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# Insights Gleaned from a Review of NMRD Profiles

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UNIVERSITY OF  
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Fast Field Cycling  
NMR Relaxometry

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**Extra Byte**  
>in spin we trust

# Origins of Relaxation

Basic aspects of complex systems, as seen by Physics:

- equilibrium states (thermodynamics)
- return paths from a non-equilibrium state towards an equilibrium
  - Radiation (radiation physics, ineffective in NMR)
  - Non-radiative relaxation (energy redistribution among eigenstates)

Relaxometry of a complex system studies the dynamics of energy transfers between its various internal degrees of freedom while it evolves towards a thermodynamic equilibrium.

# Relaxation in condensed-phase NMR

We usually accept Weston Anderson's approximation and formally separate any studied system into:

- One or more spin subsystems described by their Spin Hamiltonians
- other degrees of freedom, referred-to as lattice (also thermal bath)

The energy exchange paths that transfer energy from the spin system to lattice give rise to spin-lattice relaxation phenomena, while those paths that exchange energy among various spin states give rise to spin-spin relaxation phenomena such as spin-diffusion.

In high magnetic fields (when the Zeeman interaction of the spins magnetic moments dominates over other terms of the spin Hamiltonian, the above terms may be identified, respectively, with longitudinal relaxation phenomena of  $T_1$  type and transversal relaxation phenomena of  $T_2$  type.

# Quantum formulation

in laboratory frame

In Liouville representation, quantum systems are described by the density operator  $\rho$ , a Hamiltonian  $H$ , and the evolution equation

$$(1) \quad \frac{d}{dt}\rho = -i\mathbf{H}\rho, \text{ where } \mathbf{H} \text{ is the super-operator } \mathbf{H}\rho \equiv [H, \rho].$$

which can be also cast into the integral form

$$(2) \quad \rho(t) = \rho(0) - i \int_0^t dt' \mathbf{H}\rho(t')$$

When  $H$  is time-invariant, the exact solution of (1) is

$$(3) \quad \rho(t) = e^{-iHt}\rho(0)e^{iHt},$$

These equations cover many aspects of *spectroscopy*, but not yet *relaxation*!

# Quantum formulation

in **rotating frame** and with the Hamiltonian containing **stochastic terms**

To explain relaxation, we need a time dependent Hamiltonian, which we split into a time-independent part and a random part with zero mean:

$$(4) \quad H(t) = H_0 + S(t), \text{ where } H_0 = \langle H(t) \rangle \text{ and } \langle S(t) \rangle = 0.$$

Now we transform  $\rho$  and  $S$  to the rotating frame

$$(5) \quad \rho^*(t) = e^{iH_0 t} \rho(t) e^{-iH_0 t}, \quad S^*(t) = e^{iH_0 t} S(t) e^{-iH_0 t} \text{ and,}$$

after some manipulation, find out the following evolution equations:

$$(6) \quad \frac{d}{dt} \rho^* = -i S^* \rho^*, \quad \rho^*(t) - \rho^*(0) = -i \int_0^t S^*(t') \rho^*(t') dt'$$

**Two time scales:**

micro (molecular motion times) and macro (relaxation times)

We need to assume that the terms  $S(t)$  are due to molecular motions occurring at time scales in the range of  $10^{-4}$  to  $10^{-10}$  seconds, while we wish to look for their “secular” effects at much longer times ( $>10^{-3}$  seconds).

# Correlations and Spectral densities

In order to describe the slow (secular) evolution of the density matrix, equation (6) must be iterated to second order (the Peano-Picard trick) and then averaged over the micro-scale time intervals.

After some more manipulations and assumptions, one obtains  
**a universal expression for relaxation phenomena:**

$$\frac{d}{dt}(\boldsymbol{\sigma}^*(t) - \boldsymbol{\sigma}_0^*) = -J(H_0)(\boldsymbol{\sigma}^*(t) - \boldsymbol{\sigma}_0^*)$$

where

$\boldsymbol{\sigma}^*(t) = \langle \boldsymbol{\rho}^*(t) \rangle$  is the rotating-frame smoothed density super-operator

$J(H_0) = \int_0^\infty d\tau e^{iH_0\tau} \mathcal{C}(\tau)$  is the spectral density super-operator ( $H_0 \approx \omega$ )

$\mathcal{C}(\tau) = \langle \mathcal{S}(0)\mathcal{S}(\tau) \rangle$  is the correlation function super-operator

**Note:** spectral densities are Fourier transforms of correlation super-operators.

# Insights - the very basics

- ✓ Rigorously speaking, in all practical cases, *the theory is far too complex* to manage numerically. At best, it can give us a heuristic guidance.
- ✓ In NMR, relaxation is driven by the presence of spin interactions that get modulated by stochastic motions occurring at the micro scale.
- ✓ The spin interactions and the stochastic motions get combined together inside the correlation functions  $C(\tau)$ .
- ✓ With respect to spin interactions, relaxation is a second-order effect.
- ✓ Observable relaxation rates are linear combinations of the spectral density functions which, in turn, are Fourier transforms of the  $C(\tau)$ .
- ✓ To explain relaxation phenomena, even just heuristically, we need:
  - to know the relevant spin Hamiltonian terms and
  - to have a model of the micro-scale motions within the sample

# Spin-Hamiltonian terms

of a generic system of nuclei

$$H = H_Z + H_{SR} + H_C + H_{DD} + H_{DE} + H_F + H_J + H_Q + \dots$$

H (energy) =

interaction with external field(s)

**Z** (Zeeman)

+ spin-rotation interactions

SR

+ chemical shifts

C, CSA

+ dipolar interactions with other nuclei

**DD**

+ dipolar interactions with electrons

**DE**

+ contact interactions with electrons

F (Fermi)

+ indirect couplings

J, JCA

+ quadrupolar interactions

**Q**

!!! All this gets **summed over all nuclides and pairs of nuclides** in a sample !!!

# Details of some spin-Hamiltonian terms

$$H_Z = \mathbf{B} \cdot \boldsymbol{\mu}_i = \hbar \gamma_i \mathbf{B} \cdot \mathbf{I}_i,$$

$\mathbf{B}$  is the external magnetic field,  $\mathbf{B} = \mathbf{B}_0 + \mathbf{G}_0 + \mathbf{G}$

$$H_C = \mathbf{B} \cdot \mathbf{C}_i \cdot \mathbf{I}_i,$$

$\mathbf{C}_i$  is the **chemical shift tensor** due to the *magnetic polarisation of the molecule* in field  $\mathbf{B}$  at the location of nucleus  $i$

$$H_{SR} = \mathbf{M} \cdot \mathbf{R}_i \cdot \mathbf{I}_i,$$

$\mathbf{R}_i$  is a **spin-rotation interaction tensor** between the molecular angular momentum  $\mathbf{M}$  and the spin of nucleus  $i$

$$H_{DD} = \mathbf{I}_i \cdot \mathbf{D}_{ij} \cdot \mathbf{I}_j,$$

$\mathbf{D}_{ij}$  is the **dipole-dipole interaction tensor** of the *direct coupling* between the magnetic moments of the nuclei  $i, j$

$$H_{DE} = \mathbf{I}_i \cdot \mathbf{E}_{ij} \cdot \mathbf{S}_\nu,$$

$\mathbf{E}_{ij}$  is the **dipole-dipole interaction tensor** between the nucleus  $i$  and the spin  $\mathbf{S}_\nu$  of an *unpaired electron*  $\nu$

$$H_F = \mathbf{I}_i \cdot \mathbf{A}_{i\nu} \cdot \mathbf{S}_\nu,$$

$\mathbf{A}_{i\nu}$  is the **hyperfine coupling tensor** due to the *Fermi contact interaction* between the nucleus  $i$  and an *unpaired electron*  $\nu$

$$H_J = \mathbf{I}_i \cdot \mathbf{J}_{ij} \cdot \mathbf{I}_j,$$

$\mathbf{J}_{ij}$  is the **indirect coupling tensor** due to the *contact interaction* between nuclei  $i, j$  and their shared *chemical bond electrons*

$$H_Q = \mathbf{I}_i \cdot \mathbf{Q}_i \cdot \mathbf{I}_i,$$

$\mathbf{Q}_i$  is the **quadrupole interaction tensor** due to the coupling between a *local molecular electric field gradient* and the *quadrupole moment* of the nucleus  $i$

# Molecular dynamics models

and their classes

I. **“Real cow”** models assume **realistic** molecular arrangements & dynamics:

- Chelated paramagnetic ions with one or more hydration spheres
- Rouse-based models for long linear molecules (polymers, liquid crystals)
- Caterpillar-like motions of long-chain molecules along surfaces,
- or wiggling through narrow channels
- 3- and more-taus models for water in pores with paramagnetic walls

II. **“Spherical cow”** models assume **idealized** geometrical arrangements:

- Rotational diffusion (Brownian) of molecules assumed to be spherical (BPP)
- Cole-Cole models, backed by a good but heuristic Kronig-Kramers argument
- Adsorbed water versus free water for systems with large surfaces

III. **“Not even a cow”** models are purely **heuristic**:

- Multi-Lorentz model corresponding to multi-exponential  $C(\tau)$ 's
- Other decaying transients  $C(\tau)$  may lead to multi-Gauss and other models

.....

# Insights

generic structure of formulas for a sample relaxation rates

Given a sample, its total nuclear magnetization evolves as a

**sum of myriads of additive terms**

The terms can be classified on the basis of distinguishable combinations of spin interactions and molecular motions. These, apart from summations over nuclei, can be classified as belonging to a

**manageable number of different types of relaxation terms,**

each requiring a distinct expression.

# Counting relaxation expression types

So far we have seen (we will for a moment assume that this is exhaustive):

$n_I = 8$  types of spin-interactions involving 1 or 2 nuclear spins

$n_M = 9$  types of molecular motions (or “motions”)

Since relaxations are second-order effects, this generates  $(n_I \cdot n_M)^2 = 72 \cdot 72 =$   
**= 5184 possible relaxation term expression types**

Usually, correlations between different motions are rather weak. Neglecting such cross-terms, we would need ‘only’  $(n_I^2 \cdot n_M) = 576$  formulas.

Finally, *combinations of two different Hamiltonian terms* also often lead to minor contribution. Neglecting those as well, the count drops to only  $(n_I \cdot n_M) =$   
**= 72 principal expressions, which is still no joke.**

In practice, people usually say, “ok, the interactions that matter in my case are just one or two, and maybe just one to three dynamics modes”. Hence, they end up with **1 – 6 expressions** to describe their particular NMRD profile.

# Insights

current state-of-the-art

In scientific literature,

**not too many of the relaxation term types were so far really worked out.**

And even those are often “recycled” in contexts other than the original one, sometimes with little critical spirit, apart from the fact that “they fit”.

This is partially due to the fact that the actual expressions exhibit a

*strong tendency to resemble each other mathematically,*

reducing the chance to distinguish them by fitting the data.

# Where does all this leave us

as developers of a universal software for the analysis of NMRD profiles  
???

The best one can do is to provide

**a bag of different elementary relaxation terms**

covering the various combinations of spin interactions and molecular motions that were so far studied.

The user may then choose

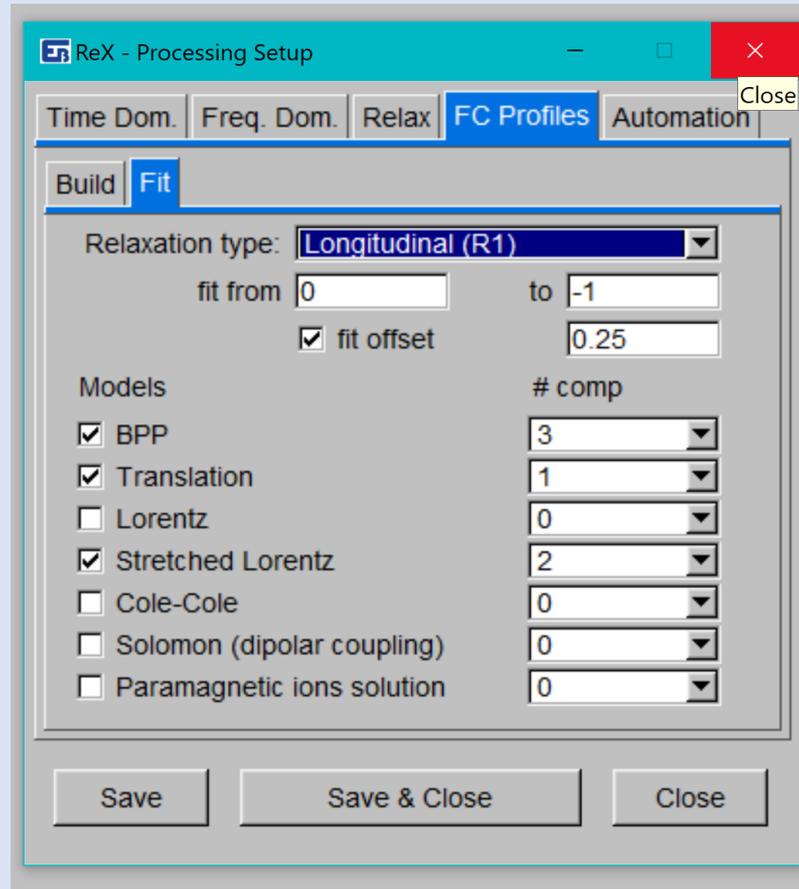
**any linear combination of such elementary terms,**

thus accepting the responsibility for the appropriateness of the choice.

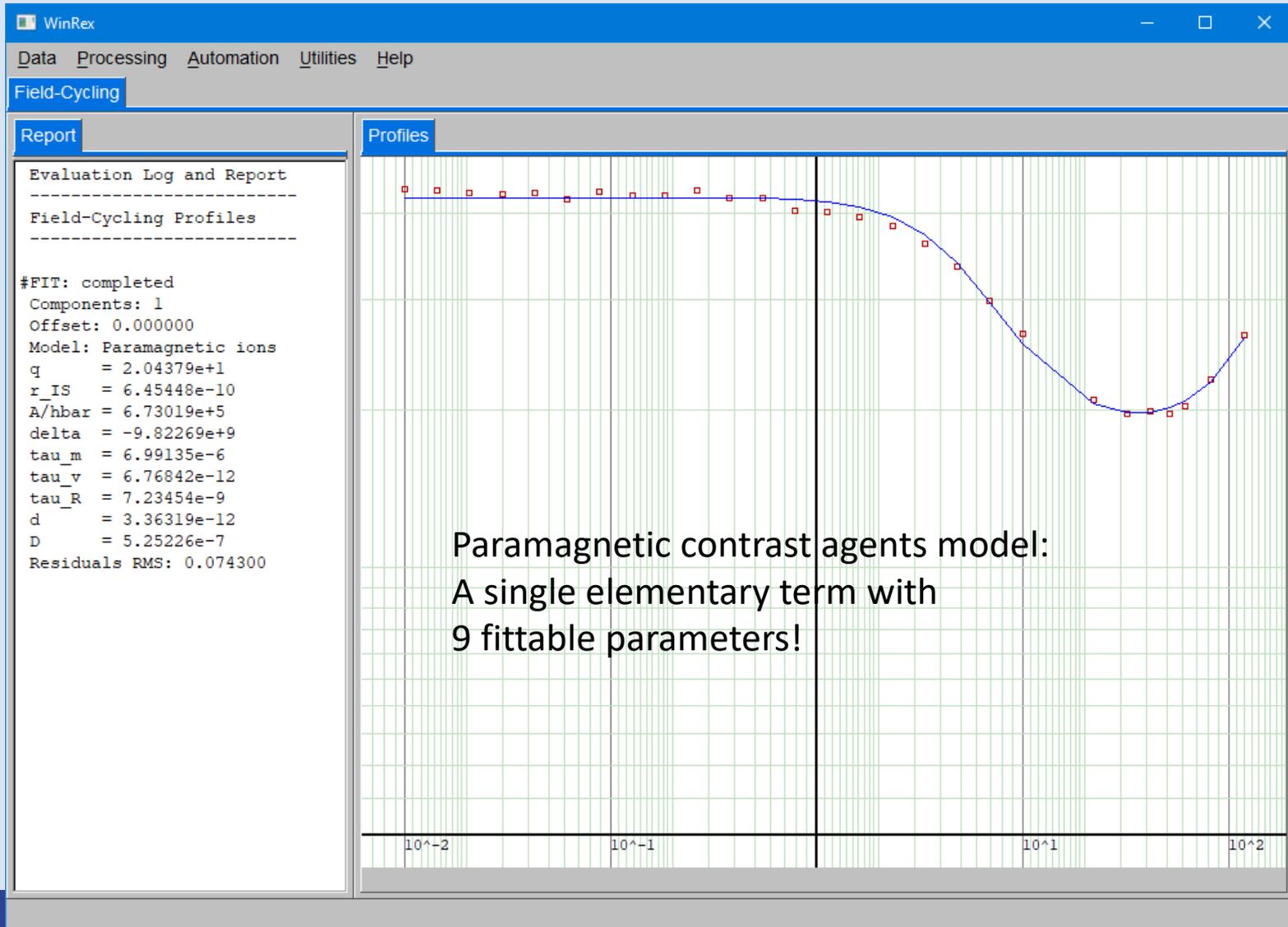
However, the bag must include as “elementary” also the sophisticated models of category I as a whole, since they can not be split onto a sum of simpler terms.

# How can this be done in practice

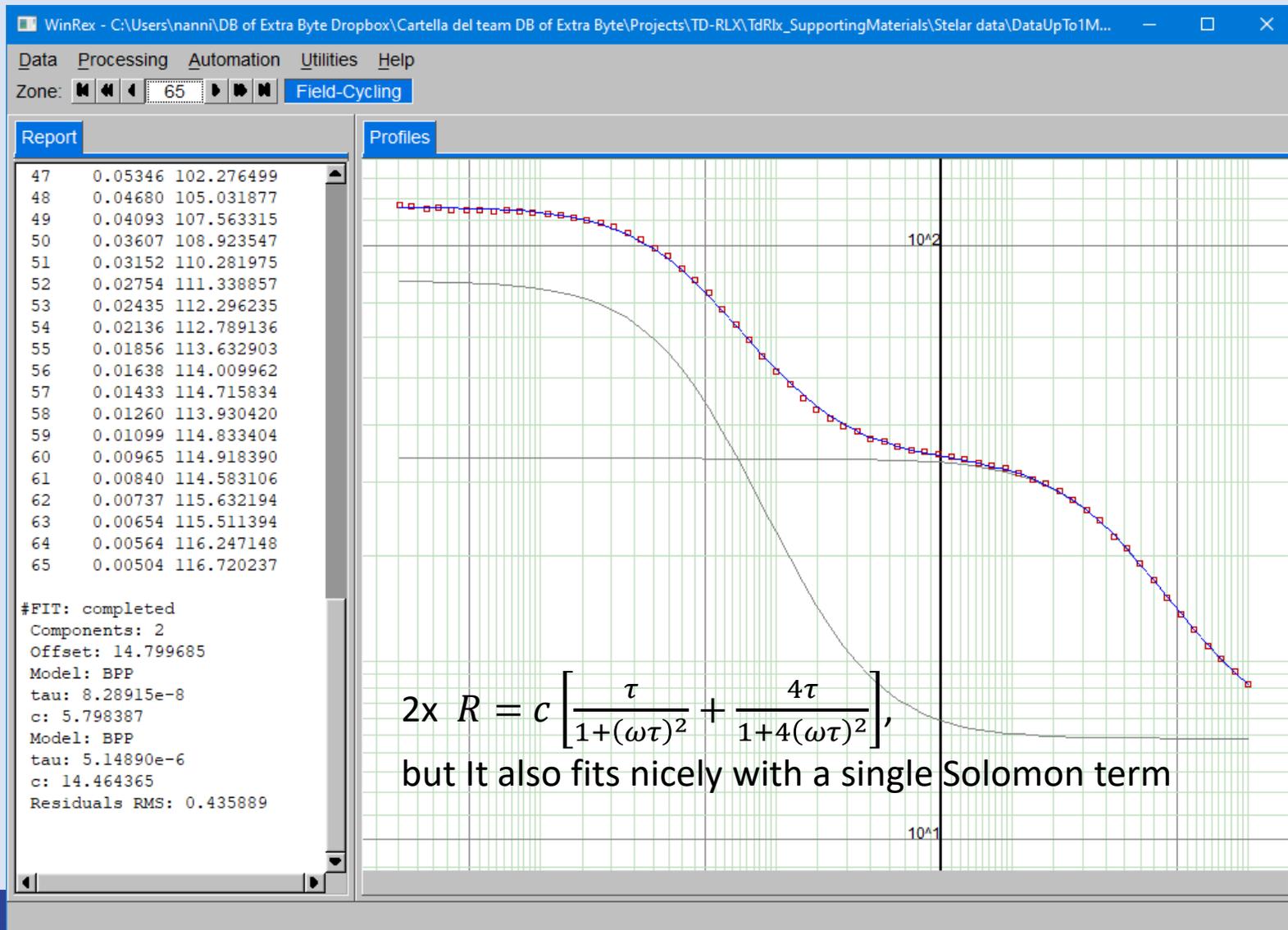
An already working, but not-yet-complete, proposal



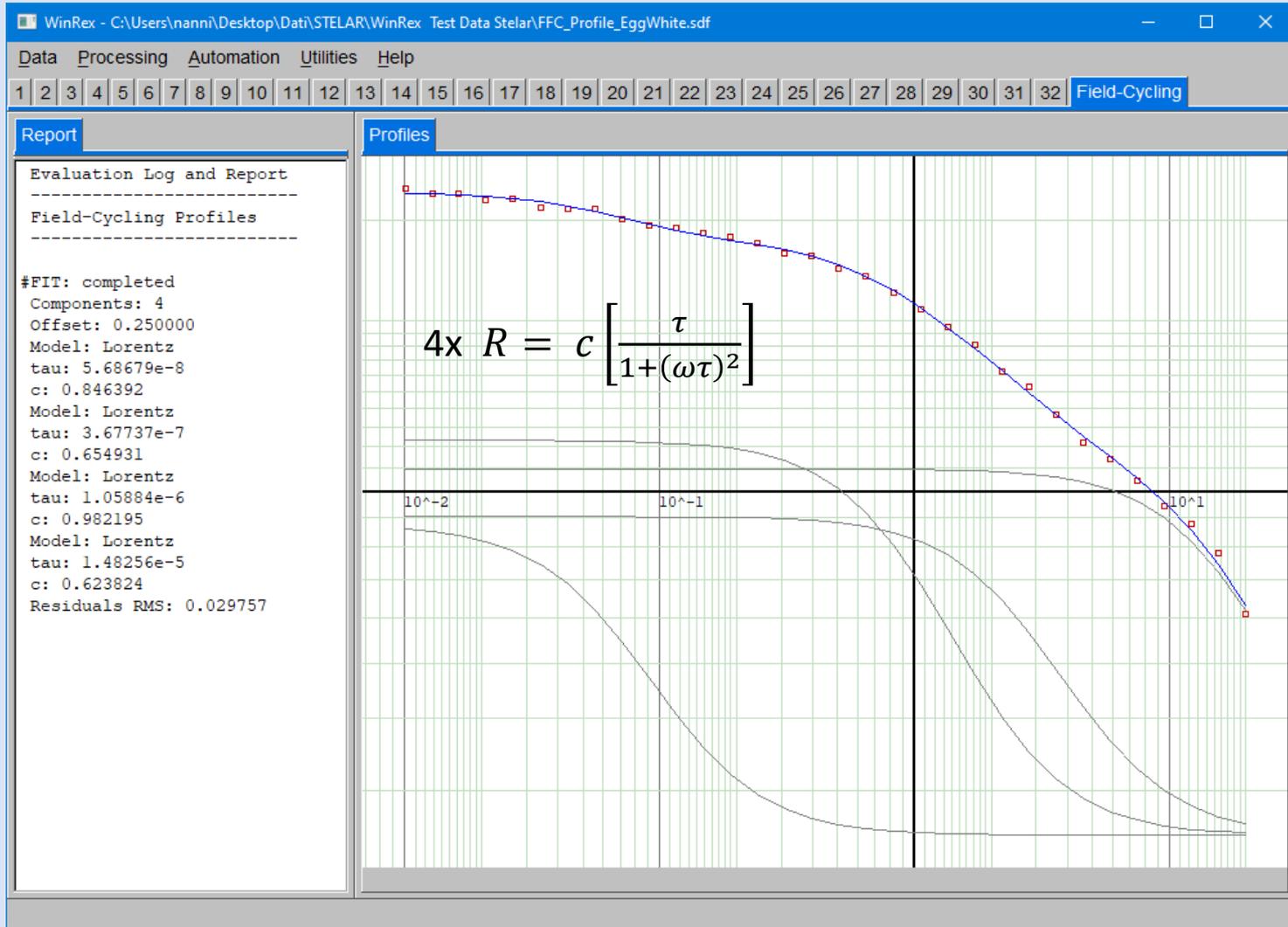
# Category I example: a gadolinium contrast agent



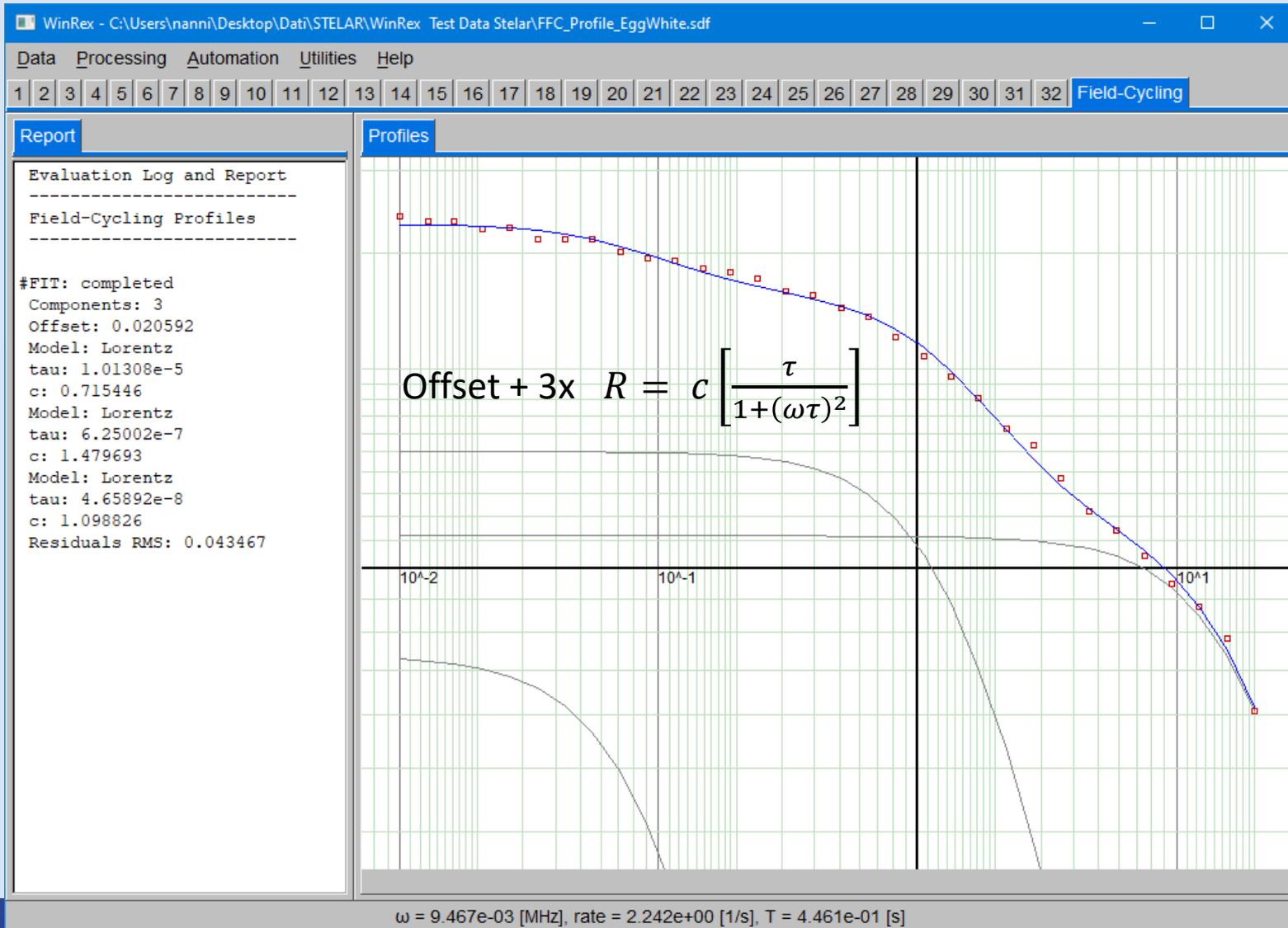
# Category II example: 2mM Mn<sup>++</sup>



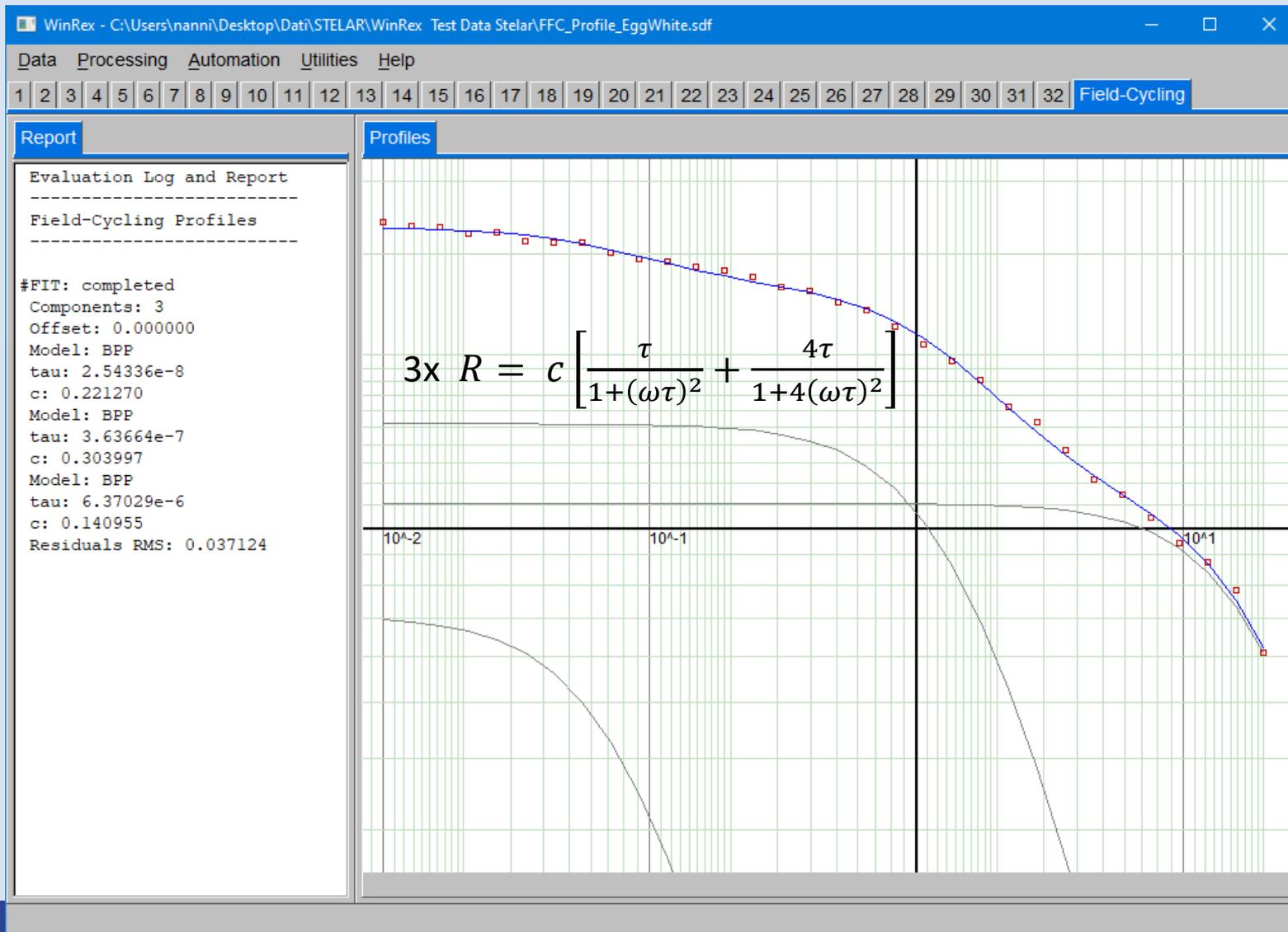
# Category III example: hen egg albumen; 4 Lorentz terms



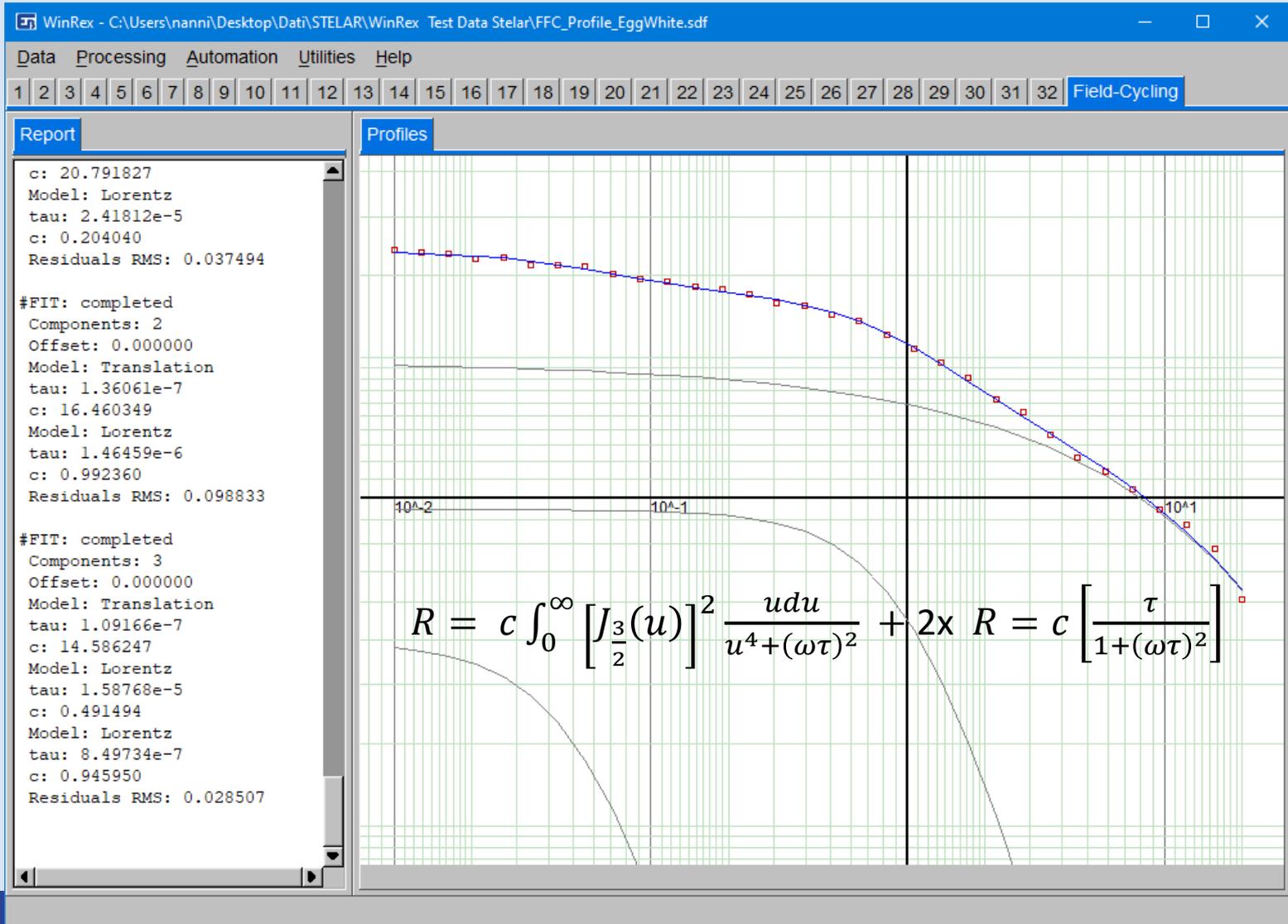
# Alternative fit: hen egg albumen; 3 Lorentz + Constant



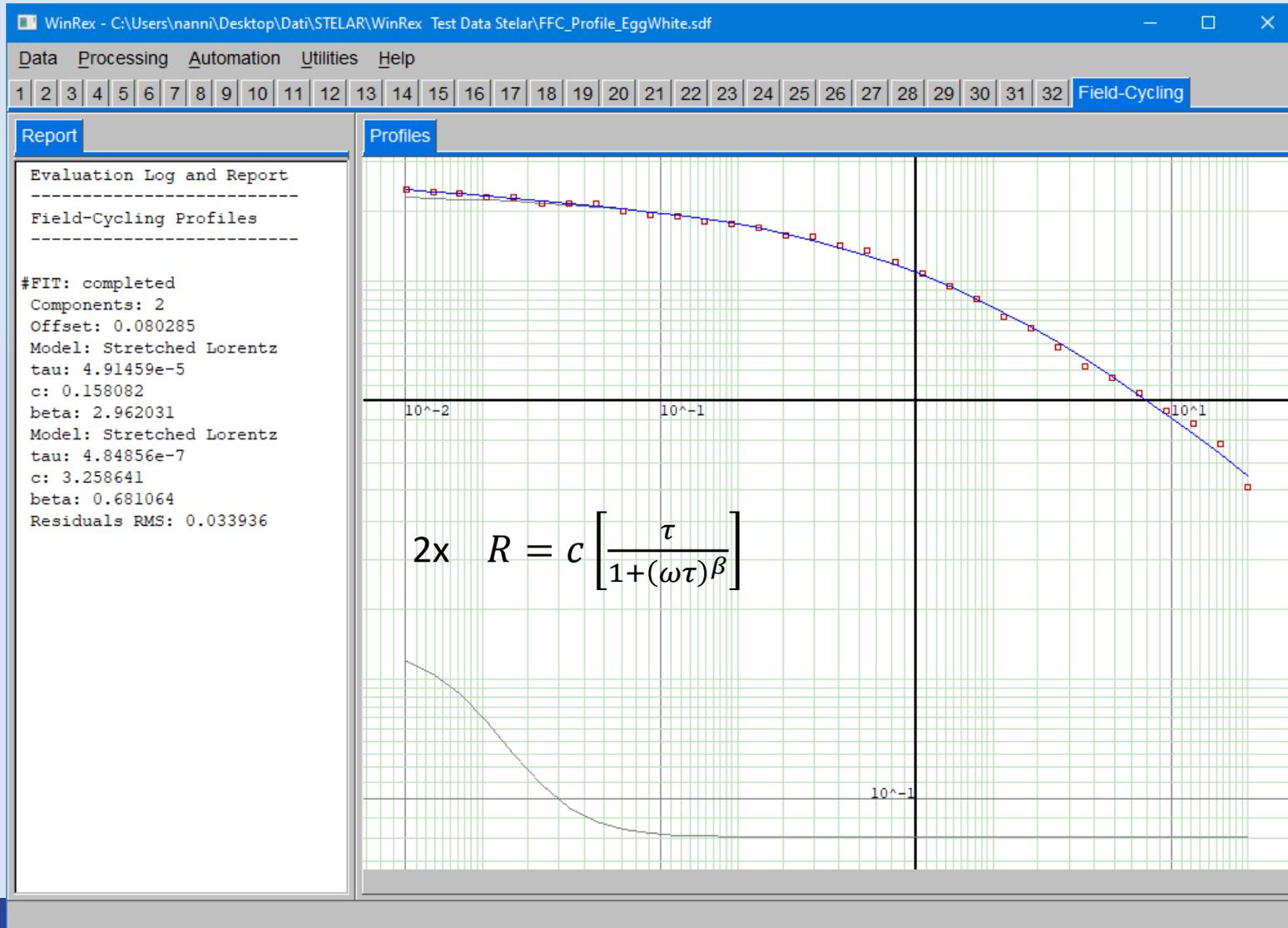
# Alternative fit: hen egg albumen; 3 BPP terms



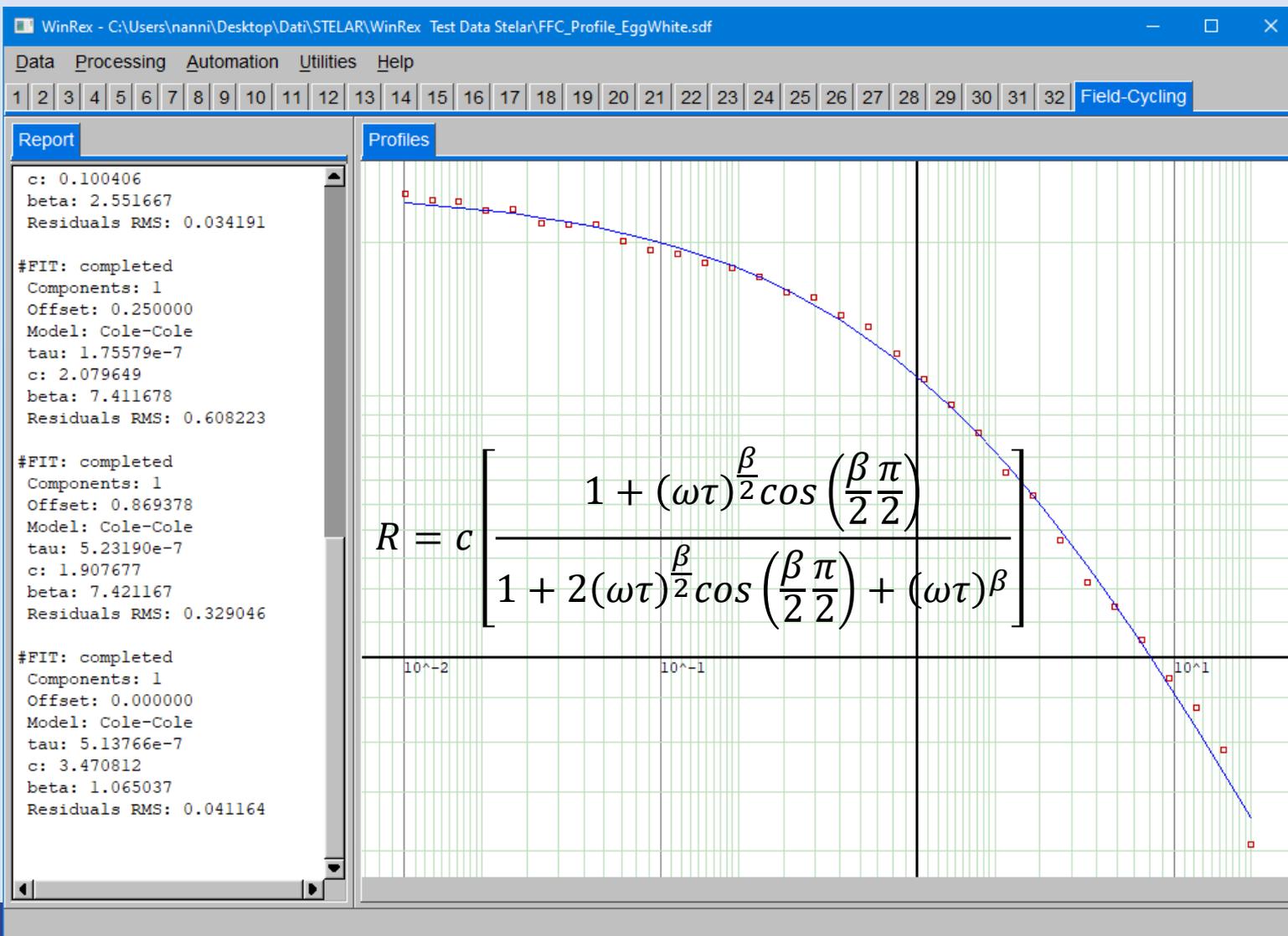
# Alternative fit: hen egg albumen; 1 Translation + 2 Lorentz



# Alternative fit: hen egg albumen; 2 Stretched Lorentz



# Alternative fit: hen egg albumen; 1 Cole-Cole



# More versatility?

Sure, it is coming

(more elementary terms and predefined taus ratios and/or coefficients ratios).

**But beware: more versatility means more indetermination!**

The real question is:

**how much “realistic” information is there in an NMRD profile?**

The rule of thumb is:

- If your motional model does not fit the data, it is wrong.
- Otherwise, it may fit but be quite wrong anyway !!!
- Choosing between two models, less fitted parameters is preferable
- Category I models, where appropriate, are more affirmative and safer.

**More suggestions? They are welcome!**

# Ways to fight the indetermination

Adding more data and fitting them all together to the same dynamic model!

In principle, what kind of data can be added?

- ✓ Same sample:
  - Variable temperature (VT profiles)
  - Measure with the same sample, but different nuclides (1H, 2D, 13C, 19F, ...)
- ✓ Early sample components separation:
  - Early separation of components in FID's
  - Prior separation of components in relaxation curves
- ✓ Pulse sequences:
  - Combined T1-T2 (2D relaxometry)
  - Pulse sequence preambles such as PERFIDI
  - Multiple quantum (MQ) relaxometry
- ✓ Sample modifications by changing:
  - Isotopic concentration (e.g. H<sub>2</sub>O/D<sub>2</sub>O mixtures)
  - Chemical concentration
- ✓ Combining with non-NMR relaxometries:
  - Dielectric relaxometry (spectra of losses)
  - Fluorescence relaxometry

# Thank You for Your Attention!

Our team:



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