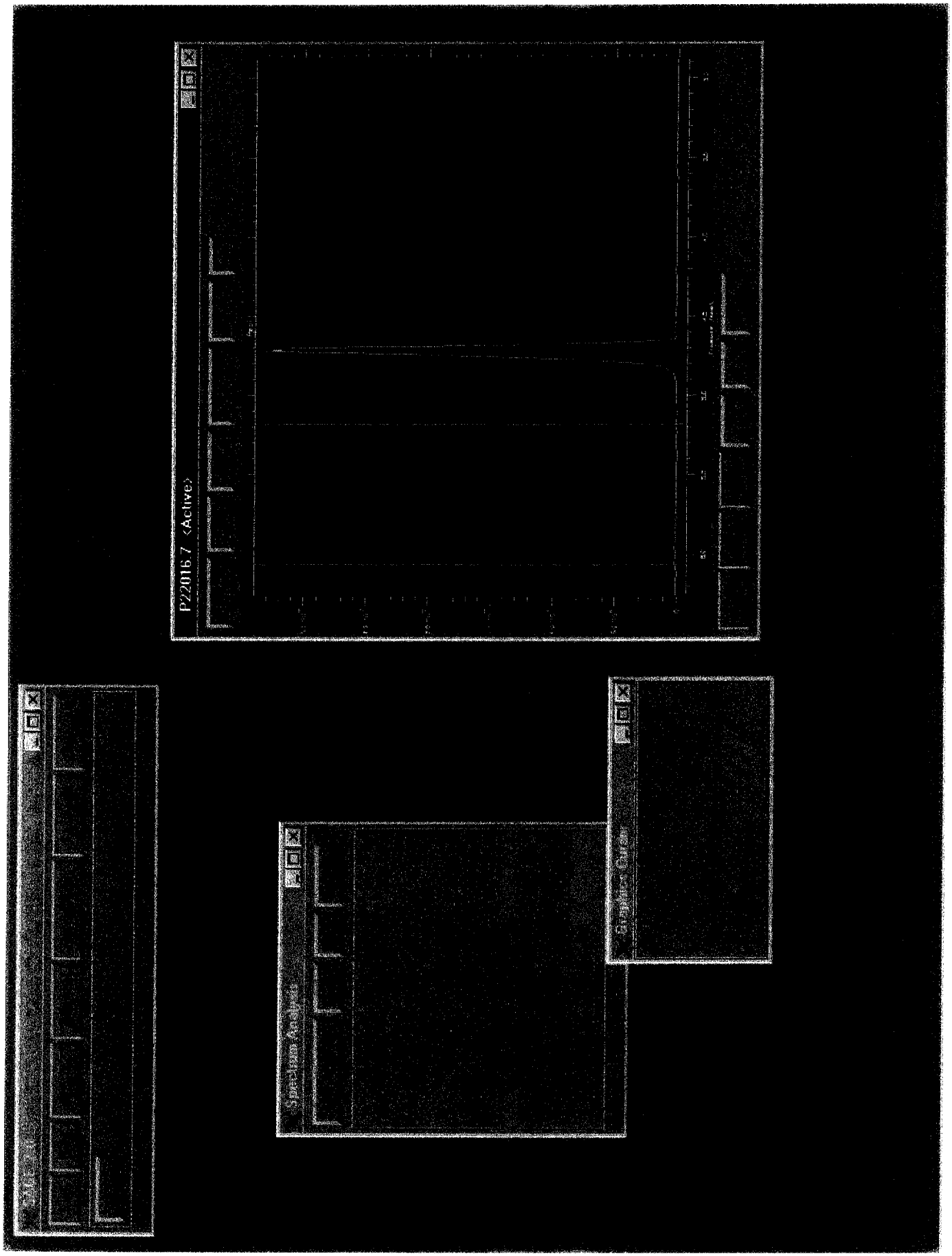

Figure 6 Analysis of noise region

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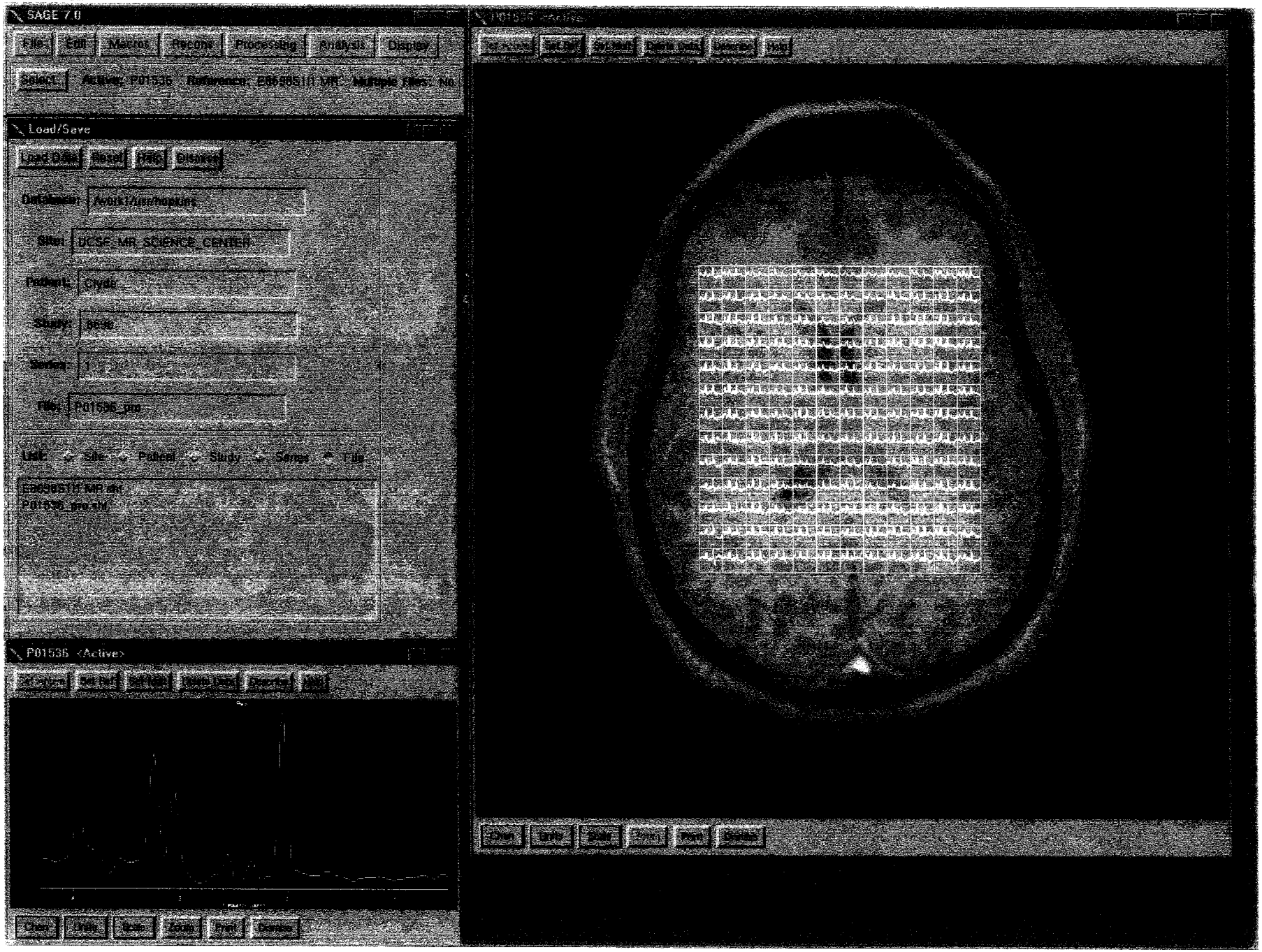

FIGURE 7

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ATTACHMENT #9

Literature

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Journal of Computer Assisted Tomography
17(5):673–680, September/October
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Direct ^{31}P Imaging in Human Limb and Brain

Thomas Ernst, Jung Hee Lee, and Brian D. Ross

Objective: This article describes two methods for direct imaging of the ^{31}P-metabolites phosphocreatine (PCr) and inorganic phosphate (P_i) and their application in human brain and muscle.

Materials and Methods: All studies were performed on a 1.5 T whole-body GE Signa scanner, using bird cage resonators double-tuned to ^{31}P and ^{1}H. The pulse sequence was based on a multiple slice, multiple echo imaging sequence. Selection of the PCr signal was achieved either by selective excitation or by the extensive chemical shift artifact in read direction. Examinations were done in two diabetic patients, in four patients with cerebral neoplasms, and in several healthy subjects.

Results: In calf muscle, images showed uniform distribution of PCr in normal muscle; deficits corresponded to bony structures and neurovascular bundles. Repeated exercise (dorsiflexion of the foot) led to selective loss of PCr in the anterior muscle compartment. A simultaneous increase in P_i appeared as a spatially distinct map. Diabetic patients showed more severe changes of PCr distribution in the calf muscle at rest and during much milder exercise. Direct imaging in the human brain with chemical shift selective excitation was completed in 5–30 min. In normal cerebral cortex, PCr was uniformly distributed around deficits marking the lateral ventricles. Tumors exhibiting moderate to severe depletion of PCr appeared as well defined deficits in the PCr image.

Conclusion: Direct imaging of PCr and P_i, with or without selective excitation of PCr, was effective in the human brain and limb. The methods described should lead to greatly improved fast phosphorus imaging. Clinical utility in peripheral ischemia and in localized energy deficits in the brain of patients with tumor, stroke, and other pathologies is anticipated.

Index Terms: Magnetic resonance imaging, techniques—Metabolites—Brain—Muscle.

The central role of phosphocreatine (PCr) in many physiological and pathological processes has been confirmed, using localized and nonlocalized ^{31}P MRS (1–4). The concentration of PCr ([PCr]) falls during muscular exercise, with the formation of equimolar amounts of inorganic phosphate [P_i] (5,6). [PCr] may also fall in the activated brain in response to visual stimulation (7). Useful information on the modulation of intracellular free [ADP] is obtained from [PCr] by the equilibrium of creatine kinase:

$$\mathrm{ADP} + \mathrm{PCr} \overset{K}{\rightleftarrows} \mathrm{Cr} + \mathrm{ATP} + \mathrm{H}^+$$

In pathology, reduced [PCr] appears to be a consistent finding in heart and skeletal muscle, as a response to ischemia, and in brain, following stroke or in many neoplasms (8–11).

Because of the importance of this metabolite and the likelihood that metabolic responses in tissues are spatially heterogeneous, a number of attempts have been made to produce metabolic images of PCr. ^{1}H spectroscopy has been used to create Cr maps of brain (12). However, these images do not directly give information on the distribution of [PCr] because the proton resonance contains variable contributions from both free Cr and PCr. The

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AUG 19 '98 08:09AM GEMS SPECTROSCOPY P.3/9
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most successful attempt to date has been ^{31}P NMR phase-encoded spectroscopy (CSI), which has the further advantage of mapping the remaining metabolites of the phosphorus spectrum (13–16). An inherent disadvantage of CSI has been the limited spatial and temporal resolution and the extensive data processing required to generate metabolite maps (or "images") from the large data sets that are obtained.

In this article, we demonstrate the effectiveness of a direct PCr imaging technique that overcomes some of these problems. The method was originally introduced by Hsieh and Balaban (17) for PCr imaging in rabbit skeletal muscle in which case selective detection of PCr is based on differences in T2, J-coupling, and concentration. This method of filtering the PCr signal does not work in brain tissue of animals, however, because of the higher T2 values and higher concentrations of the remaining metabolites. Therefore, the selection of the signal of PCr has to be based on chemical shift. An obvious solution is to excite only PCr using a chemical shift selective pulse. This was suggested by Mora et al. (18) and led to usable PCr images of primate brain within 30 min at 4.7 T.

We also explore another approach for selecting PCr and develop the method for use on standard chemical images at lower field (1.5 T). The experiment utilizes the fact that, to achieve optimal signal/noise (S/N) ratio, very small read gradients are used for direct phosphorus imaging. In conjunction with the extensive chemical shift in the ^{31}P spectrum, this leads to a chemical shift "artifact" (offset) big enough to separate the images of individual metabolites completely. This technique, which we call FRACTAL (FRequency Artifact Coded Tomography ALgorithm), thus encodes both chemical shift and spatial information in the same axis.

With use of these techniques, the anticipated heterogeneity of PCr distribution in both muscle and brain was readily demonstrated in normal subjects and selected patients. A preliminary account of these findings was presented at SMRM 1991 and 1992 (19,20).

MATERIALS AND METHODS

In addition to a number of young healthy volunteers, three studies were performed in two diabetic patients (aged 65 and 69 years) with Doppler-proven peripheral vascular disease and in four patients with CT- and MRI-verified cerebral neoplasms (three primary, one secondary lung carcinoma; 45–80 years). Institution review board approval (Huntington Memorial Hospital, Pasadena, CA, U.S.A.) and written consent were obtained from all subjects prior to examination.

All studies were performed on a 1.5 T whole-body GE Signa scanner (Milwaukee, WI, U.S.A.) with shielded gradients and spectroscopy (4.7 or 4.8) package. The RF coils used were two bird cage resonators—internal diameter 14 and 27 cm, respectively (J. Tropp, GE Fremont) (21)—double-tuned to the resonance frequencies of ^{31}P (25.86 MHz) and protons (63.88 MHz). To achieve highest S/N ratio, the phosphorus channel was built for quadrature detection, whereas the proton circuit was for linear detection only.

Shimming could easily be performed on the water signal of the region of interest without moving the patient. For the limb, only the linear terms x, y, and z were used for optimizing the B_0 homogeneity. In the brain, the higher-order terms x^2–y^2, xy, and z^2 were also adjusted after optimizing x, y, and z on a STEAM-selected voxel over a volume of >200 ml.

Measurements were also performed on an aqueous solution (phantom) of ~0.25 M inorganic phosphate (P_i; chemical shift 4–5 ppm) and 0.2 M Na pyrophosphate (PP_i; chemical shift −4.5 ppm). Throughout this article, PCr is assigned a chemical shift of 0 ppm.

The phosphorus images presented here are based on a multiple slice multiple echo imaging sequence as used for standard proton imaging (GE). Using a slice selective excitation pulse and four slice selective refocusing pulses, the sequence generates four SEs at equidistant TE values (see Figs. 2c–d and 5c–f). The bandwidth of the 180° pulses is greater than that of the 90° pulses so that the slice profile is defined by the profile of the excitation. Stimulated echoes and other indirect echoes are suppressed. The original pulse sequence was modified to allow acquisition of all four SEs at variable TE and variable bandwidth. Further modifications were necessary for running the experiment on the broadband channel of the Signa scanner. All phosphorus images shown were acquired with a TE increment of 91 ms and a TR of 5 s. In the read direction, acquisition of 256 data points with a bandwidth of ±1,953.1 Hz leads to an acquisition window of ~65 ms. Spatial resolution in the second dimension was achieved using 32 phase-encoding steps. All images shown were acquired in an axial orientation.

The resulting data sets were reconstructed online using standard Signa reconstruction algorithms and appeared as standard images that could be filmed. The raw data were additionally transferred to a SUN 3/470 computer (SUN Microsystems, Mountain View, CA, U.S.A.) for further processing on the SA/GE spectroscopy processing platform (GE). This off-line processing comprised zero filling to 64 or 128 phase-encoding steps, moderate Gaussian multiplication in read and phase direction, and two-dimensional Fourier transformation (2DFT). The resulting images were displayed in magnitude mode.

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Selective Excitation

For selective excitation of PCr in the human brain, the standard SE imaging sequence described above was modified. The slice selective excitation pulse was replaced by a 53.3 ms chemical shift selective 90° sinc pulse with a bandwidth of 75 Hz, corresponding to ±1.5 ppm in the ^{31}P spectrum. The suppression of signals at ±2.5 ppm is >10. By applying a spatially nonselective RF pulse, the multiple slice capability of the experiment is lost. Slice selection was achieved by the use of spatially selective refocusing pulses, all of which have the same bandwidth. The TE interval used was identical to that of the standard SE sequence, i.e., 91 ms.

FRACTAL

In an MR experiment employing a read gradient, a chemical shift difference Δ between two spin species is translated into a spatial offset d of the corresponding images:

$$d = \frac{\Delta N}{BW} \quad (1)$$

where N is the number of datapoints sampled and BW is the acquisition bandwidth. In regular imaging experiments, the chemical shift artifact d is kept to a minimum by using high receiver bandwidths. The FRACTAL technique, on the other hand, utilizes the rather high offset caused by small receiver bandwidths and the considerable chemical shifts in the phosphorus spectrum to maximize the chemical shift offset.

The FRACTAL images shown in this article were acquired with the standard SE sequence described above. With a resolution of 15.625 Hz/pixel (4 kHz bandwidth, 256 points), the chemical shift difference between PCr and P_i (5 ppm = 130 Hz) causes a spatial offset of 8.3 pixels, which, depending on the object size, is sufficient to separate the two images completely.

RESULTS

Measurements on Phantoms

The FRACTAL method can easily be validated on a phantom consisting of two spin species with differing chemical shift. Figure 1 shows the result of scanning a sample containing P_i and PP_i. The chemical shift difference between the two nuclei (8.5 ppm) leads to a spatial offset in the read direction large enough to separate the corresponding images completely. As Eq. 1 predicts, a receiver bandwidth of ±2 kHz leads to an effect twice as great as a bandwidth of ±4 kHz (14 pixels offset vs. 7 pixels).

FIG. 1. FRACTAL ^{31}P Image of a bottle containing inorganic phosphate (P_i) and pyrophosphate (PP_i). The chemical shift difference between these two compounds leads to an offset in read direction large enough to separate the two images (left = P_i; right = PP_i) completely. The effect is inversely proportional to the receiver bandwidth used: ±2 kHz (lower pair of images) and ±4 kHz (upper pair of images).

Phantom measurements were also performed to compare the FRACTAL SE technique with the experiment using selective excitation. Centering the chemical shift selective excitation pulse (bandwidth ± 1.5 ppm) on the frequency of inorganic phosphate leads to complete disappearance of the pyrophosphate signal (images not shown). The signal intensity of the first echo with selective excitation is ~10% lower than that of the SE experiment. This is very likely the result of differences in the slice profile, which is defined by the 90° excitation pulse with SE (see Materials and Methods), but by the first 180° refocusing pulse with selective excitation.

Normal Brain

Figure 2 shows ^{31}P spectra of the human brain acquired with a DRESS (22) experiment (TR 5 s) and a slice selective two pulse SE sequence at a TE of 91 ms (TR 5 s). At the long TE, the spectrum is dominated by the PCr signal with its long T2 of ~400 ms. The other ^{31}P resonances are reduced due to their shorter T2 values and, in the case of ATP, J-coupling. However, as Fig. 3a demonstrates, the signals of these other metabolites are visible in the images even at TE of 91 ms. Particularly, the image of phosphodiesters (PDEs) with a chemical shift offset of ~6 pixels may overlap with that of PCr. With selective excitation of PCr, the "artifacts" disappear to allow direct PCr imaging in the human brain (Fig. 3b). The image intensity in the later echoes (Fig. 2d) (TE 182 ms) drops rather fast with an apparent T2 much smaller than 400 ms. Therefore, these images were not used for averaging. Phantom studies showed that the fast signal decay in the later echoes is caused by imperfections in the multiple slice selective refocusing pulses. However, this is a peculiarity of the imaging sequence used rather than an intrinsic limitation of chemical shift selective excitation. Improved experiments can be devised

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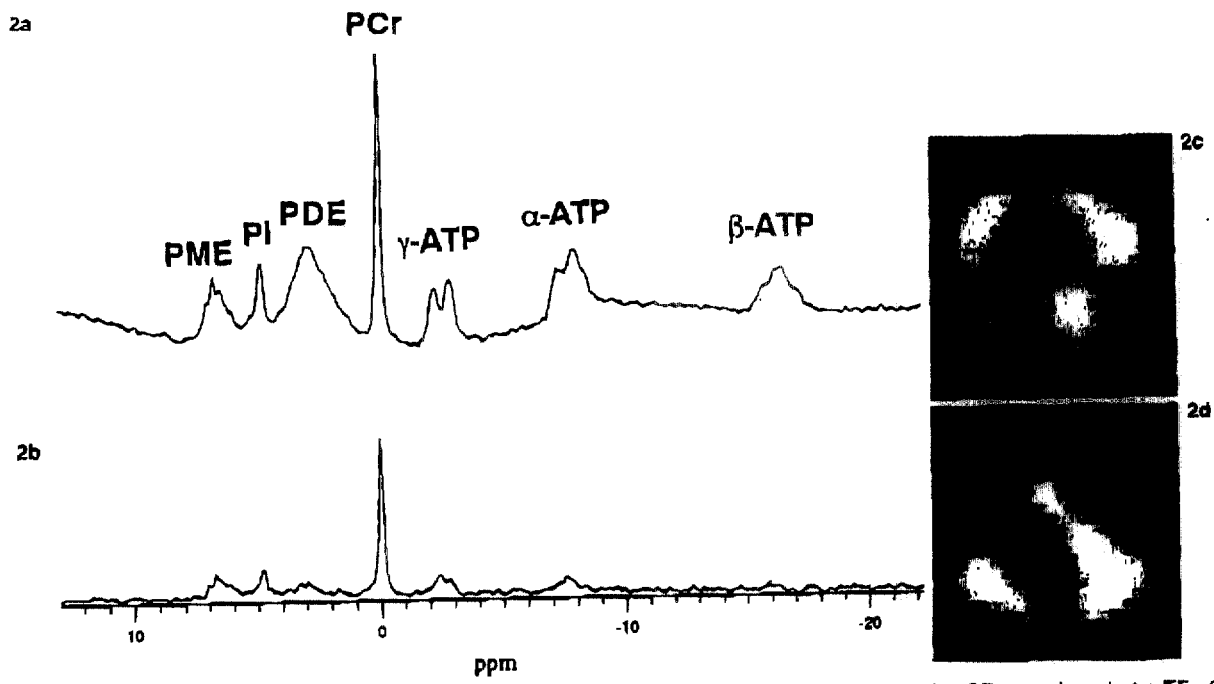

FIG. 2. ^{31}P spectra of the human brain acquired with a DRESS sequence (a) and with a two pulse SE experiment at a TE of 91 ms (TR 5 s) (b). The resonances of phosphomonoester (PME), P_i, phosphodiester (PDE), phosphocreatine (PCr), and ATP can be identified in the DRESS spectrum (a). In the SE experiment at longer TE, the spectrum is dominated by PCr; the other resonances are reduced due to their short T2 values and J-coupling. Axial ^{31}P brain images generated with the multiple echo experiment at TE values are also shown, with first echo = 91 ms (c) and second echo = 182 ms (d), in-plane resolution of 25 × 25 mm^2, slice 30 mm, TR 5 s, TE 91 ms, and 10 NEX (27 min). The intensities in the two images are not normalized. The second echo is acquired under an inverted read gradient, so that artifacts due to B_0 inhomogeneities are considerably different from those in the first echo. The poor image quality of the second echo can also be attributed to a low signal/noise ratio. The third and fourth echoes still contain signals, but are not shown here.

rather easily (increasing the bandwidth of the second and following 180° pulses).

A second problem in ^{31}P imaging of the human brain is B_0 inhomogeneity, which can be considerable in the frontal region of the brain (23). Depending on strength and orientation relative to the read gradient, nonlinear field variations can lead to signal loss and spatial misregistration in the read direction. This was investigated in several volunteers. The B_0 inhomogeneities in the frontal lobes lead to artifacts that vary with sign and orientation of the read gradient. When shimming was performed only on the posterior part of the selected slice, the artifacts were less pronounced if the read gradient was applied in the anteroposterior direction. This orientation is probably better adapted to the left–right symmetry of the brain and was used for the other brain scans shown in this article.

Figure 4 shows a PCr image of a healthy volunteer acquired with in-plane resolution of 30 × 30 mm^2 and 30 mm slice thickness in 15 min. The PCr image is relatively uniform around a deficit that corresponds to the lateral ventricles in this 3 cm thick brain slice. Some increase in PCr intensity is usually noticed laterally and corresponds to the temporalis muscle.

Normal Limb

Figure 5 shows a ^{31}P spectrum of the human calf muscle acquired with a DRESS experiment and with a slice selective SE sequence at TE 100 ms (TR 5 s). With the DRESS experiment, the spectrum is dominated by the signal of PCr, which has a concentration of ~25 mM. The other resonances, such as P_i and ATP, are also visible. As Fig. 5b demonstrates, at a TE of 100 ms, the spectrum in the SE experiment contains only the PCr signal, whereas the resonances from other metabolites are absent. Therefore, nonselective excitation is possible for the direct PCr imaging in the human calf muscle. In contrast to the situation in the human brain, B_0 inhomogeneities in the calf muscle are less pronounced, so that high-order shimming was unnecessary. Figure 5d–f shows ^{31}P images of human calf muscle for the later echoes. Unlike the situation in the brain with chemical shift selective excitation, the intensity of the later echoes is quite satisfactory for most experiments. Thus, adding all echoes leads to an improvement in S/N of ~1.5 compared with the first echo (Fig. 5c). Despite this improvement, only the first echo will be displayed in the remaining figures.

FIG. 3. Axial
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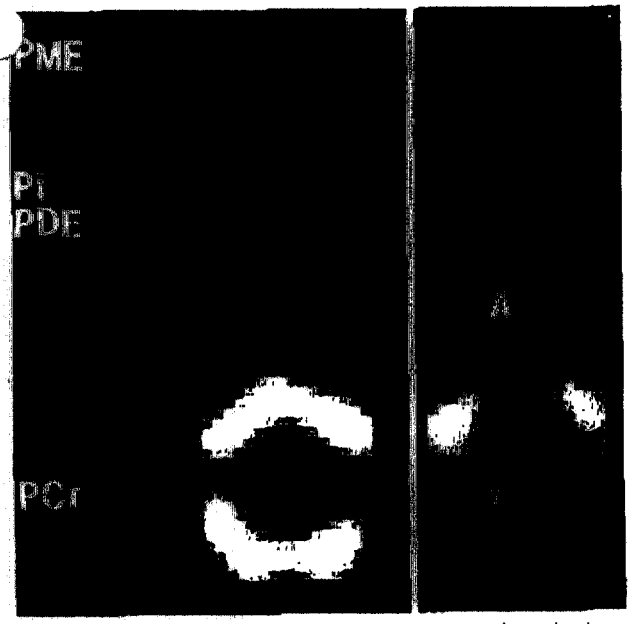

FIG. 3. Axial phosphorus brain images of a healthy volunteer using the FRACTAL technique, i.e., nonselective excitation [in-plane resolution 25 × 25 mm², slice 25 mm, TR 5 s, TE 91 ms, and 10 NEX (27 min)] (a). The image is dominated by the signal of phosphocreatine (PCr). The images of other metabolites, though considerably suppressed, are also visible and partially overlap. This "artifact" completely disappears if selective excitation of PCr is employed (b). (*Please note*, left side of the brain is on the left.) PME, phosphomonoester; PDE, phosphodiester.

Figure 6b shows a PCr image of a healthy volunteer acquired with in-plane resolution of 6 × 6 mm² (slice 25 mm) in 81 min. The PCr arises from the anterior and posterior muscle compartments; deficits correspond accurately to bony structures and the neurovascular bundles (Fig. 6a). A further modest inhomogeneity represents the main muscle masses and may reflect different [PCr] values of individual muscle groups.

Figure 7 demonstrates that PCr imaging is also possible around the knee. The phosphorus image, acquired with in-plane resolution of 8 × 8 mm² (slice 25 mm) in 27 min, shows that the areas of high [PCr] nicely correspond to muscle in the proton image (Fig. 7a).

FIG. 4. Axial phosphocreatine image of a healthy volunteer acquired with selective excitation. The phosphorus image has an in-plane resolution of 30 × 30 mm² and 30 mm slice thickness; total scan time was 15 min (TR 5 s, TE 91 ms, 6 NEX).

Brain Pathology

Selective excitation was used for scanning an 80-year-old patient with a secondary cerebral neoplasm (Fig. 8). The large hyperintense lesion seen in the proton image obtained at a separate examination exhibits severe depletion or complete absence of PCr, while the surrounding "normal" brain is represented accurately by the PCr image. This examination was done in under 30 min. Similar findings were achieved in the two other patients with primary cerebral neoplasms. Parallel ^{1}H MR spectra were acquired to quantify local [Cr] in the tumor and in the contralateral normal brain. The loss of local PCr intensity in the phosphorus image varies in the patients according to intratumor [Cr] (not shown).

Effects of Exercise and Peripheral Ischemia in Human Muscle

The PCr imaging with FRACTAL demonstrates the regional effect of exercise on the energy metabolism of muscle in the lower leg of a normal individual. For this proposed imaging, time was reduced to 5.5 min, with corresponding sacrifice of in-plane resolution. Exercise started ~1–2 min before the scan. Due to the low "duty cycle" of the experiment (0.5 s total data acquisition followed by 4.5 s waiting period), the exercise can be continued throughout scanning, by timing flexions to occur only within the waiting periods.

Phosphocreatine is uniformly distributed at rest (Fig. 9a). However, a new region of heterogeneity appears during repeated vigorous dorsiflexion of the foot (Fig. 9b). Phosphocreatine is lost from the anterior muscle compartment (peroneus longus, extensor digitorum longus, and tibialis anterior muscles). Noteworthy is a P_i image of the corresponding muscle groups (marked by arrows on the two figures), chemically and spatially shifted in the appropriate dimension. Upon recovery, the P_i image is no longer seen and the full and uniform intensity of the PCr image is restored, indicating metabolic recovery in all muscle groups (not shown). Particularly significant is the stability of the PCr content of the flexor compartment, including soleus and gastrocnemius, during vigorous exercise, in this and other normal subjects.

Phosphocreatine imaging demonstrates significant differences in a diabetic subject with peripheral ischemia without rest pain. At rest, in accordance with the proton images (Fig. 10a), somewhat greater heterogeneity in the PCr images is demonstrable (Fig. 10b), defining regions of muscle that are hypoperfused or replaced by fibrosis. Mild exercise induced pain and, within 1–2 min, loss of PCr in the

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112

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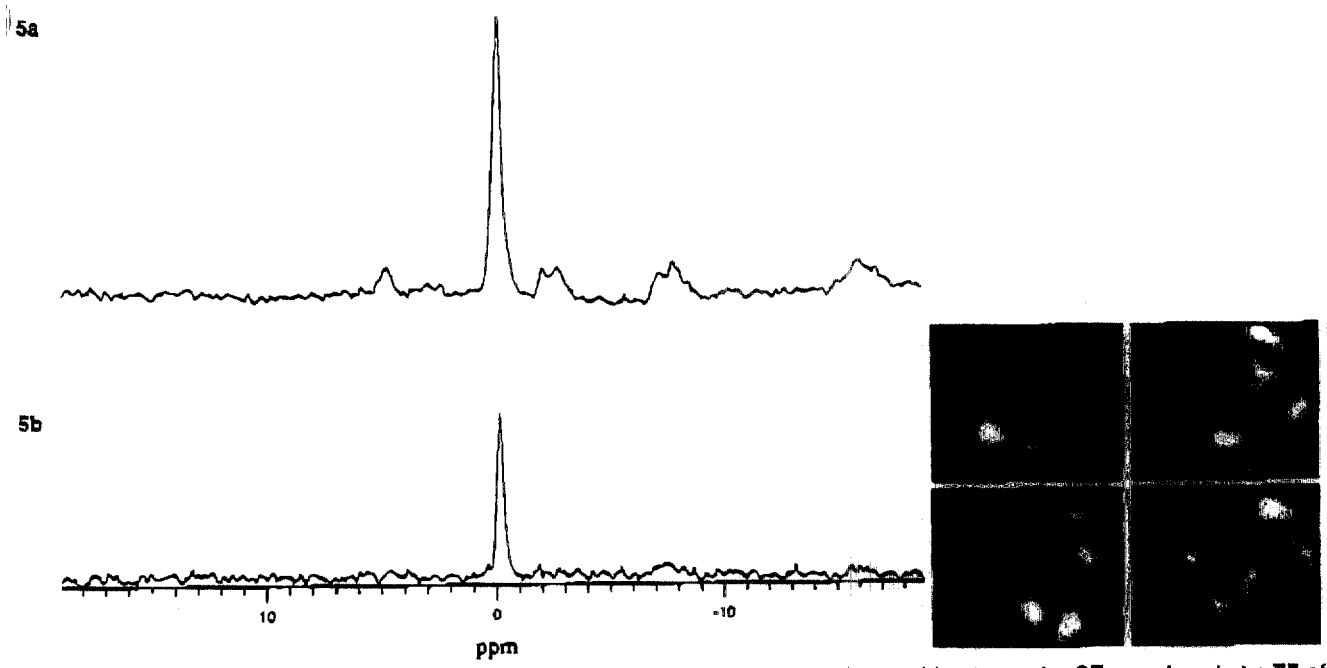

FIG. 5. ^{31}P spectra of human calf muscle acquired with a DRESS sequence (a) and with a two pulse SE experiment at a TE of 100 ms (TR 5 s) (b). The resonances of P_i, phosphocreatine (PCr), and ATP can be identified in the DRESS spectrum (a). In the SE experiment at longer TE, the only visible signal is PCr; the other resonances are absent due to their short T2 values, J-coupling, and low concentration. Axial ^{31}P images of human calf muscle generated with the multiple echo at equidistant TE values (91, 182, 273, and 364 ms, first to fourth echoes) (c–f), with in-plane resolution of 8 × 8 mm², slice 25 mm, TR 5 s, TE 91 ms, and 10 NEX (27 min).

anterior muscle compartment (Fig. 11). The anatomically shifted image of P_i is again seen in this FRACTAL study. Interestingly, with repeated plantar flexion, depletion of PCr was also detectable in muscles of the flexor compartment, probably the tibialis posterior and flexor hallius longus and possibly regions of the gastrocnemius (not shown). Elevation of P_i was manifest in the chemically shifted image of a corresponding anatomical region. Together these findings indicate early regional ischemia in the muscles of the extensor compartment not detectable even at much more vigorous exercise loads in the normal individual.

DISCUSSION

This article demonstrates the feasibility of direct PCr imaging in humans. In the limb, a conventional imaging experiment without selective excitation leads to excellent results. The high S/N ratio achievable with this technique can be used either to acquire images with a high enough spatial resolution to observe anatomical variations or to perform dynamic studies demonstrating the conversion of PCr into P_i in selective muscle groups during exercise. The resulting images are available immediately after

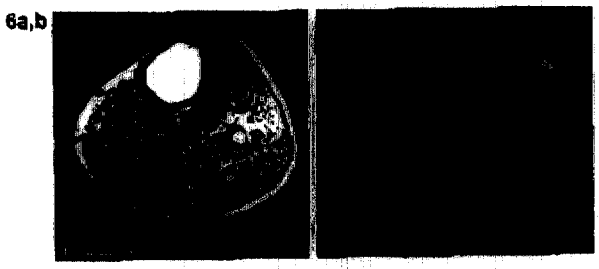

FIG. 6. Axial proton (a) and phosphocreatine (PCr) (b) image of the calf acquired on a healthy volunteer. An in-plane resolution in the PCr image of only 6 × 6 mm² with a slice thickness of 25 mm was achieved with a total scan time of 81 min (SE, nonselective excitation, TR 5 s, TE 91 ms, 3 × 10 NEX). Relative size of the images is indicated.

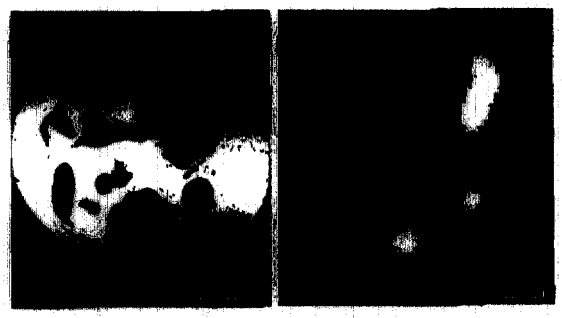

FIG. 7. Proton image (a) and corresponding phosphocreatine image (b) of an axial slice through the knee acquired on a healthy volunteer in 27 min. The in-plane resolution is 8 × 8 mm² with a slice thickness of 25 mm (SE, nonselective excitation, TR 5 s, TE 91 ms, 10 NEX). Relative size of the images is indicated.

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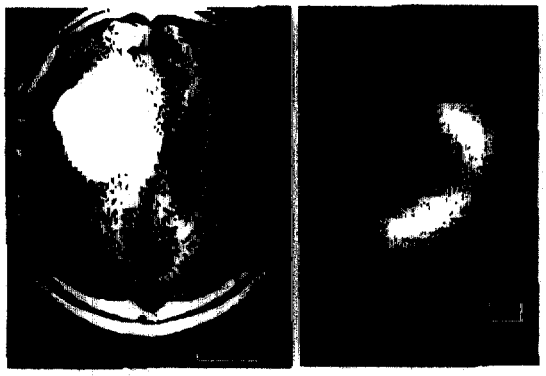

FIG. 8. Axial proton (a) and phosphocreatine (PCr) (b) image of the *brain* acquired with the double-tuned head coil in a patient with a secondary cerebral neoplasm using selective excitation [in-plane resolution of 25 × 25 mm², slice 30 mm, TR 5 s, TE 91 ms, 10 NEX (27 min)]. The large hyperintense lesion seen in the ^{1}H image corresponds to an area of severely depleted PCr, as expected for a secondary tumor. The PCr images of primary tumors varied with somewhat less demonstrable deficits in accordance with their higher PCr content. Relative size of the images is indicated.

scanning, since no special reconstruction algorithms are required. We predict their utility in the investigation of peripheral vascular disease and in further studies of muscle physiology.

In the human brain, direct PCr imaging using the techniques described is more difficult and the S/N ratio is, as expected, less ([PCr] ~5 m*M* in brain vs. 25 m*M* in skeletal muscle). To suppress artifacts from metabolites other than PCr, chemical shift selective excitation has to be employed. The major difficulties lie in B_0 inhomogeneities, however. Because the reconstruction algorithm for 2DFT assumes a linear relationship between frequency and spatial coordinates, local field variations may result in spatial misregistration. The resulting artifacts depend on direction and sign of the read gradient. Choosing correct parameters reduces the artifacts considerably, as does high-order shimming. It should be mentioned that CSI does not show these artifacts, because spatial mapping by phase encoding is not sensitive to B_0 variation.

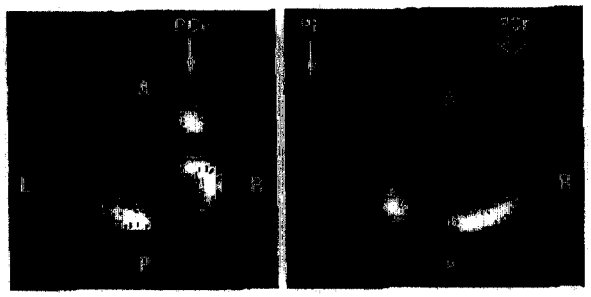

FIG. 9. Effect of exercise on regional energy metabolism in the lower leg of a healthy volunteer. The axial phosphocreatine (PCr) images were acquired at rest (a) and during vigorous dorsiflexion exercise of the foot (b), leading to loss of PCr only from the anterior muscle compartment (arrow). The ^{31}P image, which was acquired with the FRACTAL technique, also shows the localized appearance of P_i in an image that is spatially shifted 8.3 pixels (130 Hz) to the left (filled arrow) and simultaneous loss of PCr in the anterior muscle compartment (open arrow). The phosphorus images, which have in-plane resolution of 12 × 12 mm² (25 mm slice), were each acquired in 5.5 min (TR 5 s, TE 91 ms, 2 NEX).

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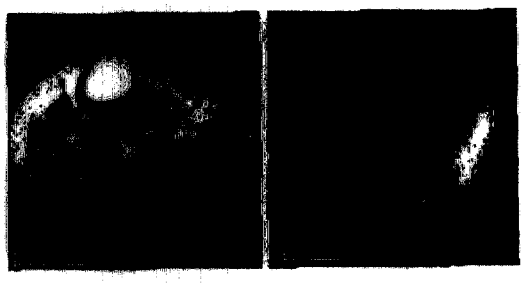

FIG. 10. Axial proton (a) and phosphocreatine (PCr) (b) images in the lower leg of a diabetic patient with peripheral vascular disease [in-plane resolution of 8 × 8 mm², slice 25 mm, TR 5 s, TE 91 ms, 10 NEX (27 min)]. Relative size of the images is indicated.

In the chemical shift selective experiments, B_0 variations may also lead to nonexcitation of the PCr signal and possibly excitation of the wrong spectral signals (PDE or P_i). The inhomogeneities would have to be considerable, however, for the latter possibility to appear.

If the intravoxel inhomogeneities exceed the strength of the read gradient used, there is partial or complete loss of the signal. The same can happen in phase-encoded CSI, because the lines become very wide and S/N ratio very low. Such strong local B_0 inhomogeneities may occur in hemorrhagic lesions, in pathologically inhomogeneous lesions, or close to interfaces between different tissue types, such as air–bone–brain. They are very hard to affect by shimming.

One possibility to improve the situation and get a better and quantitative understanding of possible artifacts is to acquire a B_0 field map after acquiring

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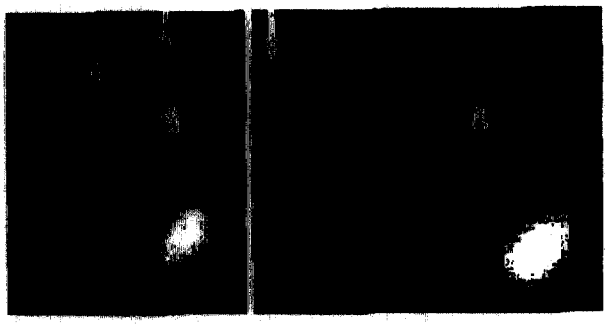

FIG. 11. Effect of exercise on regional energy metabolism in the lower leg of a diabetic patient with peripheral vascular disease (same patient and image location as in Fig. 10). The FRACTAL images were acquired at rest (a) and during mild dorsiflexion exercise of the foot (b), leading to loss of phosphocreatine (PCr) (arrow, a) and appearance of P_i (arrow, b) in the anterior muscle compartment [in-plane resolution of 12 × 12 mm², slice 25 mm, TR 5 s, TE 91 ms, 2 NEX (5.5 min)].

114

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the phosphorus images. Various methods (24–26) have been suggested. Such an approach would allow identification of areas (voxels) within which the inhomogeneity is great enough to cause signal voids. Furthermore, B_0 maps might be used to correct the metabolite images for spatial misregistration and thus to improve image quality. This would, however, complicate image reconstruction considerably.

A second approach for improving the situation would be the application of the RARE technique (27). This technique acquires several phase-encoding steps within one single echo train and is intrinsically T2 weighted. It could easily be combined with chemical shift selective excitation. Because higher read gradients could be applied, artifacts due to B_0 inhomogeneities would be reduced considerably. Furthermore, RARE would be very likely to result in still improved S/N ratio so that a spatial resolution of 2 cm^3 in the human brain seems possible with scan times of ~30 min.

Despite all of these technical limitations, our first attempts with direct ^{31}P imaging in the human brain were very promising. Clear anatomic detail, reflecting heterogeneous distribution of PCr, could be demonstrated in normals (due to ventricles) and in patients with cerebral neoplasms. In infants, FRACTAL may be able to resolve phosphomonoesters, P_i, and PCr images (unpublished work). These techniques may have wider application in strokes and transient ischemic attacks, as well as in the investigation of physiological responses to brain activation.

Finally, the techniques described in this article should be applicable to nuclei other than ^{31}P. ^{13}C and ^{15}N might be well suited for imaging with the FRACTAL technique, due to their large chemical shifts.

Acknowledgment: We are grateful for the support of the L. K. Whittier Foundation and the Ida Jameson Foundation of California. Work on diabetes supported by the McFarlane Trust.

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115

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THE EFFECT OF BI-LEVEL PROTON DECOUPLING ON THE MEASUREMENT OF PHOSPHORUS METABOLITE RATIOS

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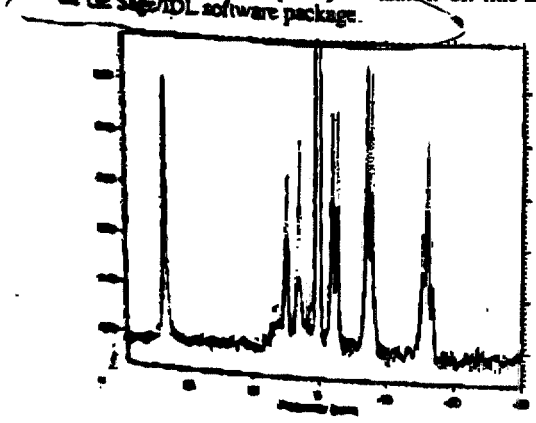
GE Medical Systems, Fremont CA 94539 and Waukesha WI 53188

Introduction

For *in vivo* applications of ^{31}P MRS, the resolution and SNR advantages of proton decoupling and nuclear Overhauser enhancement, nOe, are well known (1,2). A common concern, however, is the question of the error introduced by a potentially unreliable level of nOe. In theory, the resolution advantage of decoupling can be exploited without the uncertain impact of the nOe on quantitative measurements. Unfortunately, slow recovery from transient nuclear Overhauser enhancement (3), generated during decoupling make this impractical in vivo. Sufficient recovery time would be prohibitive and correction for these transient effects would not only require accurate metabolite T_1's but also ^1H-^{31}P cross relaxation rates for each of the metabolite signals. On the other hand, if metabolite ratios proved relatively insensitive to full steady-state nOe, then quantitative information could be obtained from decoupled enhanced spectra with the dual advantages of improved resolution and sensitivity. Therefore, we set out to examine carefully the effect of bi-level decoupling (decoupling with nOe) on metabolite ratios.

Methods

In over 50 separate exams obtained over a period of 2 months, control and proton decoupled spectra were obtained from the gastrocnemius muscle of 5 normal healthy volunteers. Data were collected on a GE Signa 1.5T MRI system equipped with broad band electronics for detection of ^{31}P and, a second exciter for proton irradiation, comprised of an integrated rf driver, a power amplifier, rf filters to protect the receiver from the decoupler carrier and out of band noise. A standard body coil was used for proton decoupling and a conforming flexible coil was used for excitation and reception of phosphorus. A SAR of less than 1 W/kg was achieved using a proton decoupling field strength, $\gamma B_2/2\pi$ of 250 Hz during signal acquisition and a field strength, $\gamma B_2/2\pi$ of 10 Hz for the remainder of the recycle time. Proton irradiation was centered at the water resonant frequency and a WALTZ-16 modulation scheme was used to cover the proton band-width. To minimize baseline distortion, ^{31}P slice selection was obtained using a self-refocused 90°-up / TE 2.5 ms spin-echo pulse (4). Spectra were collected with a TR of 5 s, with the first 20 s of data collection discarded to allow for full steady-state nOe. Metabolite T_1 relaxation times were determined via inversion recovery. Data were automatically processed, phased, integrated and frequency domain fit off-line using the GE Sage/IDL software package.



An nOe-free reference signal was obtained by attaching a proton-free phosphorus sample to the outside of the flexible ^{31}P coil. This sample consisted of 0.4 M phosphonitrillic chloride trimer in 25 ml 99.8% deuterated chloroform. The T_1 of the reference was reduced to 7.3 seconds by addition of 350 µg/ml CrACAC.

Results

Spectra from a typical exam are shown in Fig. 1. The nOe-free reference signal at 24 ppm is unchanged in the bi-level (dashed line) versus control (solid line), consistent with good rf isolation. A 69% increase in the PCr signal and smaller enhancements of the other metabolite resonances is consistent with previous observations in vivo (2). Metabolite nOe's (Table 1) and ratios with γATP (Table 2) are summarized for the two volunteers with the largest metabolite differences.

Conclusions

It has been previously suggested that while proton nOe improves SNR, it leads to a larger error in the measurement of metabolite ratios, or that both accurate metabolite T_1's and ^1H-^{31}P cross-relaxation times must be known for quantitation in the presence of nOe. In the case of normal resting muscle we find this not to be true. From our data we conclude that:

- Pi, γATP and αATP all get the same level of nOe (η_0 = 0.45 - 0.60).
- PDE (primarily GPC) also receives the same level of nOe as γATP but with a larger standard error. Better resolution due to decoupling is a big advantage here.
- PCr gets the most enhancement (η_0 = 0.60 - 0.72). A PCr/γATP correction factor of 0.93 fits all of the data.
- βATP is the least enhanced at 0.4. A βATP/γATP correction factor of 1.07 fits all of the data.
- The standard deviations of metabolite peak areas are significantly reduced in the higher SNR spectra obtained by applying bi-level decoupling.

In general, given enough SNR, quantitative NMR data is best collected fully relaxed and without signal enhancement. However, at the SNR-time limit realized in vivo, the use of typical correction factors for saturation and nOe can lead to improved precision without significant impact on accuracy of the measurement.

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Table 1. nOe (η_0)

	PCr	gamma	alpha	beta	pi	PDE
1/Mid	[illegible]	.51(.08)	.48(.10)	.43(.10)	.46(.10)	.46(.10)
2/Mid	[illegible]	[illegible]	.45(.06)	.41(.06)	.51(.06)	.47 (.12)

Table 2. Metabolite Ratios (uncorrected)

	PCr:gam	Pi:gam	PDE:gam	alpha:gam	beta:gam
1-Ctrl	3.12 (.10)	.71(.06)	.56(.06)	1.27(.06)	1.03(.06)
1-Dec	[illegible]	.69(.02)	.54(.02)	1.23(.03)	0.97(.05)
1-Corr	0.92	NS	NS	NS	1.07
2-Ctrl	3.72 (.10)	.61(.05)	.46(.03)	1.26(.04)	0.95(.04)
2-Dec	[illegible]	.61(.04)	.44(.03)	1.10(.03)	0.88(0.2)
2-Corr	0.92	NS	NS	NS	1.06

116

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NOTES

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Short *TE* Phosphorus Spectroscopy Using a Spin-Echo Pulse

Kelvin O. Lim, John Pauly, Peter Webb, Ralph Hurd, Albert Macovski

***In vivo* phosphorus spectroscopy requires very short acquisition delays in order to capture the signal from components with short transverse relaxation times (T_2). The echo time typical of standard slice selective spin-echo pulses are too long for this application, so hard pulse, free induction decay (FID) acquisitions have frequently been used instead. With FID, however, there is an interval between the time of coherence and data acquisition (acquisition delay), with resulting baseline distortions. In this paper we describe the design of a new short *TE*, slice-selective, composite spin-echo pulse with echo times as short as 2.5 ms. With a long *TR*, fully relaxed, multislice spectra can be collected. This technique will be useful for assessing, *in vivo*, changes in brain phospholipid activity associated with psychiatric and neurological diseases.**

Key words: ^{31}P; spectroscopy; spin-echo pulse.

INTRODUCTION

Much work is currently underway to exploit the potential of phosphorus magnetic resonance spectroscopic (^{31}P MRS) techniques for quantifying, *in vivo*, disease related changes in human brain phospholipid metabolism by examining changes in phosphomonoesters (PME) and phosphodiesters (PDE) (1, 2). *In vivo* ^{31}P MRS techniques have suggested significant alterations in brain phospholipid metabolism in patients with schizophrenia (3, 4), autism (5), and AIDS (6). These studies have used a range of methods for localizing spectra, including surface coils for adjacent areas of brain (3, 5), volume coils and whole slice excitation sequences (6), or modified ISIS techniques for exciting specific volumes of interest (VOI) (4). Regions of the brain analyzed have included the temporal lobes (4), dorsal prefrontal cortex (3, 5) or whole axial sections (6).

The potential of ^{31}P MRS is limited by the low concentrations of the relevant compounds, as well as their short T_2 components, and the inherently low NMR sensitivity of phosphorus. These factors all contribute to low signal to noise ratios and poor spatial resolution. Furthermore, because of the lack of component-specific T_1 data, investigators have generally used reference T_1 values (7) derived from limited samples for purposes of peak quantification, even though there is evidence that there are age-dependent T_1 changes in normal brain (8).

The short T_2 of the ^{31}P metabolites of interest requires short acquisition delays in order to collect useful data. The free induction decay (FID) acquisition technique allow short acquisition delays (9), but the minimum selective RF pulse widths available on clinical imaging hardware, and additional delays imposed by slice refocusing and phase encoding, lead to loss of the initial data points. This then requires the application of algorithms to correct for the resulting baseline distortion. Methods have been developed to compensate for the missing data points (10), but may be subject to errors under poor signal-to-noise ratio (SNR) or other conditions found with ^{31}P (11).

The use of a spin-echo sequence avoids the problem of baseline distortion caused by missing data points, but at the expense of a longer T_2 decay time. A ^{31}P spectroscopic imaging (SI) method using a nonselective spin-echo excitation has recently been developed (11). Using hard RF pulses and splitting the phase encoding lobes, Maudsley *et al.* obtained an echo time of 2.9 ms. A phase encoded FID acquisition gave them T_2 decay time of 2.4 ms. Comparing their spin-echo and FID acquired data, they concluded that the slightly longer T_2 decay time with spin-echo was not detrimental to the signal. However, because they used nonselective pulses, a 3D phase encoding was required in order to obtain spatial localization.

Most current ^{31}P imaging approaches use nonselective pulses. The ^{31}P spectrum is very broad, extending across 600 Hz at 1.5 T, and use of selective pulses will result in spatial displacement of the slice profiles of the different ^{31}P components. Since many acquisitions are required to obtain an acceptable SNR ratio, due to the low sensitivity of ^{31}P, the number is usually large enough for full three dimensional Fourier (3DFT) encoding.

Our approach to ^{31}P imaging has focused on developing clinically feasible techniques for accurately measuring the rapidly decaying components with specific attention to the PME and PDE. For reliable clinical applications, it is important that the imaging method be easy to use, T_2 decay times be relatively brief, and post-processing requirements be minimal. To meet these requirements, we decided to use a slice-selective composite spin-echo pulse. Because the components of interest (PME and PDE) are relatively close in frequency, we were not especially concerned about chemical-shift slice displacement. Because the acquisition is a spin-echo, baseline distortion is avoided and only zero-order phase cor-

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rection is required. This eliminates the risk that first-order phase correction will produce errors in the estimates of the rapidly decaying components, and makes the measurements far more robust. An additional advantage of using slice-selection is that three-dimensional Fourier encoding is no longer required. Indeed, the 2D acquisition mode produces better slice profiles than the 3DFT, which are not particularly good unless a substantial number of phase encodes are collected. Using a long *TR* allows many slices to be acquired in a multislice mode and provides for the collection of more fully relaxed spectra.

METHODS

Hardware capabilities and desired data characteristics constrained the design process. Our goal was 27 cc (3cm × 3cm × 3cm) spatial resolution. All measurements were performed on a 1.5 T GE Signa clinical scanner (GE Medical Systems, Milwaukee, WI). A dual tuned (^{31}P quadrature, ^{1}H linear) birdcage head coil was used for excitation and reception. For ^{31}P, this coil required a 250 μs hard RF pulse to generate a $\pi/2$ nutation, corresponding to a B_1 field of 1000 Hz. The maximum gradient strength was 1 Gauss/cm with a maximum slew rate of 2 Gauss/cm/ms. For the desired spatial resolution of 3 cm in a 24-cm FOV, the gradient constraints dictated a triangular phase encoding pulse width of 500 μs for the highest spatial frequency phase encode.

Spin-Echo Pulse-Pair Design

The RF pulse used in this sequence is a composite of an initial α pulse followed by a refocusing 180° pulse. If these two pulses are designed separately the echo time is limited by the lengths of the individual pulses. The short T_2 phosphorus components will then suffer substantial decay. The approach we take here is to specify the echo time and slice profile, and then solve for the RF pulse that produces this echo. In this case the α and 180° pulses will overlap for short echo times, and the echo may be at any time after the end of the RF pulse.

The RF pulse design method (12) is based on the Shinnar-Le Roux (SLR) algorithm for pulse design. The SLR algorithm reduces pulse design to the design of two polynomials. The spin-echo profile can be described as a product of these two terms. We take the approach of directly designing the product which defines the slice profile. This product is then factored into its two components. The inverse SLR transform then computes the RF pulse that produces that profile at the specified echo time.

These pulse pairs are distinct from self-refocused pulses (13). Self-refocused pulses perform an α degree rotation in-slice, a zero degree rotation out-of-slice, with a smooth transition between the two. The spin-echo pulse pairs differ in that the transition is not smooth, due to a dephased component caused by parasitic excitation from the 180° pulse. The practical difference is in the RF power required. The self-refocusing pulse power increases rapidly with increasing echo time. The spin-echo pulse pairs, on the other hand, always require essentially the same RF power, that of an α and a 180° pulse. For the case of a zero delay, the self-refocusing pulses and the spin-echo pulse pairs are identical.

For phosphorus imaging we would like as short a T_2 decay time (echo time) as possible. The minimum delay from the end of the RF pulse to the echo is determined by the time required for the phase encoding lobe–500 μs for our application. The other major constraint is the peak RF amplitude produced by the RF coil, which essentially specifies the main-lobe width of the 180° pulse. The spin-echo pulse is then designed by incorporating the desired echo delay into the design. The resulting 90° pulse is plotted in Fig. 1. Here we have designed the 90° and the 180° pulse to be in quadrature. The echo time, for T_2 decay purposes, is essentially the time between the peak of the 90° pulse and the echo coherence point. It is actually somewhat less because the magnetization is not in the transverse plane for the entire time.

Many of the metabolites of interest in the phosphorus spectrum have very long T_1s. To maximize SNR the RF pulse should be at the Ernst angle (14). If the Ernst angle is θ, we want the pulse pair to consist of an 180°–θ pulse followed by the 180° pulse. Because the α and 180° components are combined into a single RF pulse, simple scaling of the pulse amplitude will not scale the flip angle; hence a specific pulse must be designed for each flip angle. Like other nonadiabatic spin-echo pulse sequences, this pulse does not work well with surface coil transmission. Examples of pulse pairs for flip angles of 30°, 45°, and 60° are also plotted in Fig. 1. To examine the effect of echo time, we designed a set of pulses at a range of echo times. In Fig. 2 we show three pulses with echo delays of 2.5 (the minimum), 4, and 8 ms, all with a flip angle of 60°.

As was mentioned above, the main difference between self-refocusing pulses and spin-echo pulse pairs is the presence of a crushed signal in the transition bands from the parasitic excitation of the 180° pulse. The phases of the two pulses in the pair can be chosen at will. We usually design the α and the 180° pulses to be in quadrature. Then we can phase cycle the α pulse by conjugating

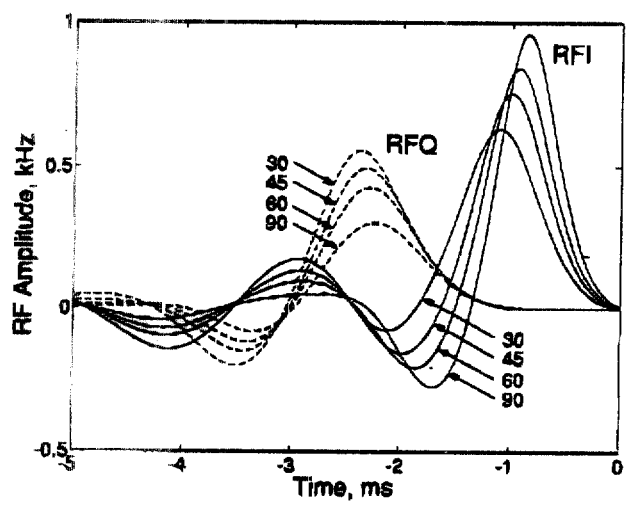

FIG. 1. Plots of the I and Q channels for spin-echo pulses at a constant echo time with varying flip angles of 30, 45, 60, and 90 degrees.

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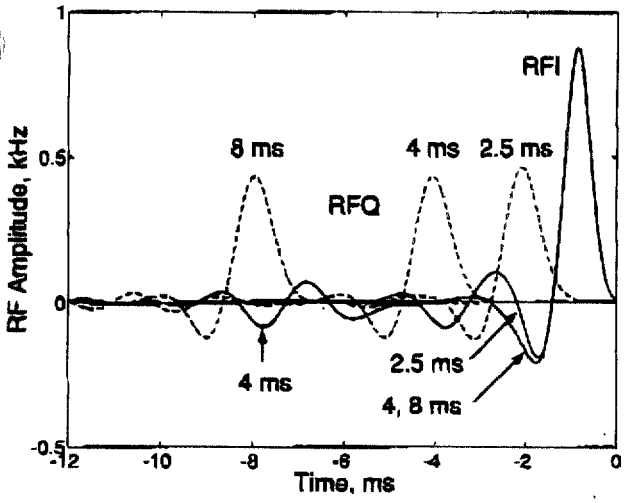

FIG. 2. Plots of the I and Q channels of spin-echo pulses for a 2.5, 4, and 8 ms echo.

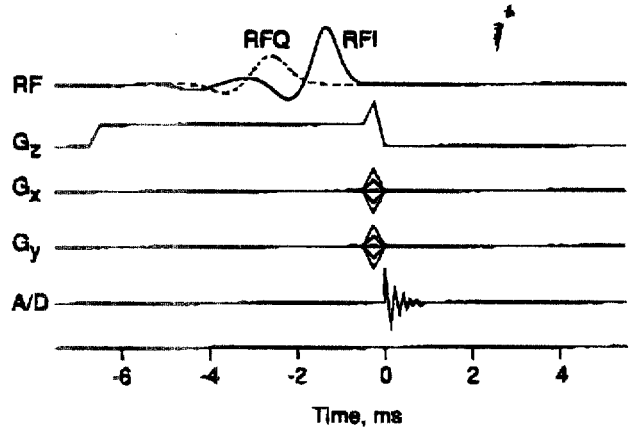

FIG. 4. 2D-SI pulse sequence using a 2.5 ms *TE* spin-echo pulse.

the RF pulse. The desired spin-echo signal changes sign, while the undesired crushed parasitic signal subtracts out. Hence, with one average the parasitic signal can be suppressed. In Fig. 3a we show the slice profile for a single excitation with a 90° pulse shown in Fig. 1. Figure 3b is the slice profile after the two phase cycled acquisitions are subtracted resulting in a very clean slice profile. Because of the design approach used, in which the pulse is designed to fit a specified slice profile, all the pulses have the identical slice profile.

Sequence Design

The spin-echo RF pulse was incorporated into the 2D phase encoded SI sequence shown in Fig. 4. Triangular phase encoding waveforms for an 8 × 8 imaging matrix were incorporated into the *X* and *Y* gradients. The slice selection gradient was placed in the *Z* gradient. The spin-echo pulse requires that the integral of the slice selection gradient from the end of the RF to the coherence point be the same as if the slice-selection gradient were left on; however, the slice selection gradient must also be turned off by the beginning of the echo. To meet these conditions and stay within gradient slew rate limits, the post RF *Z* gradient was divided into two ramps with the total area meeting the constant integrated gradient requirement and the down going ramp meeting slew rate constraints.

DATA COLLECTION AND RESULTS

In order to demonstrate the capabilities of this pulse sequence, a variety of acquisition parameters were used on consenting, healthy control subjects. In general the following steps were taken when acquiring data. Proton MRI was first performed to guide the placement of the axial spectroscopic slice. Automatic shimming on water was performed over the desired region (15). The hardware was then switched to ^{31}P mode and pulse tuning performed by maximizing the signal peaks from a whole slice. The spectral width was 2500 Hz and 512 points were collected, corresponding to about a 250 ms data acquisition window. Raw data were transferred from the scanner to a Sun SPARCStation (Sun Microsystems, Mountain View, CA) for further processing using the

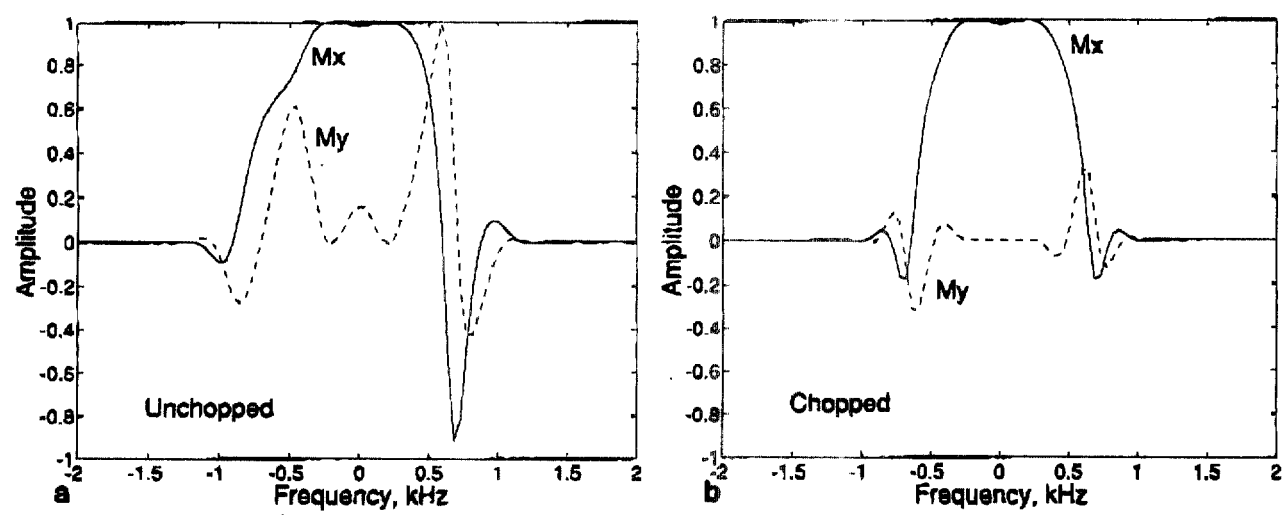

FIG. 3. Slice profiles for (a) unchopped and (b) chopped pulses.

119

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SA/GE software package (GE Medical Systems, Milwaukee, WI). The data were zero filled to 1024 points, line broadened, and then Fourier transformed. Zero order phasing was done but first order phasing was unnecessary because no initial points were lost during data collection. Initial starting values for the peaks were manually defined and then automatically fitted with Lorentzian lines.

To illustrate the different echo times achievable by this pulse sequence, whole-slice brain spectra were collected using three different spin-echo pulses with *TE*s of 2.5, 4.0, and 8.0 ms shown earlier in Fig. 2. *TR* was 2000 ms, flip angle 60°, slice thickness 33 mm. Spectra were line-broadened by 5 Hz, then zero order phase corrected. The spectra are shown in Fig. 5. As expected, the broad component, stretching from the PME to the βATP peaks, decreases with increasing *TE* (16).

To examine saturation effects, whole slice acquisitions, 35 mm thick, with *TR*s of 2 and 4 s were performed. Scan time was the same for both, 256 s. In Fig. 6 are plotted the spectra from a 4-s *TR*, a 2-s *TR*, and the difference signal from the two spectra, all plotted with the same scale.

Spectroscopic imaging data were collected using 8 × 8 phase encodes, a 28-cm field of view, *TR* 4000 ms, *TE* 2.5 ms, flip angle 60°, slice thickness 35 mm, 2048 points, and eight averages for a total scan time of 34 min. Ten Hz line-broadening was applied followed by FT reconstruction. Sample 2D spectra superimposed on the corresponding anatomical image are shown in Fig. 7. In Fig. 8, the raw spectrum, fitted spectrum and difference signal are shown for the starred voxel in Fig. 7. A total of 12 Lorentzian lines were used for the fitting, including a broad component for the baseline.

DISCUSSION

The use of a spin-echo pulse for selective excitation in ^{31}P spectroscopy provides several advantages over FID excitation approaches and over 3D acquisitions. First, it combines flexibility in slice selection with the benefits of a short T_2 decay time found in an FID excitation approach. With a 250 ms data acquisition window, multiple slices can be collected in a *TR* of 2 s. This approach potentially allows the time-efficient collection of fully relaxed spectra from multiple slices. Second, unlike FID, no initial data points are lost, permitting quantification free of FID-induced baseline distortion. Furthermore, this spin-echo pulse produces an excellent slice profile without use of spoiling gradients. The spatial resolution and SNR of spectra collected with our sequences compare favorably with those published by other groups (11, 17). The lack of distortion of the collected spectra allows excellent fitting with Lorentzian lines using only zero order phase correction.

For clinical applications, multislice SI is preferable to fixed VOI imaging. Multislice SI enables assessment of

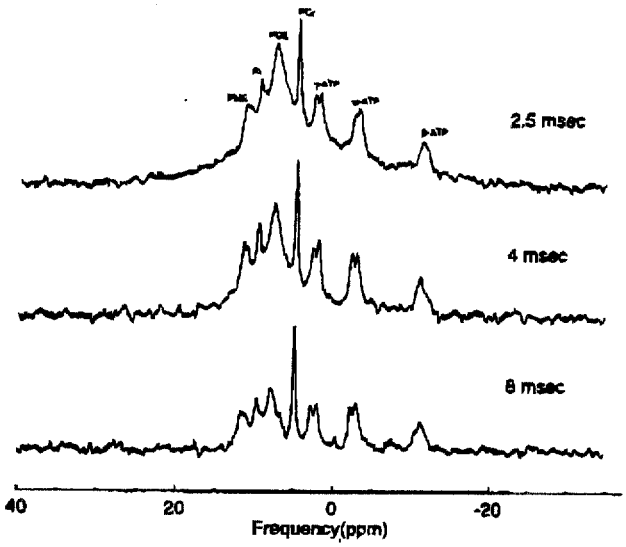

FIG. 5. Spectra from 33 mm axial slice through the brain at *TR* 2000 ms and echo times of 2.5, 4, and 8 ms.

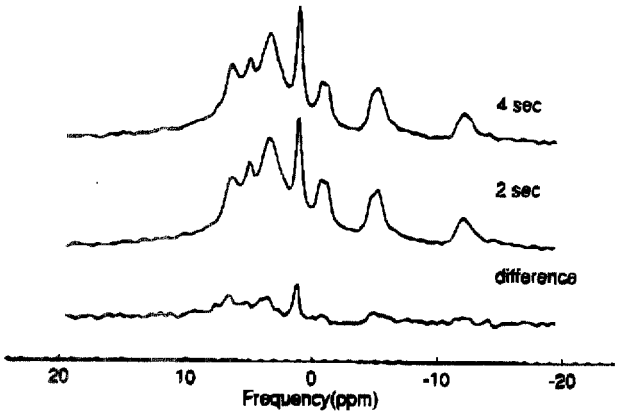

FIG. 6. Whole slice spectra collected with a *TR* of 4 s (top), *TR* of 2 s (middle), and the difference (bottom).

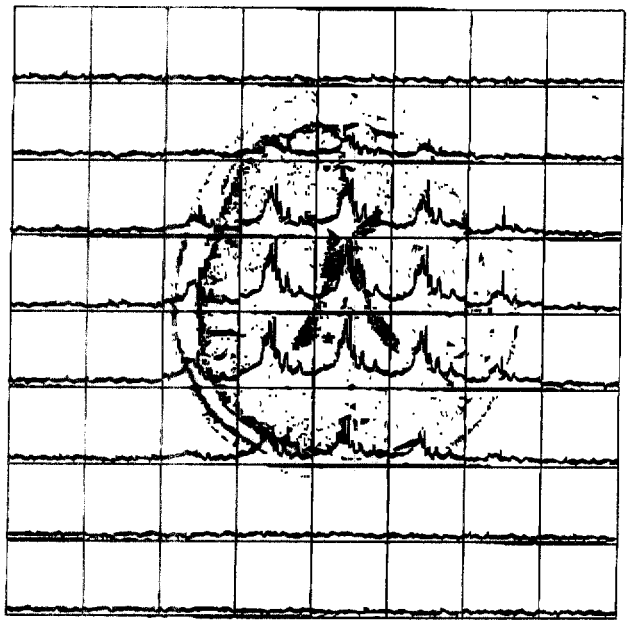

FIG. 7. 8 × 8 2D-SI ^{31}P data set superimposed on the corresponding edges from an anatomical axial MRI. *TR* of 4 s, *TE* of 2.5 ms, FOV of 28 cm, slice thickness of 35 mm and scan time of 34 min.

120

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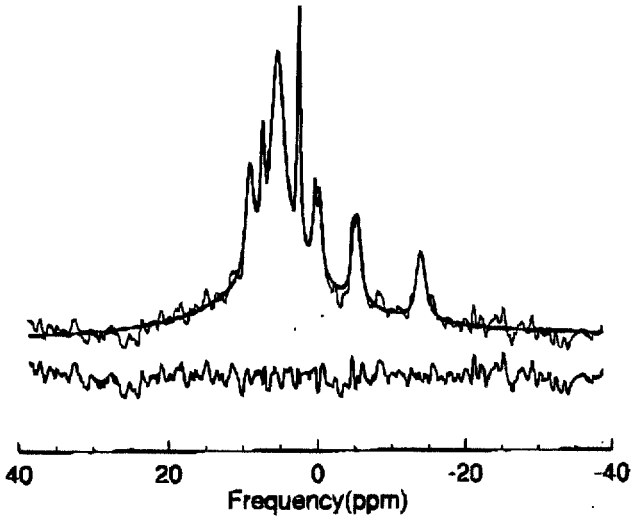

FIG. 8. Spectrum from the starred voxel in Fig. 7. Plots of raw spectrum and fitted spectrum (heavy line) including a broad component are shown along with the difference signal (bottom) between the raw spectrum and the fitted spectrum.

the regional or neuroanatomic distribution of observed phospholipid metabolites. Such regional information is important for obtaining a better understanding of their biological significance, and elaborating upon different results obtained from different brain regions, e.g., (3, 4). An additional advantage of SI is the potential it offers for being combined with high resolution morphological brain data obtained with proton imaging to make corrections for partially volumed spectroscopic voxel. The typical voxel, approximately 30 cc, in many *in vivo* ^{31}P MRS studies usually must encompass both white and gray matter (as well as CSF). However, *in vitro* spectroscopic analysis of samples of calf white and gray matter, have shown that white matter yields much higher PDE values than gray matter (18). Thus PME and PDE values reported in existing clinical studies may be influenced by the ratio of white and gray matter in the voxel.

One limitation of selective excitation is that it can result in potential slice misregistration for different spectral components. This is related to the RF bandwidth (RFBW) and the chemical shift range (CSR) of interest. The maximum frequency offset would be CSR/RFBW. A CSR of 500 Hz would correspond to approximately 19 ppm at 1.5 Tesla. With an RFBW of 1000 Hz, this would result in a maximum spatial shift of one half of a slice; in this case 15 mm. For the PME and PDE components of interest in this study, the 5 ppm difference corresponds to a spatial shift of approximately 4 mm.

Another way to reduce slice misregistration is to increase RFBW. There are several approaches to this while still remaining within peak power constraints. As evident from Fig. 1, decreasing the flip angle decreases the required peak RF power. Hence, for the same peak power the smaller flip angle pulses can be of shorter duration, increasing the RFBW. However, the pulse has to be redesigned to preserve the desired echo time. The use of RF phase modulation can also be used to decrease the peak power requirements. This again allows the pulse pair to be played in a shorter time, thereby increasing the RFBW. In Pauly and Macovski (12) an example is shown where the peak RF amplitude was reduced by a factor of two. This would allow the pulse to be played in half the time, doubling the RFBW.

By collecting fully relaxed spectra, we avoid the need to make any assumptions about component and state-specific T_1 values, assumptions which are best avoided, especially in studies of patients with possible brain pathology. Figure 6 illustrates that significant saturation effects are present at a *TR* of 2 s, primarily affecting the PCr, PME, and PDE peaks. With partially relaxed spectra, information on the T_1 of each of the components being examined is needed for quantification. Collection of specific T_1 data for each component and state is complicated and time consuming, so standard values are frequently used, even though few studies have assessed *in vivo* T_1s of these components.

Collection of fully relaxed data involves compromises between SNR, scan time and amount of saturation contamination. The Ernst angle relationship provides the angle for optimum SNR for a given *TR* and T_1, however saturation effects are not part of the optimization. For a given *TR* and T_1, decreasing the angle will decrease saturation contamination of the spectra, but at the expense of SNR. Because this is a monotonic function, no optimum exists and one must select the amount of saturation contamination and SNR acceptable for the specific application. A guide might be to match the amount of saturation contamination to the SNR so that one would be hidden by the other.

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121

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A Quantitative Assessment of Liver Metabolites in Jaundice Using Three-Dimensional Phosphorus Chemical Shift Imaging

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Introduction

In patients with jaundice due to obstruction of the biliary tree, the incidence of morbidity and mortality following surgery is high (1). The object of this study was to determine whether jaundice influenced energy metabolism in the liver. To non-invasively monitor the effect of bile duct obstruction in a rat model, 3D-^{31}P Chemical Shift Imaging (CSI) (2) was performed using an external standard for quantitation.

Methods

All studies were performed on a 4.7 Tesla Bruker-CSI spectrometer. Each animal was anaesthetized by isoflurane inhalation and placed prone over a 31 mm diameter ^{31}P surface coil. Located at the center of the coil was a standard containing methylene diphosphonic acid (MDP). The animal/surface coil was positioned inside a proton-tuned birdcage coil for proton imaging.

T1-weighted scout images were acquired, followed by shimming. The spectrometer frequency was centered on the MDP standard and a fully relaxed unlocalized FID was acquired with a flip angle of 90° to provide a reference for metabolite quantitation. The spectrometer frequency was then centered on the PME region and 3D-CSI was performed over a 72 cm field of view with 8x8x8 phase encodes resulting in a voxel size of 729 mm^3. The pulse sequence consisted of a hard pulse, phase-encoding gradients, and data acquisition. The flip angle at the liver voxel of interest was 40-60°. With a repetition time of 1s and 6 averages, the CSI acquisition required 54 minutes. Five jaundiced animals were scanned at weeks 1, 2, and 3 post-bile duct ligation. Five normal control animals were also studied. ^{31}P T1 measurements were performed on a separate group of 4 normal rats using a partial-saturation pulse sequence localized by 3D-CSI with TR = 100, 350, 600, 900, and 6000. In separate groups of jaundiced and pair fed rats (N=5-10 in each), hepatic metabolites were analyzed by HPLC.

NMR data were processed using SAGE/IDL software (GE, Milwaukee WI, RSI, Boulder, CO) for voxel shifting, Fourier transform, spectral grid/image overlay and single voxel FID extraction. The extracted FID was fit in the time domain using the MRUI-VARPRO analysis package (3). Software for mapping the 3-dimensional B_1 field and overlaying the B_1 data on the images for calculation of flip angle and receive B_1 sensitivity over the liver voxel was written in IDL. Intracellular pH was calculated from the P_i/α-NTP chemical shift. Metabolite concentrations were calculated from peak areas according to:

$$[M] = \frac{PA(m) \times Q(s) \times NEX(s) \times B_{1rec}(s)}{PA(s) \times NEX(m) \times PE(m) \times B_{1rec}FA(m) \times (1 - BF)}$$

[M] = metabolite concentration (mMoles/liter),
m,s refer to metabolite and standard, respectively,
PA = peak area,
Q = millimole quantity,
NEX = number of averages,
PE = total number of phase encode steps,
$B_{1rec}(s)$= normalized coil receive field sensitivity at standard,
$B_{1rec}FA$ = B_1-flip angle factor accounting for saturation and $B1_{rec}$ which vary over the voxel.
BF = fraction of voxel occupied by bile duct: In some jaundiced rats, the bile duct remnant could not be avoided in placing the liver voxel. Hence the fraction of voxel occupied by bile duct was included in the analysis. This remnant was found to contain no metabolites of interest for the analysis

Results

Liver metabolite concentrations and pH for normal and jaundiced rats are shown in Table 1. At week 3, P_i and γ-NTP were significantly reduced compared to control values ($p<0.01$ and $p<0.05$, respectively). At weeks 2 and 3, pH was elevated ($p<0.05$ and $p=0.01$, respectively). α-NTP and β-NTP were unchanged. HPLC data showed no change in ATP although hepatic energy charge (ATP + 1/2ADP)/(AMP + ADP + ATP) was significantly lower at days 2,21 and 28.

Discussion

These data indicate that jaundice may affect liver ^{31}P metabolism, especially at 2-3 weeks. The physiological significance of the changes in P_i and pH is currently under investigation. Although γ-NTP appeared to decrease at week 3, the unchanged α and β-NTP indicate that this result may be fortuitous, and assessment of NTP alone may not provide pertinent information about metabolism in jaundice.

The calculated concentrations of NTP in normal rats were substantially greater than those reported in the literature (>50%) (4). The CSI point spread function (PSF) is a likely source of error. Based upon the voxel size relative to the sensitive tissue volume, we estimate that the PSF would result in at least a 20% overestimation of concentration and possibly greater than 50% (5,6). However, because the tissue geometry was similar in all experiments, this does not alter the significance of the changes found relative to controls.

Table 1. Liver metabolite concentrations (mMole/liter) calculated from 3D-CSI localized ^{31}P spectra.

		PME	P_i	γ-NTP	pH
	N	mean ± sdev	mean ± sdev	mean ± sdev	mean ± sdev
baseline	5	4.7 ± 1.1	5.0 ± 0.7	5.9 ± 0.7	7.18 ± 0.04
week 1	5	5.0 ± 1.6	6.0 ± 2.3	6.2 ± 1.6	7.20 ± 0.12
week 2	5	5.4 ± 0.8	6.6 ± 2.0	6.3 ± 0.6	7.26 ± 0.05*
week 3	5	4.8 ± 0.6	4.0 ± 0.4*	4.5 ± 0.4*	7.42 ± 0.15*

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123

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