INADEQUATE

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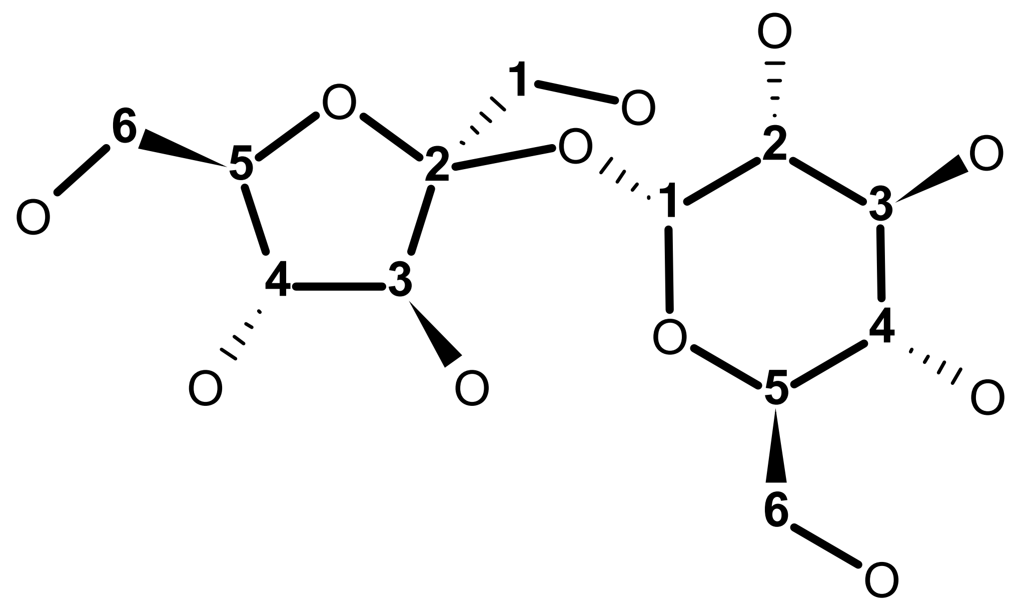
(with Alex Bain, Sean Watson, Anuroop Sharma)

Small Molecules



- biological products
- possible medical applications
- want to know structure
- look at C-C bonds, double-quantum structure

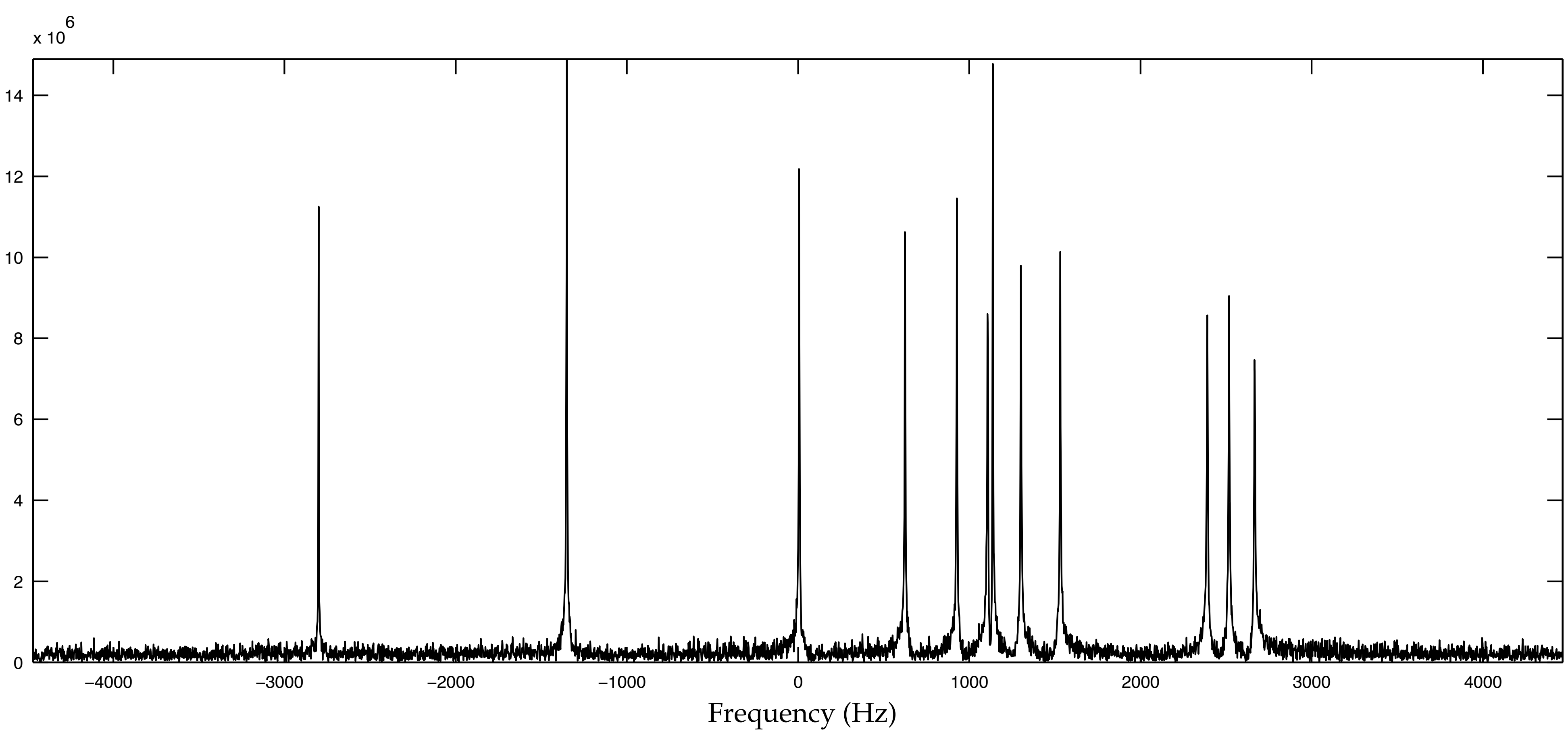
Single Quantum

- Single Quantum = Bloch Equations
- Complex Form

$$\frac{d}{dt}\begin{pmatrix} \rho_{+1} \\ \rho_0 \\ \rho_{-1} \\ \rho_{eq} \end{pmatrix} = -\begin{pmatrix} i\omega + R_2 & i\frac{\gamma B_1}{\sqrt{2}} & 0 & 0 \\ i\frac{\gamma B_1}{\sqrt{2}} & R_1 & i\frac{\gamma B_1}{\sqrt{2}} & -R_1 \\ 0 & i\frac{\gamma B_1}{\sqrt{2}} & -i\omega + R_2 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}\begin{pmatrix} \rho_{+1} \\ \rho_0 \\ \rho_{-1} \\ \rho_{eq} \end{pmatrix}$$

Step 1

- measure C spectrum



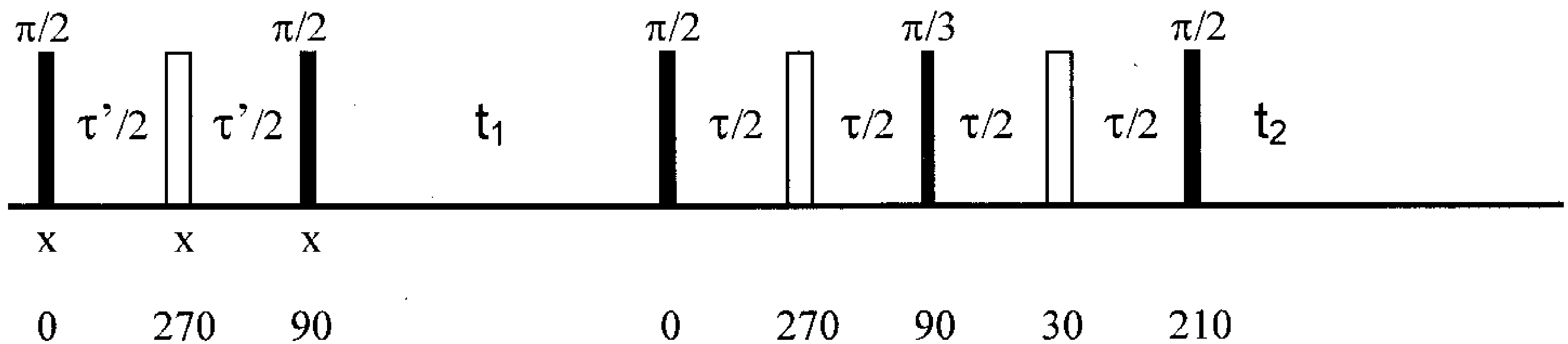
Double Quantum

- two nuclei, arrange by coherence level

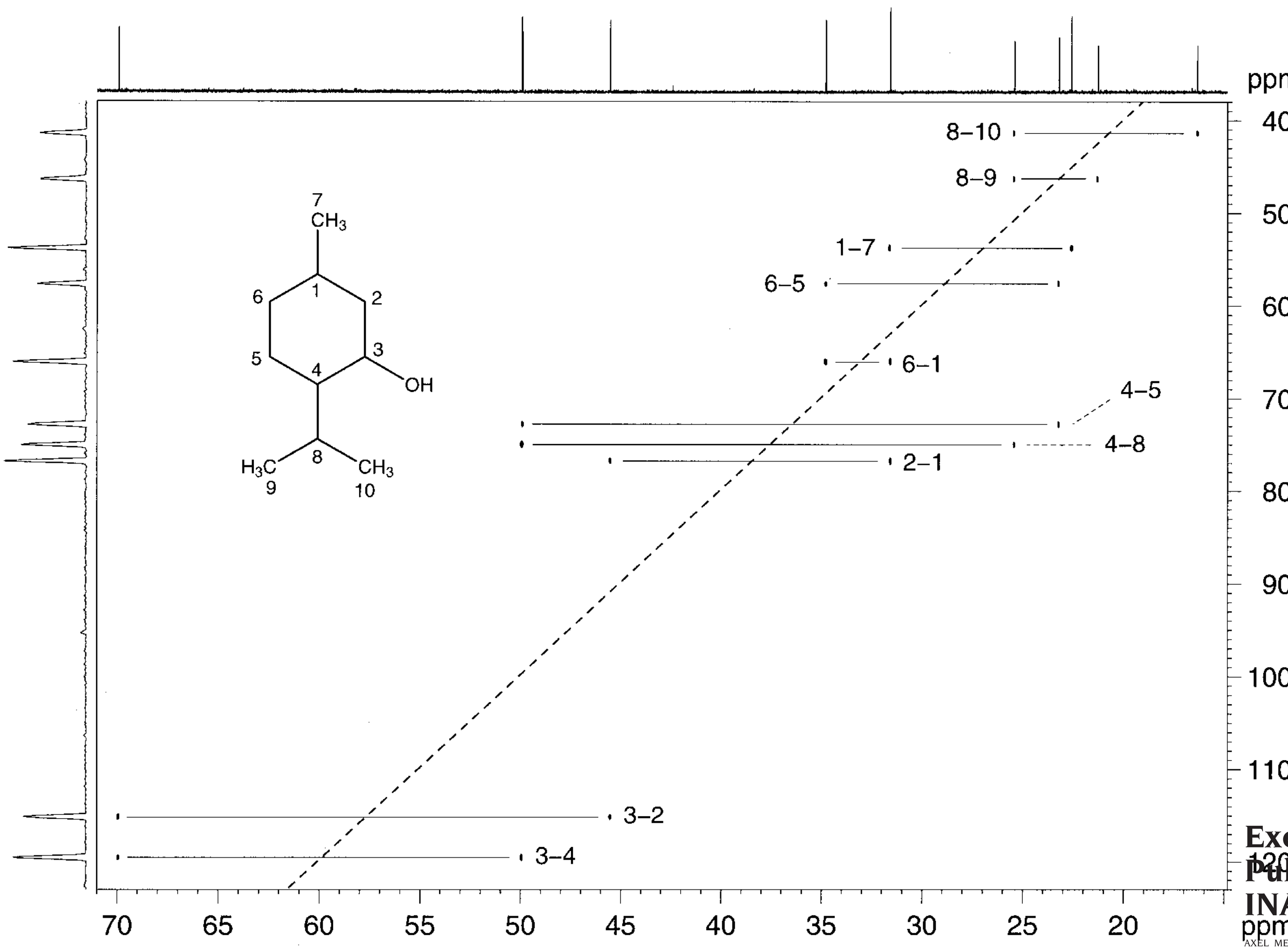
$$
\begin{pmatrix}
A+B & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & A & \frac{J}{2} & 0 & -\frac{J}{2} & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & \frac{J}{2} & A & -\frac{J}{2} & 0 & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & 0 & -\frac{J}{2} & B & \frac{J}{2} & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & -\frac{J}{2} & 0 & \frac{J}{2} & B & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & -A+B & 0 & \frac{J}{2} & -\frac{J}{2} & 0 & 0 & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & 0 & 0 & 0 & 0 & 0 & 0 & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & \frac{J}{2} & 0 & 0 & 0 & 0 & -\frac{J}{2} & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & -\frac{J}{2} & 0 & 0 & 0 & 0 & \frac{J}{2} & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & 0 & 0 & 0 & 0 & 0 & 0 & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & 0 & 0 & -\frac{J}{2} & \frac{J}{2} & 0 & A-B & \cdot & \cdot & \cdot & \cdot & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & -A & -\frac{J}{2} & 0 & \frac{J}{2} & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & -\frac{J}{2} & -A & \frac{J}{2} & 0 & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0 & \frac{J}{2} & B & -\frac{J}{2} & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \frac{J}{2} & 0 & -\frac{J}{2} & B & \cdot \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & -A-B
\end{pmatrix}
\begin{pmatrix}
|0)|0) \\
|1_{+1})|0) \\
|1_{0})|0) \\
|1_{-1})|0) \\
|0)|1_{+1}) \\
|1_{+1})|1_{+1}) \\
|1_{0})|1_{+1}) \\
|1_{-1})|1_{+1}) \\
|0)|1_{0}) \\
|1_{+1})|1_{0}) \\
|1_{0})|1_{0}) \\
|1_{-1})|1_{0}) \\
|0)|1_{-1}) \\
|1_{+1})|1_{-1}) \\
|1_{0})|1_{-1}) \\
|1_{-1})|1_{-1})
\end{pmatrix}
\quad \text{permute} \rightarrow \quad
\begin{pmatrix}
|1_{+1})|1_{+1}) \\
|1_{+1})|0) \\
|1_{+1})|1_{0}) \\
|0)|1_{+1}) \\
|1_{0})|1_{+1}) \\
|1_{-1})|1_{+1}) \\
|0)|0) \\
|1_{0})|0) \\
|0)|1_{0}) \\
|1_{0})|1_{0}) \\
|1_{+1})|1_{-1}) \\
|1_{-1})|0) \\
|1_{-1})|1_{0}) \\
|0)|1_{-1}) \\
|1_{0})|1_{-1}) \\
|1_{-1})|1_{-1})
\end{pmatrix}
$$

Measure 2Quantum

- create 2Q spin
- let it evolve (delay 1)
- put it back into 1Q
- measure (readout 2)



Isolated Signal

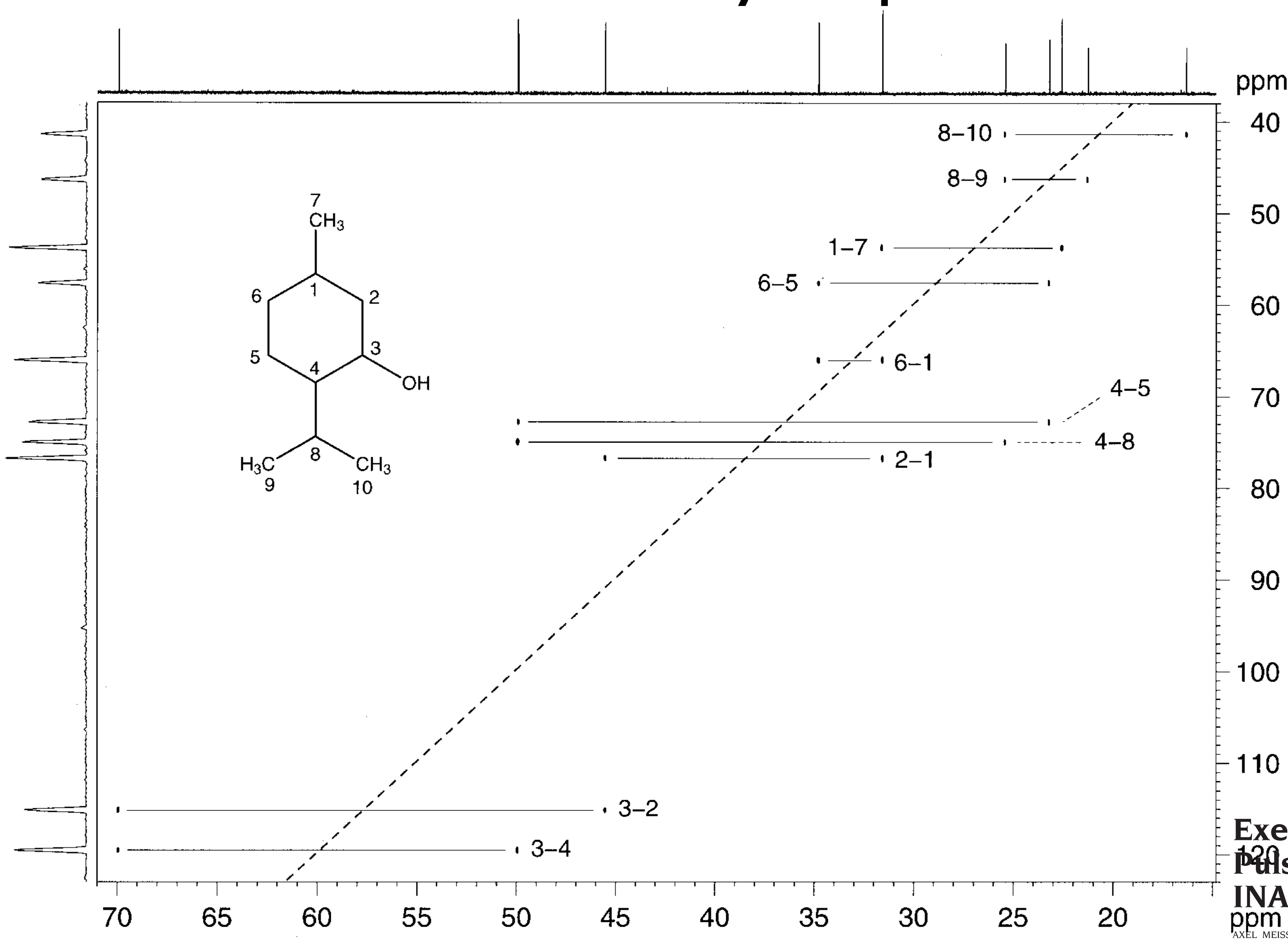


Exercise in Modern NMR Pulse Sequence Design: INADEQUATE CR

AXEL MEISSNER, OLE WINNECHE SØRENSEN

Isolated Signal

readout = directly acquired



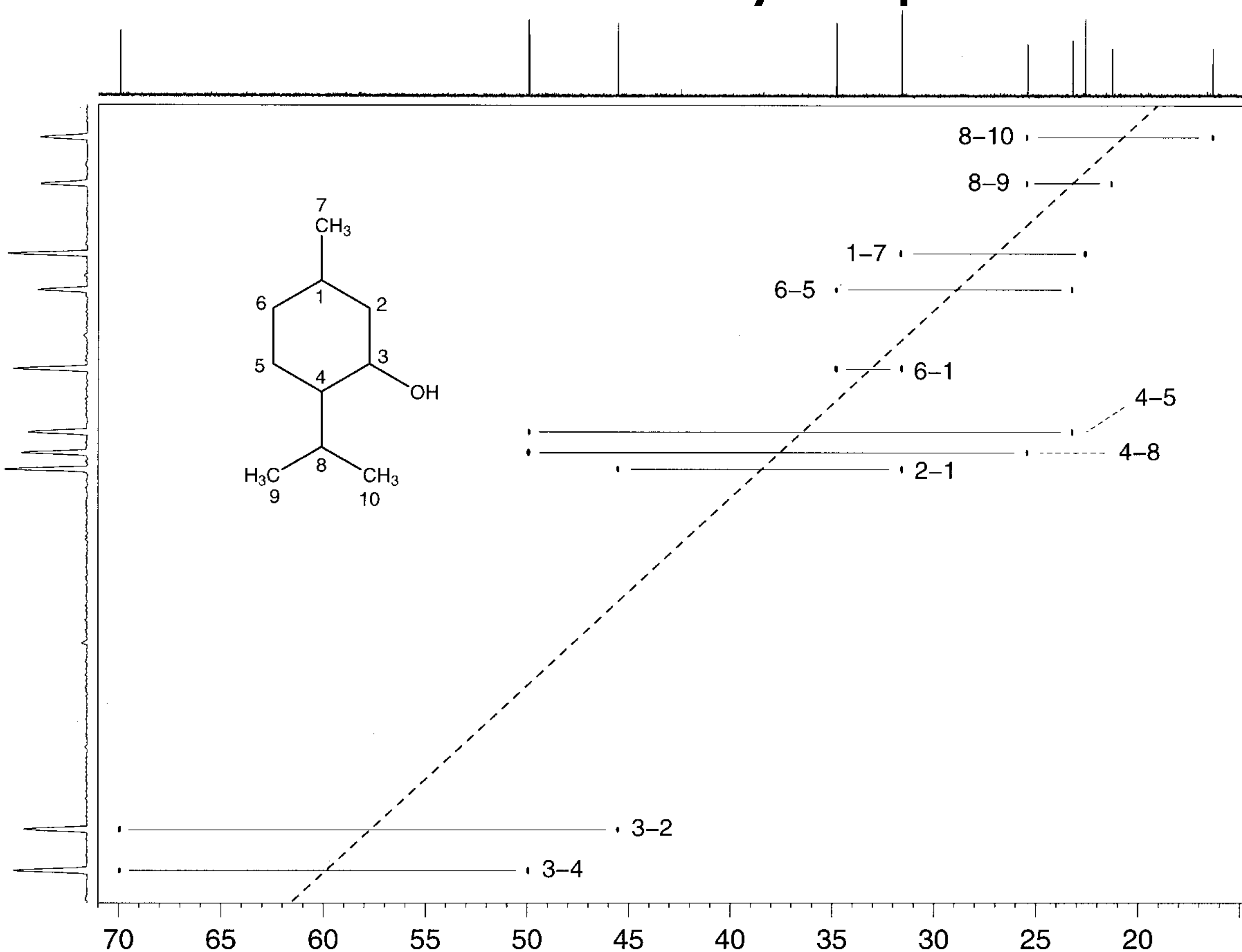
Exercise in Modern NMR Pulse Sequence Design: INADEQUATE CR

AXEL MEISSNER, OLE WINNECHE SØRENSEN

Isolated Signal

readout = directly acquired

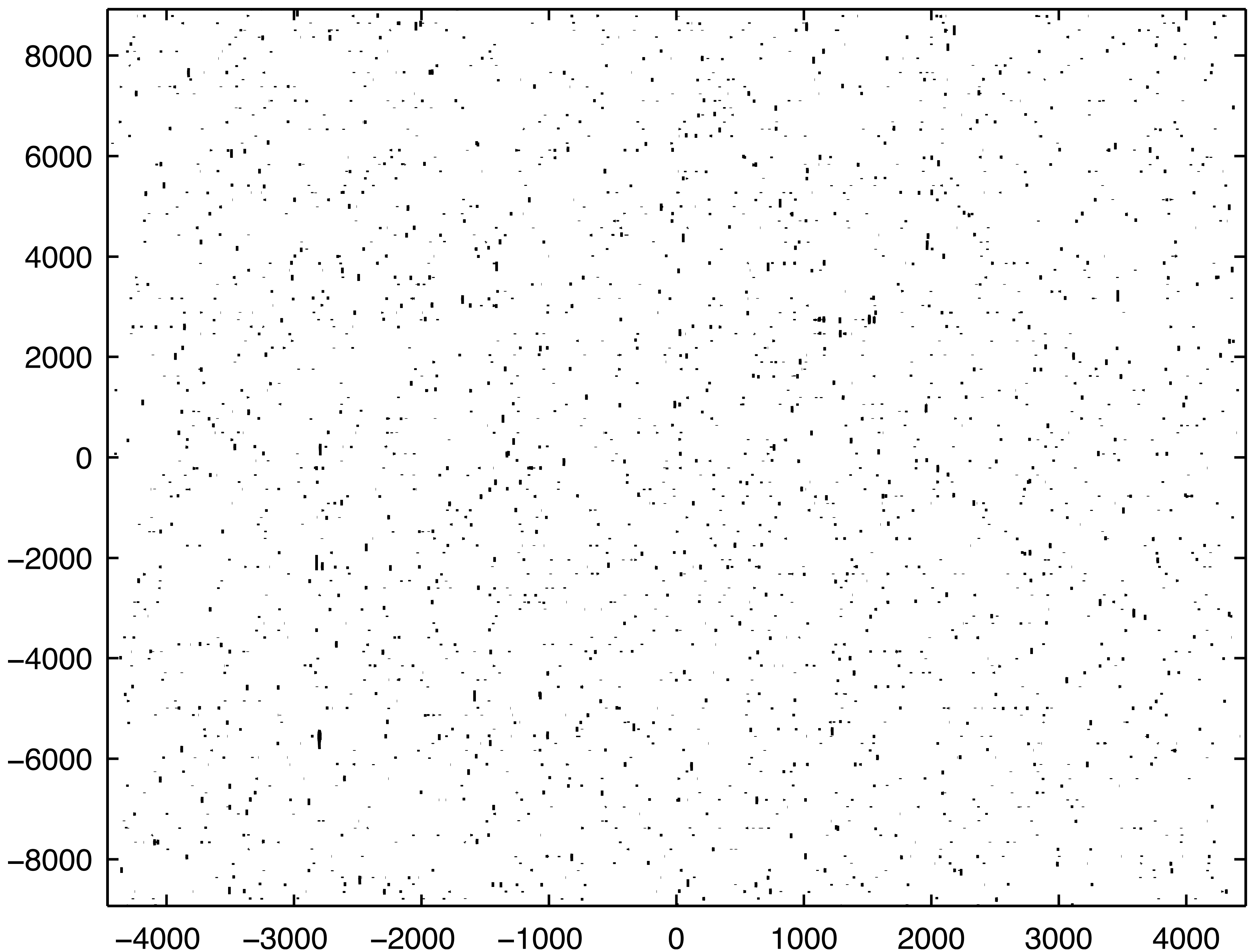
delay = indirectly acquired



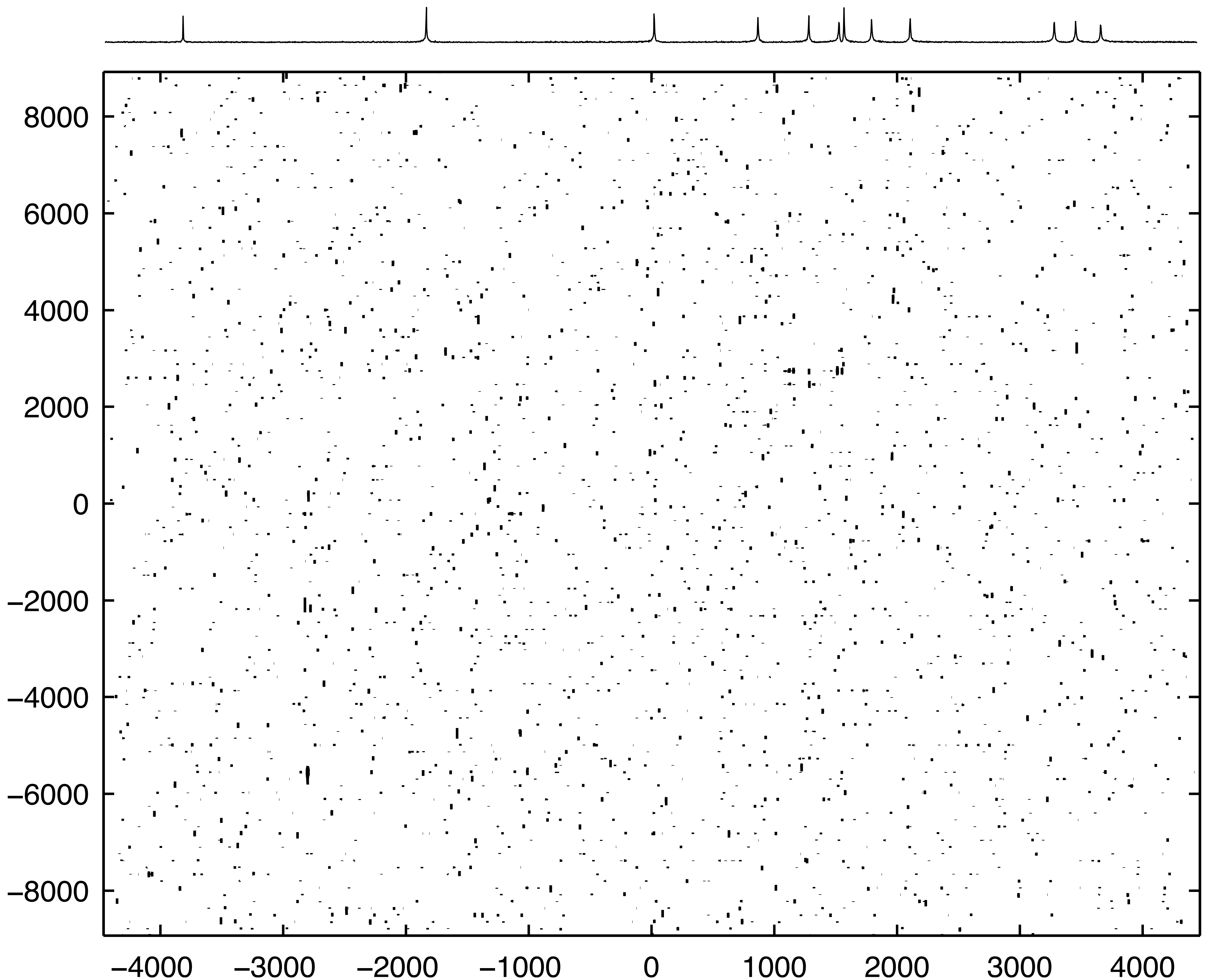
Exercise in Modern NMR Pulse Sequence Design: INADEQUATE CR

AXEL MEISSNER, OLE WINNECHE SØRENSEN

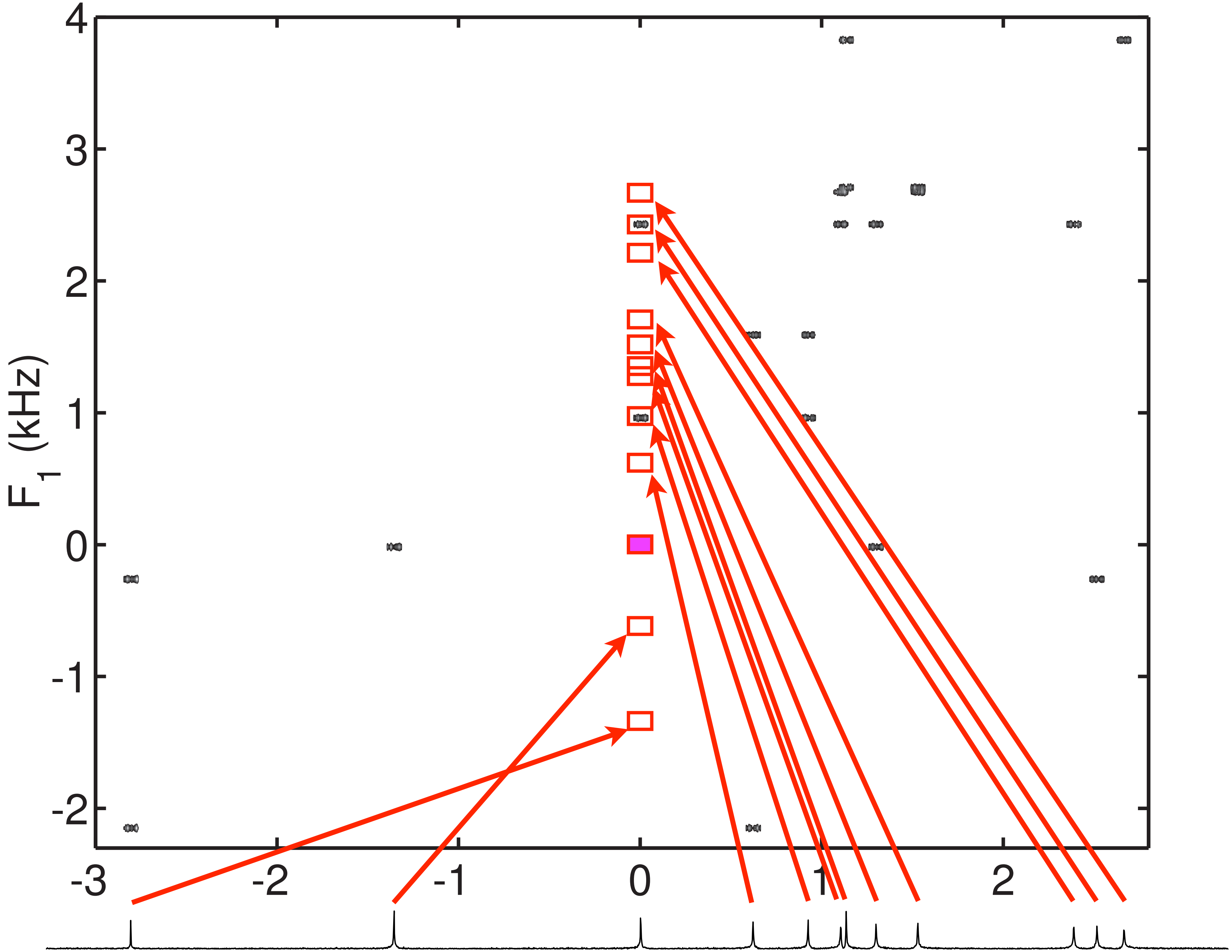
Problem: Noise



Problem: Noise



Box the Signal $\mathcal{S}_{ij}$



$$\min \|m - \mathcal{S}\|^2 \tag{2}$$
$$+ \lambda_1 ||\delta_x \mathcal{S}||^2 \tag{3}$$
$$+ \lambda_2 \sum_{ij} (1 - p_{ij})^2 ||\mathcal{S}_{ij} + \mathcal{S}_{ji}||^2 \tag{4}$$
$$+ \lambda_3 \sum_{ij} (||\mathcal{S}_{ij}||^2 - ||\mathcal{S}_{ji}||^2)^2 \tag{5}$$
$$+ \mu_1 \sum_{i} \left(2 - \sum_{j \neq i} p_{ij} \right)^4 \tag{6}$$
$$+ \mu_2 \sum_{ij} p_{ij} \tag{7}$$
$$\text{s.t. } p_{ij} \geq 0 \tag{8}$$
$$p_{ij} \leq 1 \tag{9}$$

$$||\delta_x \mathcal{S}||^2 = \sum_{\substack{i \\ \text{s.t. } s_i \text{ and } s_{i+1} \text{ are horizontally} \\ \text{adjacent in the same box}}} (s_i - s_{i+1})^2$$

Too Hard

- Non-quadratic + bi-quadratic terms
- takes to long to solve
- solve alternately for S and p (Gauss-Seidel)

Solve for S

$$\min_{\mathcal{S}} ||m - \mathcal{S}||^2 + \lambda_1 ||\delta_x \mathcal{S}||^2 + \lambda_2 \sum_{ij} (1 - p_{ij})^2 ||\mathcal{S}_{ij} + \mathcal{S}_{ji}||^2$$

$$+ \lambda_3 \sum_{ij} (||\mathcal{S}_{ij}||^2 - ||\mathcal{S}_{ji}||^2)^2$$

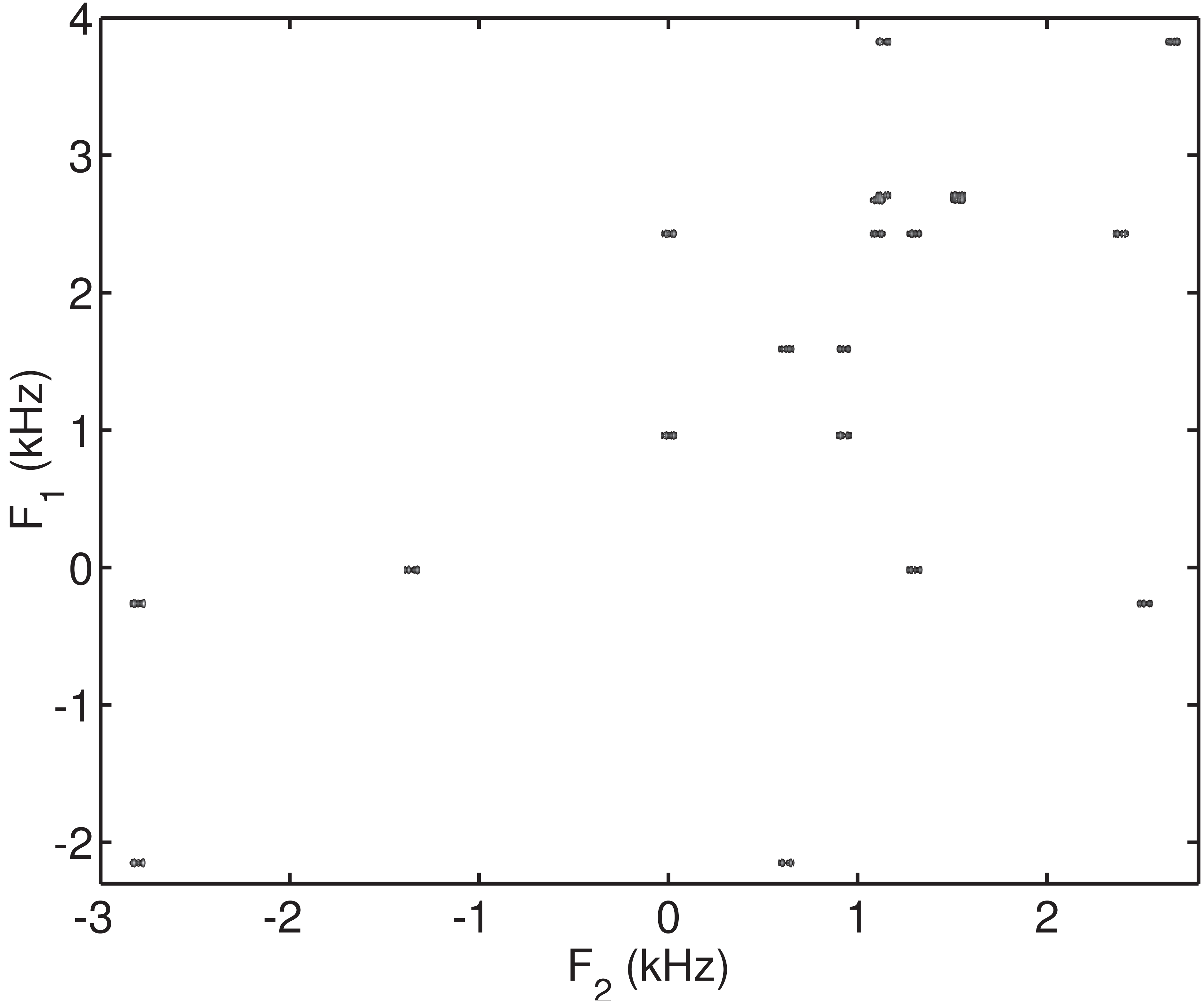
Solve for p

$$\min_{p_{ij}} \sum_{ij}(1-p_{ij})^2||\mathcal{S}_{ij}+\mathcal{S}_{ji}||^2 + \mu_1 \sum_i \left(2 - \sum_{j\neq i} p_{ij}\right)^4 + \mu_2 \sum_{ij} p_{ij}$$

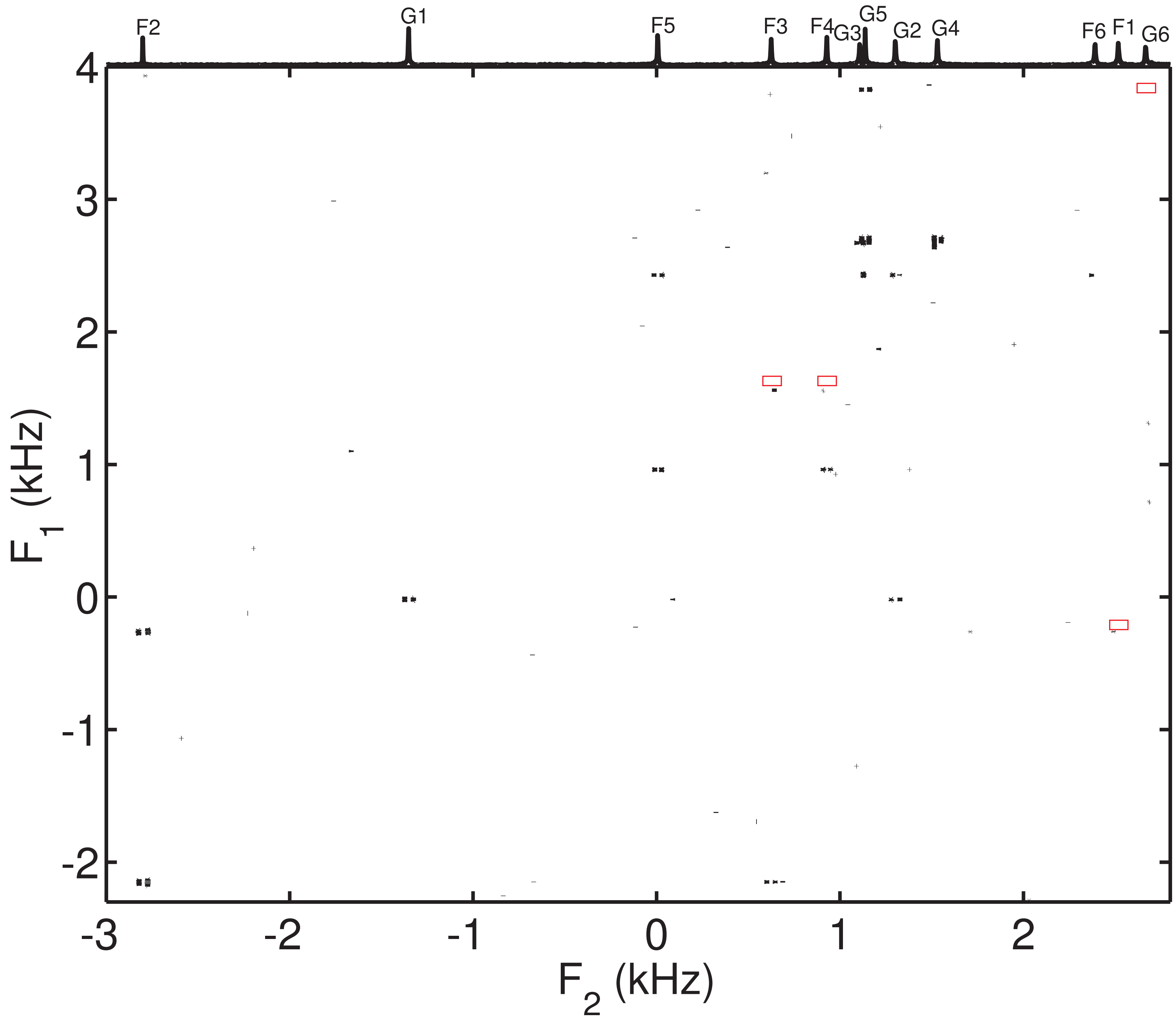
$$\text{s.t. } p_{ij} \geq 0$$

$$p_{ij} \leq 1$$

Result



Without Regularization



Results

- **> 4X** reduction in scan time
    - compared to skilled interpretation

Problems

- Can’t see past O, N, etc.
- Still takes too long

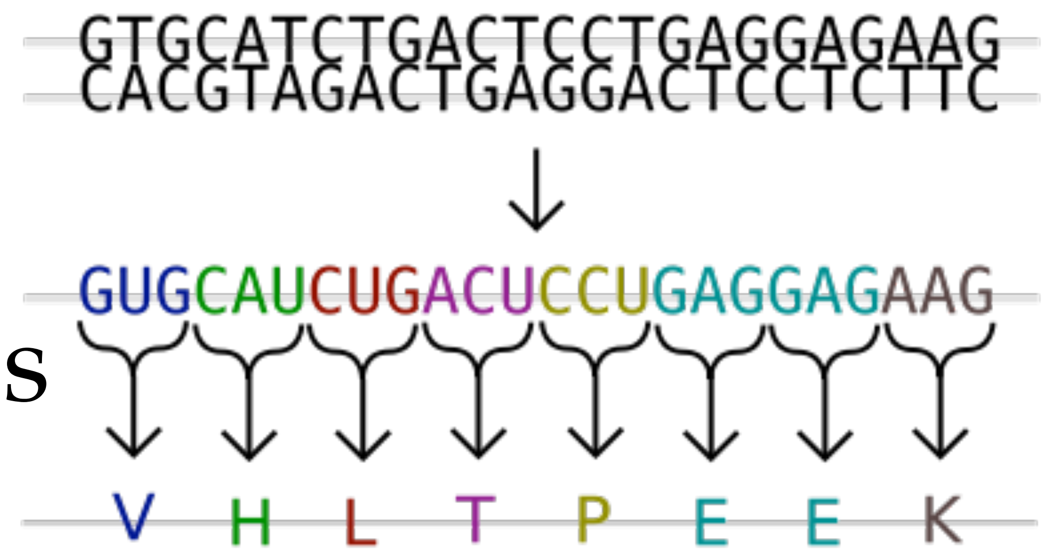
Solutions

- Can't see past O, N, etc.
  - go Multi-Nuclear
- Still takes too long
  -

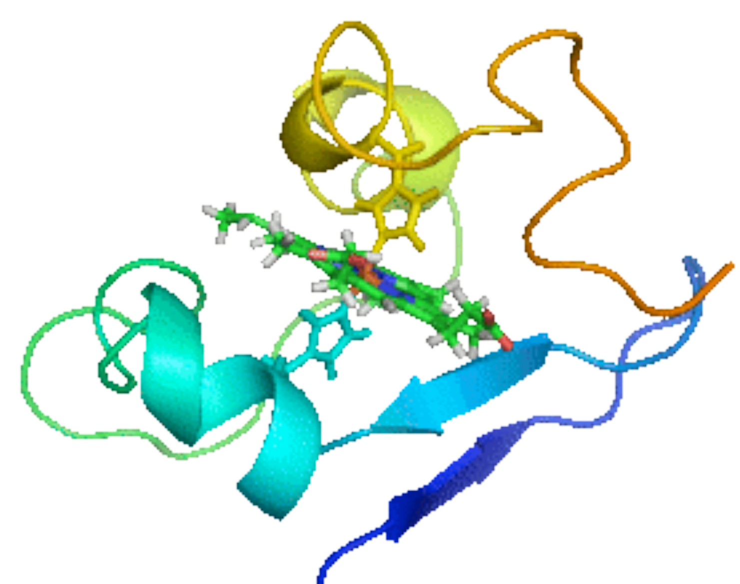
Solutions

- Can’t see past O, N, etc.
  - go Multi-Nuclear
- Still takes too long
  - Optimize delay times (k-space sampling)

Protein NMR



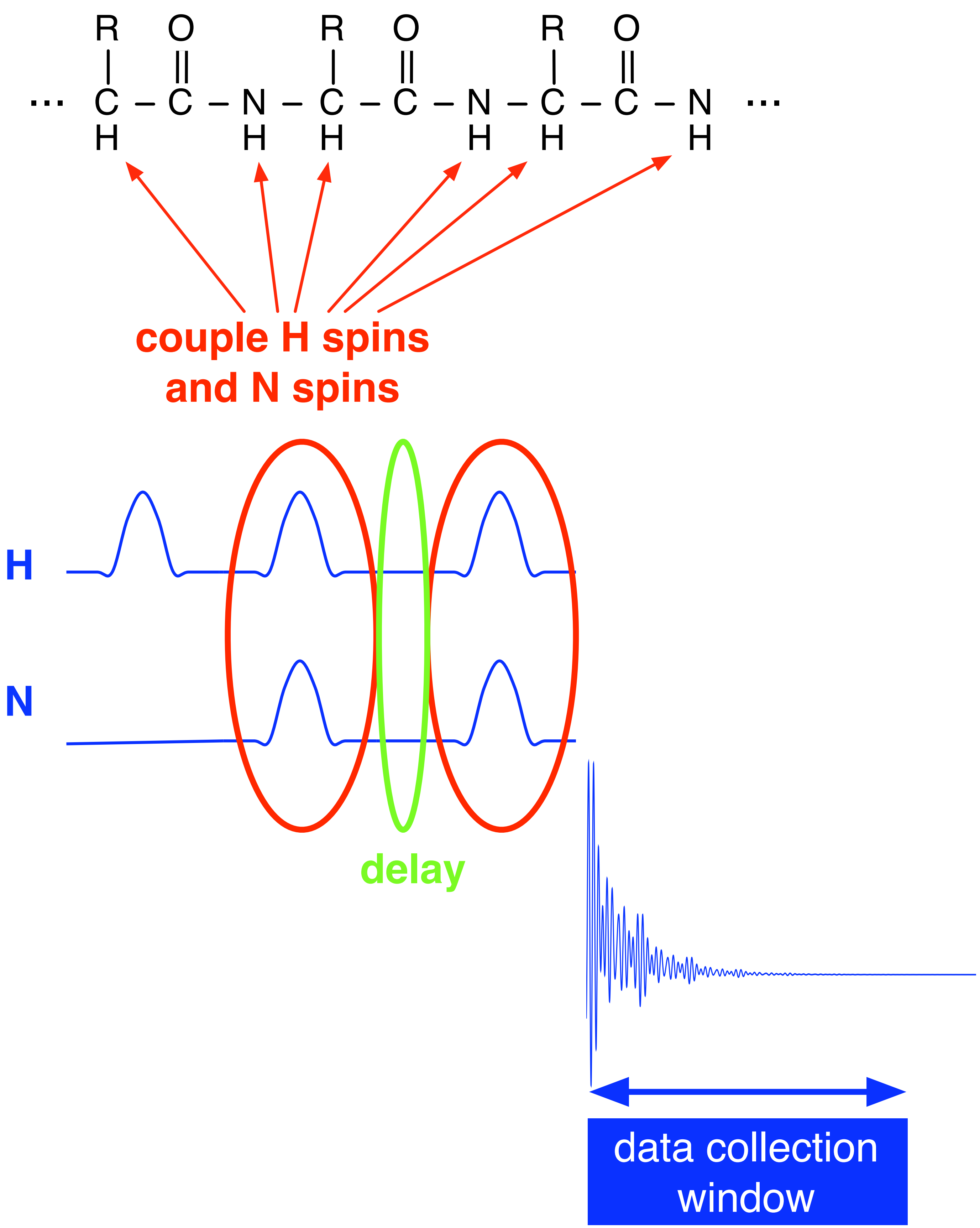
- Know DNA Sequences
- Defines Strings of Amino Acids
- Missing Info:
  - Protein Structure
    - only works if folded
  - **Protein Function**
    - **interaction = wiggling**



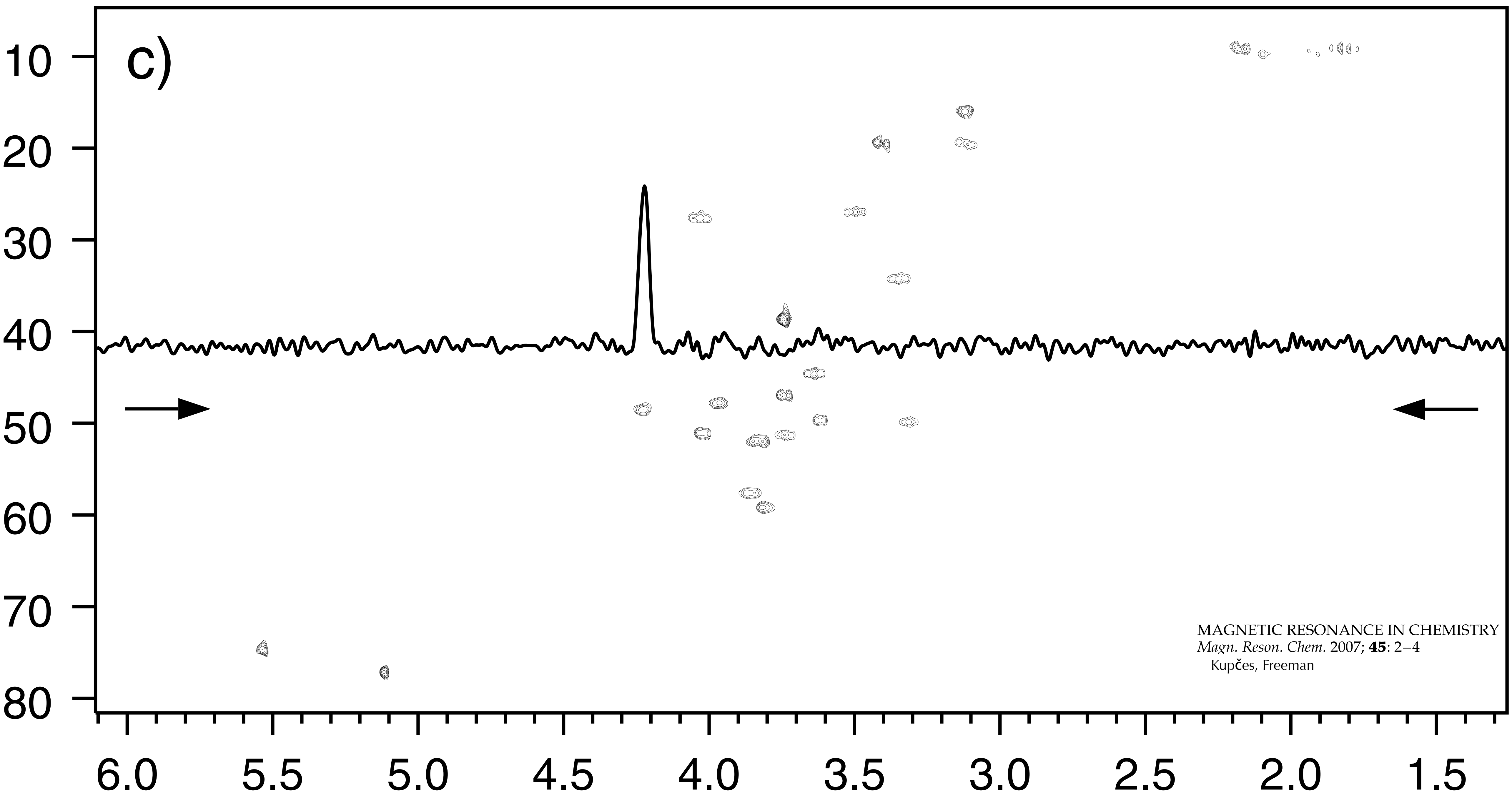
http://en.wikipedia.org/wiki/Protien

2-d NMR

- pulse @ 2 frequencies
- transfer spin state H-N-H
- phase variation proportional to delay (indirect)



2-d C-H


c)
10
20
30
40
50
60
70
80
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. 2007; 45: 2–4
Kupčes, Freeman

Linear Forward Problem

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$$\tilde{f}(k_i) = \sum_{j=1}^{m} f(x_j) e^{\sqrt{-1}\langle k_i, x_j \rangle}$$

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$$\begin{pmatrix} \tilde{f}(k_1) \\ \vdots \\ \tilde{f}(k_n) \end{pmatrix} = S \begin{pmatrix} f(x_1) \\ \vdots \\ f(x_m) \end{pmatrix} + \begin{pmatrix} \epsilon_1 \\ \vdots \\ \epsilon_n \end{pmatrix}$$

Linear Forward Problem

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$$\begin{pmatrix} \tilde{f}(k_1) \\ \vdots \\ \tilde{f}(k_n) \end{pmatrix} = S \begin{pmatrix} f(x_1) \\ \vdots \\ f(x_m) \end{pmatrix} + \begin{pmatrix} \epsilon_1 \\ \vdots \\ \epsilon_n \end{pmatrix}$$

$$S_{i,j} = e^{\sqrt{-1}\langle k_i, x_j \rangle}$$

Linear Forward Problem

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$$S_{i,j} = e^{\sqrt{-1}\langle k_i, x_j \rangle}$$ is *linear*

Moore-Penrose Inverse

$$\begin{pmatrix} f(x_1) \\ \vdots \\ f(x_m) \end{pmatrix} = (S^*S)^{-1}S^* \begin{pmatrix} \tilde{f}(k_1) \\ \vdots \\ \tilde{f}(k_n) \end{pmatrix}$$

Moore-Penrose Inverse

$$\begin{pmatrix} f(x_1) \\ \vdots \\ f(x_m) \end{pmatrix} = (S^* S)^{-1} S^* \begin{pmatrix} \tilde{f}(k_1) \\ \vdots \\ \tilde{f}(k_n) \end{pmatrix}$$

- can invert with M-P pseudo-inverse

Moore-Penrose Inverse

$$\begin{pmatrix} f(x_1) \\ \vdots \\ f(x_m) \end{pmatrix} = (S^* S)^{-1} S^* \begin{pmatrix} \tilde{f}(k_1) \\ \vdots \\ \tilde{f}(k_n) \end{pmatrix}$$

- can invert with M-P pseudo-inverse
- optimize {k} for M-P

Worst-Case Noise ~ Conditioning of

$$(S^*S)_{i,j} = \sum_{l=1}^{n} e^{\sqrt{-1}\langle k_l, x_j - x_i \rangle}$$

Worst-Case Noise ~ Conditioning of

$$(S^*S)_{i,j} = \sum_{l=1}^{n} e^{\sqrt{-1}\langle k_l, x_j - x_i \rangle}$$

- expected maximum error
  ~ 1/ minimal eigenvalue

Worst-Case Noise ~ Conditioning of

$$(S^*S)_{i,j} = \sum_{l=1}^{n} e^{\sqrt{-1}\langle k_l, x_j - x_i \rangle}$$

- expected maximum error
  ~ 1/ minimal eigenvalue
- constraining eigenvalues
  = Semi-Definite Programming (SDP)

Real SDP

$$\min_{\{k_i\}} \quad -\lambda$$

$$\text{subject to} \quad A - \lambda I \succeq 0$$

$$A_{2i-1,2j-1} = \sum_{l=1}^{n} \cos\langle k_l, x_j - x_i\rangle$$

$$A_{2i,2j} = \sum_{l=1}^{n} \cos\langle k_l, x_j - x_i\rangle$$

$$A_{2i,2j-1} = \sum_{l=1}^{n} \sin\langle k_l, x_j - x_i\rangle$$

$$A_{2i-1,2j} = -\sum_{l=1}^{n} \sin\langle k_l, x_j - x_i\rangle$$

Trust Region + SDP Step

$$\min_{k} \quad -\lambda$$

$$\text{subject to} \quad A|_{\tilde{k}} + \sum_{\substack{\alpha = 1 \ldots n \\ \beta = 1 \ldots r}} (k_{\alpha,\beta} - \tilde{k}_{\alpha,\beta}) \left. \frac{\partial A}{\partial k_{\alpha,\beta}} \right|_{\tilde{k}} - \lambda I \succeq 0$$

$$\frac{\partial A_{2i-1,2j-1}}{\partial k_{\alpha,\beta}} = - (\sin\langle k_\alpha, x_j - x_i \rangle)(x_{j,\beta} - x_{i,\beta})$$

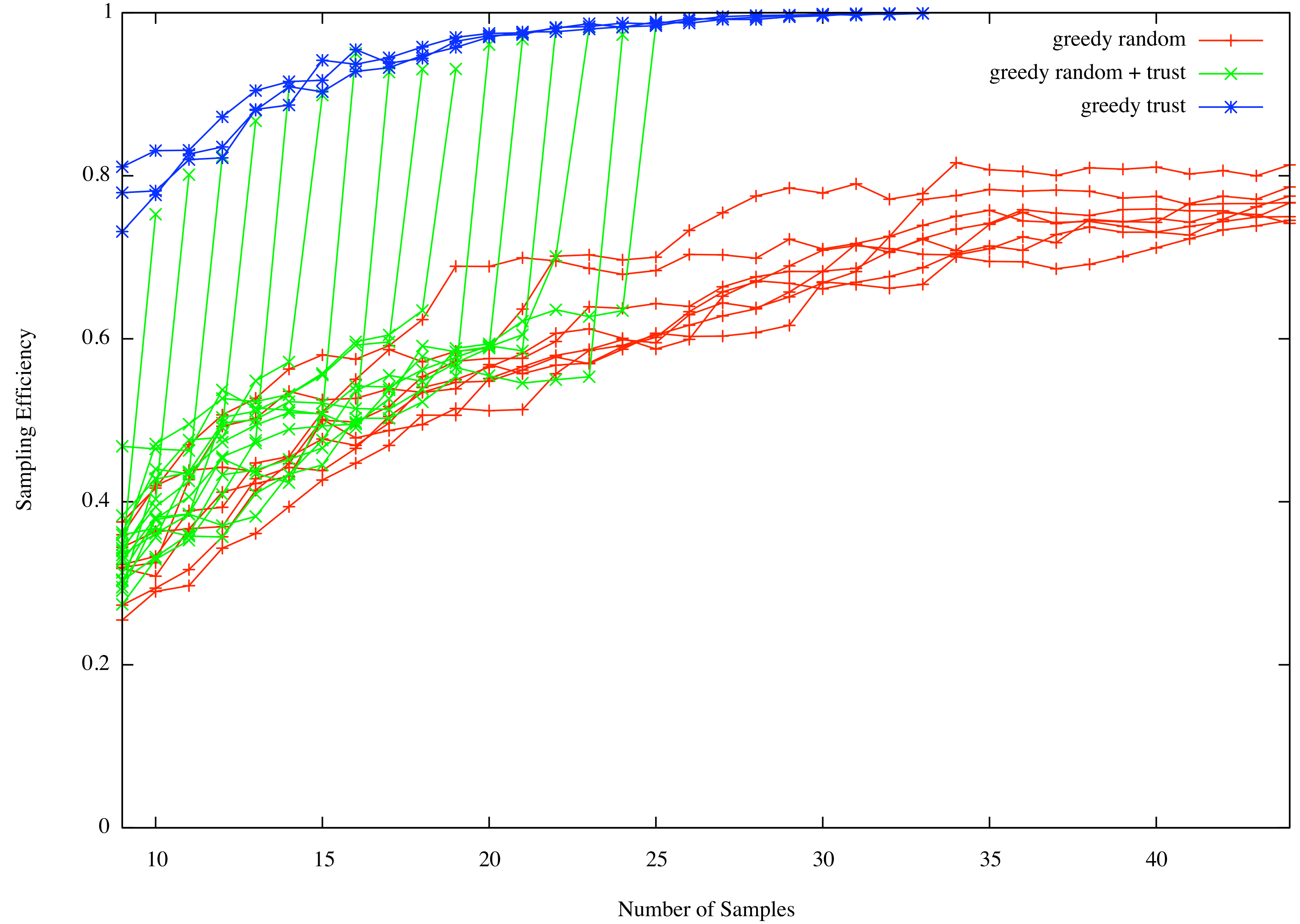
$$\frac{\partial A_{2i,2j}}{\partial k_{\alpha,\beta}} = - (\sin\langle k_\alpha, x_j - x_i \rangle)(x_{j,\beta} - x_{i,\beta})$$

$$\frac{\partial A_{2i,2j-1}}{\partial k_{\alpha,\beta}} = \quad (\cos\langle k_\alpha, x_j - x_i \rangle)(x_{j,\beta} - x_{i,\beta})$$

$$\frac{\partial A_{2i-1,2j}}{\partial k_{\alpha,\beta}} = - (\cos\langle k_\alpha, x_j - x_i \rangle)(x_{j,\beta} - x_{i,\beta})$$

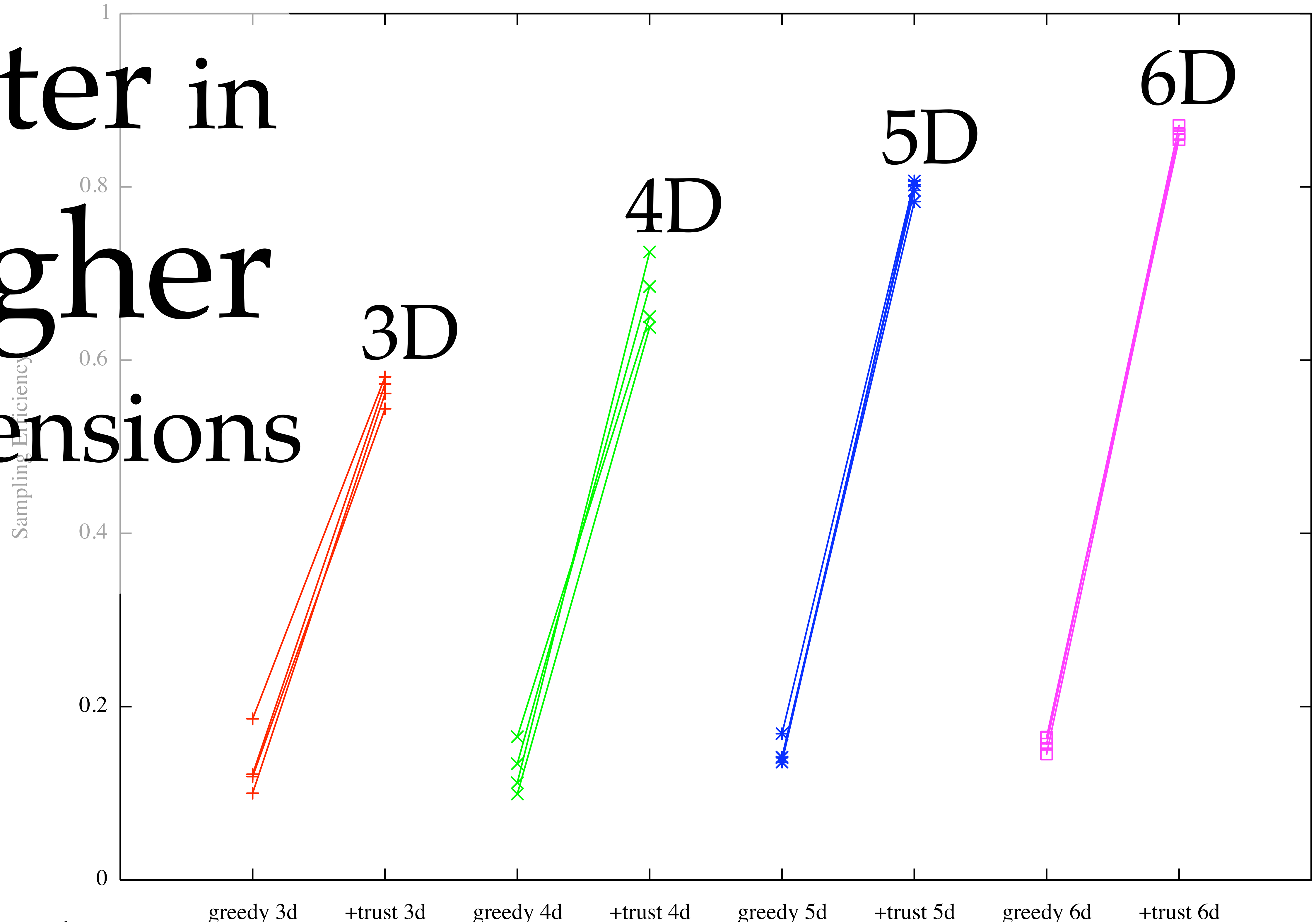
$$|k_{\alpha,\beta} - \tilde{k}_{\alpha,\beta}| \leq \frac{\pi/2}{\max|x_{j,\beta} - x_{i,\beta}|}$$

Works well in 3D!



- SDP optimization = **100% efficient**
- greedy random < 80% efficient
- 2x more samples with greedy random

Better in Higher Dimensions



- 17 peaks with full frequency information
- Efficiency increases with dimension (34 samples)
- *fewer* samples required in higher dimensions

To Do

- Celebrate 4X faster experiments
- Design mixed C-O-N experiments
- Make delay optimization numerically robust

Thanks to

- Adrian, Dhavide, Hongmei for the invitation
- MITACS and Field's the conference
- NSERC and IBM for funding
- my students for their hard work