Development of Frequency Domain Multidimensional Spectroscopy

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CMDS

The Wright Group focuses on the development and usage of Coherent MultiDimensional Spectroscopy (CMDS).

CMDS is a family of related nonlinear spectroscopic experiments.

Why CMDS?

[A BUNCH OF COOL PUBLICATIONS—FOCUSING ON COHERENCE TRANSFER, MECHANISMS ETC] [MORE APPLICATIONS]

Coherence in Energy Transfer and Photosynthesis

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Analytical

But wait! I'm an *Analytical* Chemist...

What am I doing in a field so rich with fundamental studies?

I hope to convince you that CMDS can be used for analytical work.

- detection (selectivity)
- unknown identification
- quantification

ACCOUNTS
of chemical research

Mixed Frequency-/Time-Domain Coherent Multidimensional Spectroscopy: Research Tool or Potential Analytical Method?

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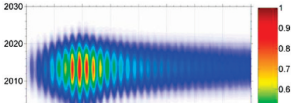
RECEIVED ON JANUARY 23, 2009

CONSPECTUS

Coherent multidimensional spectroscopy (CMDS) is now the optical analogue of nuclear magnetic resonance (NMR). Just as NMR heteronuclear multiple-quantum coherence (HMQC) methods rely on multiple quantum coherences, achieving widespread application requires that CMDS also excites multiple quantum



Pakoulev et al. (2009)

Spectroscopy forms the heart of the analytical methodology used for routine chemical measurement. Of all the analytical spectroscopic methods, NMR spectroscopy is unique in its ability to correlate spin resonances and resolve spectral features from spectra containing thousands of peaks. For example, heteronuclear multiple quantum coherence (HMQC) spectroscopy achieves this capability by exciting ^{1}H, ^{15}N, ^{13} C=O, and ^{13}Cα spins to form a multiple quantum coherence characteristic of a specific position in a protein's backbone. Three excitations define a specific residue, and a fourth defines the coupling to an adjacent residue. Not only does it decongest the spectra, it defines the couplings and connectivity between the different nuclear spin states. Coherent multidimensional spectroscopy (CMDS) has emerged as the optical analogue of nuclear magnetic resonance (NMR), and there is great interest in using it as a general analytical methodology.

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Generation of Simplified Protein Raman Spectra Using Three-Color Picosecond Coherent Anti-Stokes Raman Spectroscopy

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The well-known and prominent marker bands of aromatic amino acids in Raman spectra of protein and peptide films are revisited in the frequency and time domains using three-color picosecond coherent anti-Stokes Raman spectroscopy (CARS). We show here that control of the probe delay allows the narrow width/long lifetime states to be observed free not only from nonresonant background and fluorescence contamination but also free from the spectral congestion that arises from the complex background of spectrally broader (shorter lifetime) vibrational modes. The reasonable limits of detection obtained indicate that such CARS methods may be useful for quantitative analysis of protein composition.

Introduction

The relative and absolute quantification of proteins and their amino acid composition from separated cell extracts is of central importance in the field of proteomics. The possibility of performing such analyses by optical means, on proteins separated, for example, by capillary electrophoresis (CZE) or

spectroscopy that helped to reduce spectral congestion of the protein spectra was the ability to select only coupled vibrational states (the fundamental feature of multidimensional vibrational spectroscopy). The method also employed picosecond delays between the excitation pulses to reduce the levels of nonresonant background relative to the desired signals.[9]

ACCOUNTS
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Biological and Biomedical Applications of Two-Dimensional Vibrational Spectroscopy: Proteomics, Imaging, and Structural Analysis

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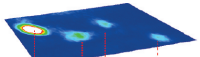
RECEIVED ON MARCH 10, 2009

CONSPECTUS



In the last 10 years, several forms of two-dimensional infrared (2DIR) spectroscopy have been developed, such as IR pump−probe spectroscopy and photon-echo techniques. In this Account, we describe a doubly vibrationally

Fournier et al. (2009)

Our protein identification strategy is based on using EVV 2DIR to quantify the amino acid content of a protein. EVV 2DIR is shown to be able to perform absolute quantification, something of major importance in the field of proteomics but rather difficult and time-consuming to achieve with mass spectrometry. Our technique can be qualified as a top-down label-free method; it does not require intensive sample preparation, the proteins are intact when analyzed, and it does not have any mass restriction on the proteins to be analyzed. Moreover, EVV 2DIR is a nondestructive technique; the samples can be kept for reanalysis in the light of further information.

Domains of CMDS

CMDS can be collected in two domains:

- time domain
- frequency domain

Time domain

Multiple broadband pulses are scanned in *time* to collect a multidimensional interferogram (analogous to FTIR, NMR).

A local oscillator must be used to measure the *phase* of the output.

This technique is...

- fast (even single shot)
- robust

pulse shapers have made time-domain CMDS (2DIR) almost routine.

Frequency domain

In the Wright Group, we focus on *frequency* domain "Multi-Resonant" (MR)-CMDS.

Automated Optical Parametric Amplifiers (OPAs) are used to produce relatively narrow-band pulses. Multidimensional spectra are collected "directly" by scanning OPAs against each-other.

This strategy is...

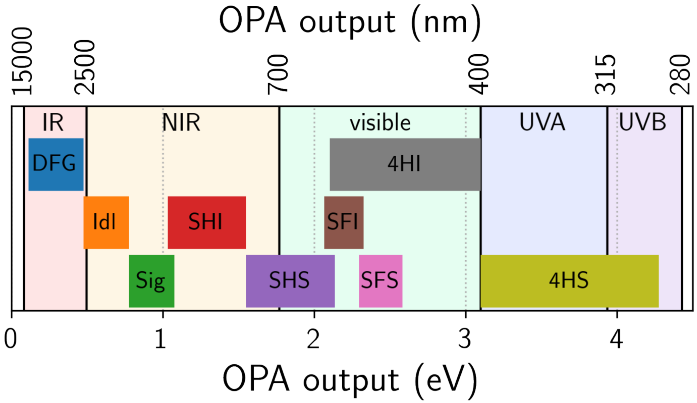
- slow (must directly visit each pixel)
- fragile (many crucial moving pieces)

but! It is incredibly flexible.

Bandwidth

MR-CMDS has no bandwidth limit!

There is just the small matter of making the source continuously tunable...



Selection rules

MR-CMDS can easily collect data without an external local oscillator.

This means... [BOYLE]

The instrument

[PICTURE OF LASER LAB]

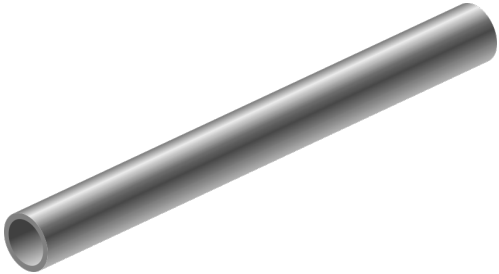
The instrument

Many kinds of component hardware

- monochromators
- delay stages
- filters
- OPAs

$\sim$ 10 settable devices, $\sim$ 25 motors.
Multiple detectors.

Pipeline



What does the “pipeline” of MR-CMDS data acquisition and processing look like in the Wright Group?

How to increase data throughput and quality, while decreasing frustration of experimentalists?

Processing

WrightTools.

Universal format

WrightTools defines a *universal file format* for CMDS.

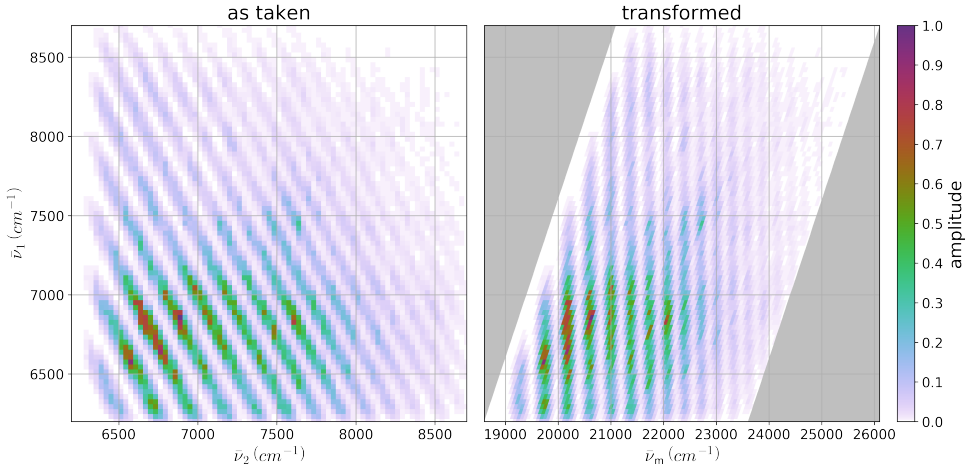
- store multiple multidimensional arrays
- metadata

Import data from a variety of sources.

- previous Wright Group acquisition software
- commercial instruments (JASCO, Shimadzu, Ocean Optics)

Flexible data model

Flexibility to transform into any desired “projection” on component variables.



Acquisition

PyCMDS—unified software for controlling hardware and collecting data.

Abstraction

Hardware—something that has a position that can be set.

Sensor—something that has a signal that can be read.

Modular hardware model

```
Hardware
├── Delay
│   ├── Aerotech
│   ├── LTS300
│   ├── MFA
│   └── PMC
├── Filter
│   └── Homebuilt
├── OPA
│   ├── OPA800/PMC
│   └── TOPAS
│       ├── TOPAS-C
│       └── TOPAS-800
└── Spectrometer
    └── MicroHR
```

Modular sensor model

Can have as many sensors as needed.

Each sensor contributes one or more channels.

Sensors with size contribute new variables (dimensions).

Central loop

Set, wait, read, wait, repeat.

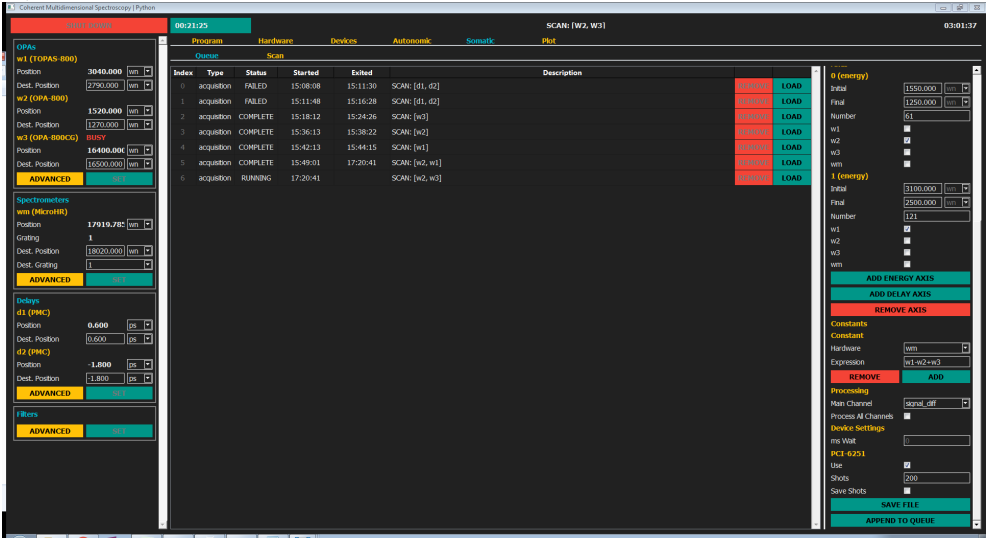
Everything is multi-threaded (simultaneous motion, simultaneous read).

Acquisitions

Acquisition—a particular set of actions.

Acquisition modules—a GUI that accepts a user instruction.

Queue.


Coherent Multidimensional Spectroscopy | Python
Select Points
00:21:25
SCAN: [W2, W3]
03:01:37
Program
Hardware
Devices
Autonomic
Somatic
Plot
Queue
Scan
OPAs
w1 (TOPAS-800)
Position 3040.000 wn
Dest. Position 2790.000 wn
w2 (OPA-800)
Position 1520.000 wn
Dest. Position 1270.000 wn
w3 (OPA-800CG) BUSY
Position 16400.00 wn
Dest. Position 16500.000 wn
ADVANCED SET
Spectrometers
wm (MicroHR)
Position 17919.785 wn
Grating 1
Dest. Position 18020.000 wn
Dest. Grating 1
ADVANCED SET
Delays
d1 (PMC)
Position 0.600 ps
Dest. Position 0.600 ps
d2 (PMC)
Position -1.800 ps
Dest. Position -1.800 ps
ADVANCED SET
Filters
ADVANCED SET
Index Type Status Started Exited Description
0 acquisition FAILED 15:08:08 15:11:30 SCAN: [d1, d2] REMOVE LOAD
1 acquisition FAILED 15:11:48 15:16:28 SCAN: [d1, d2] REMOVE LOAD
2 acquisition COMPLETE 15:18:12 15:24:26 SCAN: [w3] REMOVE LOAD
3 acquisition COMPLETE 15:36:13 15:38:22 SCAN: [w2] REMOVE LOAD
4 acquisition COMPLETE 15:42:13 15:44:15 SCAN: [w1] REMOVE LOAD
5 acquisition COMPLETE 15:49:01 17:20:41 SCAN: [w2, w1] REMOVE LOAD
6 acquisition RUNNING 17:20:41 SCAN: [w2, w3] REMOVE LOAD
0 (energy)
Initial 1550.000 wn
Final 1250.000 wn
Number 61
w1
w2
w3
wm
1 (energy)
Initial 3100.000 wn
Final 2500.000 wn
Number 121
w1
w2
w3
wm
ADD ENERGY AXIS
ADD DELAY AXIS
REMOVE AXIS
Constants
Constant
Hardware wm
Expression w1-w2+w3
REMOVE ADD
Processing
Main Channel signal_diff
Process All Channels
Device Settings
ms Wait 0
PCI-6251
Use
Shots 200
Save Shots
SAVE FILE
APPEND TO QUEUE

Queue

This strategy can be incredibly productive!

- Soon after the queue was first implemented, we collected more pixels in two weeks than had been collected over the previous three years.

Tuning

Conclusion

MR-CMDS theory

Mixed domain

[FIGURES FROM DAN'S PAPER]