Challenges in the decomposition of 2D NMR spectra of mixtures of small molecules

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*A*midex project BIFROST*

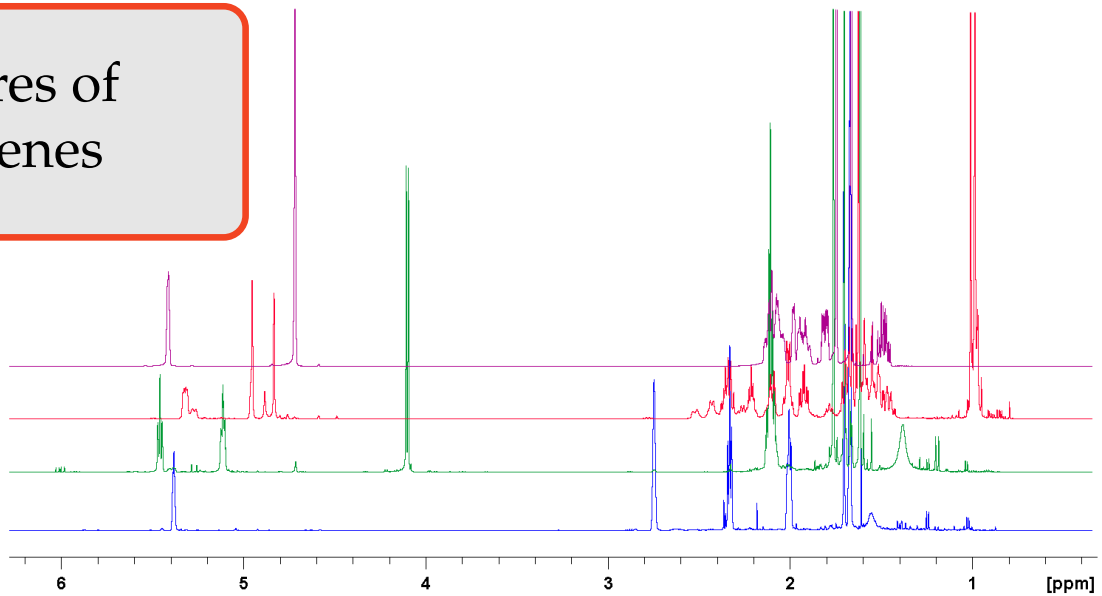
CNRS and Aix-Marseille Univ.

NMR Analysis of complex mixtures

NMR spectroscopy : tool of choice for the analysis of complex mixtures

- structural information and quantification within one spectrum

Mixtures of
4 terpenes



Issues

Sample complexity involves more overlaps of signals
=> Signal assignment is more difficult

NMR ways to solve these issues

NMR solutions

- To suppress signal multiplicity through decoupling techniques (i.e. ^{13}C decoupled from ^{1}H or pure shift spectrum)
- To improve spectral resolution adding more spectral dimensions (ultrafast methods to reduce acquisition time)

Remarks

- Spectra simplified but no help for signal assignment
- Automated identification methods available but rely on reference compound library

Proposed approach

Use of blind source separation tools to decompose mixture into pure spectra

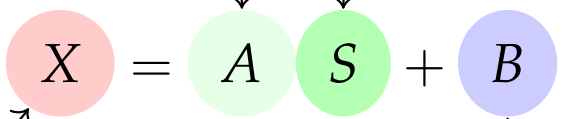
Mathematical tools: modeling

Mixing matrix

(Concentrations)

Pure spectra

(unknown: to be estimated)



Observations

Spectra of mixtures
(solutions)

Gaussian noise

$B \sim \mathcal{N}(0, \sigma^2)$
zero mean - variance σ^2

Mathematical problem

Find an estimation $(\hat{A}, \hat{S})$ of A and S from X.

Mathematical tools: proposed approach

Variational approach

$$\underset{A,S}{\text{minimize}} \quad \underbrace{\frac{1}{2}\|X - AS\|_F^2}_{\text{Model adequation}} + \underbrace{f_A(A)}_{\text{A priori on A}} + \underbrace{f_S(S)}_{\text{A priori on S}} \quad ,$$

$$\text{under constraints} \quad A \geq 0,\ S \geq 0\ .$$

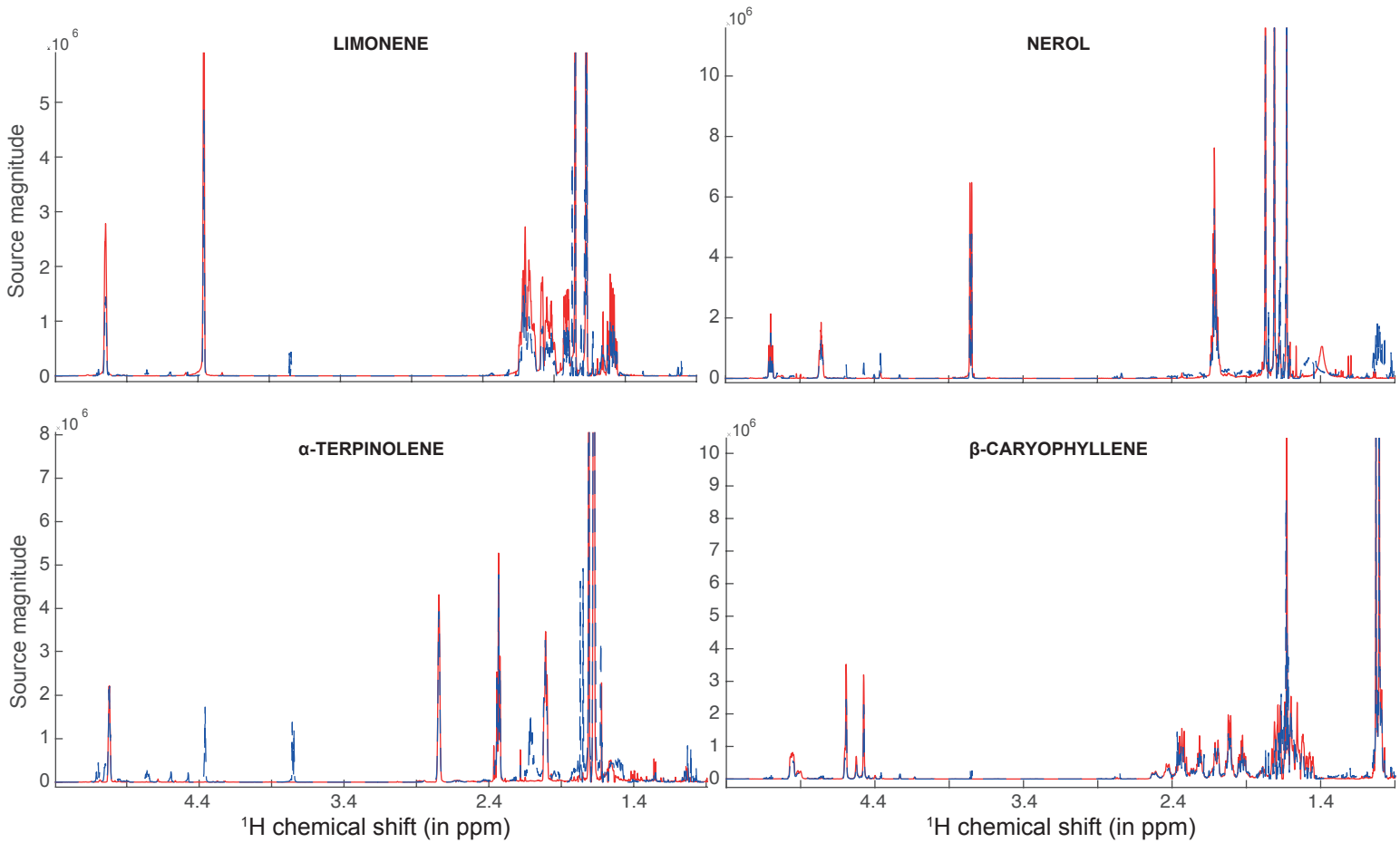
Algorithm

- Alternating minimization on A and S;
- Iterative procedure.

Performance evaluation

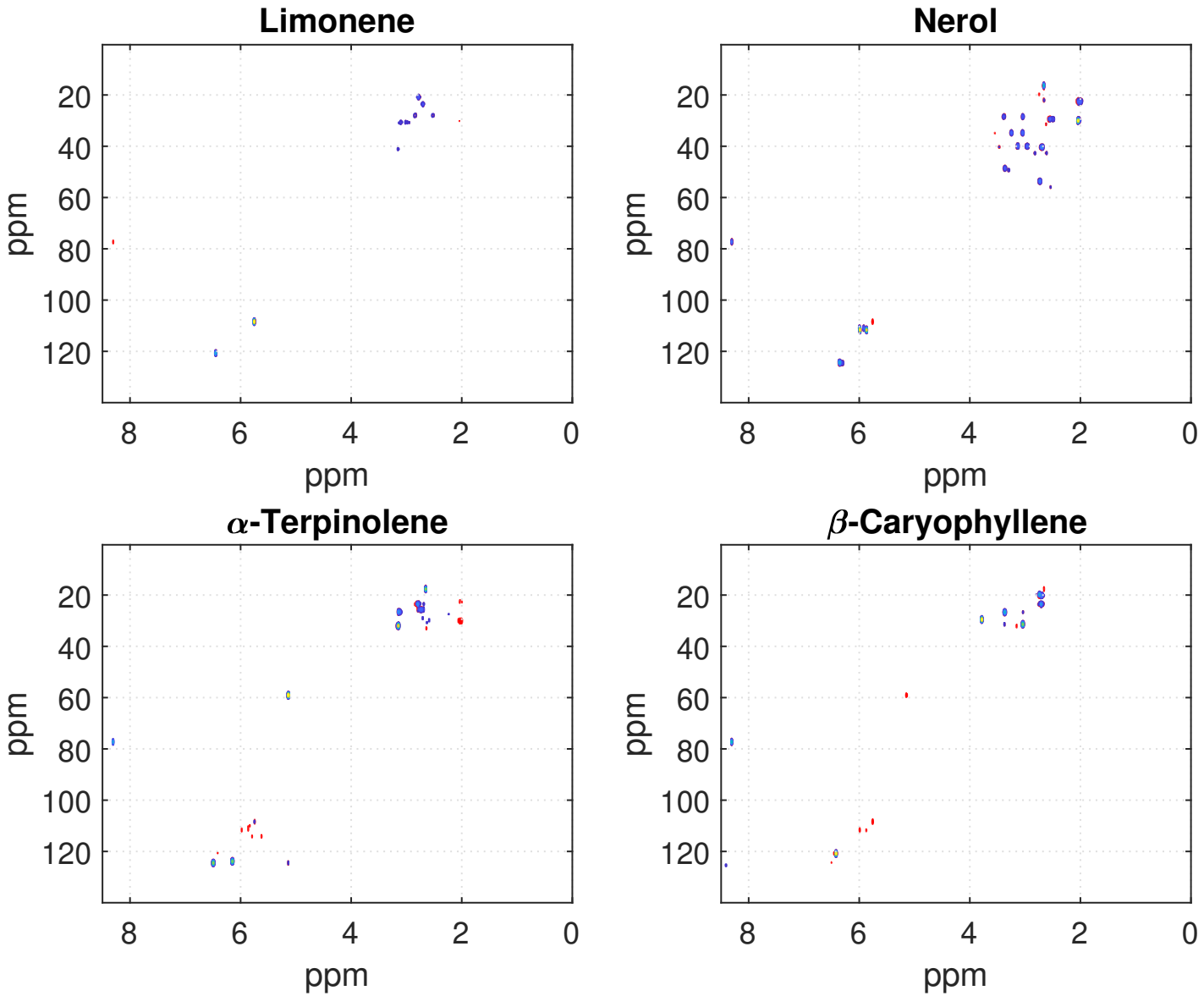
- Amari index: are A and $\hat{A}$ close ?
- Signal to interference and signal to distortion ratios: are sources in $\hat{S}$ well separated ? Are the sources noise free ?

Results on ^{1}H NMR spectra



Estimated sources versus real sources.
(5 mixture spectra of 4 metabolites)

Results on 2D ^{1}H-^{13}C HSQC spectra



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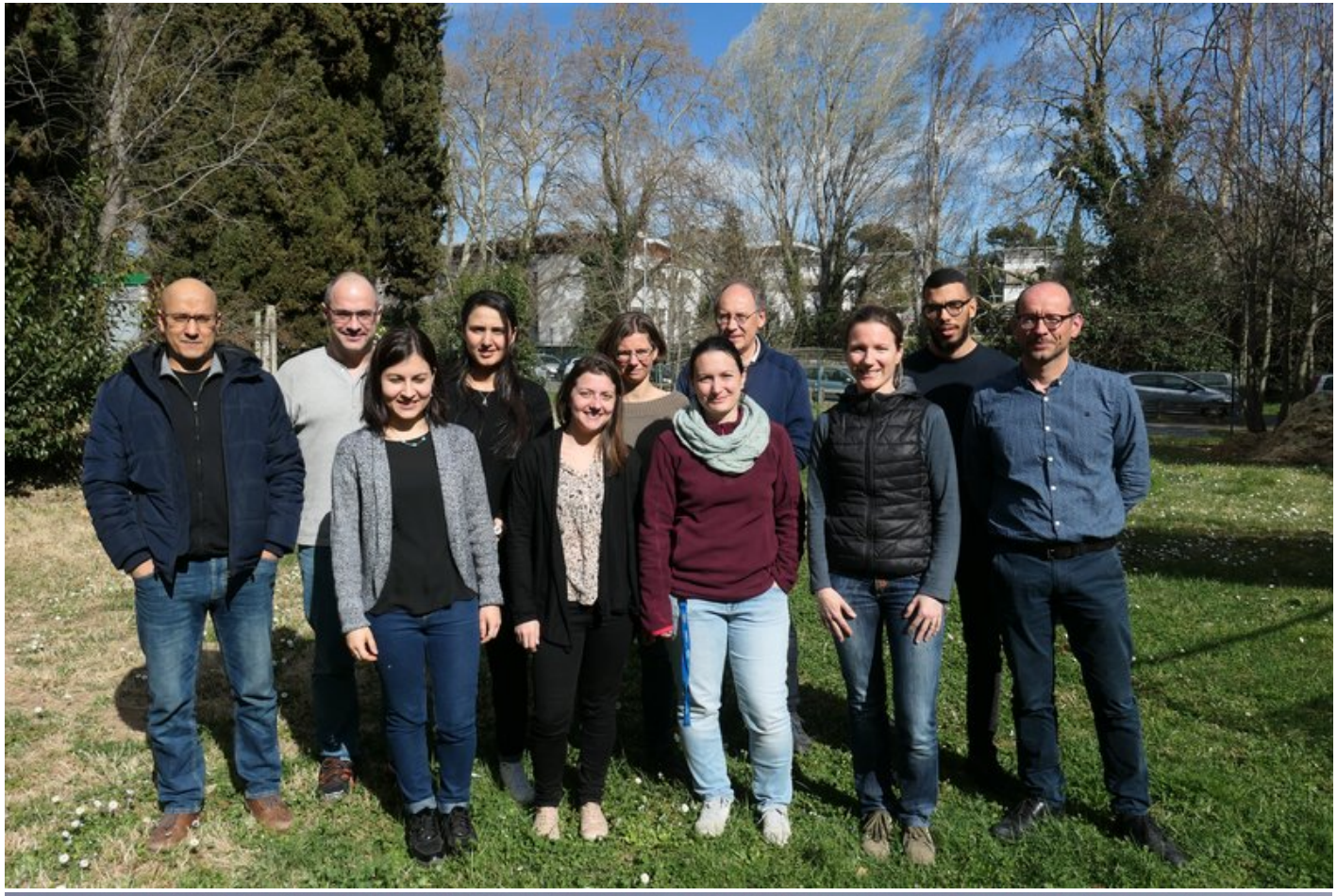
Interdisciplinary team: bifrost project



http://www.i2m.univ-amu.fr/project/bifrost/

BIFROST

Blind Identification, Filtering & Restoration On Spectral Techniques

Appendix

Numerical results on ^{1}H NMR spectra

	Limonene	Nerol	$\alpha-$Terpinolene	β-Caryophyllene
Solution 1	12.34 %	25.61 %	-9.03 %	-4.33 %
Solution 2	4.05 %	-6.68 %	1.11 %	26.27 %
Solution 3	-47.70 %	1.91 %	-0.53 %	-32.53 %
Solution 4	16.36 %	-69.78 %	1.54 %	-11.15 %
Solution 5	-55.03 %	-14.94 %	4.74 %	-4.70 %

Table: ^{1}H NMR spectra (real case): relative errors in the estimated concentrations (in %) using BC-VMFB with $\lambda = \sigma$. The corresponding Amari index equals 0.081.

	Limonene	Nerol	$\alpha-$Terpinolene	β-Caryophyllene
SIR	13.1	15	20.2	14.8
SDR	9.7	9.9	4.8	6.8

Table: ^{1}H NMR spectra (real case): SIR and SDR indices (in dB) comparing true and estimated source spectra with the BC-VMFB algorithm with $\lambda = \sigma$.

Numerical results on 2D ^{1}H-^{13}C HSQC spectra

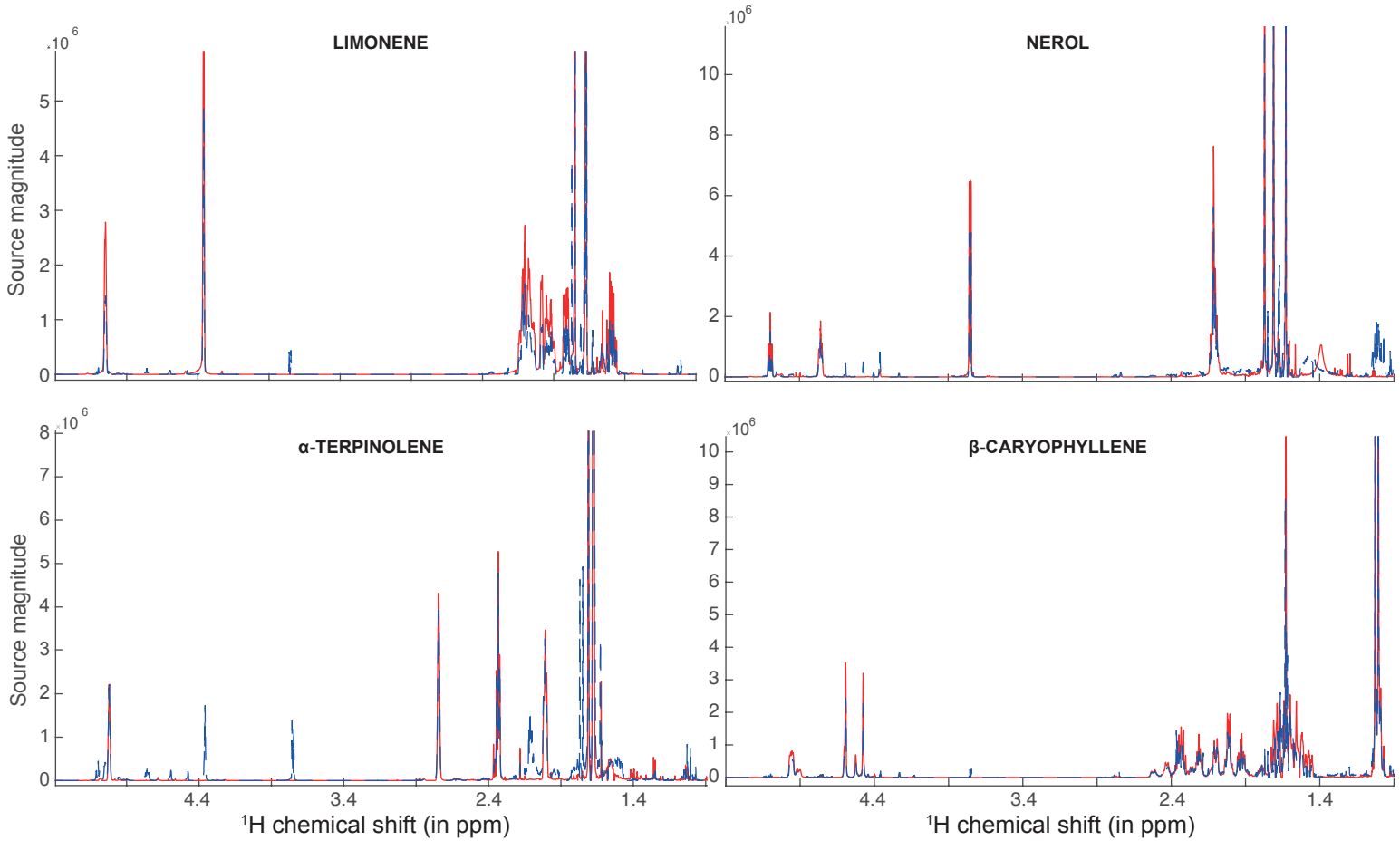
	Limonene	Nerol	$\alpha-$Terpinolene	β-Caryophyllene
Solution 1	-0.39 %	3.16 %	-7.02 %	9.53 %
Solution 2	-8.56 %	-3.43 %	-2.66 %	10.90 %
Solution 3	5.84 %	8.42 %	2.94 %	6.68 %
Solution 4	5.74 %	-14.40 %	3.47 %	-12.84 %
Solution 5	-3.65 %	-6.89 %	0.03 %	-11.00 %

Table: 2D ^{1}H-^{13}C HSQC spectra (real case): relative errors in the estimated concentrations (in %) using wavelet-based BC-VMFB with $\lambda = 10\sigma$. The corresponding Amari index equals 0.042.

	Limonene	Nerol	$\alpha-$Terpinolene	β-Caryophyllene
SIR	46.3	25.2	22.7	32.1
SDR	8.5	13.1	9.4	9.4

Table: 2D ^{1}H-^{13}C HSQC spectra (real case): SIR and SDR indices (in dB) comparing pure and estimated source spectra using wavelet-based BC-VMFB with $\lambda = 10\sigma$.

Results on ^{1}H NMR spectra



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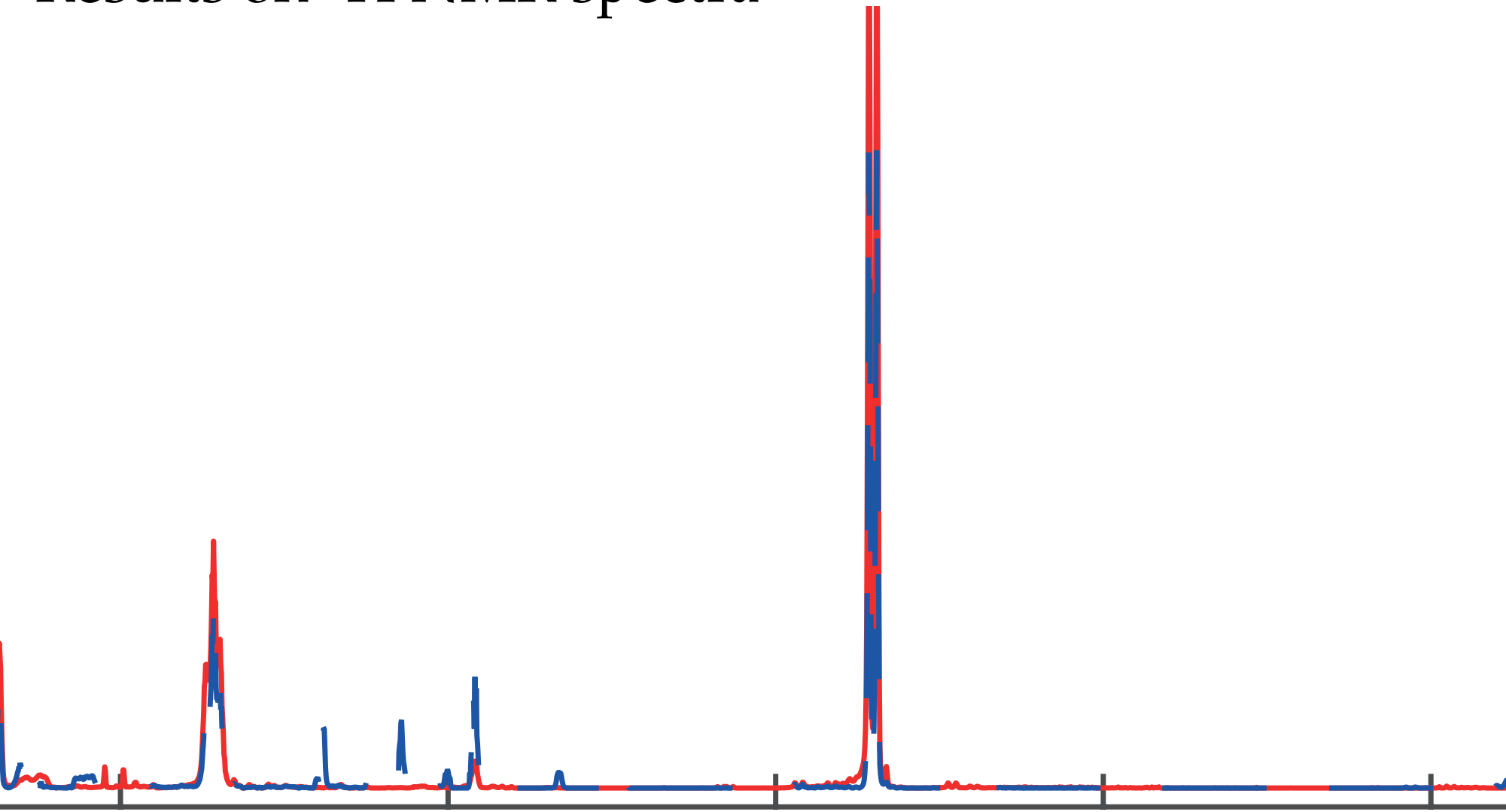

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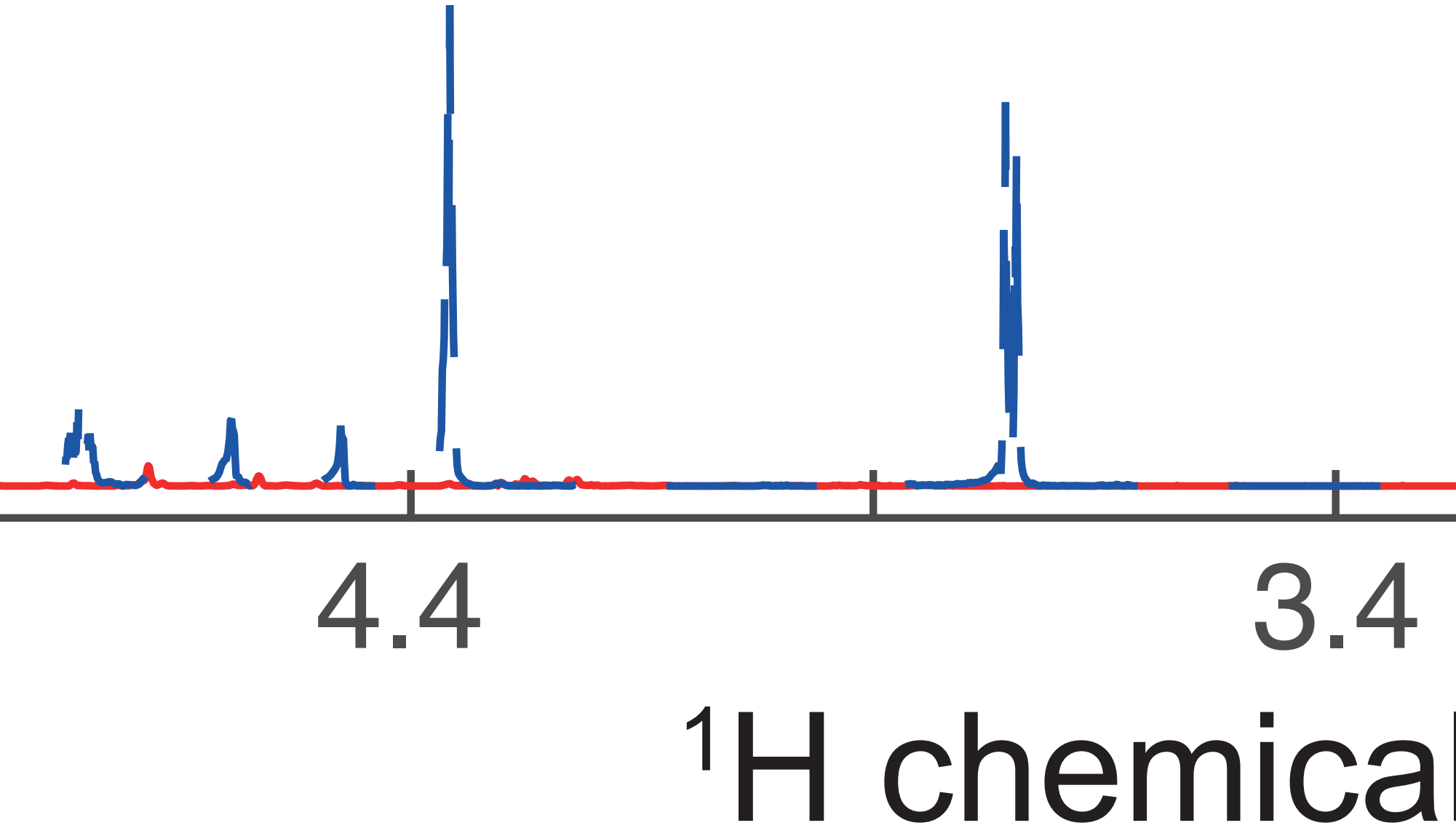

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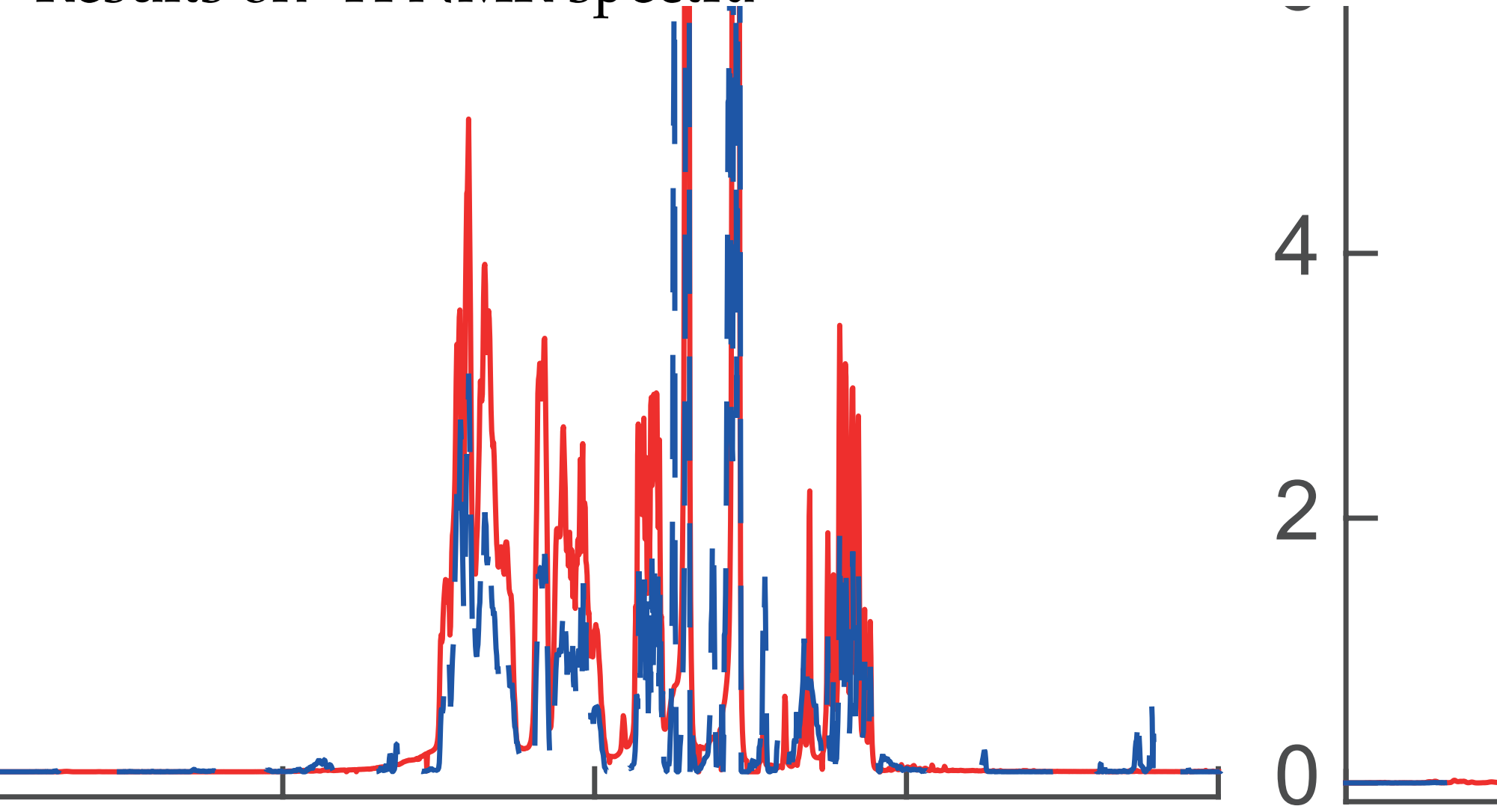

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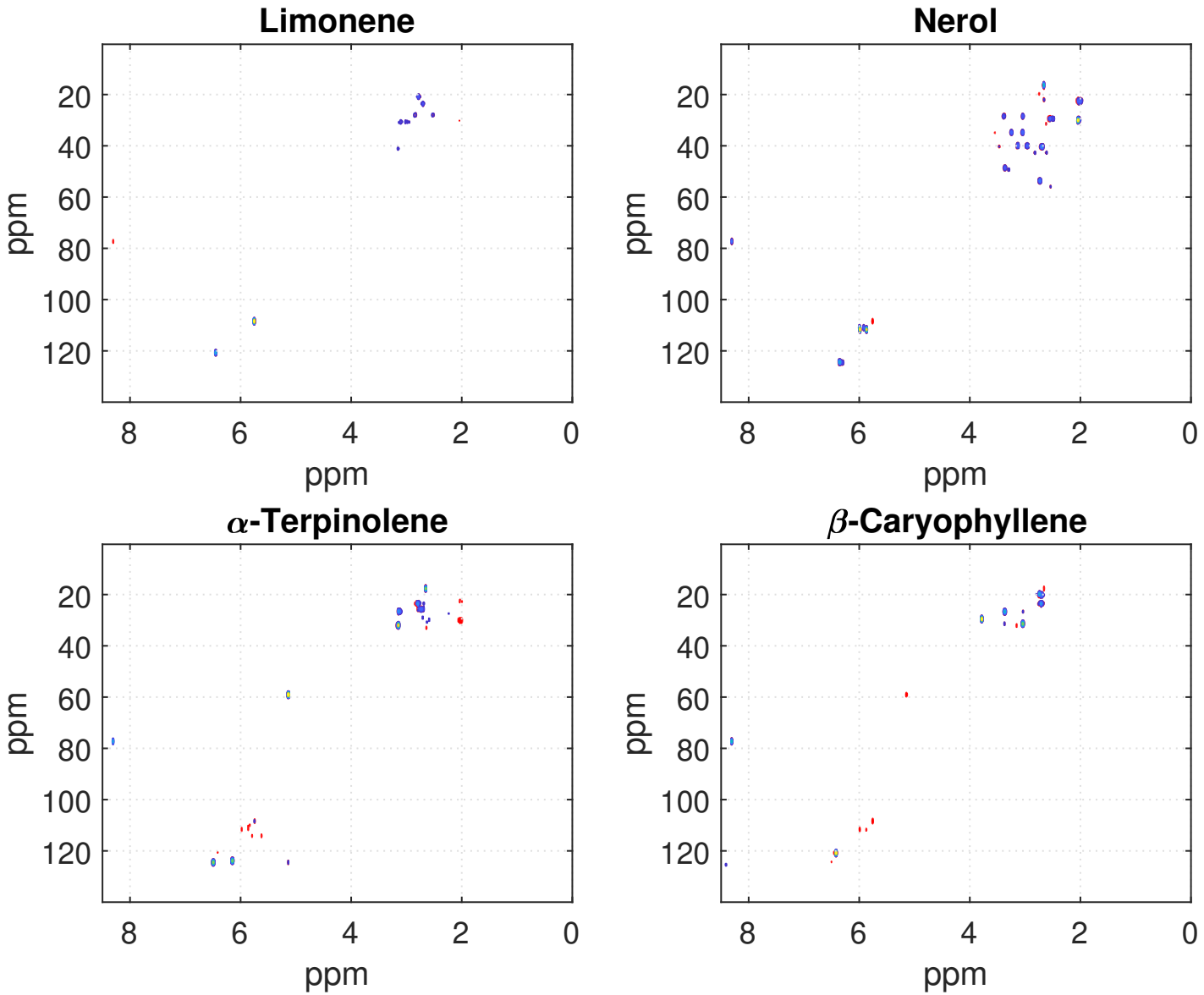

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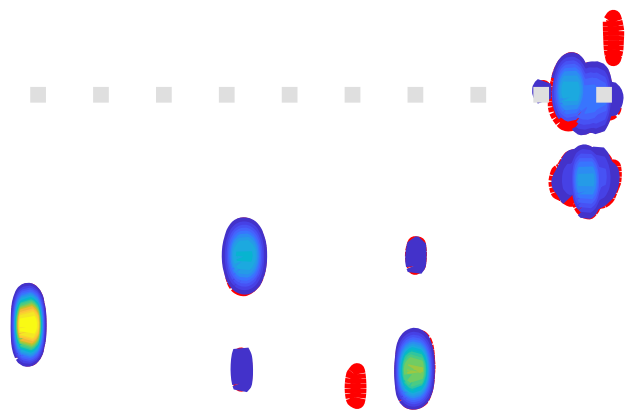

Results on 2D ^{1}H-^{13}C HSQC spectra