FELIX example was presented in Turku XXXIX Finnish NMR symposium, June 7-9th 2017*

LARGE AND VERY LARGE SPIN-SYSTEMS

Reino Laatikainen and Pekka Laatikainen,
SpinDiscoveries Ltd.

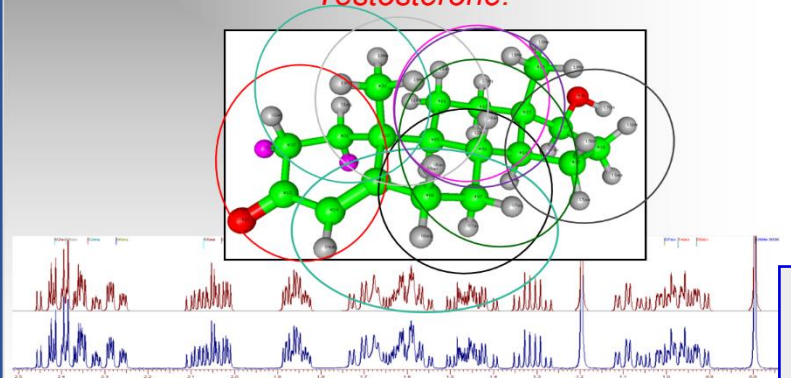
*See also, S.K.Ahola, L.P.Ingman, R.Laatikainen, J.Sinkkonen & J.P.Jokisaari, ^{21}Ne and ^{131}Xe NMR study of electric field gradients and multinuclear NMR study of the composition of a ferroelectric liquid crystal. *J.Chem.Phys*. **149**, 234901 (2018); https://doi.org/10.1063/1.5052499

Background: Cyclosporine A (slide 6)

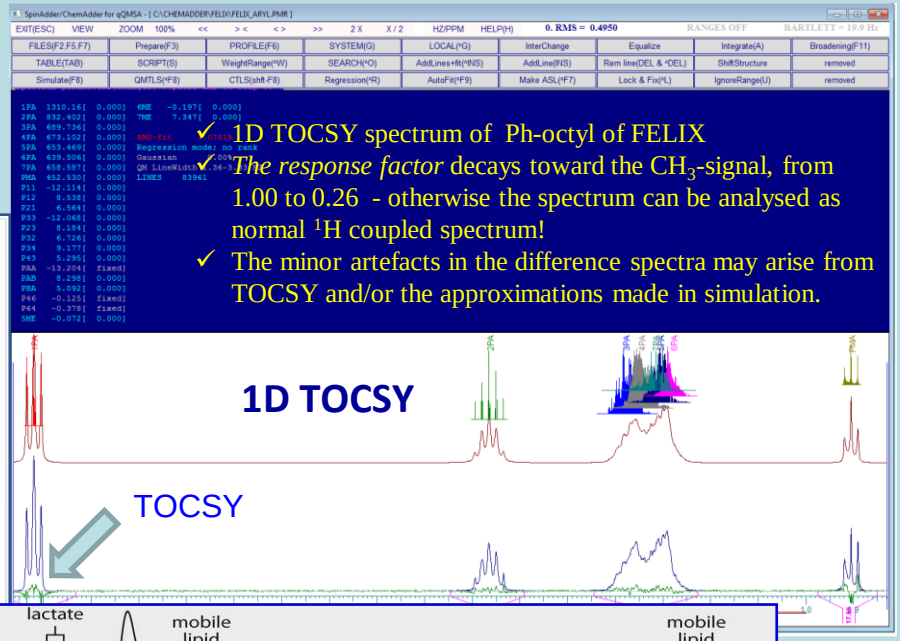
➢ LARGE and SPECIAL SPIN-SYSTEMS

Large Spin-networks can be simulated by automate splitting into sub-systems

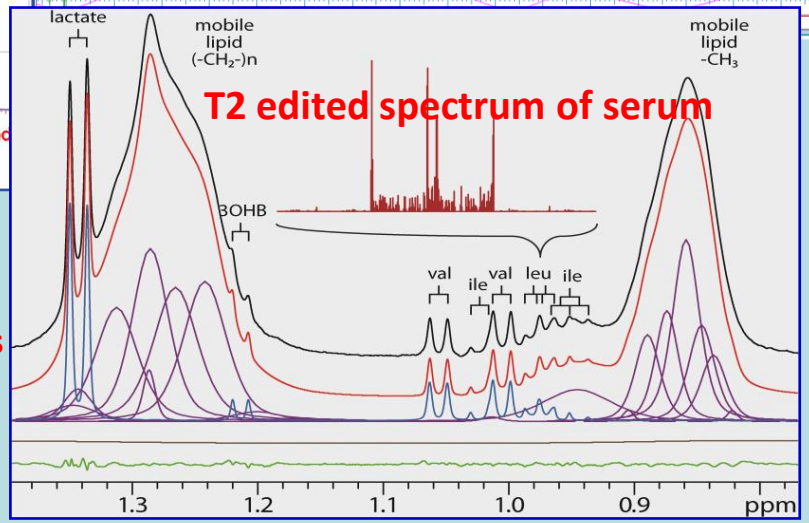
Testosterone:



24 Spin-particles with 28 protons => 13 sub-systems (circled) => 688 non-degenerated spectral lines, only ! Simulation time ca. 4 s.



- ✓ 1D TOCSY spectrum of Ph-octyl of FELIX
- ✓ *The response factor* decays toward the CH_3-signal, from 1.00 to 0.26 - otherwise the spectrum can be analysed as normal ^1H coupled spectrum!
- ✓ The minor artefacts in the difference spectra may arise from TOCSY and/or the approximations made in simulation.



Signals from lipids and macromolecules or any unknown source can be fitted by using EXTRA lines - automatically just by defining the range and the number of lines to be used:

News 10.07.2018

qQMSA of 1000+1 SpinParticles

208 Compounds with > 1500 nuclei

~~Simulation time 7 sec !~~

More news soon ..follow this channel

15.04.2019 Simulation time < 2 sec !

EXIT(ESC) VIEW ZOOM 100% << > < < > >> 2 X X / 2 HZ/PPM HELP(H) **1. RMS = 0.0000** PCR=N **WidthMode=A JFIX=DEF Ranges=ON REAL** BARTLETT= 20.0

FILES(F2,F5,F7)	PREPARE(F3)	PROFILE(F6)	SYSTEM(G)	LOCAL(^G)	InterChange	Equalize	Integrate(A)	Broadening(F11)
TABLE(TAB)	SCRIPT(S)	WeightRange(^W)	SEARCH(^O)	AddLines+fit(^INS)	AddLine(INS)	Rem line(DEL & ^DEL)	ShiftStructure	ReadOriginal(F4)
SIMULATE(F8)	QMTLS(^F8)	CTLS(shft-F8)	REGRESSION(^R)	AutoFit(^F9)	Make ASL(^F7)	Lock & Fix(^L)	IgnoreRange(U)	BASELINE(B)

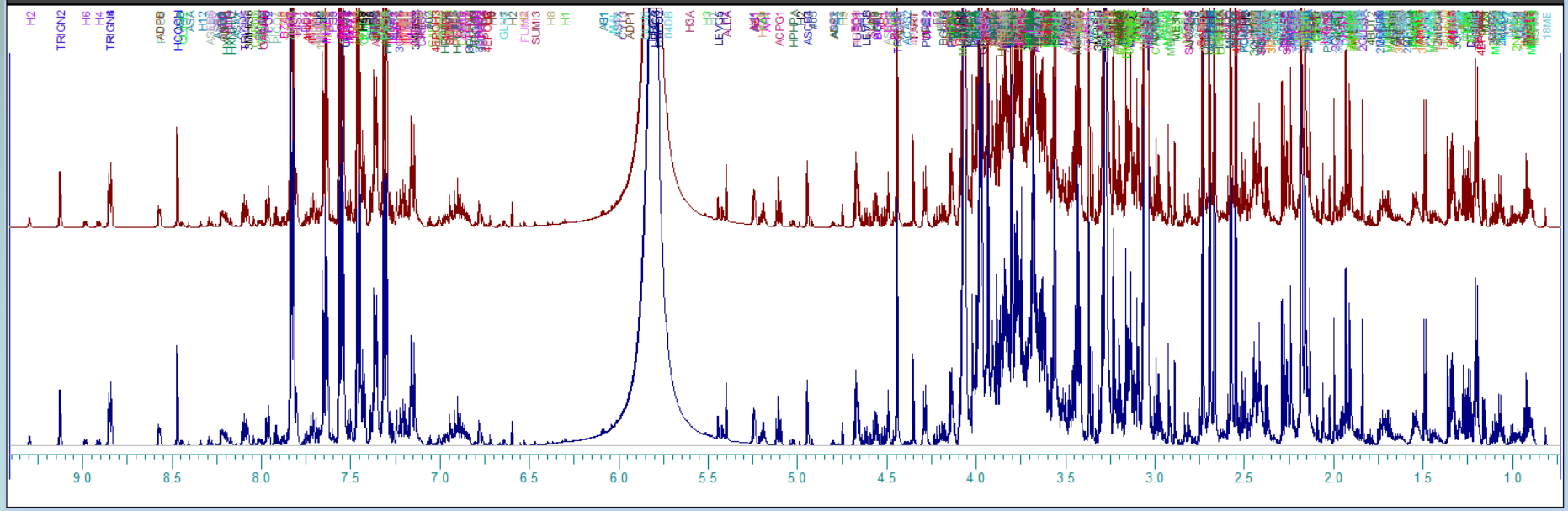
Molar% & [changes] ..press TAB to skip to parameters

TSP	0.6441[0.5589]	MANNITOL	0.5919[-0.0031]	ACETATE	0.2385[-0.0003]	XYLITOL	0.1612[0.0069]	MALTOSE	0.1103[0.0001]	3OHBUTYRA..	0.0658[-0.0003]
13NH2-PRO..	0.0223[0.0003]	TRIGONELL..	0.5681[-0.0030]	GLYCEROL	0.2408[0.0020]	DIMESULFO..	0.1464[-0.0006]	1-METHYLN..	0.1060[-0.0005]	..list continues				
CHOLINE	0.0092[-0.0551]	ACAMINOPH..	2.5352[-0.0101]	CYSTINE	0.2292[-0.0003]	GLUCARATE	0.1528[-0.0015]	CARNITINE	0.0914[-0.0004]	Total	99.356[0.1939]			
CREATININE	26.958[-0.1108]	ME2AMINE	0.5631[-0.0025]	DEOXYTHRE..	0.2249[-0.0010]	ACAMINOPH..	0.6093[-0.0040]	TRANS-ACO..	0.1207[-0.0005]	mg/ml	81.907			
UREA	22.459[-0.0923]	PSURIDN	0.5246[-0.0061]	ASCORBIC	0.5944[-0.0025]	SUCROSE	0.1342[-0.0017]	BALANINE	0.1080[-0.0003]	Structure area%				
HIPPURATE	4.1879[-0.0175]	HCOOH	0.4994[-0.0020]	GALACTOSE	0.1[illegible]	3OHPHACET..	0.1[illegible]	4ABUTYRA..	0.1[illegible]					
CITRATE	3.7127[-0.0152]	THREONICA..	0.4794[-0.0[illegible]	LACTIC	0.1[illegible]	4CBUTYRA..	0.1[illegible]	5OXOPRAL..	0.1[illegible]	Calculated area 0.15181E+04				
GLYCINE	1.9339[-0.0128]	3NH2IBUTY..	0.4754[-0.0021]	LACTATE	0.2139[0.0009]	HYPOXANTH..	0.1318[-0.0005]	PYROCATEC..	0.0853[-0.0010]	Calculated/obsd 100.026%				
ME3AMINEO..	1.6643[-0.0068]	SER	0.4620[-0.0026]	BETAINE	0.2103[-0.0008]	HOMOCITRU..	0.1369[-0.0009]	PHENOL	0.0877[-0.0004]	Background/obsd 0.000%				
TAURINE	1.4811[-0.0064]	INDOXL	0.4099[-0.0015]	FUCOSE	0.2139[-0.0028]	ANSERINE	0.1273[-0.0012]	ME2GLY	0.0806[-0.0002]	Spectrum/obsd 100.026%				
CYS	1.2039[-0.0054]	MYOINOSTOL	0.4045[-0.0069]	OHPROPION..	0.2247[-0.0011]	3OHISOVAL..	0.1247[-0.0002]	BENZOATE	0.0760[-0.0003]	2M species/Spec 100.000%				
CREATINE	0.8342[-0.0024]	ALANINE	0.4[illegible]	[illegible]	0.[illegible]	PROLYCOL	0.122[illegible]	[illegible]	0.0891[-0.0083]	Complexes/Spec 0.000%				
HIS	0.784[-0.0056]	GLUCON.C..	0.[illegible]	TARTRAT	0.2158[-0.0009]	PHE	0.117[illegible]	3OHPHPROR..	0.1370[-0.0011]					
GLYCOLICAC	0.7687[-0.0026]	CISACONAT..	0.3823[-0.0015]	ASPARTATE	0.2121[-0.0119]	TRP	0.1149[illegible]	PUROYLSER..	0.0723[-0.0011]	RMS-Fit 0.0060%				
GUANIDEAC	0.7584[-0.0092]	THREONIN	0.2440[-0.0002]	SORBITOL	0.1780[-0.0038]	2-AMINOAD..	0.1262[-0.0079]	MEAMINE	0.0732[-0.0003]	R-FACTOR(%) = 99.9989%				
ISOCITRIC	0.8586[-0.0026]	PYROGLUTA..	0.3678[-0.0124]	ASPARAGINE	0.1829[-0.0008]	3MPXANTHI..	0.1130[-0.0008]	N-ACASPAR..	0.0735[-0.0004]	POP Regression - no rank				
GLUCOSE	0.6833[-0.0[illegible]	THREITOL	0.3[illegible]	[illegible]	0.1[illegible]	HOMOVANIC	0.[illegible]	ACETONE	0.[illegible]	PM Rank = 0 / 2				
GLUTAMIN	0.6791[-0.0[illegible]	XYL	0.3[illegible]	URACIL	0.1[illegible]	HPHPA	0.[illegible]	2HYDROXY..	0.[illegible]	Threshold= 1.000%				
ETHANOLAM..	0.6746[-0.0049]	LYSINE	0.3164[0.0005]	OXOPURINOL	0.2432[-0.0010]	SUCCINICA..	0.1069[-0.0032]	MEHYDANTO..	0.0895[-0.0004]	Gaussian 0.00%				
MEOH	0.6767[-0.0028]	3MEHIS	0.3024[-0.0006]	GLUCURONA..	0.1779[-0.0003]	4OHPHEAC	0.1011[0.0001]	SCYLLITOL	0.0768[-0.0003]	Line-width 1.500HZ				
PHACGLN	0.6182[-0.0062]	GLYCEAC	0.3006[0.0086]	GLUTAMAT	0.1542[-0.0019]	NACNEURAM..	0.0989[-0.0003]	IBUTYRATE	0.0642[-0.0001]	LINES 39046				
ERYTHRITOL	0.6175[0.0041]	ALLATOIN	0.2817[-0.0011]	ARG	0.1787[0.0208]	CARNOSINE	0.1005[-0.0005]	INDOLEAC	0.0616[-0.0009]					
2OHGLUTAR..	0.6039[-0.0021]	CYSTATHION	0.2672[-0.0027]	1MEHIS	0.1534[0.0010]	QUINOLINE	0.0950[-0.0005]	VALINE	0.0620[-0.0005]					
ARABITOL	0.5462[-0.0378]	ARABINOSE	0.2438[-0.0004]	PICOLINE	0.3548[-0.0015]	LEVOGLUCO..	0.1828[-0.0008]	METHYLSUC..	0.0589[0.0001]					

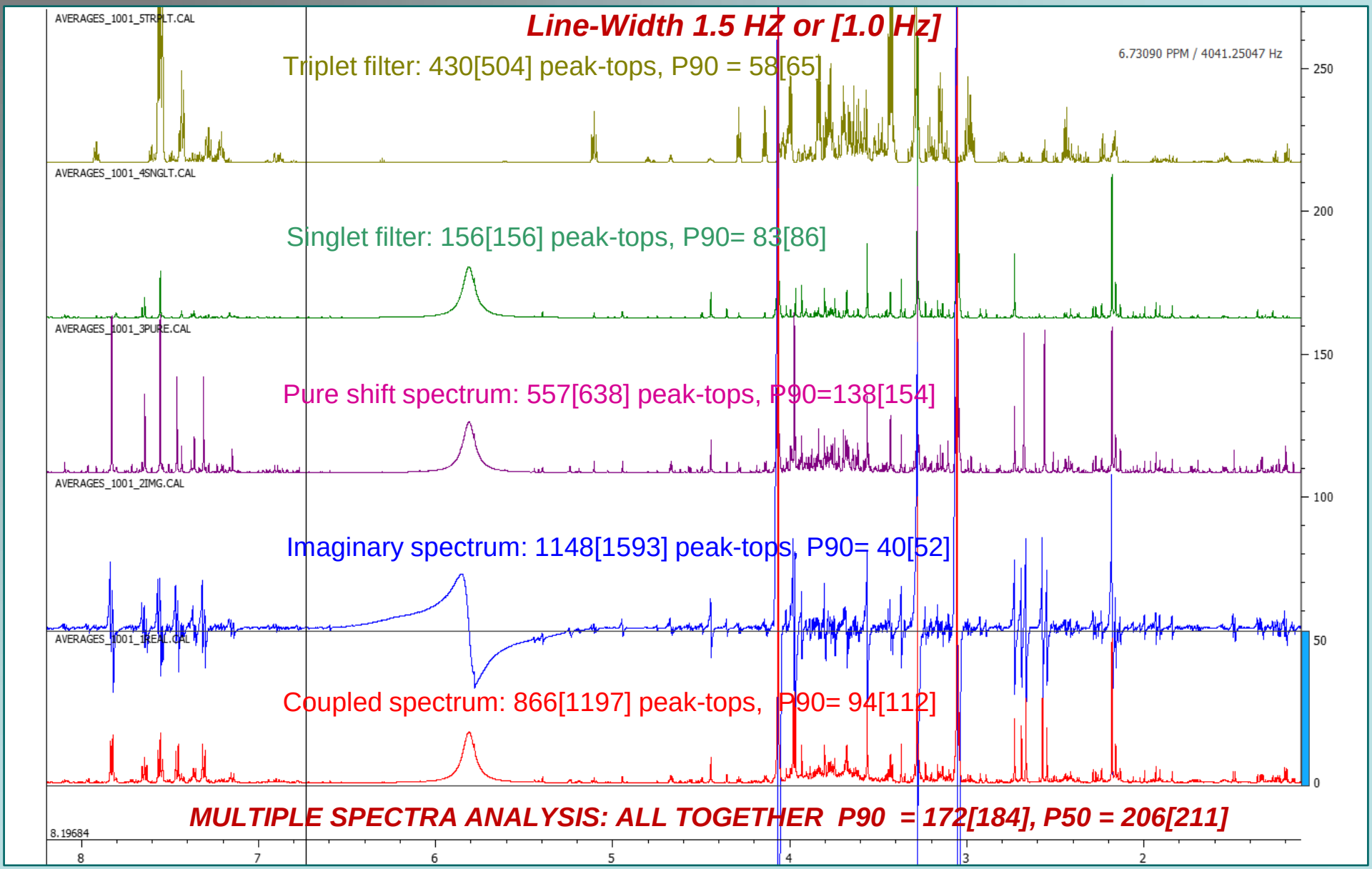
214 Compounds, 270 spin systems

1000 1H Spin Particles, 1546 nuclei (^{1}H, ^{31}P, ^{14}N)

Simulation time < 2 sec - far less multitasking



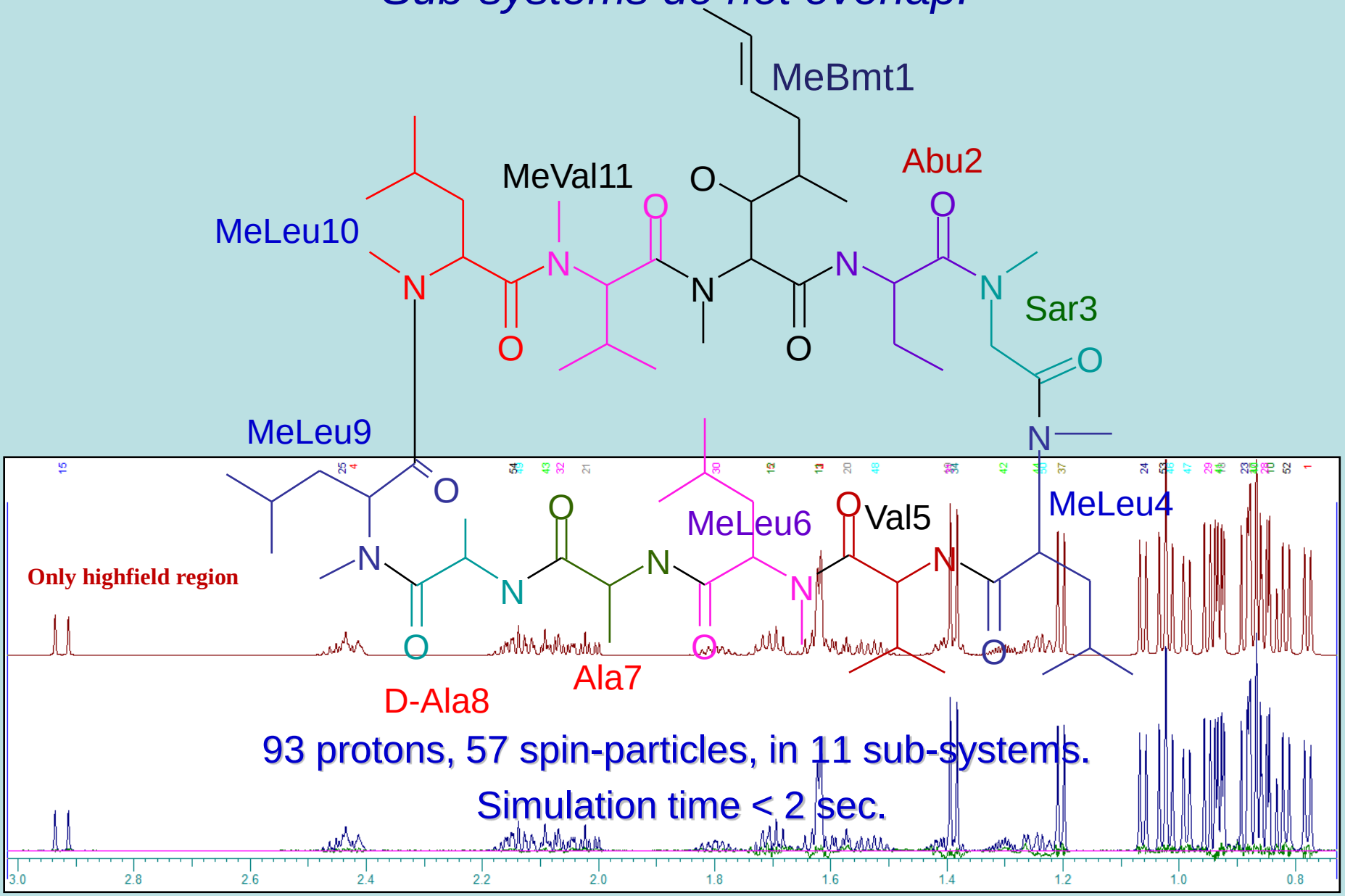
URINE 1000+1 particles, simulated spectra of 214 metabolites



P90 = No. of compounds having at least one 90% purity signal

Peptides: Cyclosporine A

Sub-systems do not overlap!



SPIN-SYSTEM DECOMPOSER

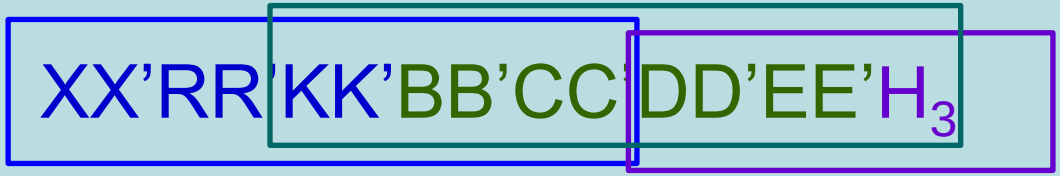
Automatic packing of large spin-networks

The simulation of octanyl $Ar(CH_2)_7CH_3$-spin system (of FELIX, see below) as

$AA'BB'CC'DD'EE'FF'GG'J_3$ – spin-system

yields > 58 000 000 allowed transitions, > 3 600 000 non-zero intensity transitions (with 99.8% of total intensity) or > 3 300 000 (97% of total) and, after packing > 76 000 non-degenerate non-zero lines !

When the system is decomposed into three overlapping sub-systems



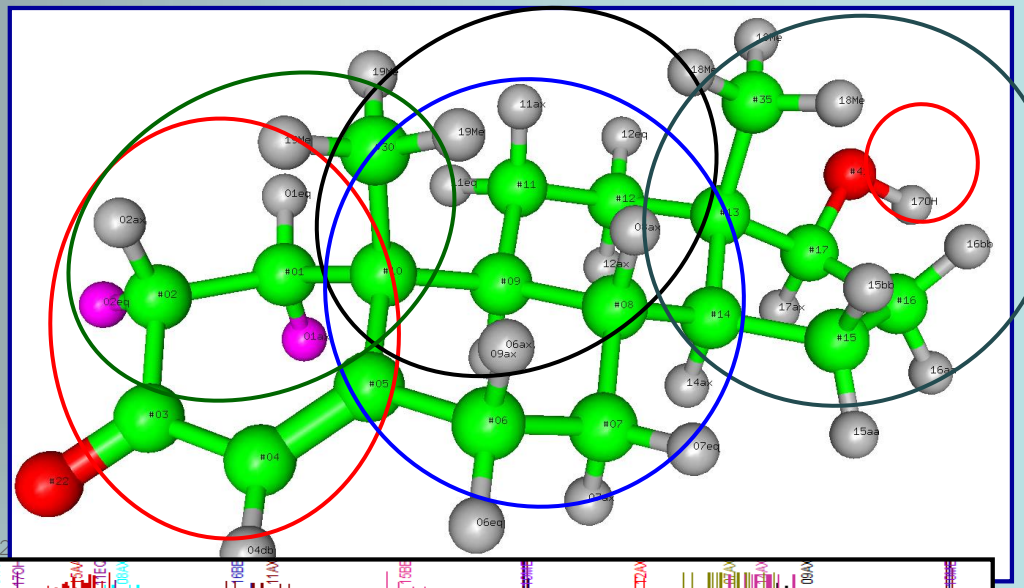
where, for example KK'BB' belongs into two sub-systems, the numbers are > 1 455 000 (allowed), > 157 800 (99.8%) and ca. 24 000 (packed) transitions !

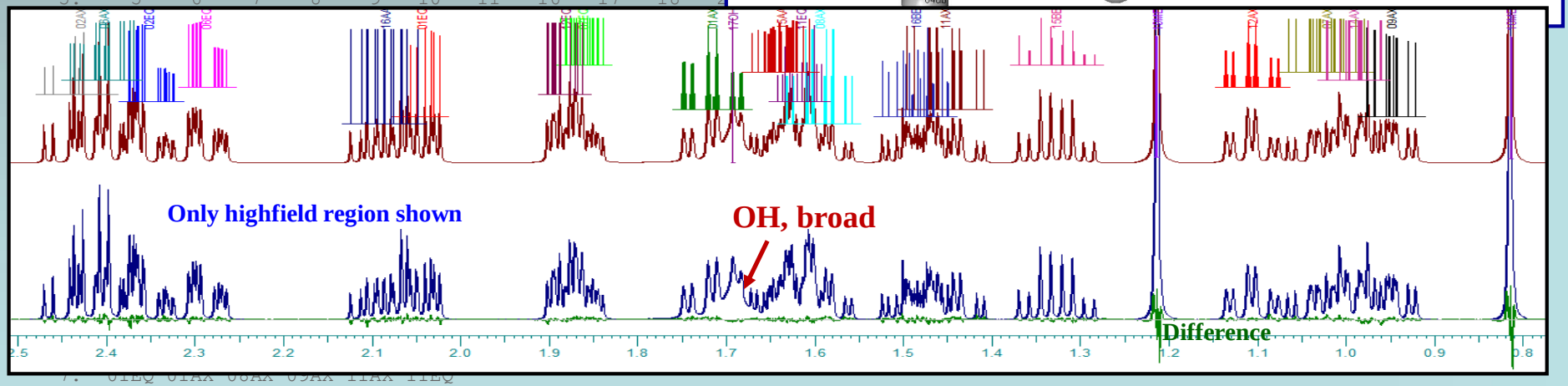
In the packing algorithm, transitions separated by < 0.01 Hz and belonging to the same species are combined, in iteration also their derivatives must be similar.

….and the simulation time drops from 64 sec to 4 sec !!

Large spin-networks: Testosterone

All the protons coupled with each others through the spin-network





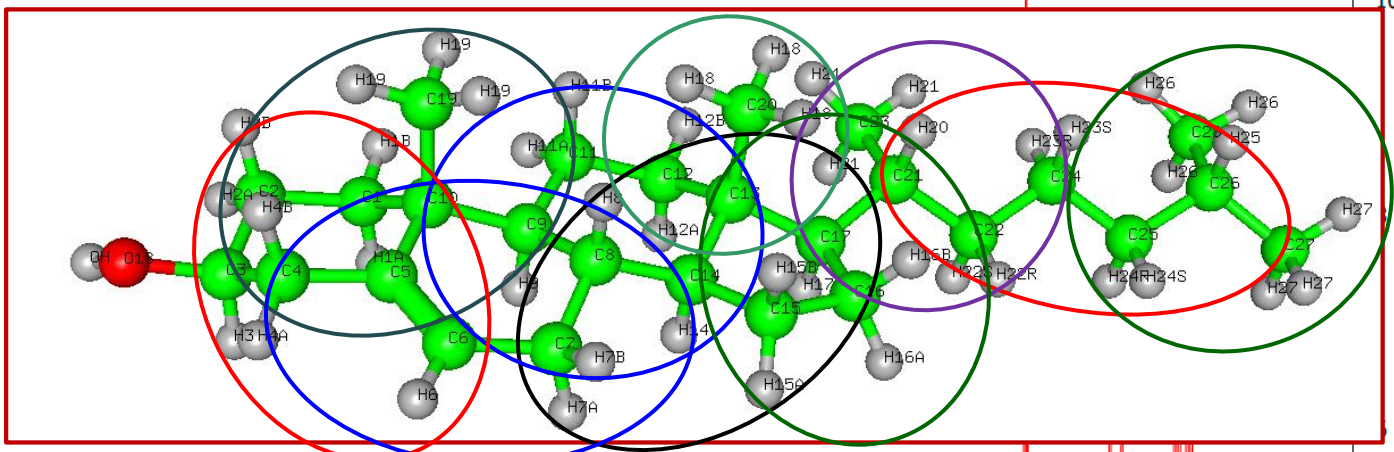
28 protons → 24-spin particles → 7 sub-systems → 25205 transitions → 1043 lines.

Simulation time < 0.7 sec, with different line-width for each particle.

CHOLESTEROL_MIX.QMT

Large spin-networks: Cholesterol

All the protons coupled with each other through the spin-network



H3, H6 and Me18 out of this range

46 protons → 36-spin particles → 14 sub-systems (not all shown above) → 368001 transitions → 9322 lines

Simulation time < 1 sec, with different line-width for each spin-particle.

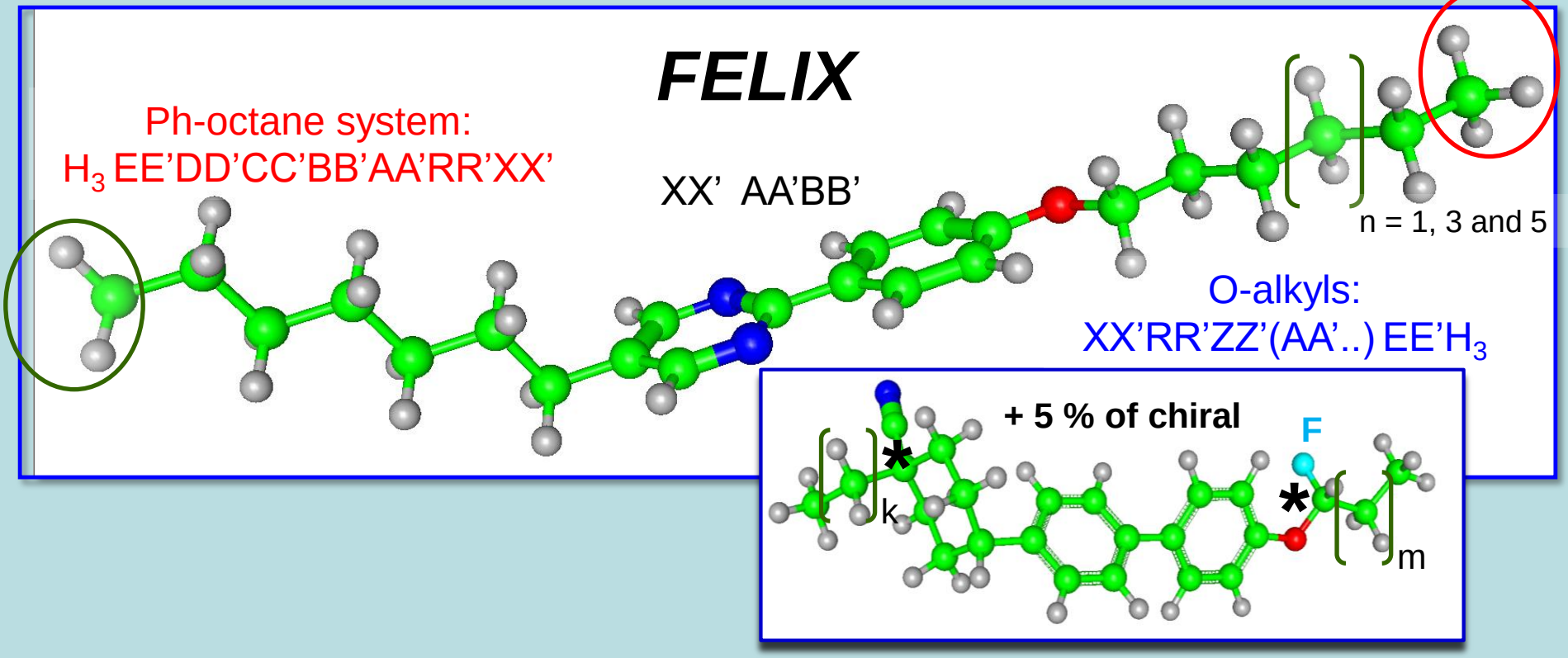
Difference

QMSA of total ^{1}H NMR and 1D TOCSY spectra of *FELIX chiral nematic solvent*

An example of large, very tightly coupled spin-systems, solved with help of QMSA of 1D TOCSY spectra of Ar-octane system and the sub-system populations derived from the Me-signals!

35 spin-particles (74 protons) in 5 sub-systems

Totally > 13 500 000 non-zero intensity transitions !



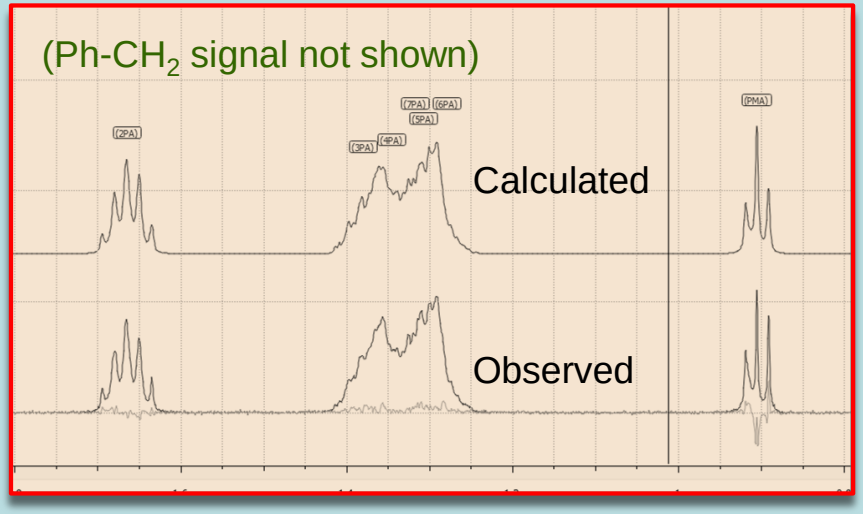
Published in

Susanna K. Ahola, L. Petri Ingman, Reino Laatikainen, Jari Sinkkonen and Jukka P. Jokisaari, *^{21}Ne and ^{131}Xe NMR study of electric field gradients and multinuclear NMR study of the composition of a ferroelectric liquid crystal.* *J.Chem.Phys.* **149**, 234901 (2018). https://doi.org/10.1063/1.5052499

QMSA of Ar-$(CH_2)_7CH_3$ **1D TOCSY**

Experimental: ^{1}H TOCSY spectrum in which proton ***response factor*** decays from 1.00 (Ar-C**H$_2$**, source of TOCSY spin-polarization) to 0.26 (C**H$_3$**).

Simulation as XX'RR'AA'BB'CC'DD'EE'K_3–system:
Simulation time: ca. 4 sec
Theoretical transitions: 5 442 2281
Non-zero intensities: 2 442 281 (99.8% of theor.)
Non-zero intensities: 2 223 827 (97% of theor.)
Lines after packing: 129 871 (packing crit. 0.010 Hz)



For AA'BB'CC'DD'EE' all the ^{2}J, ^{3}J and ^{4}J are not well-defined by the spectrum, they were taken from analysis of heptane (*Magn.Reson.Chem.,* 2012, 50, 598) and kept fixed during iteration.

All the CH_2 shifts are well-defined, see the shift order: A-B-C-E-D-K !
Analysis explains the odd shape of **CH_3-SIGNAL** (593 non-degenerate lines within 18 Hz) !

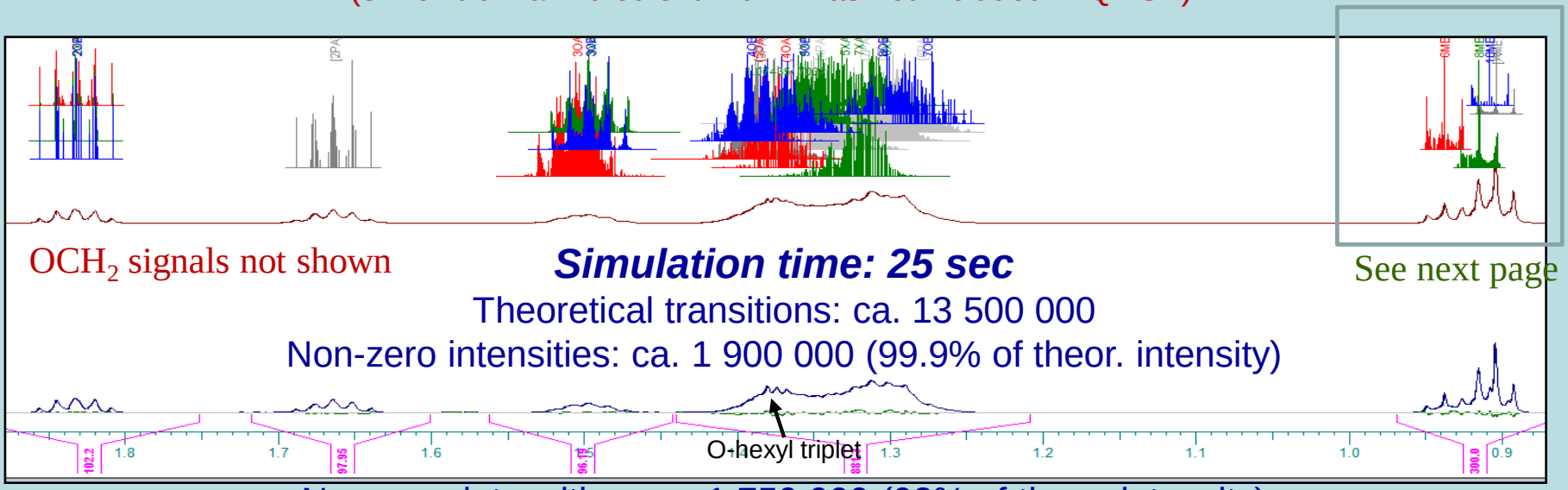
FELIX of MILLIONS TRANSITIONS

Experimental: normal ^{1}H spectrum,

Spin-system:

XX'RR'AA'BB'CC'DD'EE' H_3(Ar-octyl) +
XX'RR'ZZ' BB'CC'H_3 (O-hexyl) +
XX'RR'ZZ' BB'CC'DD'EE'H_3 (O-octyl) +
XX'RR'ZZ'BB'$(CC')_3$DD'EE'H_3 (O-decyl) +
XX'YY'ZZ'

(5 mol% *chiral incredient w*ith F was not included in QMSA)



OCH_2 signals not shown

Simulation time: 25 sec

See next page

Theoretical transitions: ca. 13 500 000

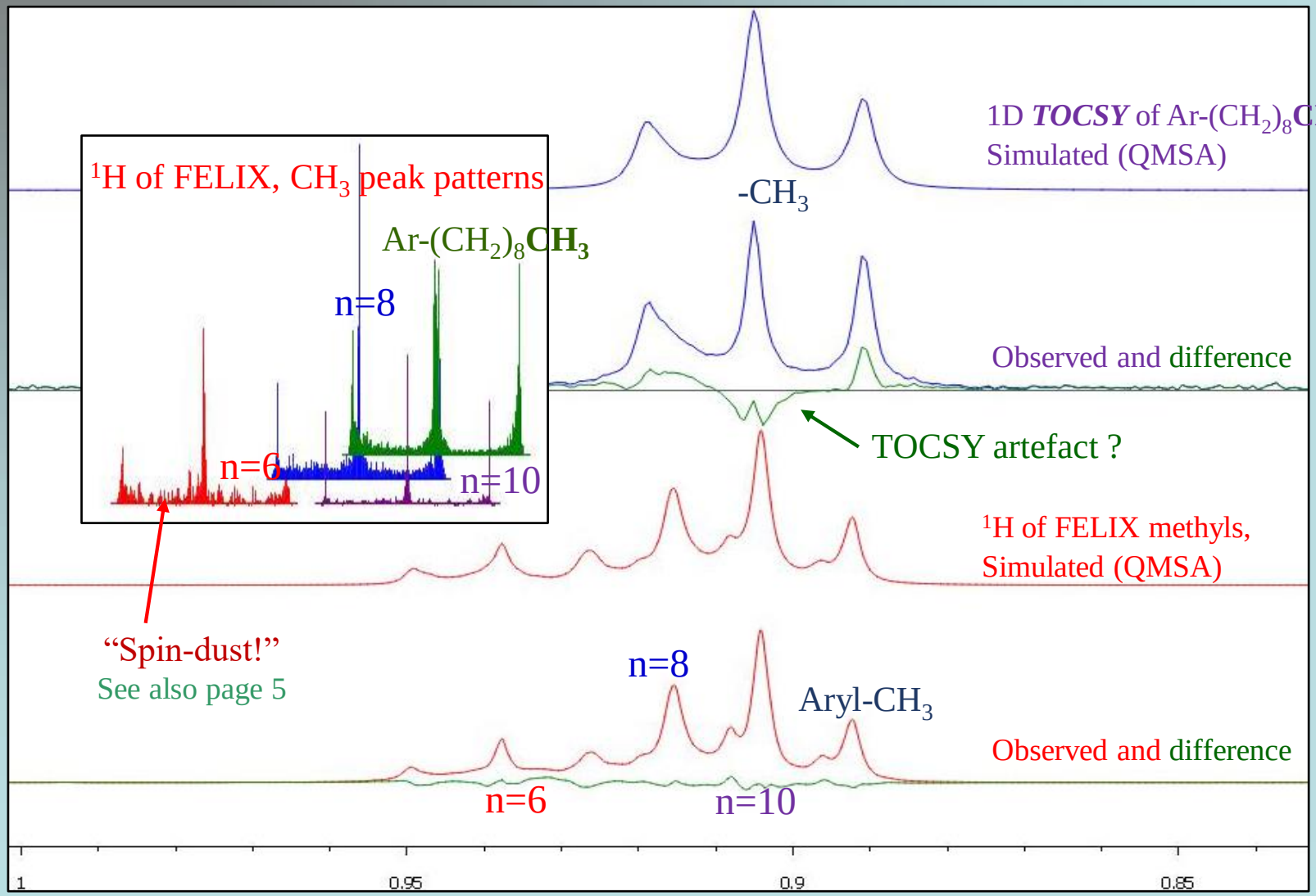
Non-zero intensities: ca. 1 900 000 (99.9% of theor. intensity)

Non-zero intensities: ca. 1 750 000 (93% of theor. intensity)

Lines after packing: ca. 135 000

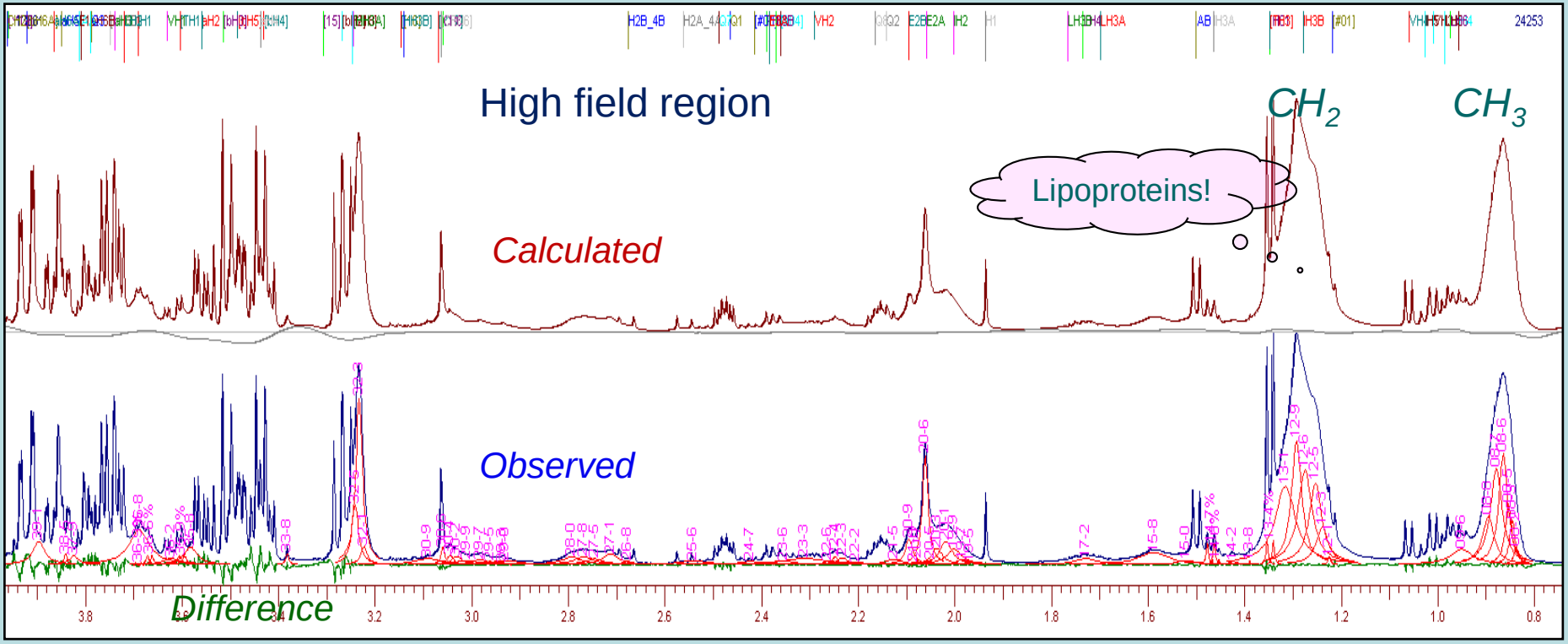
Although the CH_2-shift order is somewhat unclear, the analysis gives the alkyl lengths with a fair confidence

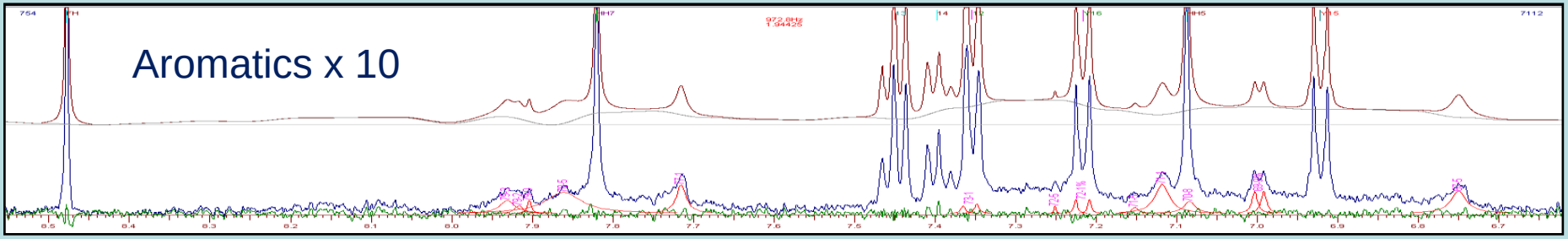
The FELIX methyl signal carries the information from the alkyl populations



qQMSA of T2 edited serum spectrum,

from *J.Magn.Reson.*, 2014, 242, 67-78





The team