2nd Workshop on Muon Science Technology and Industry, CSNS, China

Muons and Life Sciences

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Outline:
- Muon in biology: review
- Electron transfer in protein
- O_2 detection, future appli. in cancer research
- Systematic study towards muon in biology
- MuSR in water: recent achievements

A.D. Pant, et al., *Phys. Rev.* B **110**, 104104 (2024)

Jan. 10-12, 2025

Collaborators: Muon in biology

Muon
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A. Koda (KEK, Japan)
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F. L. Pratt (RAL, ISIS, UK)
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K. Nagamine (KEK, Japan)
K. Shimomura (KEK, Japan)

Biophysics & Biochemistry
B. Geil (Univ. Gottengen, Germany)
Y. Sugawara (Kitasato U. Japan)
J. S. Schultz (Houston Univ., US)

Medical/clinical
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Surendra B. Chand
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Theory: DFT, PIMD
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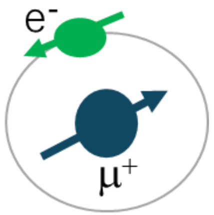
K. Kuwahata (Yokohama City Univ., Japan)
Roshan Pudasaini (KU, Nepal)
R. Adhikari (KU, Nepal)
Anjan Dahal (CDP, TU, Nepal)
Anup Shrestha (CDP, TU, Nepal)
H.S. Mallik (CDP, TU, Nepal)

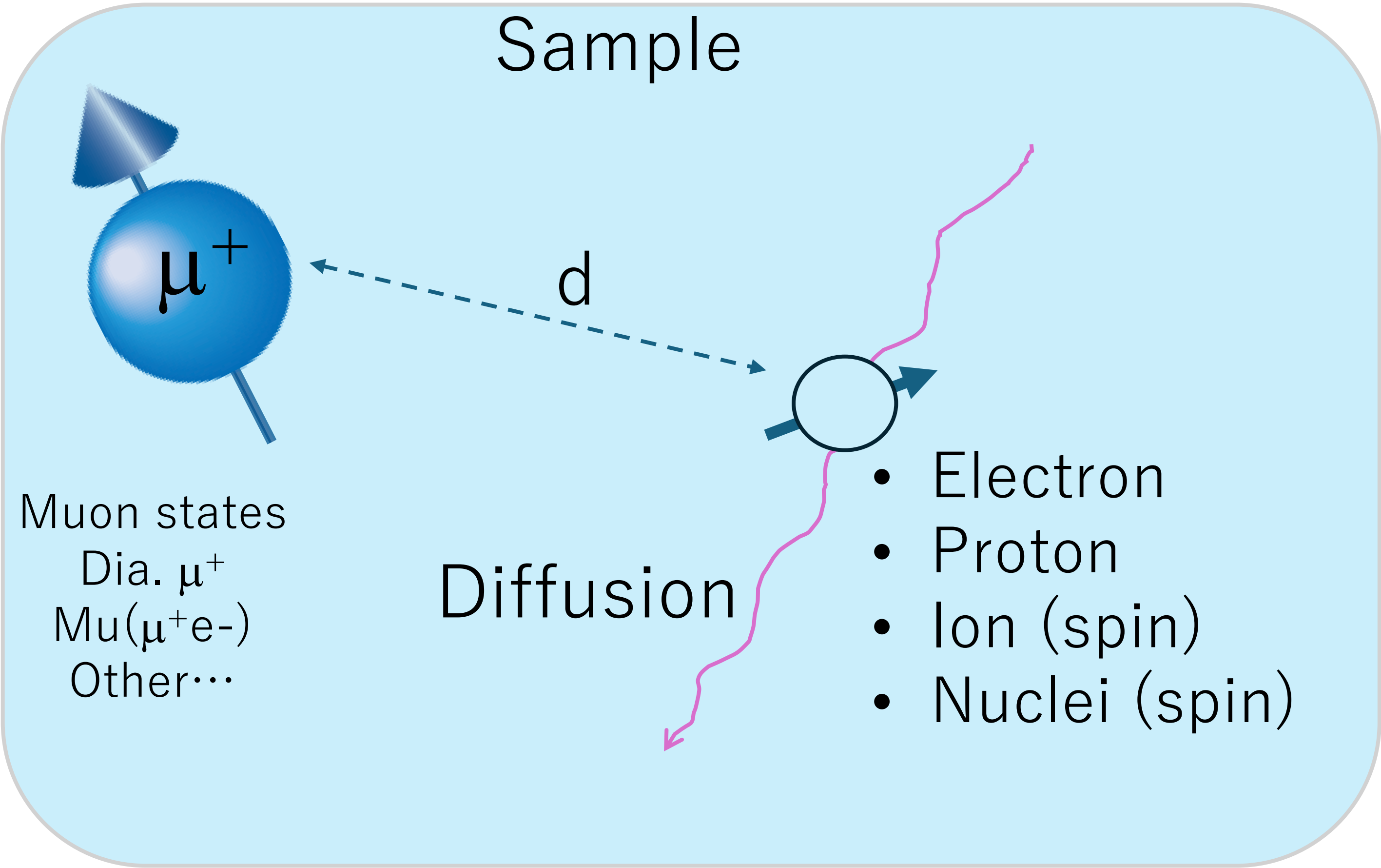
科研費 KAKENHI
JSPS, MEXT, KAKENHI Grant 21K15583
"Applications of muon in cancer research"

Muon as a sensitive local probe

Muon, μ^+
Spin 1/2
$m_\mu \sim 1/9\ m_p$
$\mu_\mu \sim 3.2\ \mu_p$
100% polarized
Asymmetric decays to e^+



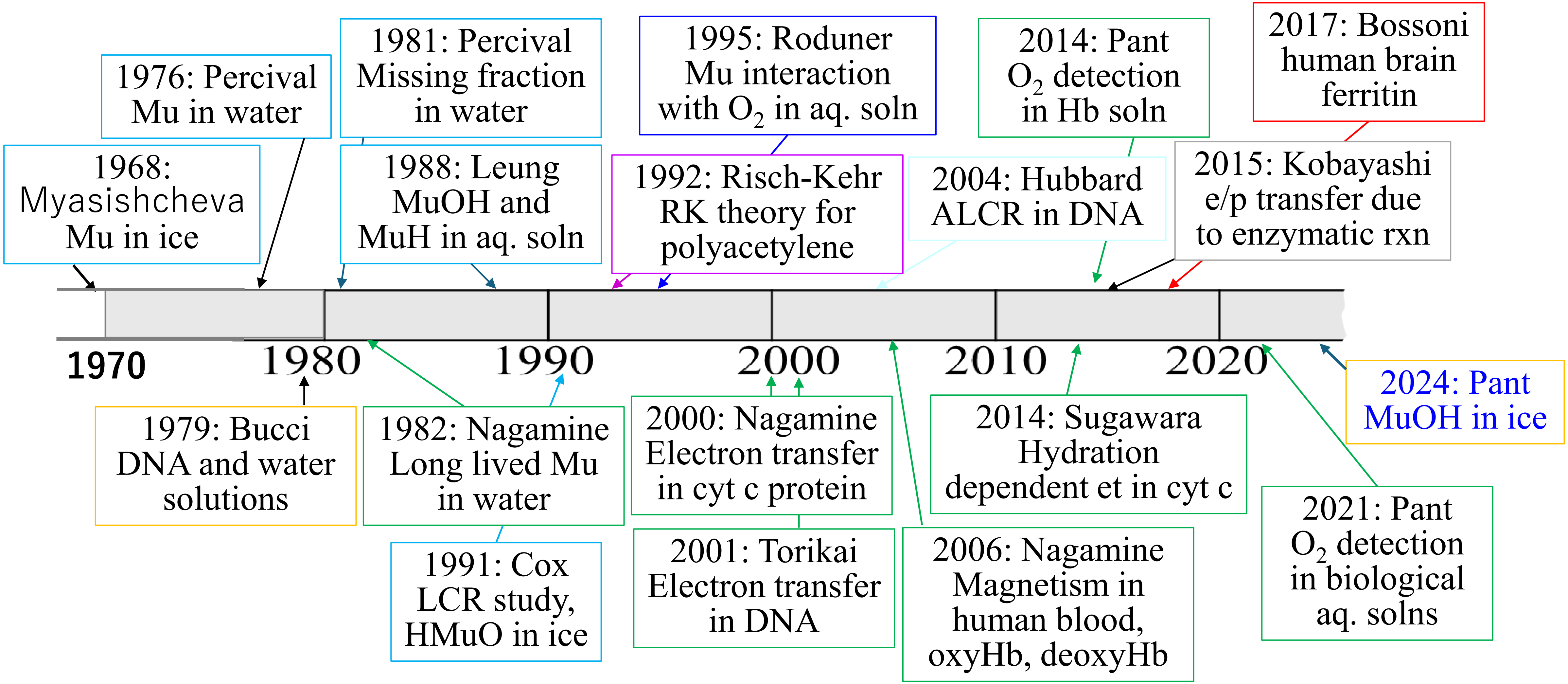
Muonium (Mu):(μ^+e^-)
Like a light isotope of H atom



Interactions:
- Spin-spin
- Hyperfine

- **Fundamentals of muon in biology and applications**
- Electron/proton transfer in bio-samples
- New noninvasive tool for cancer research

Muon in biology related studies: updates (~55 years)

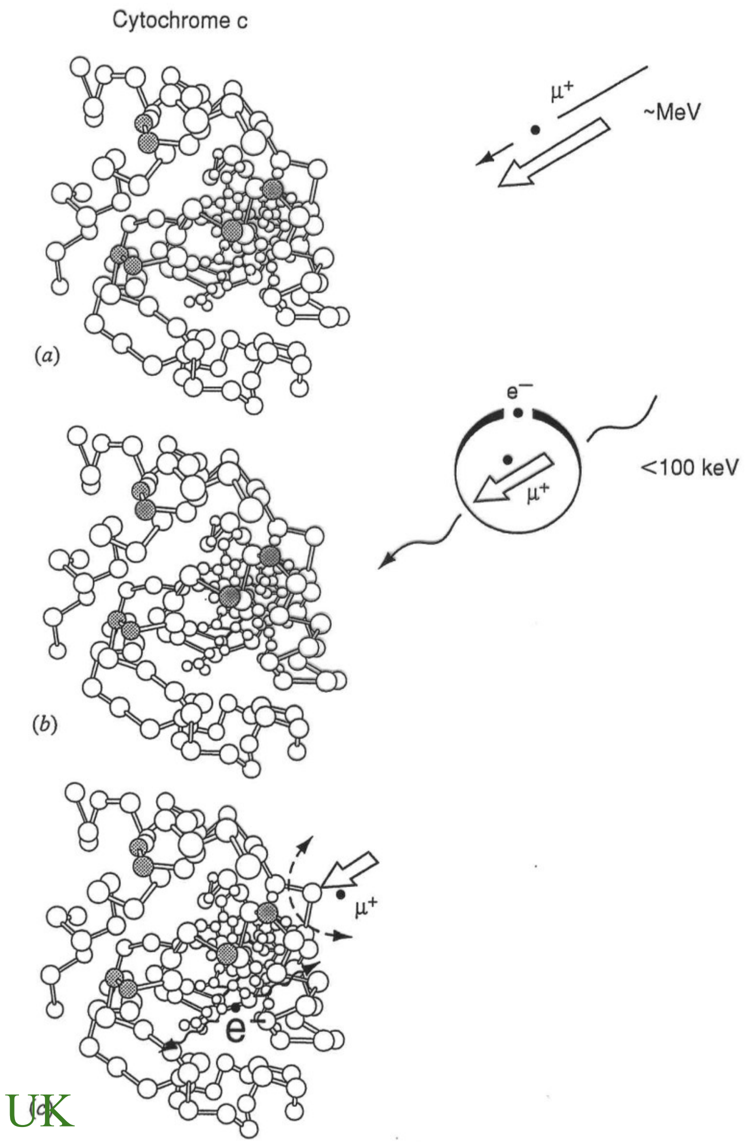


Electron transfer in proteins/DNA

Electron transfer in biomaterial: Electron labelled method

Pioneered by K. Nagamine and coworkers in 1984-85

- Pick up electron during slowing-down of injected μ^+
  → formation of Mu
- Thermalization of the Mu, and stops in electronegative sites in the molecule
- Depending on the nature of the molecule/environment, the electron brought-in by the μ^+ will,
  - Localize to form a radical state,
  - Motion (1-D, 2-D, 3-D) in material
  - Hopping (one step/multi-step)
  - Behavior depends on conditions (nature of materials , field, temperature, humidity, etc.)



Tsukamoto T et al, Chem. Phys. Lett. **441** (2007) 136-142
Jianping L et al, SCIENCE, **310** (2005) 25
Torikai E et al, Physica B **374-375** (2006) 441–443
Nagamie K et al, Physica B **289-290** (2000) 631-635
Nagamine K, Introductory Muon Science, (2007) Cambridge University Press, UK

Theoretical background of labelled electron method

Stochastic theory by Risch-Kehr (for polyacetylene), muon spin relaxation function

$$G(t) = \exp(\Gamma\, t)\mathrm{erfc}(\Gamma\, t)^{1/2}$$

where, Γ is RK relaxation parameter

$$\Gamma = \lambda / (1 + (2\omega_e\lambda)^{1/2} D_{\parallel} / \omega_0^2)^2,$$

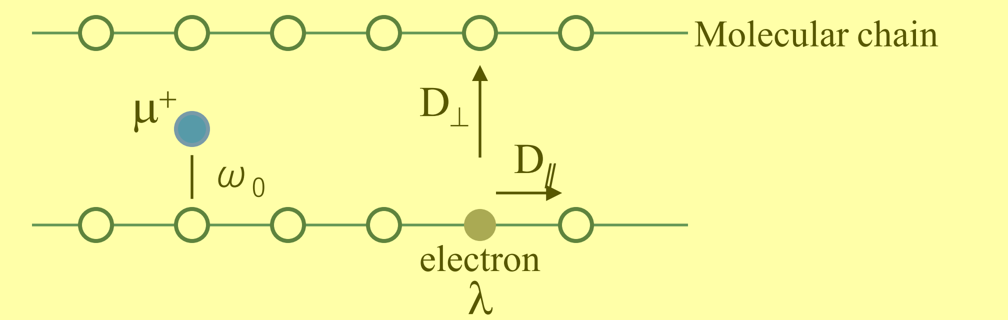
In the fast diffusion, $D_{/\!/} \gg \omega_0^2/(2\omega_e\lambda)^{1/2}$

$$\Gamma = \omega_0^4 / 2\omega_e D_{/\!/}^2$$

$D_{/\!/} = \omega_0^2/(2\gamma_e B\,\Gamma)^{1/2}$ independent on λ,

$\Gamma \propto 1/B$, 1D intrachain diffusion

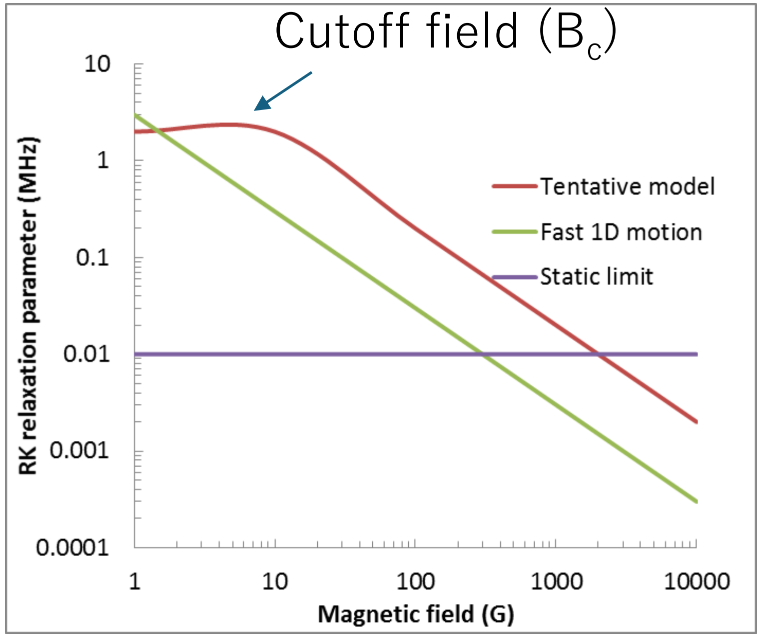
No quantum theory on diffusion topology due to 2D or 3D electron diffusion



ω_0 muon-electron hyperfine coupling
$D_\perp$ interchain diffusion rate, $D_{/\!/}$ intrachian diffusion rate
λ electron spin flip rate

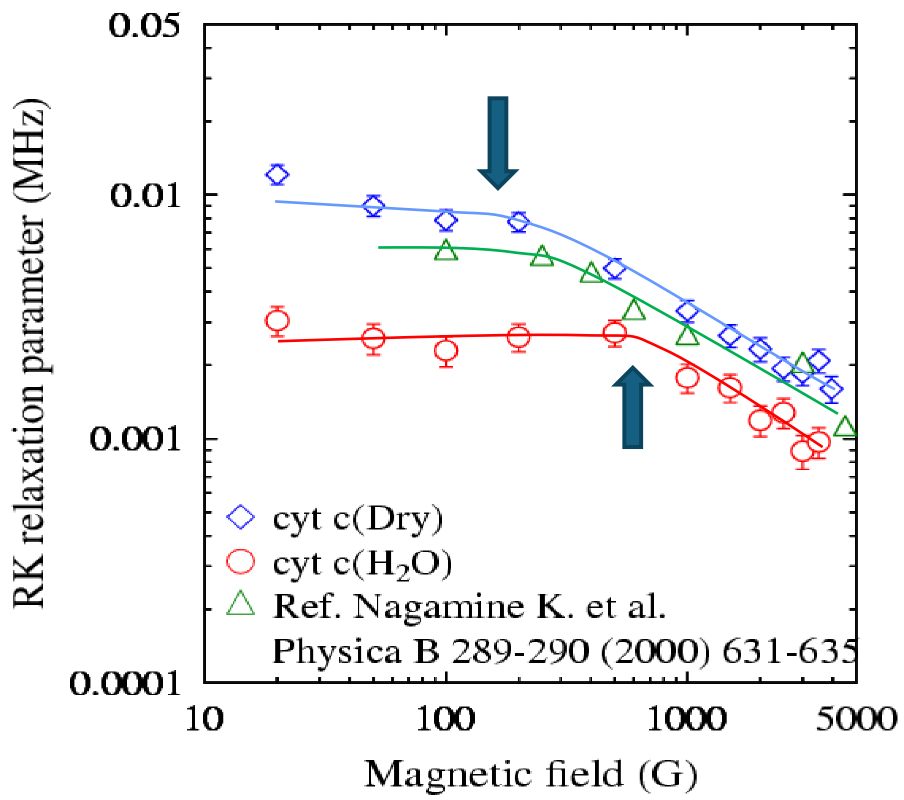
Temporal proposal, $D_\perp = \gamma_e B_c$

Conceptual image



Nagamine K et al, Phys. Rev. Lett. **53** (1984) 1763
Risch R and Kehr K W, Phys. Rev. B **46** (1992) 5246
Pratt FL et al, Phys. Rev. Lett. **79** (1997) 2855
Nagamine et al, Physica B **289-290** (2000) 631
Pratt FL, J. Phys.: Condens. Matter **16** (2004) 54779
Discussion with K Nagamine.

Hydration effect on electron transfer process

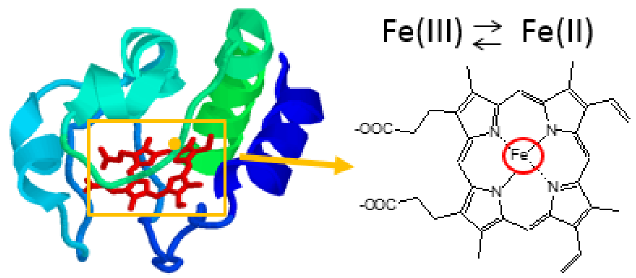


RT	$D_{\parallel}$ (rad s^{-1})	$D_{\perp}$ (rad s^{-1})	$D_{\parallel}/D_{\perp}$
Wet(20%rh)	2.1×10^{12}	1.6×10^{10}	**1.3×10^{2}**
Dry (5%rh)	1.6×10^{12}	0.9×10^{10}	**1.8×10^{2}**
D_{wet}/D_{dry}	1.3	1.7	

Electron movement is activated by water - which is essential for life

K. Nagamine et al., Physica B 289-290 (2000) 631-635
A. D. Pant et al., JPS *Conf. Proc.* **8** (2015) 033007-5
Y. Sugawara, A. D. Pant, et al., *JPS Conf. Proc.* **2** (2014) 010310-5

- Muon stopping site ?
- Complexity of biomacromolecule

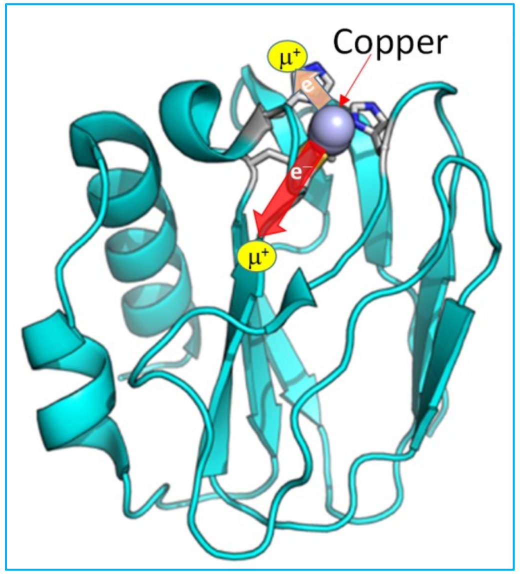


Cytochrome c from horse heart
(104 amino acids with Fe-hem; MW 12500)

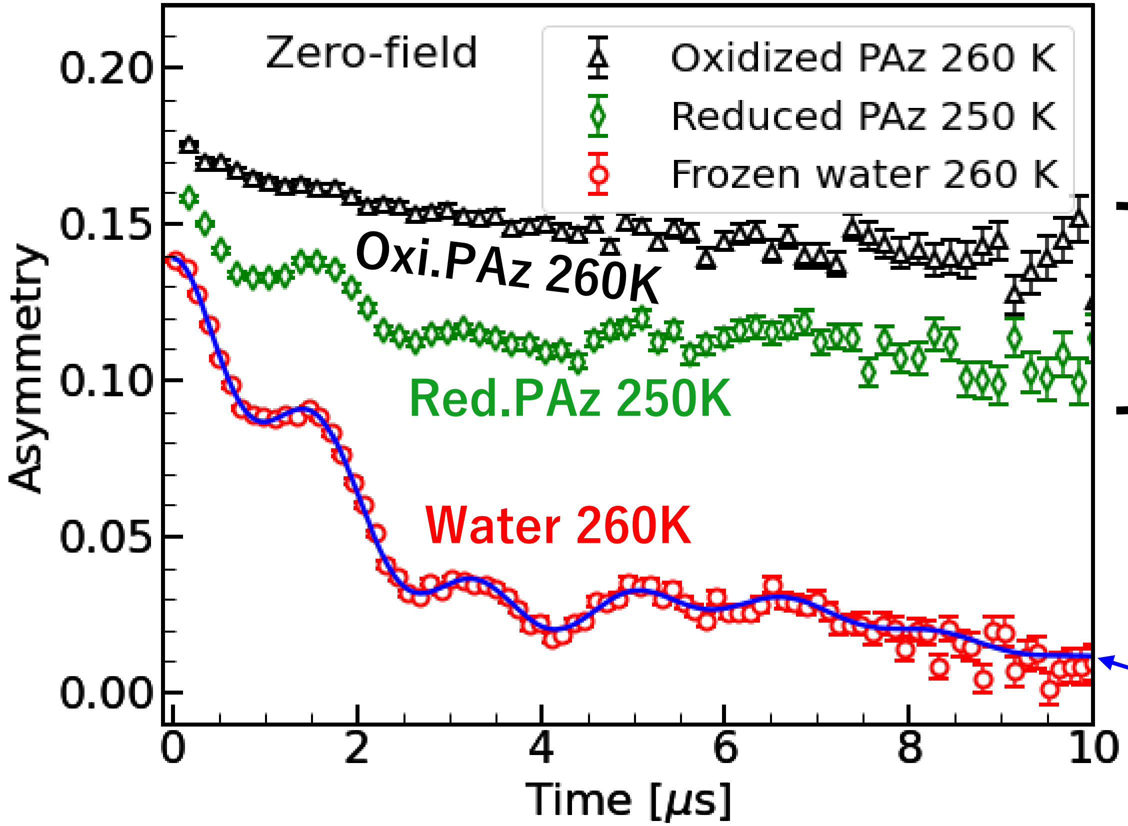
Electron transfer in single active center copper protein, PAz

A. D. Pant, T. Yamaguchi, et al., *KEK Prog. Rep.* (2019), 2020-4, 112-113

Pseudoazurin copper protein



PAzCu
Single active center
Conc. ~ 3mM, Vol. 700 uL
Aq. solution



MuSR in water before,

- Reduced & oxidized
- ET mechanism

A. D. Pant *et al. Phys. Rev.* B **110** (2024) 104104

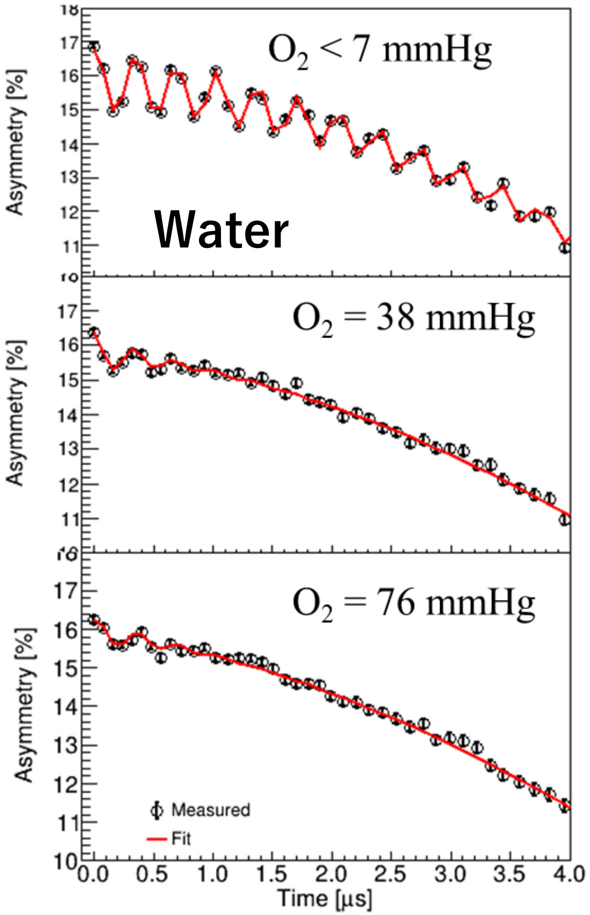
Reduced Pseudoazurin ($PAzCu^{1+}$, diamagnetic)
Oxidized Pseudoazurin ($PAzCu^{2+}$, paramagnetic)

Collaboration with Prof. Kohzuma et al @ Ibaraki University

Muon applications for hypoxia (low oxygenation) detection in cancer research: O_2 detection

O_2 detection in buffer solutions of proteins using muon

Relaxation of muonium in water in the presence of O_2



- **Spin-exchange interaction**

Mu(↑↑) + O_2 → Mu(↑↓) + O_2

- **Chemical reactions**

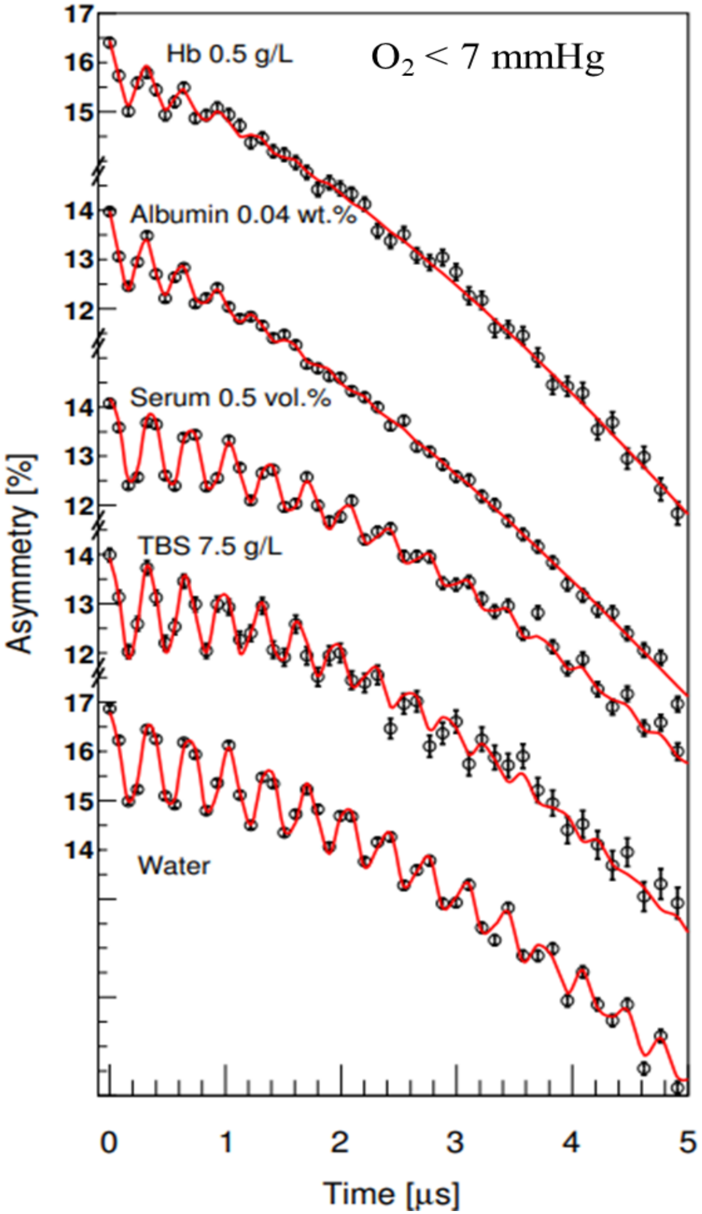
Mu + O_2 → MuO_2

Both cause relaxation of Mu

pO_2 in tumors in human body is heterogeneous, **less than 5 mmHg**

Measurable partial pressure by μSR = 0.3 to 300 (mmHg)

Sensitivity of MuSR matches perfectly with O_2 in hypoxic region (<10 mmHg)



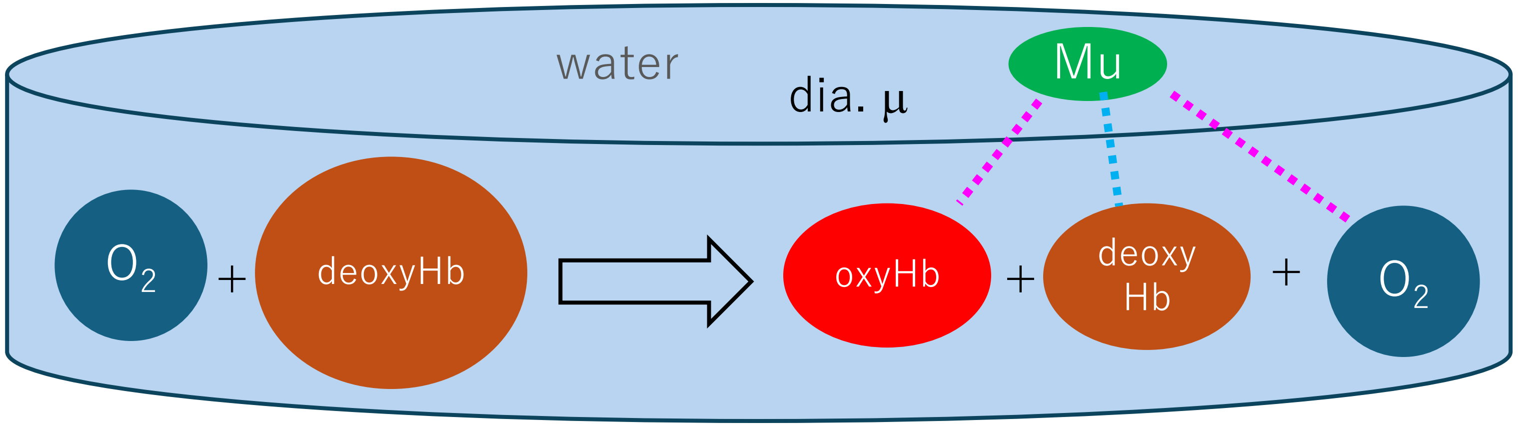
A.D. Pant, *et al.*, *J. Phys.: Conf. Ser.*, **551** (2014) 012043

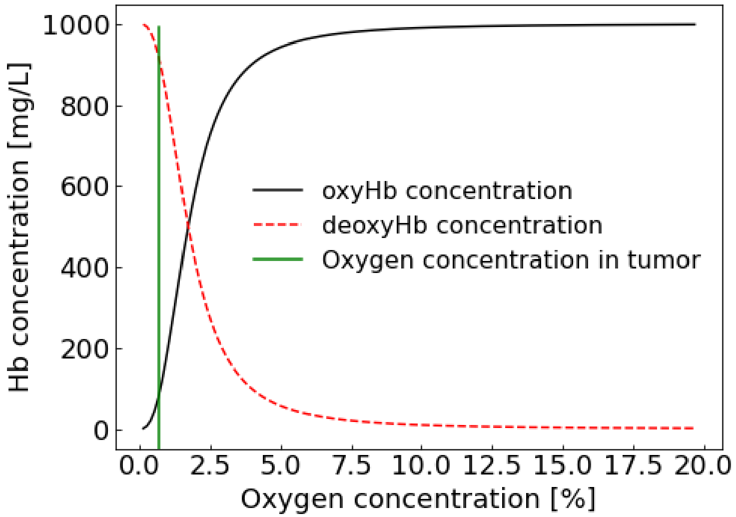
A.D. Pant et al., *Nuclear Inst. and Methods in Physics Research*, A **1011** (2021) 165561

μSR experiment performed in **ARGUS, ISIS**, RAL, UK

O_2 detection in Hb aqueous solution

Estimation using Hills Eq.





Fraction of deoxyHb
Using Hills Equation

$$\frac{\text{deoxyHb}}{\text{total}} = \frac{k^n}{k^n + p^n}$$

At 25 °C, $k = 13$, $n = 2.62$
p = partial pressure of O_2

Assumption, (l, m and r are numbers of corresponding molecules)

$$l\ O_2 + m\ \text{Hb} \rightarrow r\ \text{oxyHb} + (m-r)\ \text{deoxyHb} + (l-4r)\ O_2$$

Mu interaction with (m-r)deoxyHb

Mu interaction with free molecular O_2

Estimated relaxation rate of Mu in solution

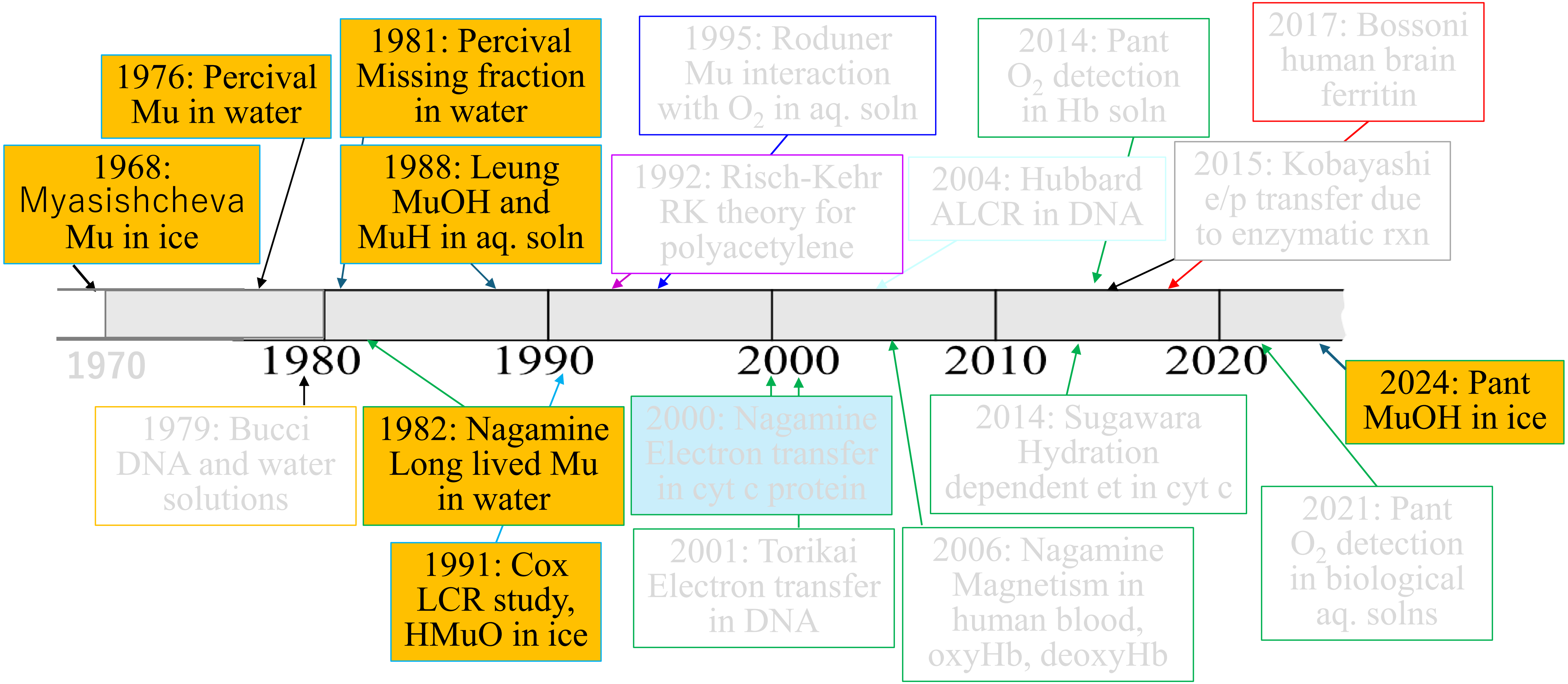
$$\lambda_{\text{estimated}} = R_{\text{Hb}}(\text{Mu}) + R_{O2}(\text{Mu})$$

Communication with Prof. JS Schultz
Hill AV, J. Physiol. **40** (1910) iv–vii.
Goutelle S et al, Fundam. Clin. Pharmacol. **22** (2008) 633-648

Behaviors of muon and its species in water, buffer, O_2, biomolecules,⋯?

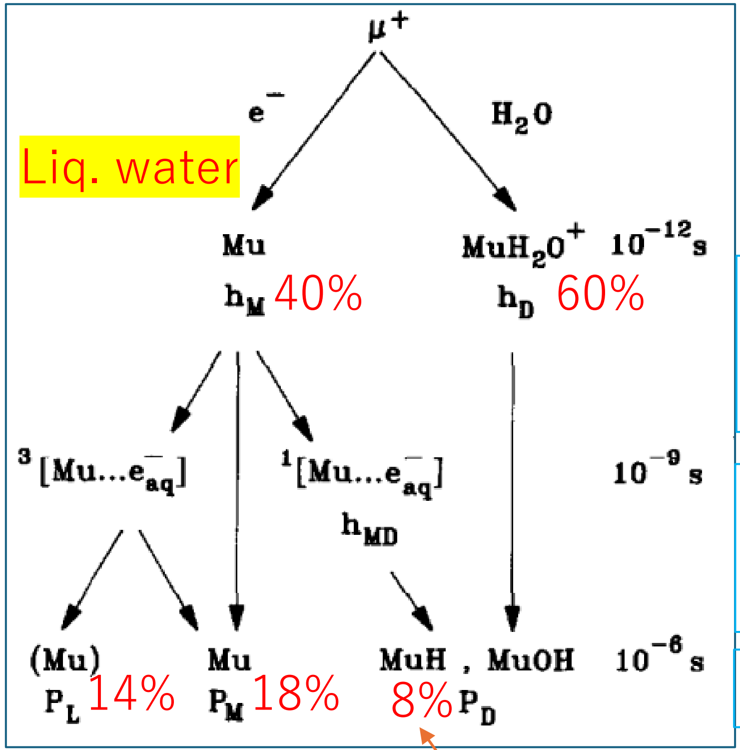
MuSR in water/ice

Muon in biology related studies: updates (~55 years)



Muon in water/ice

Percival group



Leung et al, Chemical Physics **121** (1988) 393-403
Percival et al, Chemical Physics **32** (1978) 353-367

We do not found MuH fraction in ice !!

$$H_2O+\mu^+ \rightarrow H_2MuO^+ ,$$
$$H_2MuO^+ + H_2O \rightleftarrows HMuO + H_3O^+$$

Defect, proton transfer

$$\mu^+ + H_2O \rightarrow MuH_2O^+,$$
$$MuH_2O^+ + H_2O \rightarrow MuOH + H_3O^+,$$

$$Mu + e^-_{aq} \rightarrow MuH + OH^-$$
$$Mu + \cdot OH \rightarrow MuOH.$$

Reaction rate, diffusion

Cox et al

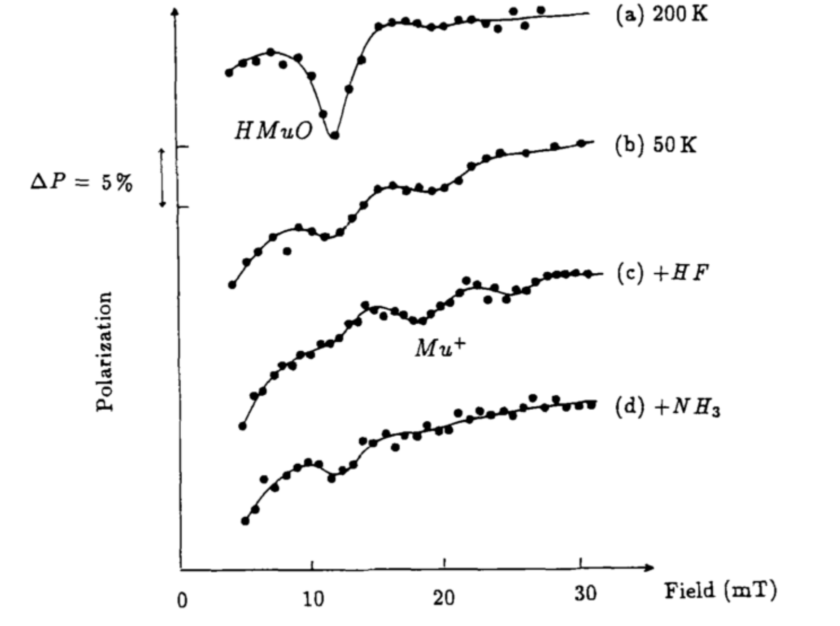


Fig. 3. Level crossing resonance spectra for ice (45% $H_2\,^{17}O$) at (a) 200 K and (b) 50 K [1,5] together with the new spectra, both at 50 K, for this material doped with (c) 0.1% HF and (d) 0.1% NH_3. Residual muon polarization is averaged over time windows 3–10 μs (a) and 6–12 μs (b–d) following muon implantation. All spectra were recorded at the ISIS Pulsed Muon Facility.

Existence of both H_2O-Mu^+-H_2O and HMuO

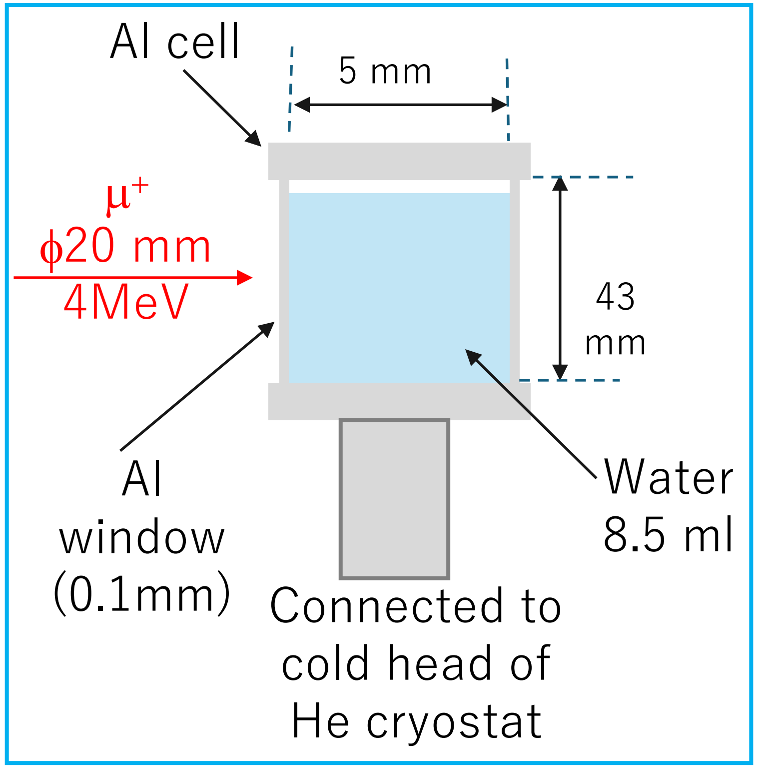
S. Cox, et al., *Hyperfine Interact.* **65** (1991) 993
Physica Scripta **1992** (1992) 292; *Hyperfine Interact.* **86** (1994) 747

HMuO signal not reported μSR in ice
Physica B **350** (2004) e451–e454,

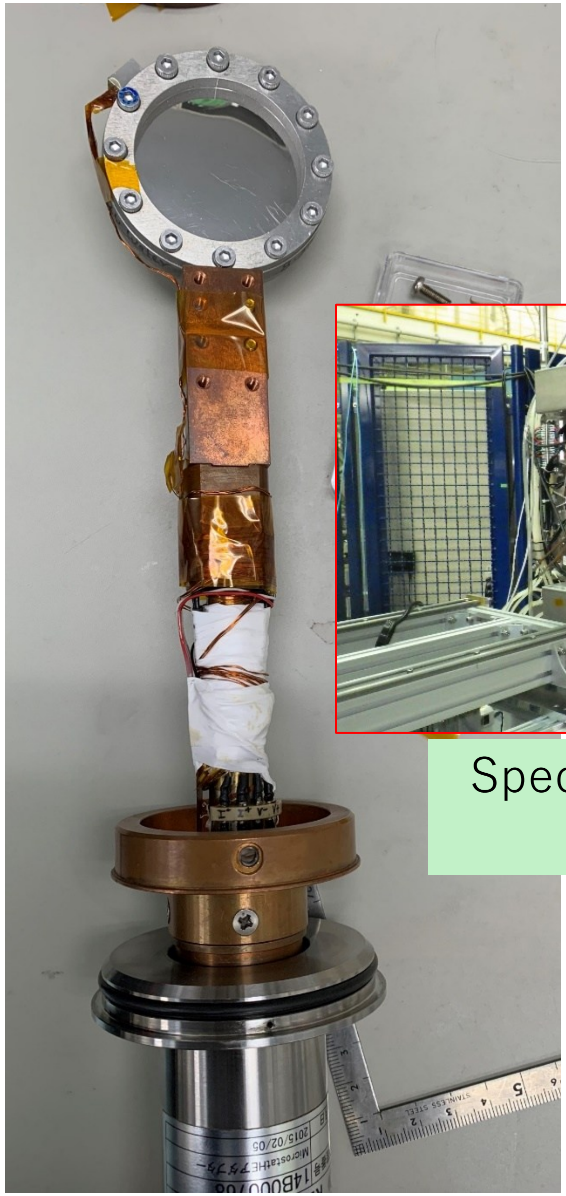
Experiment Set-up overview

Water from Milli-Q

Distill twice

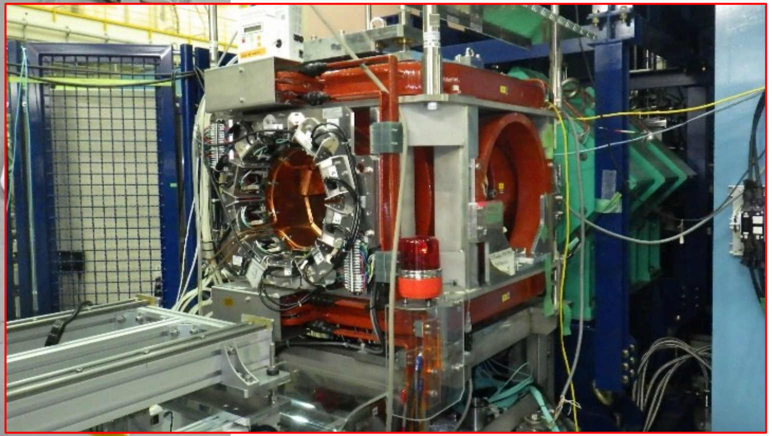


O_2 control (bubble by N_2 or O_2) and seal in Al cell



Connect to micro-cryostat head and use thermal shield

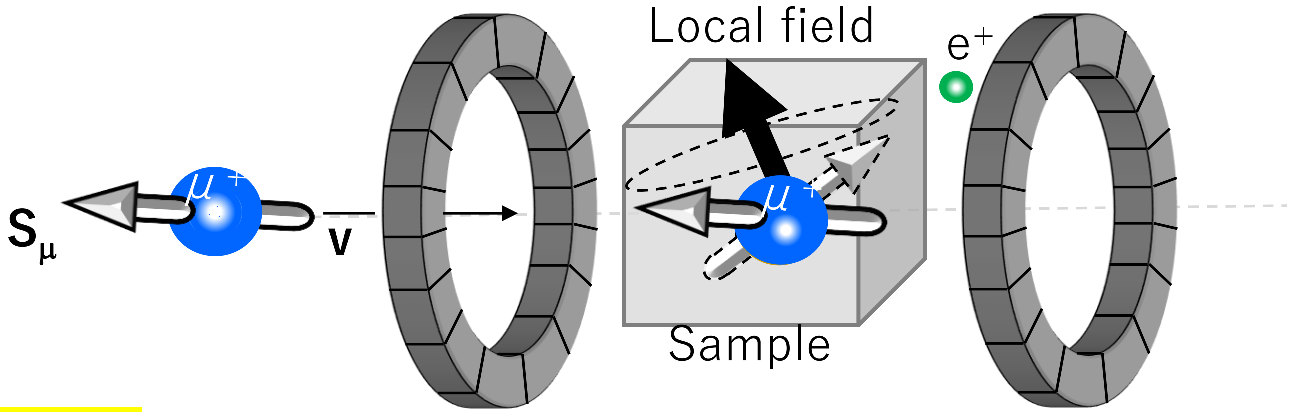
Field: Zero field, TF < 20 G
T: 100 K – 300 K

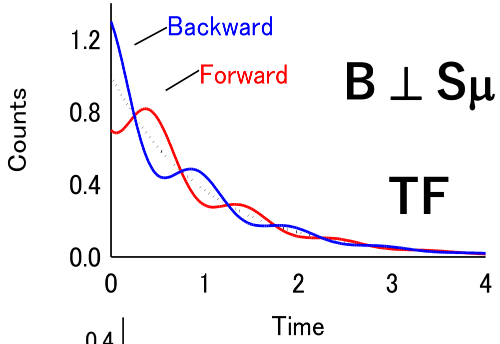


Spectrometer at S1 area, MLF, J-PARC

Muon method

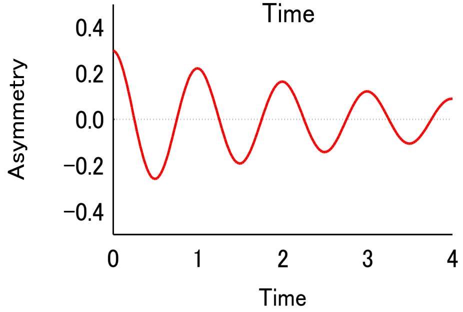
Muon spin rotation, relaxation and resonance (μSR) method





B ⊥ Sμ

TF



$\mu^+ \rightarrow e^+ + \nu_e + \overline{\nu_\mu}$

- $m_\mu \sim 1/9\ m_p$, $207 m_e$
- **Spin polarized (100%)**
- $\mu_\mu \sim 3.1\ \mu_p$
- **Asymmetric decay to e^+**
- Muonium, Mu = μ^+e^-
- Mu, 100 times more sensitive than μ
- Mu, light isotope of H

Counts detected by counters

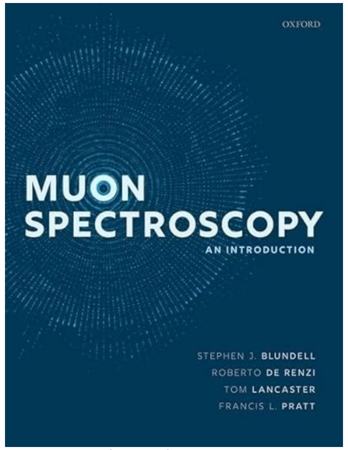
$$N(\theta, t) = N_0 \exp\left(-\frac{t}{\tau}\right)\left[1 + A G_X(t)\cos(\theta - w_0 t)\right]$$

Asymmetry,

$$A(t) = A_0\, P(t) = \frac{N_F(t) - \alpha\, N_B(t)}{N_F(t) + \alpha\, N_B(t)}$$

where, **P(t) is polarization function**,
α is balance parameter between the two detectors,
A_0 is initial asymmetry at t=0,
N_B and N_F are backward and forward counts, respectively.

A. D. Hillier, et al., *Nat. Rev. Methods Primers* **2**, 4 (2022)



Text book

PHYSICAL REVIEW B **110**, 104104 (2024)

Formation and structure of *Mu*OH in ice studied by muon spin rotation

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[3]*Institut für Physikalische Chemie, Universität Göttingen, Tammannstrasse 6, 37077 Göttingen, Germany*
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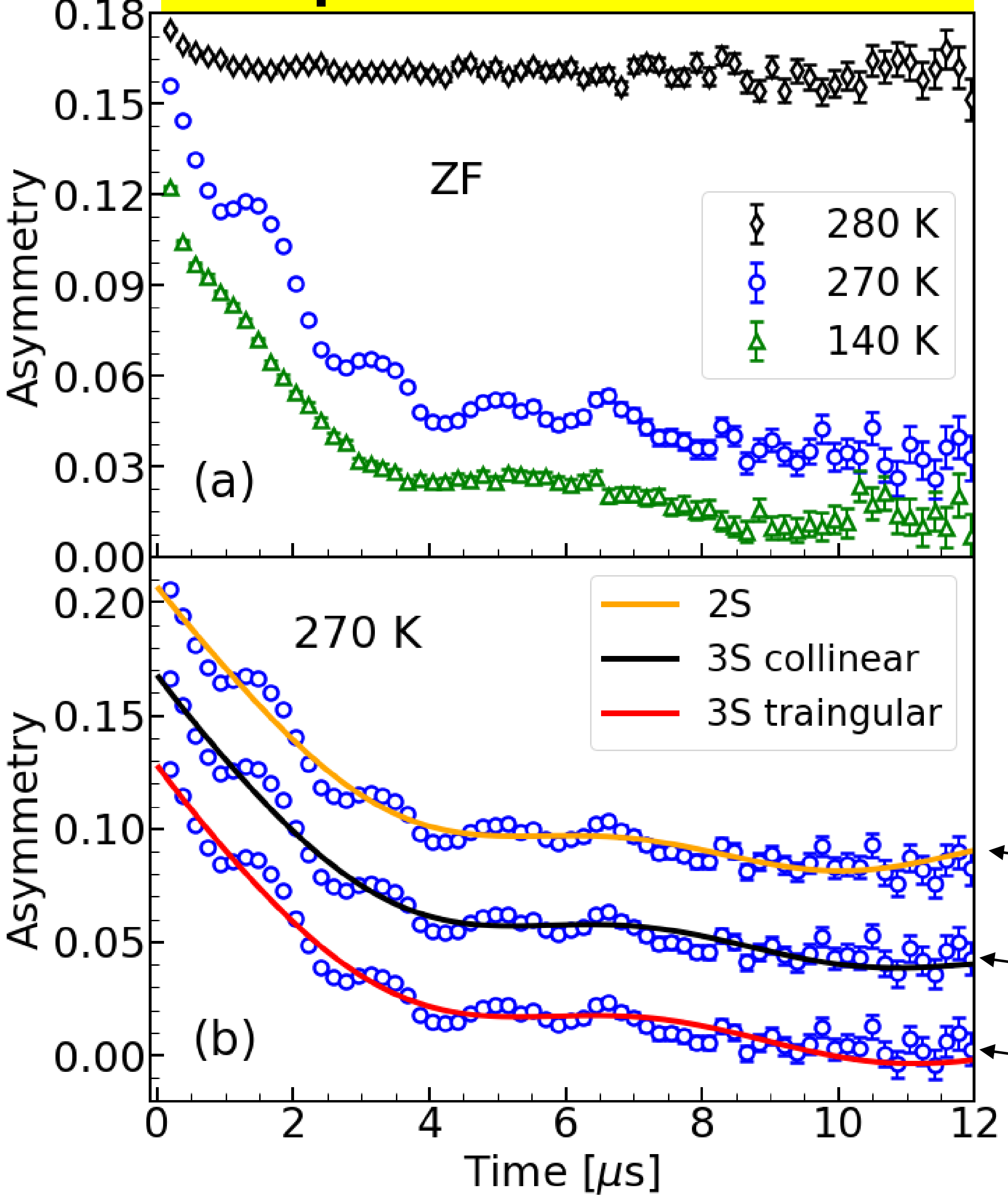
(Received 19 April 2024; revised 22 August 2024; accepted 28 August 2024; published 11 September 2024)

The behavior of muons in water and ice is investigated by measuring spin rotation and relaxation of positive muons in water at 140–300 K, where we successfully observe oscillation in the zero-field spectra of muons in ice. The oscillation is attributed to the spin–dipole interactions between the muon in *Mu*OH and neighboring protons and to hyperfine transitions of triplet states of axially symmetric anisotropic muonium in ice. The *Mu*–H distance in *Mu*OH exceeds the H–H distance in H_2O by 5% in ice.

DOI: 10.1103/PhysRevB.110.104104

ZF spectra in water/ice



Wang et al., *Physica* B **350** (2004) e451–e454

Fig. 1 shows the temperature dependence of the zero field relaxation rates λ_1 obtained by using an exponential decay function

$$P_z(t) \propto e^{-\lambda_1 t} = e^{-t/T_1}.$$

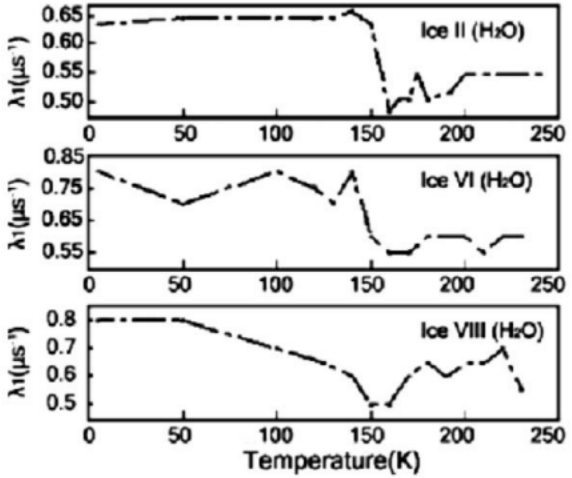


Fig. 1. The temperature dependences of the zero field relaxation rate λ_1.

T dependent ZF in ice phases

Brewer, J. H., et al, PRB **33** (1986) 7813-7816
Kadono, R., et al. PRL **100**(2008) 026401.
Sugiyama, J., et al. PRB **82** (2010) 214505.

$A(t) = F_{Mu}(t) + F_{2S}(t)$

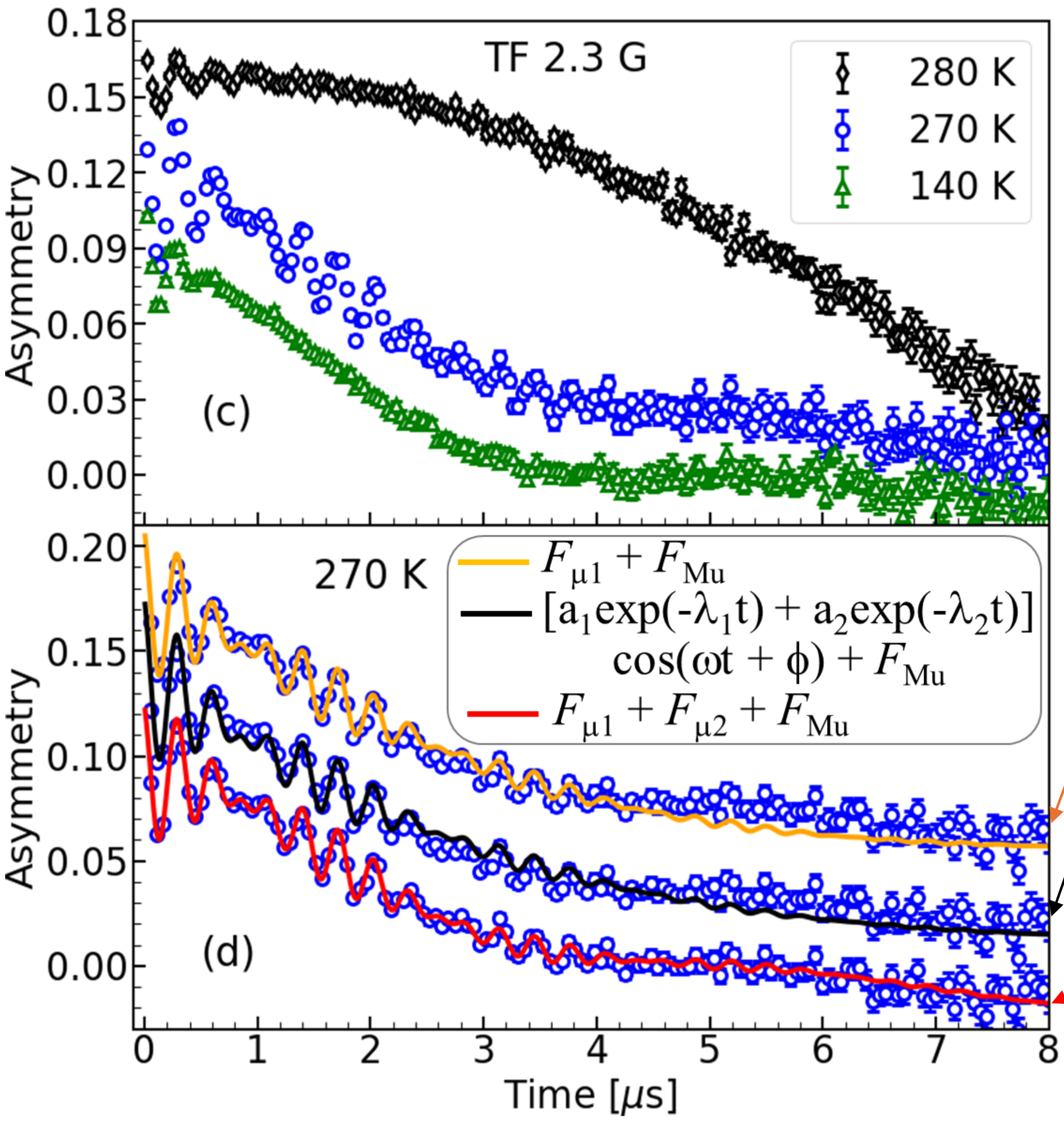
$A(t) = F_{Mu}(t) + F_{3Scol}(t)$

$A(t) = F_{Mu}(t) + F_{3Stri}(t)$

Where,
$F_{Mu}(t) = A_{Mu} \exp(-\lambda_{Mu}\, t)$
$F_{iS}(t) = A_{iS} \exp(-\lambda_{iS}\, t)\, G_{iS}(t)$

Need of new model !

TF 2.3G spectra in water/ice



W. Percival, P., et al, Chem. Phys. **95**(1985)321-330

Axially symmetric anisotropic Mu

- Single crystal ice
- Polycrystalline ice

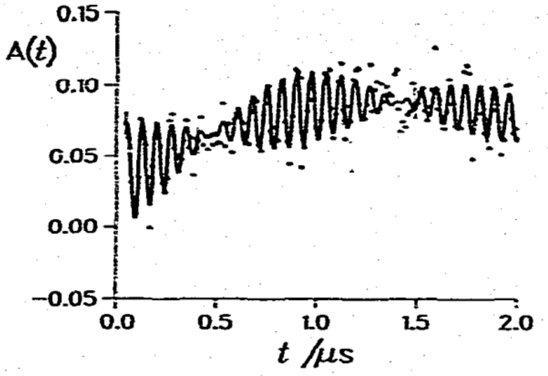


Fig. 3. Muon asymmetry in an H_2O crystal at 263 K oriented with its c-axis parallel to the field of 10 G. The two-frequency muonium signal was fitted by eq. (5).

$$A(t) = \underline{D(t) + M(t)}$$

$$D(t) = A_D e^{-\lambda_D t}\cos(\omega_D t + \phi_D)$$

$$M(t) = \tfrac{1}{2}A_M e^{-\lambda_M t}\{\cos[(\omega_M - \tfrac{1}{2}\delta)t + \phi_M] + \cos[(\omega_M + \tfrac{1}{2}\delta)t + \phi_M]\}.$$

Two diamagnetic muon states in solutions of manganous nitrate hexahydrate in acetone and in methanol

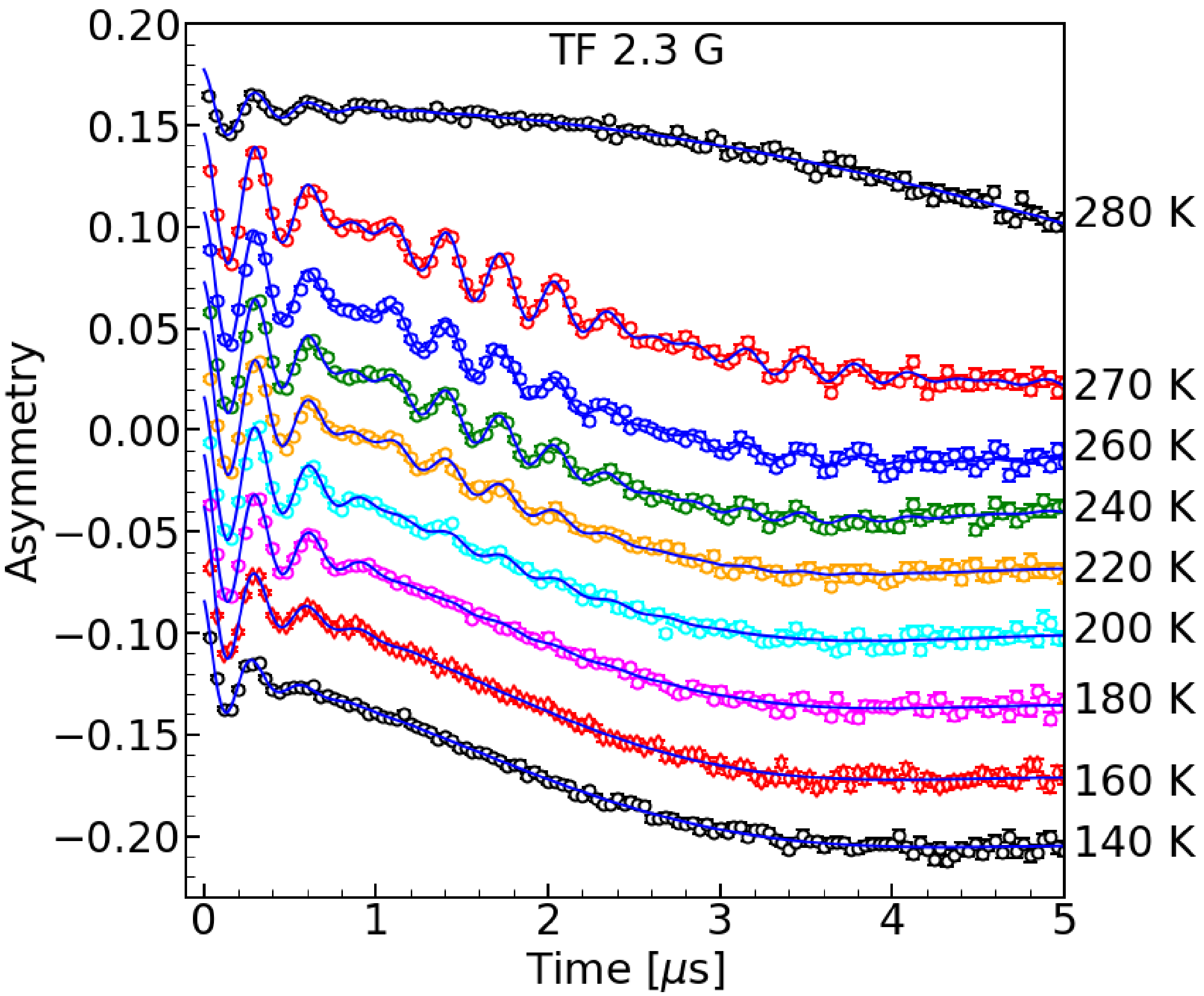
$$A(t) = \underline{F_{\mu 1}(t) + F_{\mu 2}(t) + F_{Mu}(t)}$$

$$F_{\mu i}(t) = A_{\mu i}\exp(-\lambda_{\mu i}t)\cos(\omega_{\mu i}t + \phi_\mu)$$

$$F_{Mu}(t) = A_{Mu}\exp(-\lambda_{Mu}t)[\cos(\omega_{Mu1}t + \phi_{Mu}) + \cos(\omega_{Mu2}t + \phi_{Mu})]$$

Proposed model

Mu signal: T dependent spectra in water



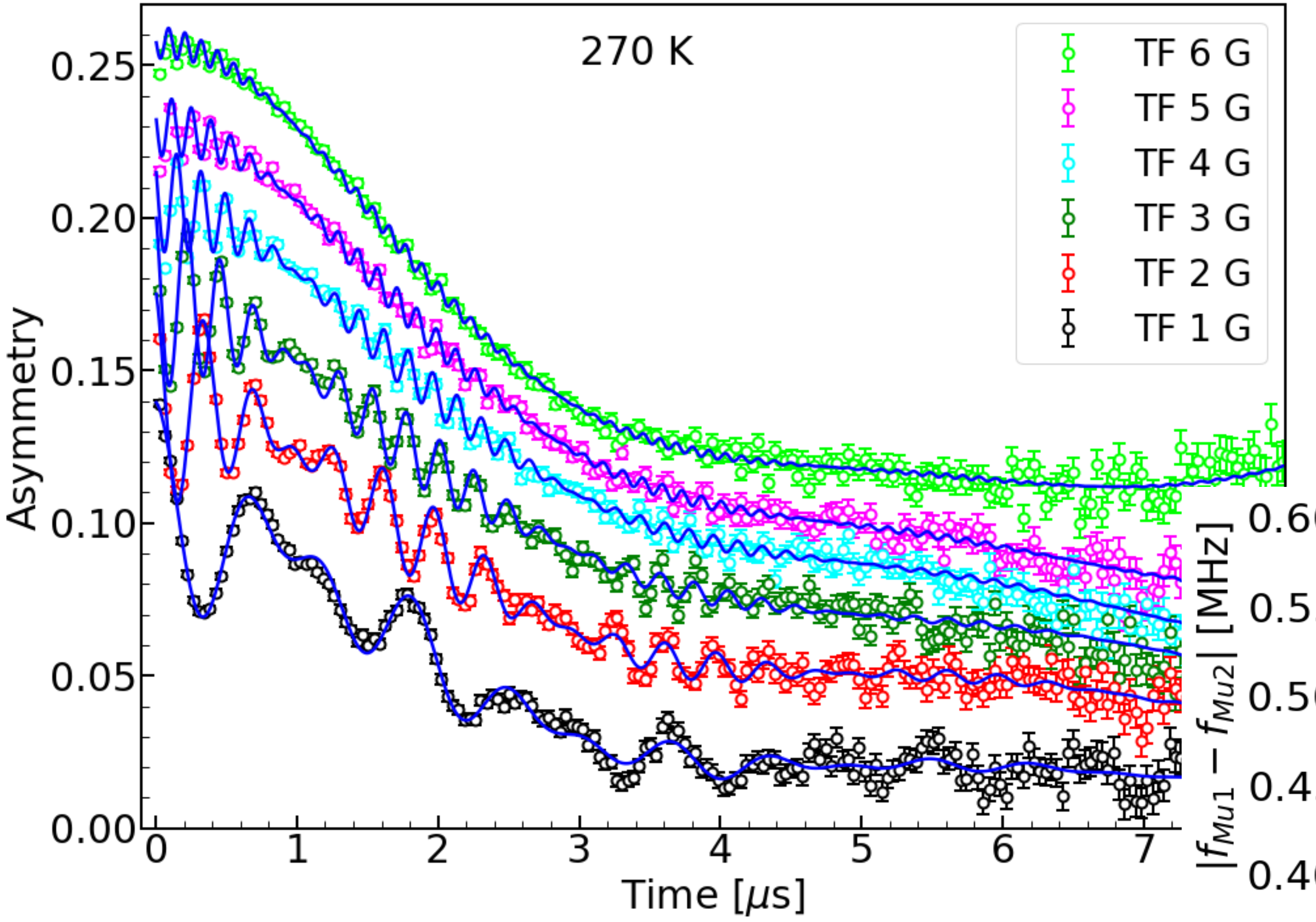
Phys. Rev. B **110**, 104104 (2024)

Proposed model

$$
\begin{aligned}
A_{TF}(t) &= F_{\mu 1}(t) + \underline{F_{\mu 2}(t)} + F_{\mathrm{Mu}}(t), \\
F_{\mu \mathrm{i}}(t) &= A_{\mu \mathrm{i}} \exp(-\lambda_{\mu \mathrm{i}} t) \cos(\omega_{\mu \mathrm{i}} t + \phi_{\mu}), \\
F_{\mathrm{Mu}}(t) &= A_{\mathrm{Mu}} \exp(-\lambda_{\mathrm{Mu}} t)[\cos(\omega_{\mathrm{Mu1}} t + \phi_{\mathrm{Mu}}) \\
&\quad + \cos(\omega_{\mathrm{Mu2}} t + \phi_{\mathrm{Mu}})],
\end{aligned}
$$

Anisotropic Mu + dia.muon2 + dia.muon1

Field dependent Mu spectra at 270 K



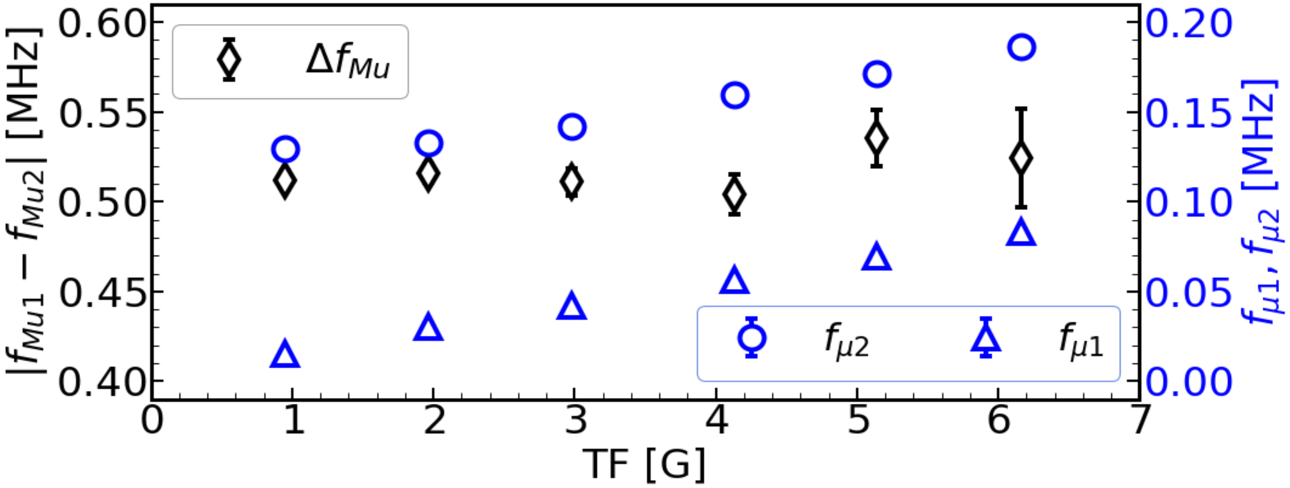
Phys. Rev. B **110**, 104104 (2024)

Proposed model

$$A_{TF}(t) = F_{\mu 1}(t) + \underline{F_{\mu 2}(t)} + F_{\mathrm{Mu}}(t),$$

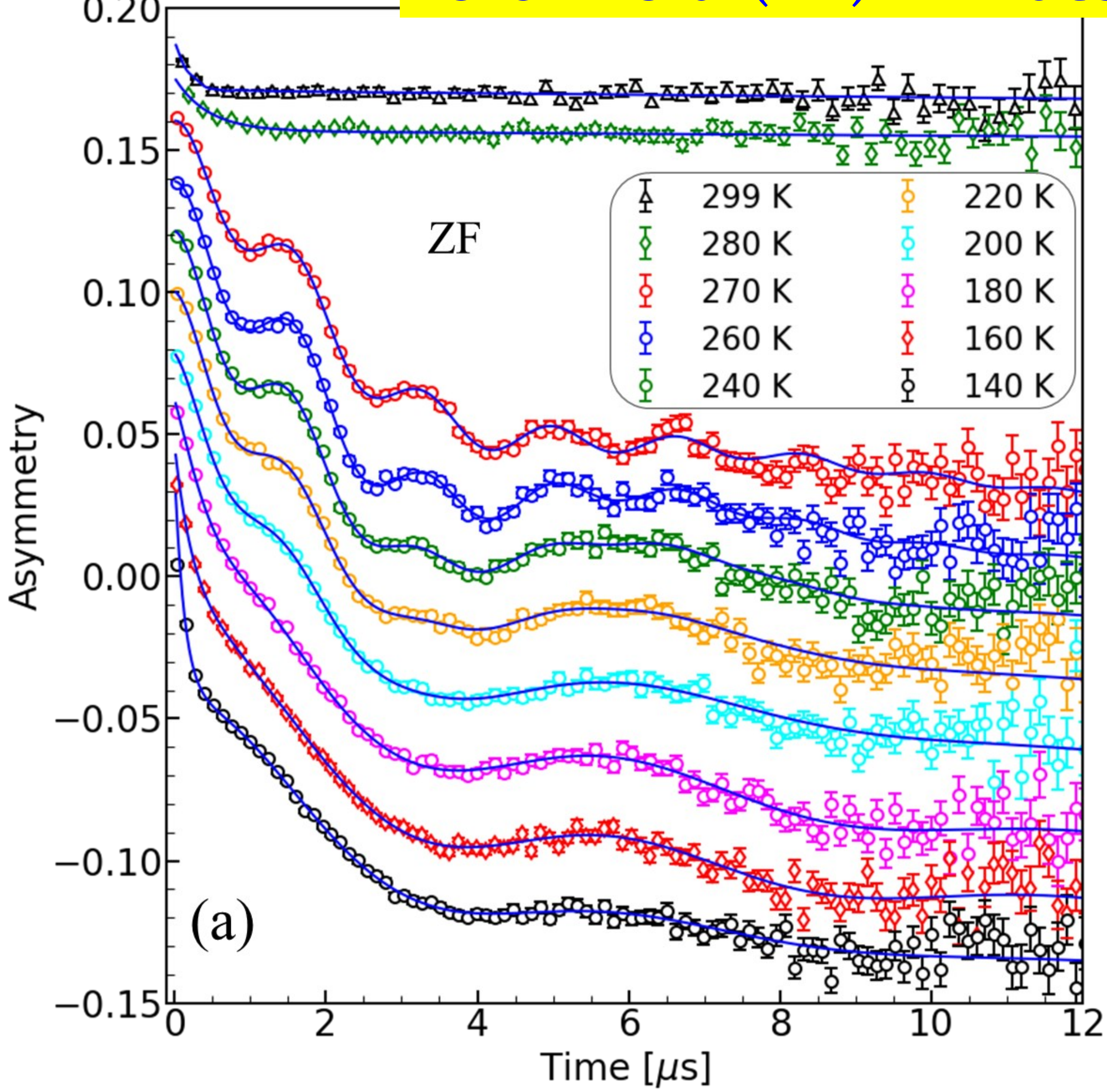
$$F_{\mu \mathrm{i}}(t) = A_{\mu \mathrm{i}} \exp(-\lambda_{\mu \mathrm{i}} t) \cos(\omega_{\mu \mathrm{i}} t + \phi_{\mu}),$$

$$F_{\mathrm{Mu}}(t) = A_{\mathrm{Mu}} \exp(-\lambda_{\mathrm{Mu}} t)[\cos(\omega_{\mathrm{Mu1}} t + \phi_{\mathrm{Mu}}) + \cos(\omega_{\mathrm{Mu2}} t + \phi_{\mathrm{Mu}})],$$



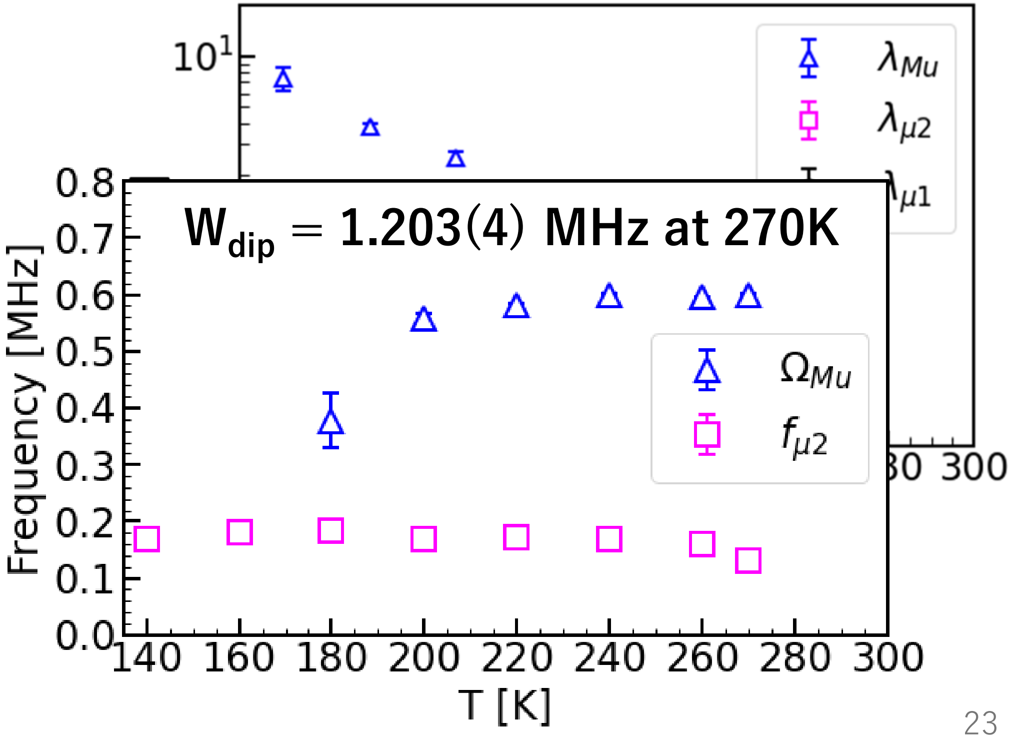
Anisotropic Mu + dia.muon2 + dia.muon1

Zero-Field (ZF) in water/ice



Model for ZF oscillation

$$A_{ZF}(t) = A_{\mathrm{Mu}} \exp(-\lambda_{Mu} t)\left[\tfrac{1}{6} + \tfrac{1}{3}\cos(\Omega_{\mathrm{Mu}} t)\right] + A_{\mu 2} \exp(-\lambda_{\mu 2} t)\cos(\omega_{\mu 2} t + \phi_{\mu}) + A_{\mu 1} \exp(-\lambda_{\mu 1} t),$$



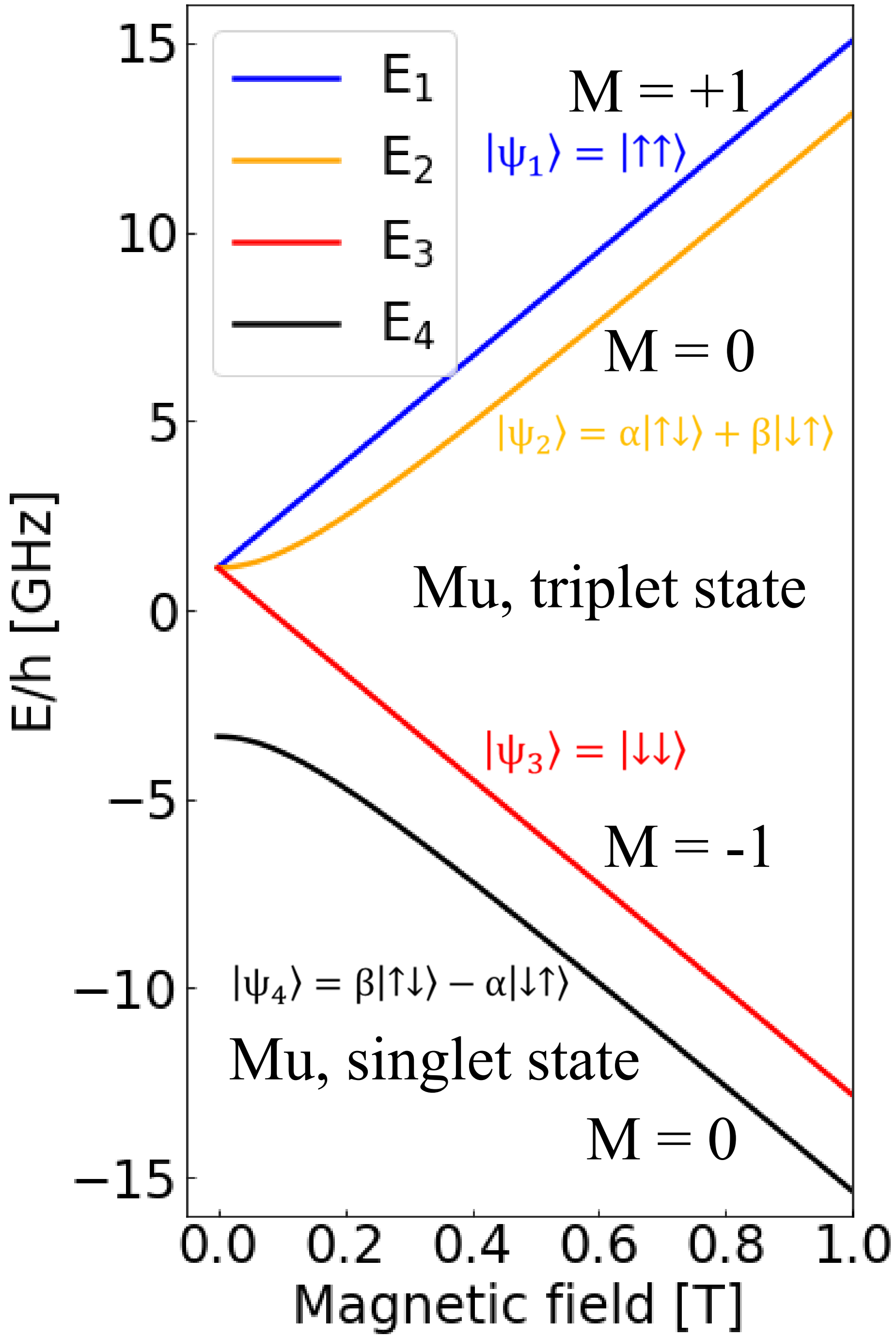
Breit-Rabi diagram for anisotropic Mu in ice

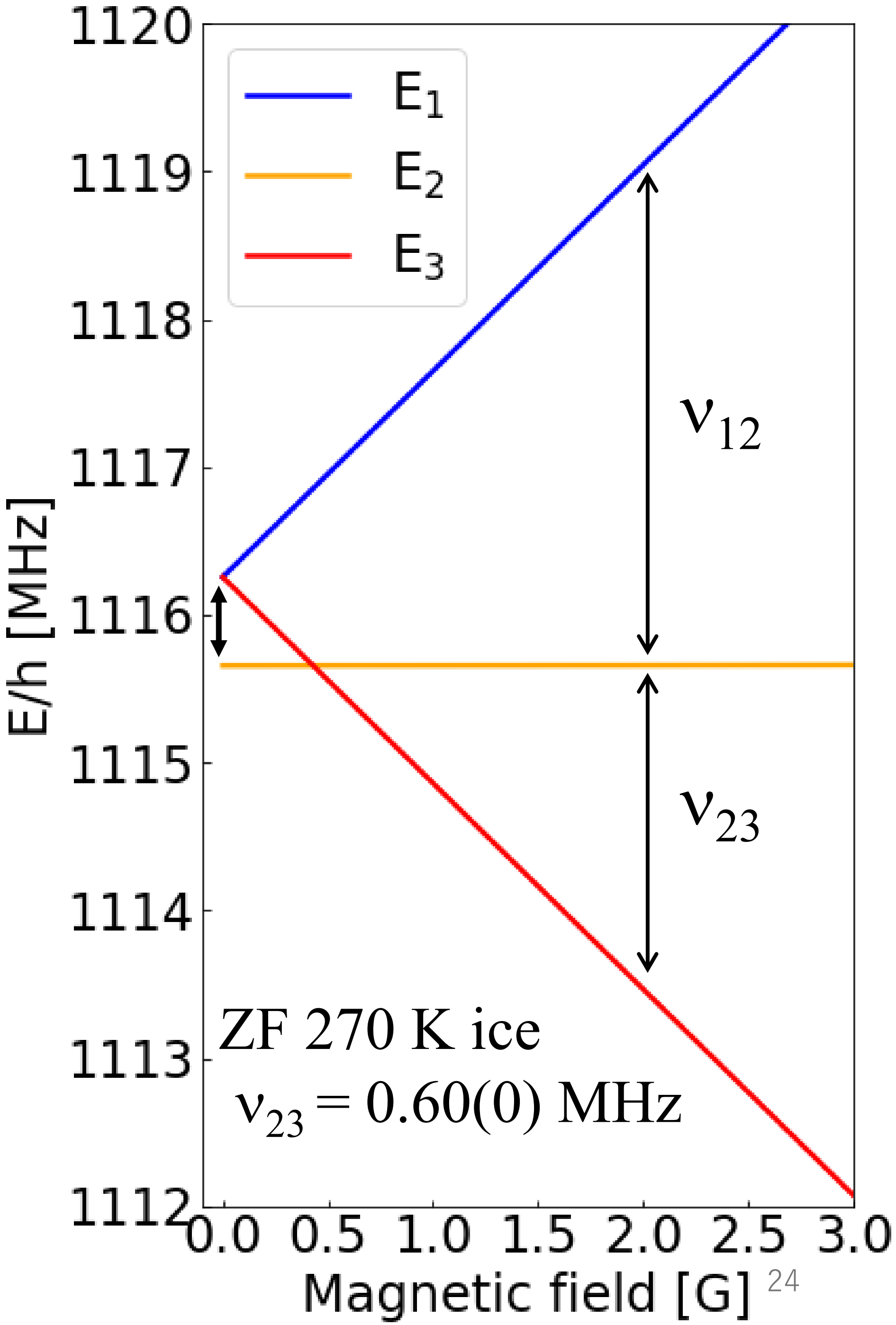
At weak TF

$f_{Mu1} = \nu_{12}$
$f_{Mu2} = \nu_{23}$
Mu beating pattern

At Zero-field,

$\nu_{12} = \nu_{23}$
$\nu_{23} = 0.60(0)$ MHz
Single freq Mu





Contribution of each muon species in ice

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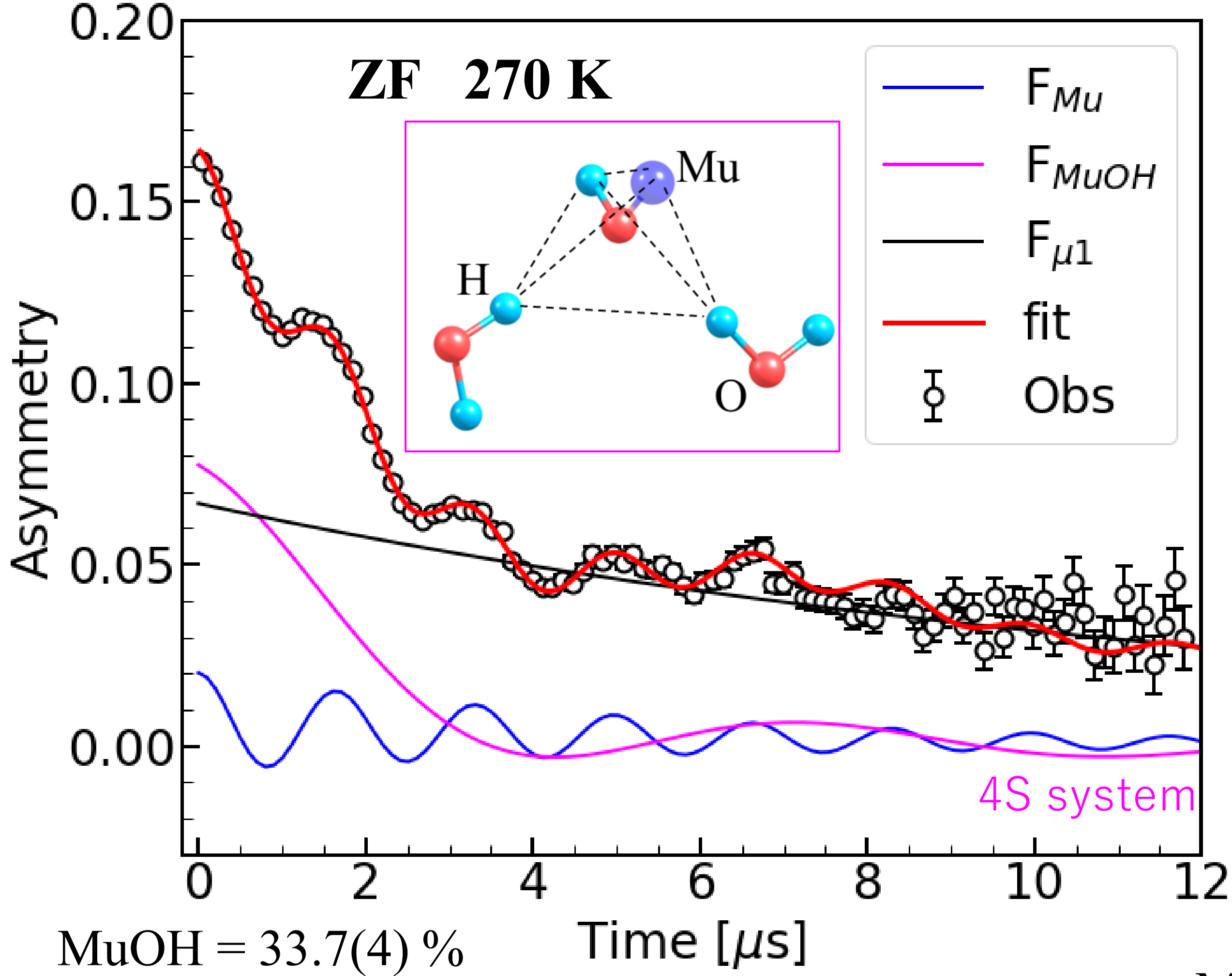

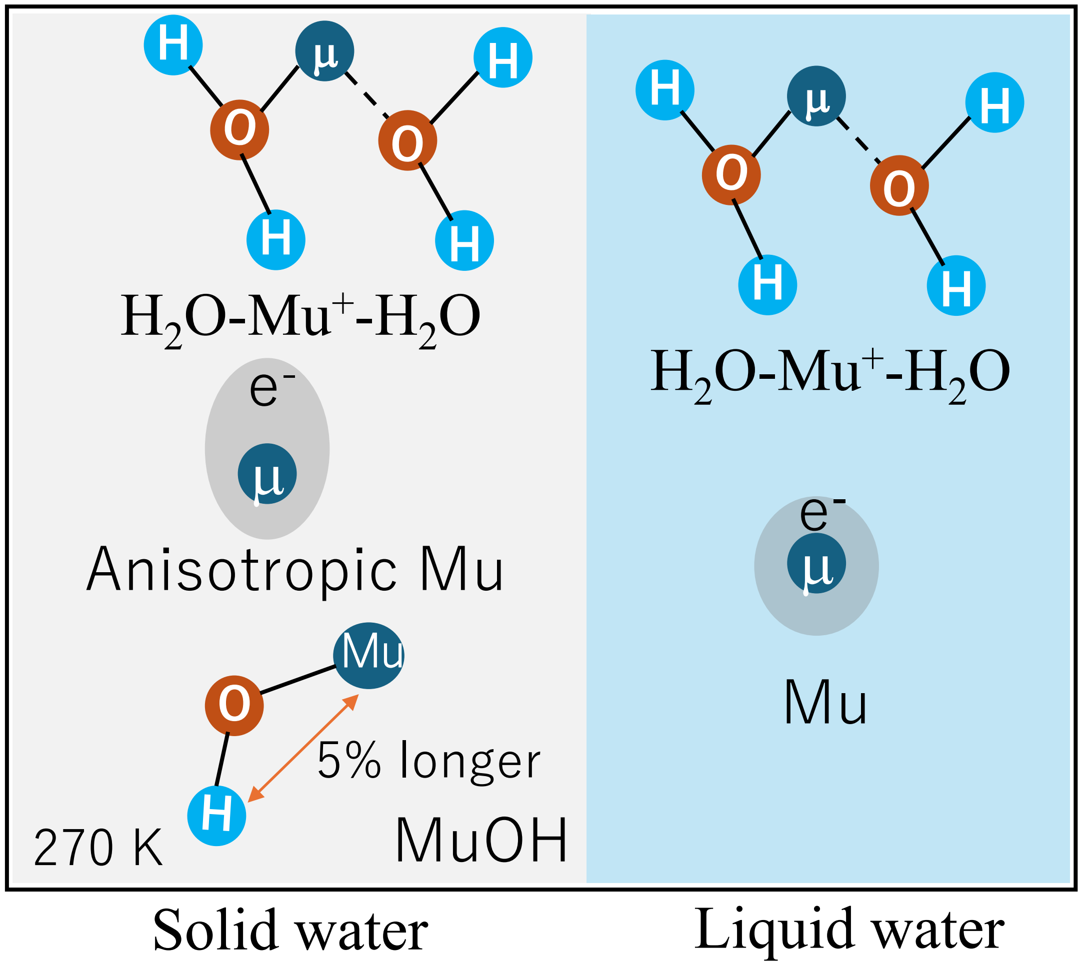

MuOH = 33.7(4) %
H_2O-Mu^+-H_2O = 29.0(5) %
Anisotroopic Mu = 17.5(6) %

Mu-H in MuOH found longer than H-H in H_2O by 5%

PIMD and quantum simulation also support the result

Provides new insights into μSR in water, help to understand the muon in biology

Summary

- ✓ **New insights into μSR in water**

- ✓ Weak TF and ZF μSR study performed in liquid and frozen water
- ✓ **Direct observation of MuOH** from time spectra in frozen water
- ✓ Anisotropic Mu, MuOH, and another diamagnetic muon (H_2O-Mu^+-H_2O) species observed in ZF and weak TF μSR in frozen samples
- ✓ μSR in water will help to understand muon in biology, systematic study in progress

- ✓ Space for biology expt. to establish **fundamentals of muon in biology** and further **applications**, cancer research, medical/clinical fields

Thank you for your attention !