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Production of hyperpolarized ^{3}He for Medical Imaging

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Leiden Cryogenics, Leiden:	*G. Frossati, A. van Waard*

Contents

1. Introduction

☐ Background and Motivation

1) Background

For long time, we have developed polarized ion sources and targets for nuclear and particle physics at RCNP, Osaka.

2) Motivation

In 2011, the nuclear reactors in Fukushima were melt down by the fatal earthquake and successive tsunami, even now a sizable part of our land is polluted by radioactivity.

In addition, a rate of medical diagnosis with X-ray, and radioisotopes per person is worst for Japan!

Therefore, it is urgent request for us to develop innovative methods of medical diagnosis free from X-ray CT, SPECT, PET, angiography, and so on.

☐ Our goal

Hyperpolarization of ^{3}He, ^{13}C, and so on by means of the Brute Force Method and PHIP (Parahydrogen Induced Polarization)

☐ Advantage of our methods

1) **Brute Force Method : use of only extremely low temperature (a few mK) and high magnetic field**

   a. Very general method. Most nuclei with spin could be hyperpolarized.
   b. No need for a microwave or a free radical required for the DNP. Note that the free radical works as depolarizing hyperpolarization.
   c. Since the Brute force method is free from the microwave cavity and depolarization caused by the free-radical, production of the hyper polarization with a large volume and long relaxation time is possible.

2) **PHIP (Parahydrogen Induced Polarization): use of Hydrogenation of organic compounds by parahydrogen and metal complex as catalyst**

   a. Simple principle based on NMR applied to organic chemistry.
   b. Cost is very cheap.
   c. Even small clinic can get it, and produce the hyperpolarized nuclei without technical difficulties.

2. Experimental methods

Brute force method:

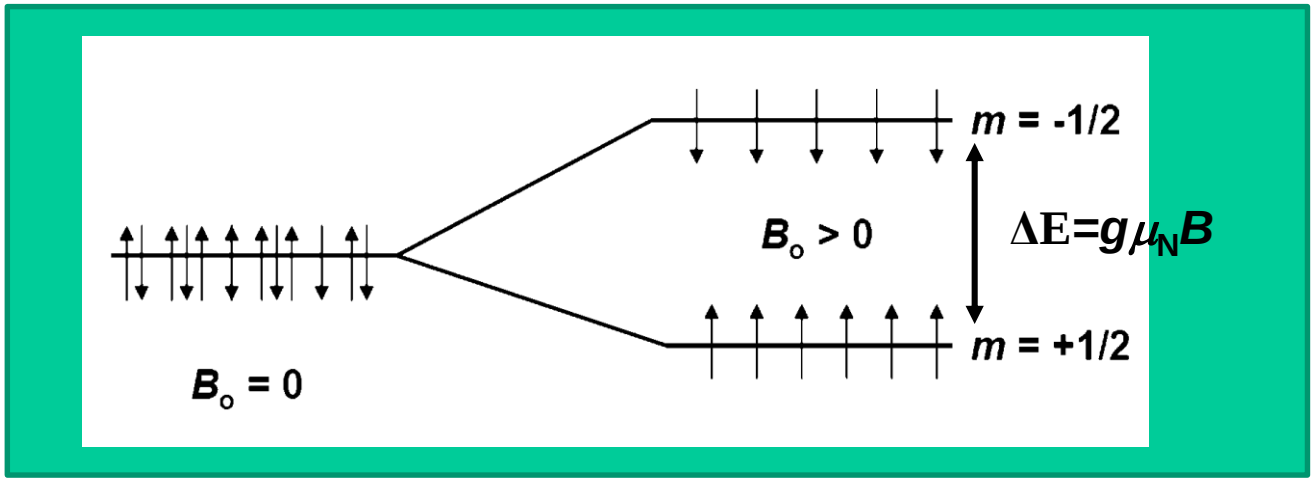
Extremely Low temperature and high magnetic field

$$P = \frac{N_+ - N_-}{N_+ + N_-} = \frac{e^{\frac{\Delta E}{2kT}} - e^{\frac{-\Delta E}{2kT}}}{e^{\frac{\Delta E}{2kT}} + e^{\frac{-\Delta E}{2kT}}} = \tanh(x)$$

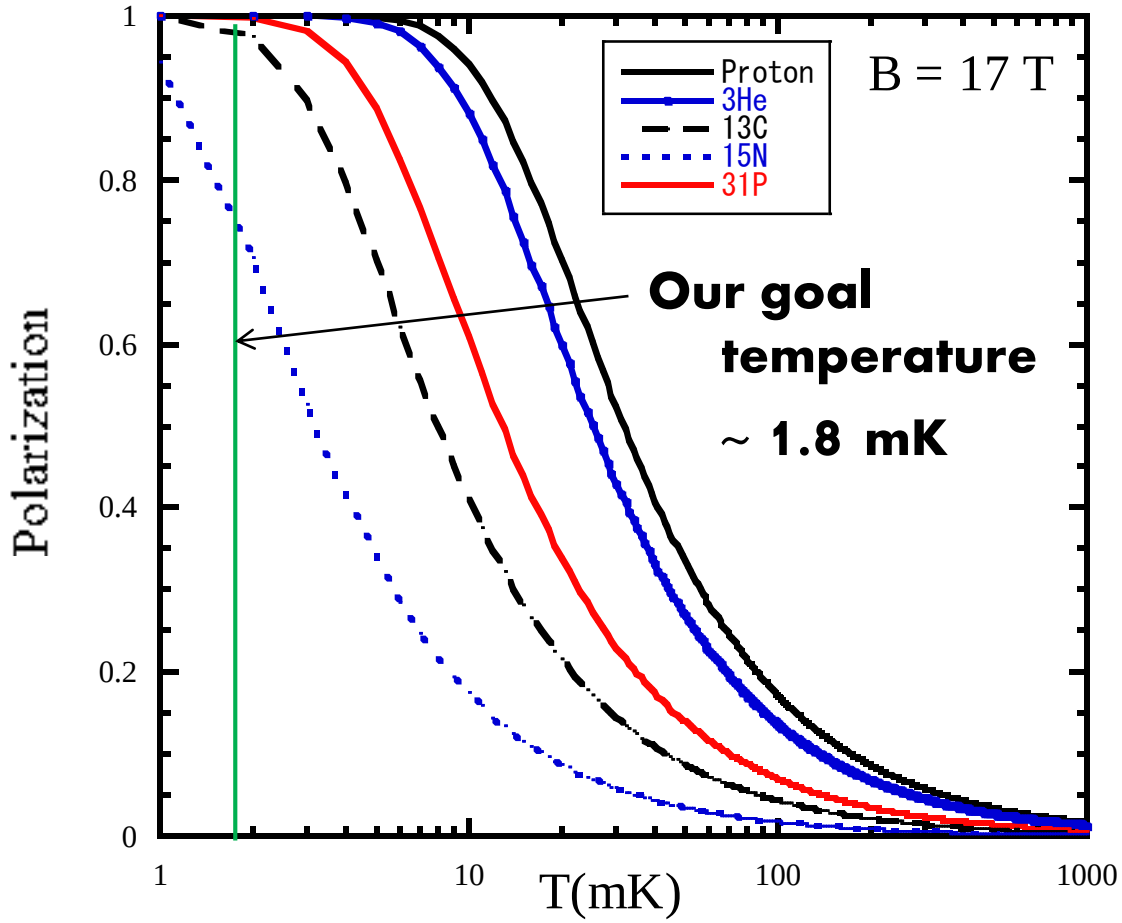
$$\sim x \quad (\text{for } x << 1)$$

$$\text{where } x = \frac{\Delta E}{2kT} = g\mu_N B/2kT$$

For I=1/2,



- **Nuclear polarization vs Temperature (mK) under the magnetic field of 17 T**



Possible candidates of hyperpolarized nuclei for medical use

Isotope	I^{π}	μ (nm)	γ (MHz/T)	Natural Abundance(%)	Existence in Living body
H	$1/2^{+}$	+2.7928	42.576	99.985	Yes
^{3}He	$1/2^{+}$	-2.1276	-32.434	0.0001	No
^{13}C	$1/2^{-}$	+0.7024	10.705	1.103	Yes
^{15}N	$1/2^{-}$	-0.2832	-4.316	0.366	No
^{19}F	$1/2^{+}$	+2.6289	40.053	100.000	No
^{29}Si	$1/2^{+}$	-0.5553	-8.466	4.67	Yes
^{31}P	$1/2^{+}$	+1.1316	17.235	100.000	Yes
^{127}I	$5/2^{+}$	+2.8133	17.155	100.000	Yes
^{129}Xe	$1/2^{+}$	-0.7780	-11.777	26.4	No

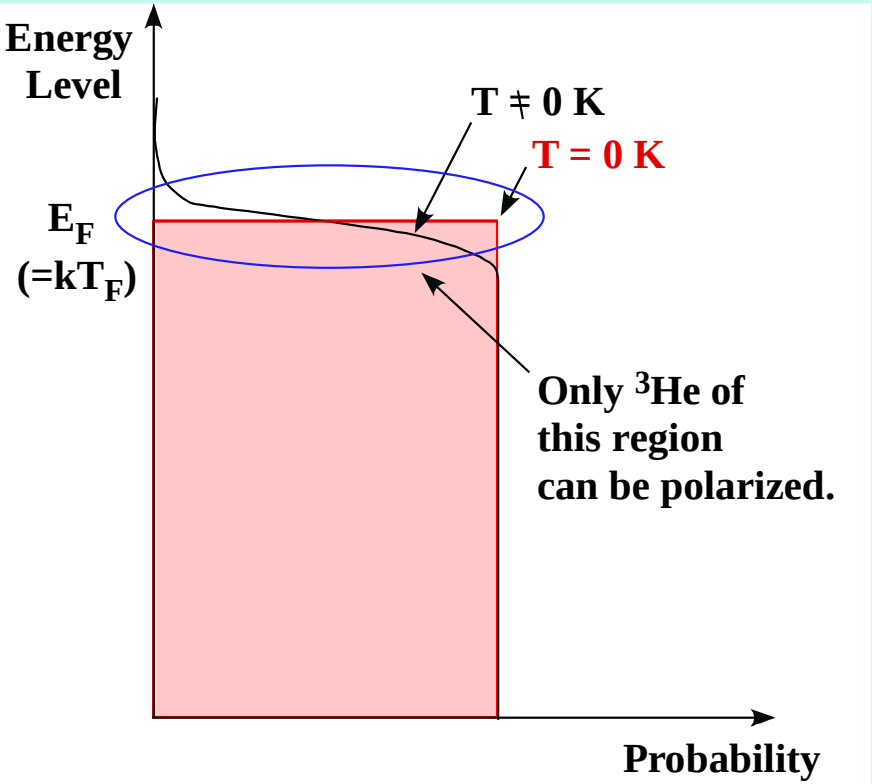
Though creation of Hyperpolarized ^{3}He has been successfully put in practice for lung imaging by the laser optical pumping, creation by the brute force method is particularly important because its production rate per day could be orders of magnitude larger than that of the optical laser pumping.

This is the primary reason why we have chosen hyper-polarized ^{3}He as a candidate of the brute force method.

Unfortunately, this was the start of unhappiness because later we have to realize that the brute force method applied to ^{3}He was the most difficult case in comparison with other nuclei, where the major difficulty comes from the fact that creation of hyper-polarized ^{3}He does not obey the simple brute force method because ^{3}He is not normal liquid but "Fermi liquid" obeying the Pauli exclusion principle as far as ^{3}He is in the liquid phase.

Only a minor part of ^{3}He near the Fermi Energy can be polarized even if the temperature is lowered than 1 mK. In other words, the polarization can never be increased beyond the value at the Fermi temperature (T_F = 179 mK).

Note that only 5% is expected with magnetic field, 17 T.



Energy Level of liquid ^{3}He

On the other hand, solid ^{3}He does not obey this rule because the overlapping of wave function for ^{3}He is limited due to the long lattice separation. In other word, ^{3}He behaves as a paramagnetic substance for which the graph of the brute force method shown in the previous slide is valid.

To overcome this difficulty, we introduced a concept of the Pomeranchuk cooling specific to ^{3}He, with which we could easily form solid ^{3}He from liquid ^{3}He.

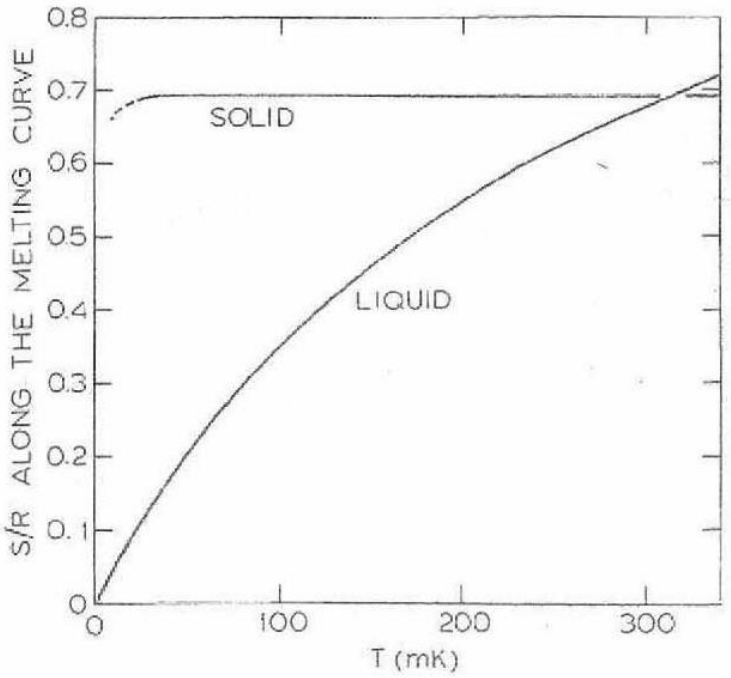
In addition, we could lower the solid ^{3}He temperature lower than 10 mK thanks to the principle of the Pomeranchuk cooling.

Principle of Pomeranchuk Cooling

1950 Pomeranchuk proposed

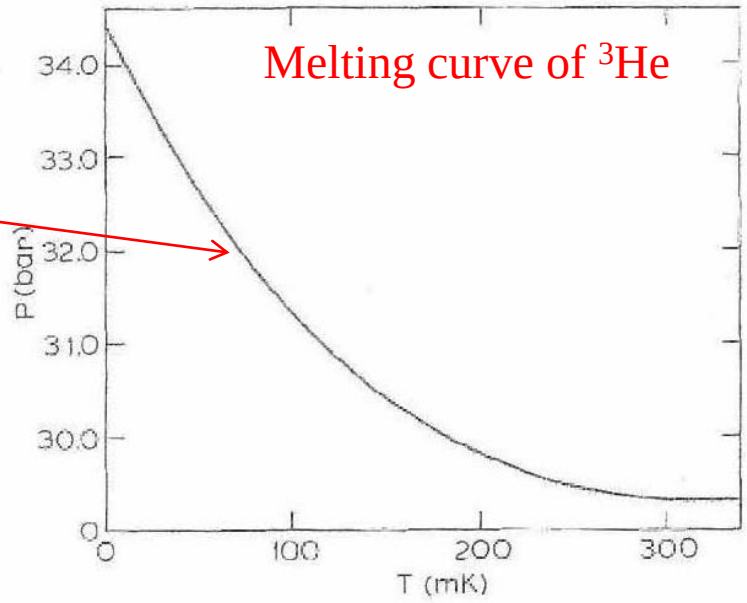
1965 Anufriev experimentally proved

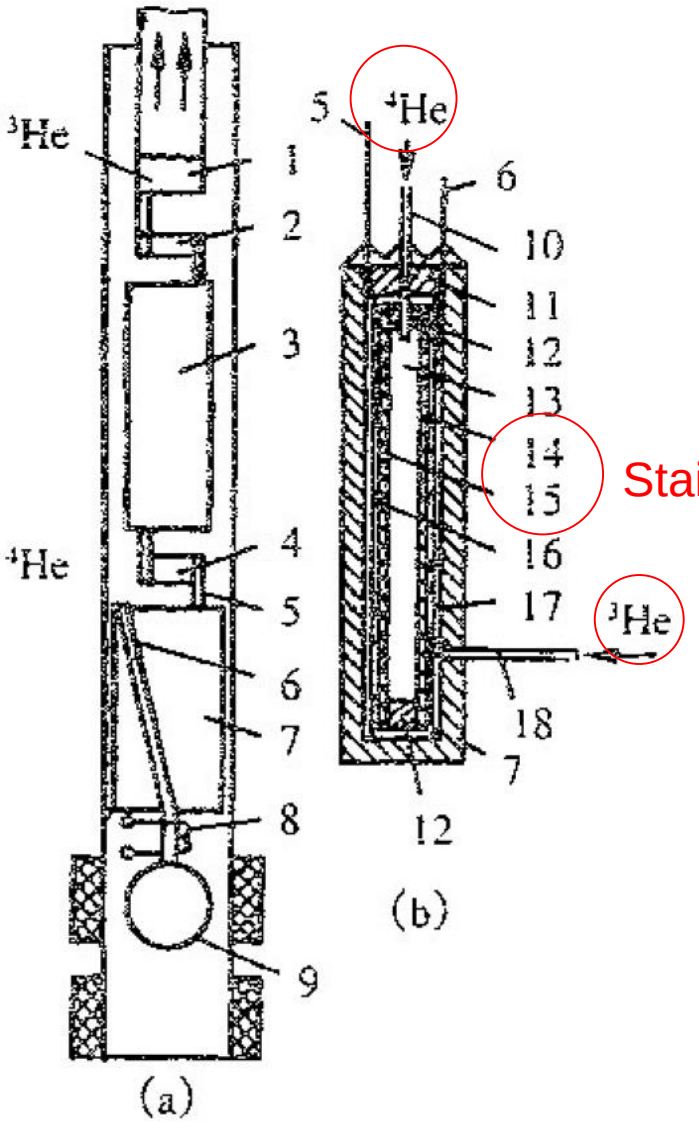
1972 Osheroff et al discovered super fluidity of ^{3}He.



Clausius-Clapeyron equation

$$\left(\frac{dP}{dT}\right)_{melting} = \frac{S_{liquid} - S_{solid}}{V_{liquid} - V_{solid}}$$



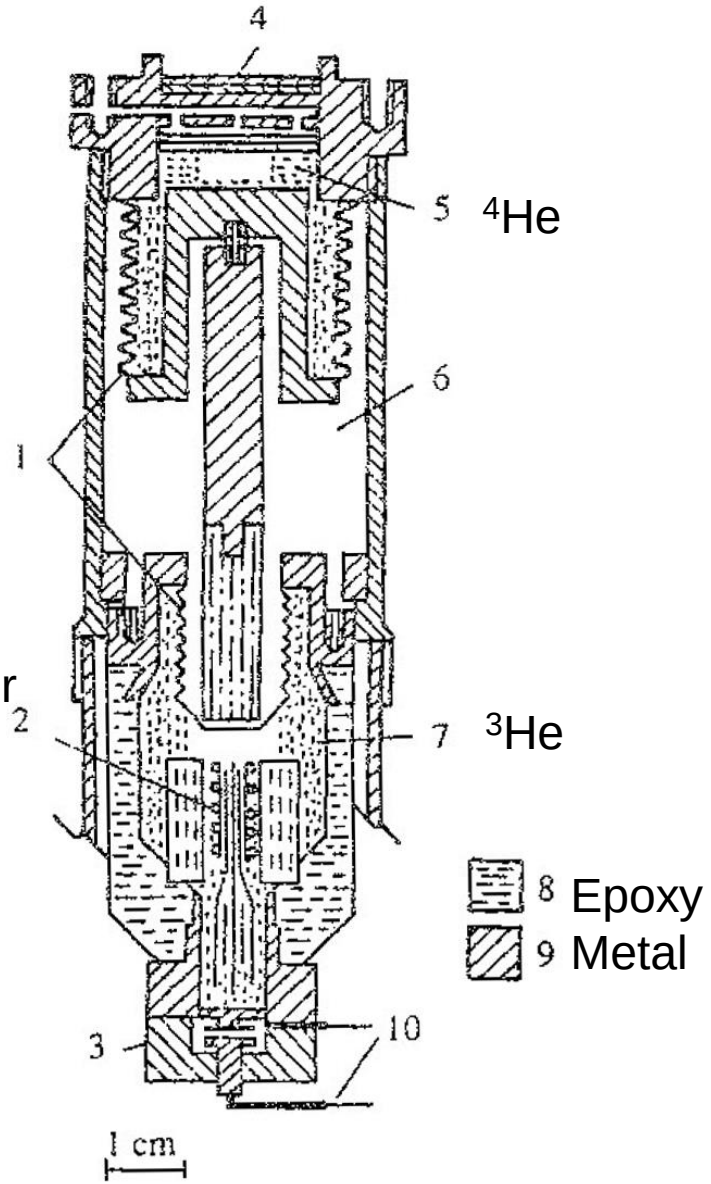


1965 Anufriev

Stainless diaphragm

Thermometer

Bellows

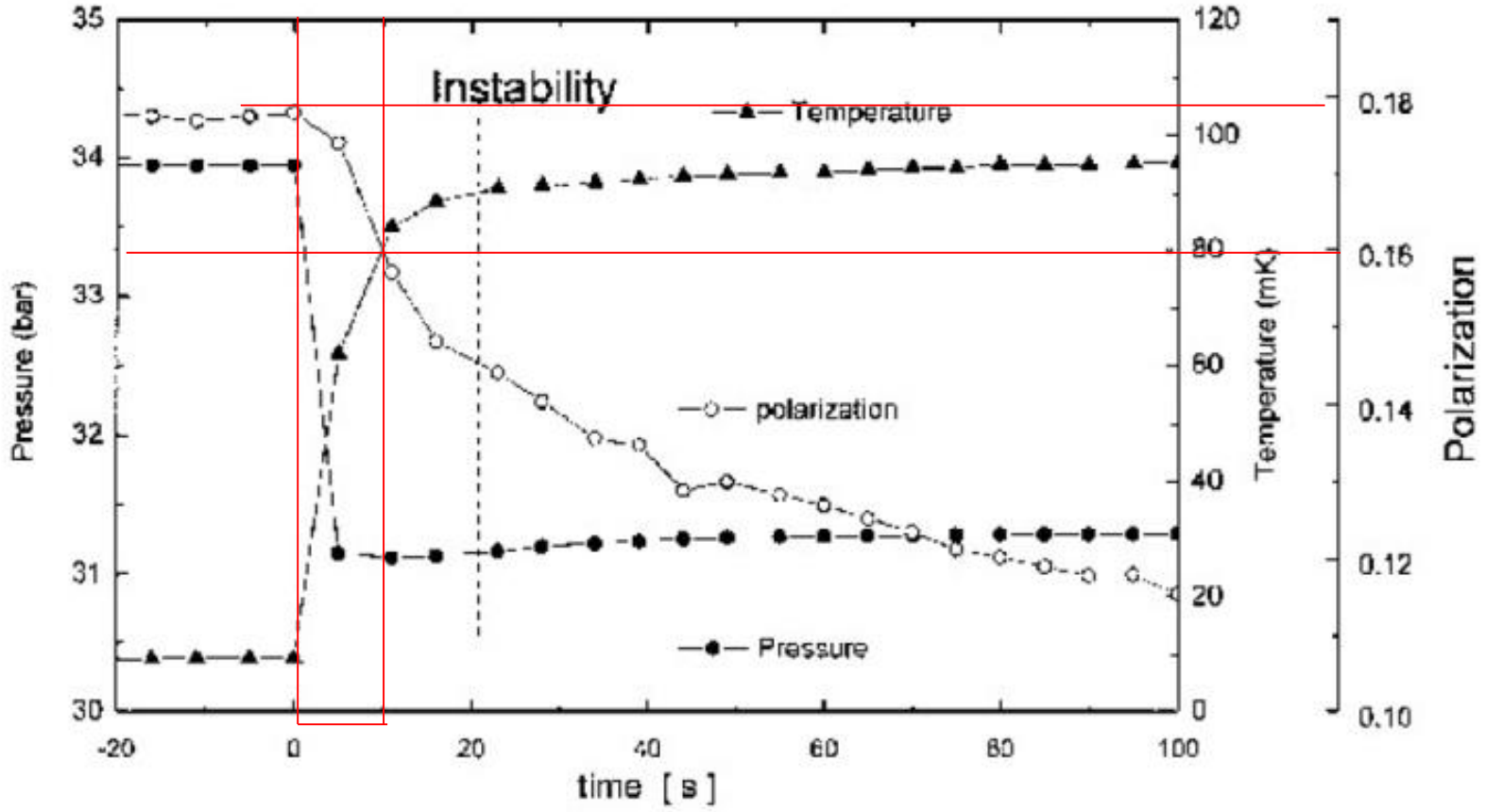


1972 Osheroff et al

Creation of highly polarized liquid and ^{3}He (Rapid melting method)

1979 Castaining and Nozieres
1979 Chapellier et al
1979 Schumacher et al
1979 Frossati
2008 Tanaka et al Restarted

To avoid the capillary blocking P<2.9 MPa and T>7~8 K



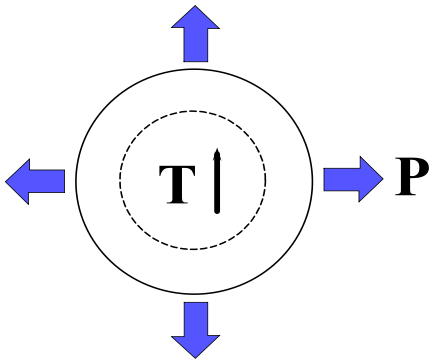
- To realize **Rapid Melting method**, i.e, Gasification of the solid ^{3}He through the liquid phase in a short time

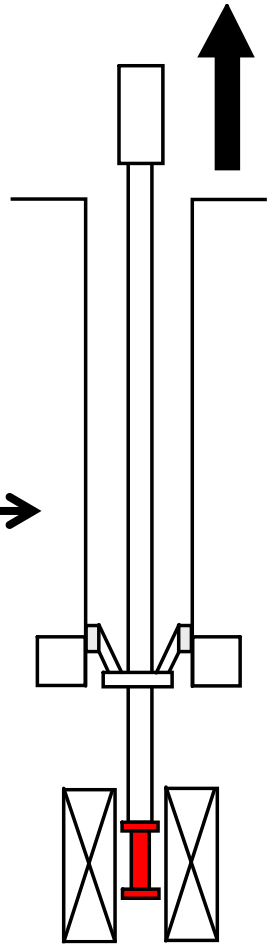
A specially designed device is needed:

1) a thermal switch

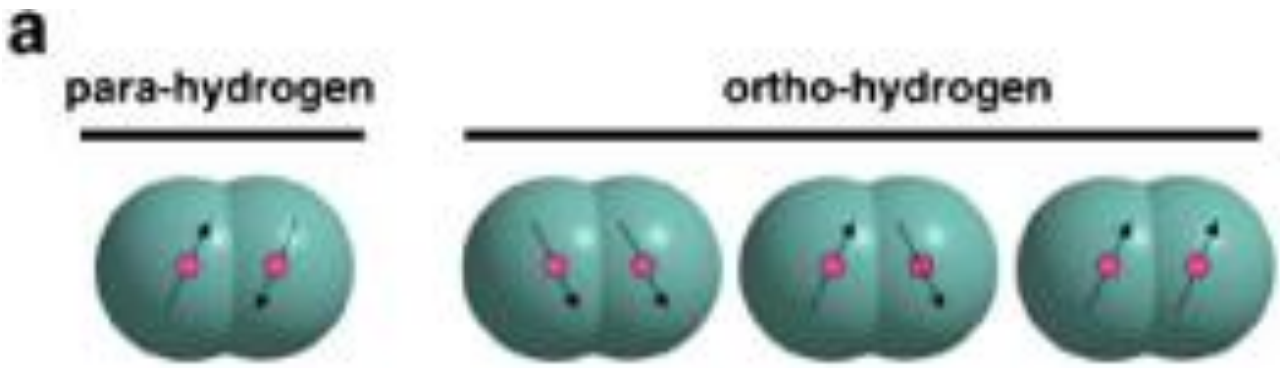
2) The Pomeranchuk cell should be moved to a place at low magnetic field and high T (7~8 K)

3) a quick decompression

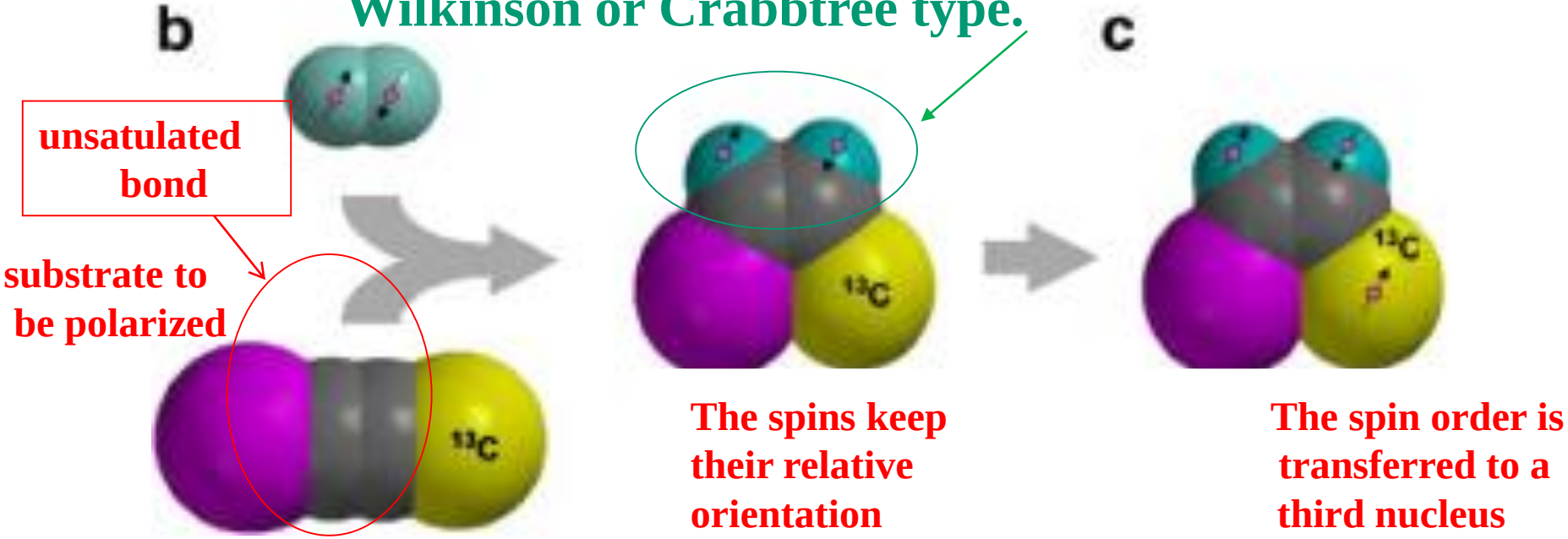




PHIP (Parahydrogen induced polarization)



Hydrogenation by homogeneous catalyst, e.g. Wilkinson or Crabbtree type.



The spins keep their relative orientation

The spin order is transferred to a third nucleus

The problem is that chemical structure may be changed.

What are we doing with PHIP?

Hyperpolarization of ^{19}F in an artificial blood.

What is an artificial blood?

PFC (Perfluoro carbon) is a candidate, which is a Polymer made of carbons and fluorines used as a blood substitute.

Why do we use the hyperpolarized PFC?

To be used for imaging, e.g. , Angiography and lung imaging.

However, PFC has saturated carbon bonds, i.e., PHIP seems to be difficult to hyperpolarize ^{19}F.

This problem will be solved by using a special catalyst.

Novel catalyst overcoming the previous drawback

R. W. Adams, et al., Science 323 (2009) 1708

Cycloocta-1,5-diene

Iridium

Cyclohexyl

$[Ir(COD)(PCy_3)(py)_3]BF_4$ $[Ir(H)_2(PCy_3)(py)_3]BF_4$ $[Ir(COD)(PCy_3)(py)_3]BF_4$

Pyridine (substrate to be polarized) or

For Chemist, this catalyst is not so important because no hydrogenation is expected.
However, physicist considers that this catalyst is the first catalyst for generating polarization in the world.

Liquid ventilation

In 1966, L. Clark proposed and performed his experiment with PFC.

A rat anaesthetised where the animal is paralysed intubated and immersed in PFC liquid.

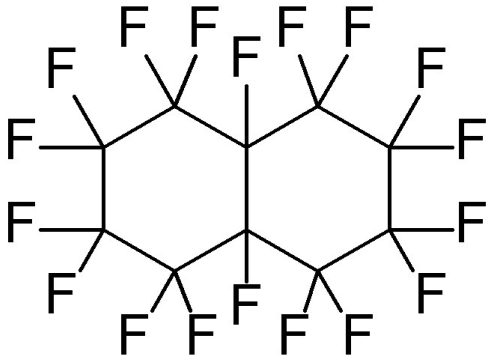
After bubbling oxygen through the liquid this is pumped into the animal's lungs and recirculated.

Fluosol – DA Artificial Blood

can play a role of red corpuscle, because it can carry oxygen and CO_2 effectively.

1) Non-ionic Surfactant
2) Phospholipid

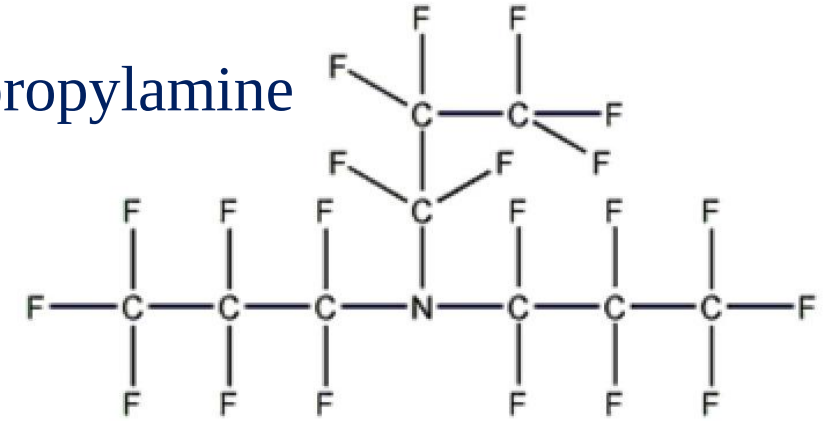
FDC
Perfluorodecalin



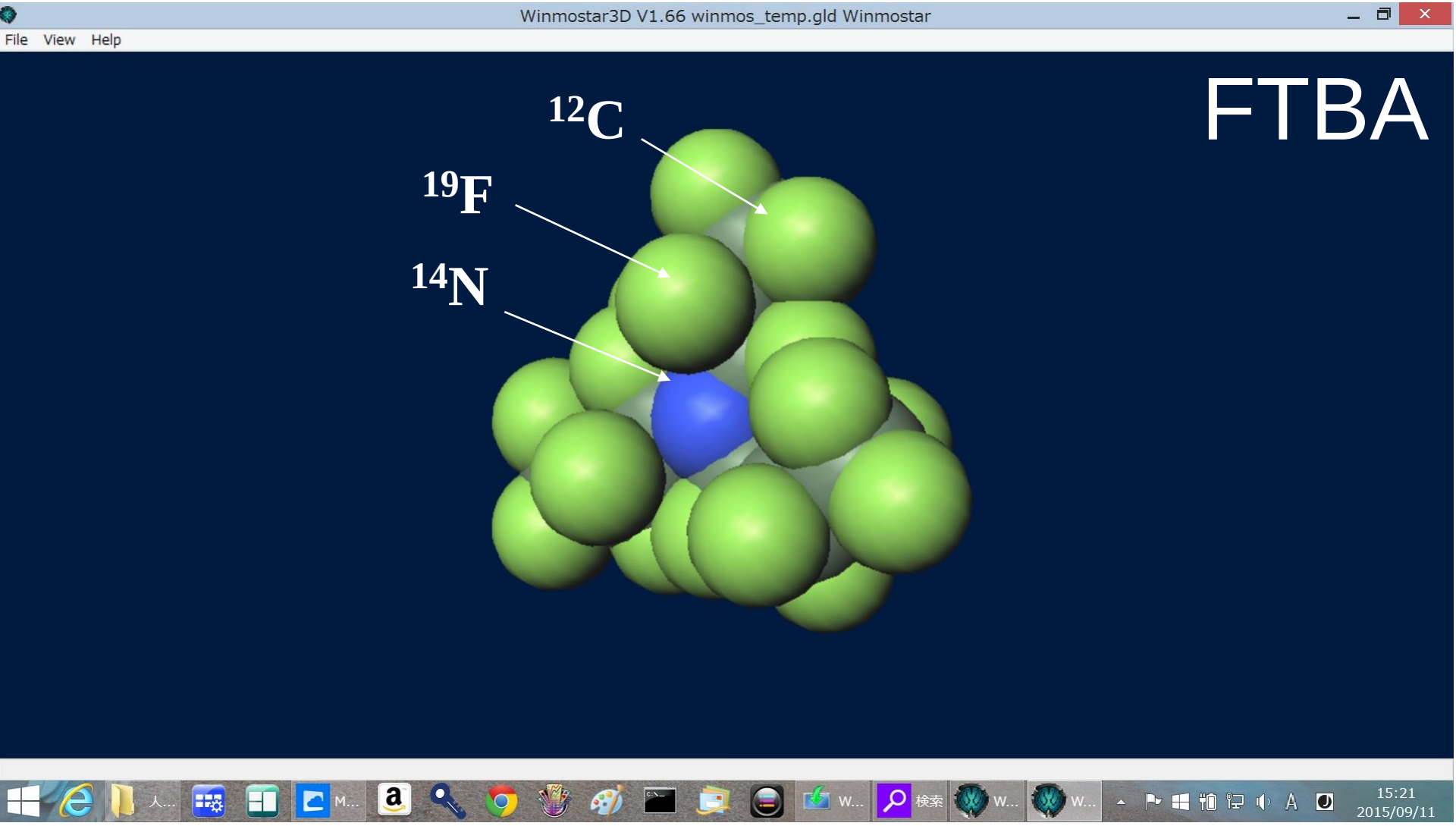
70%

Emulsified

FTPA
Perfluorotripropylamine

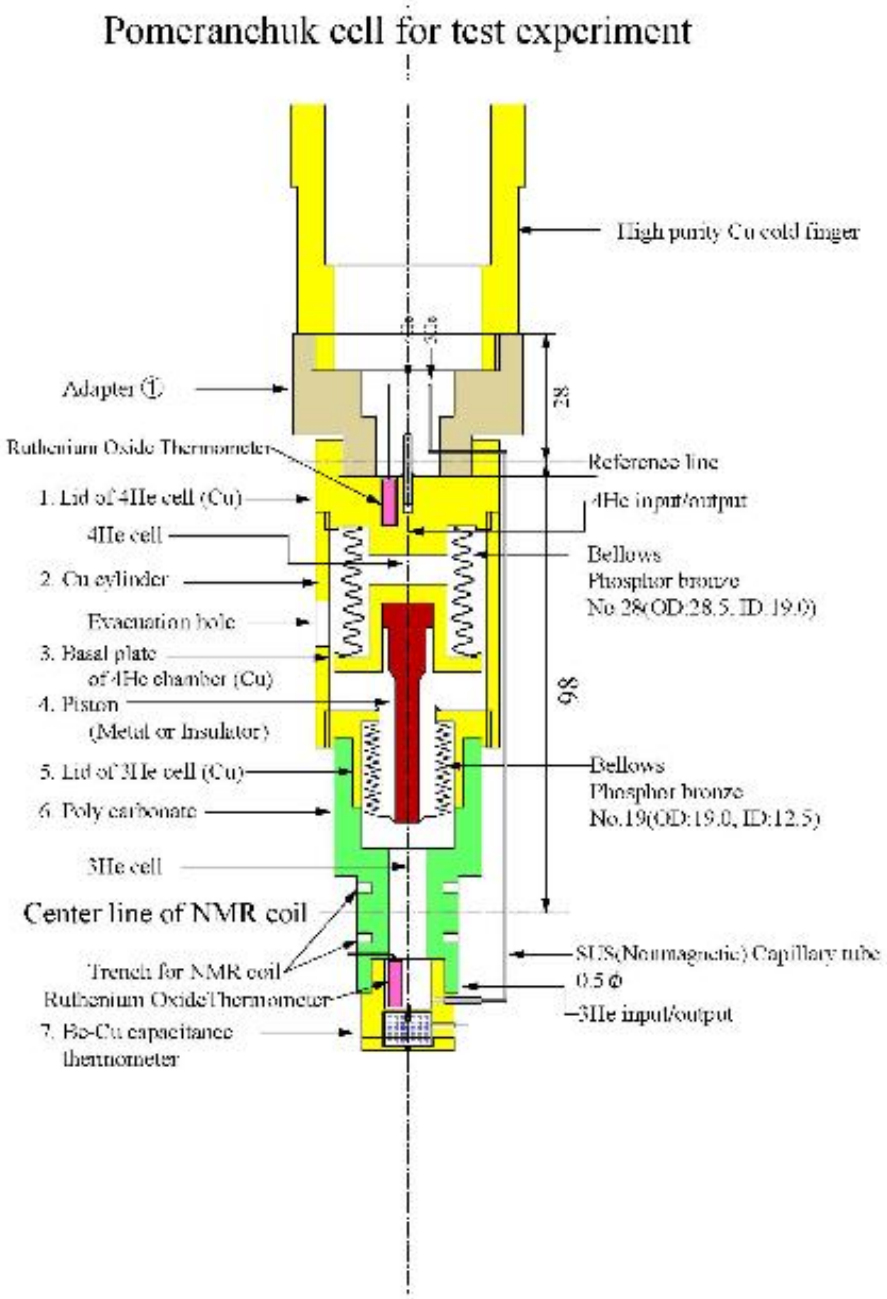


30%

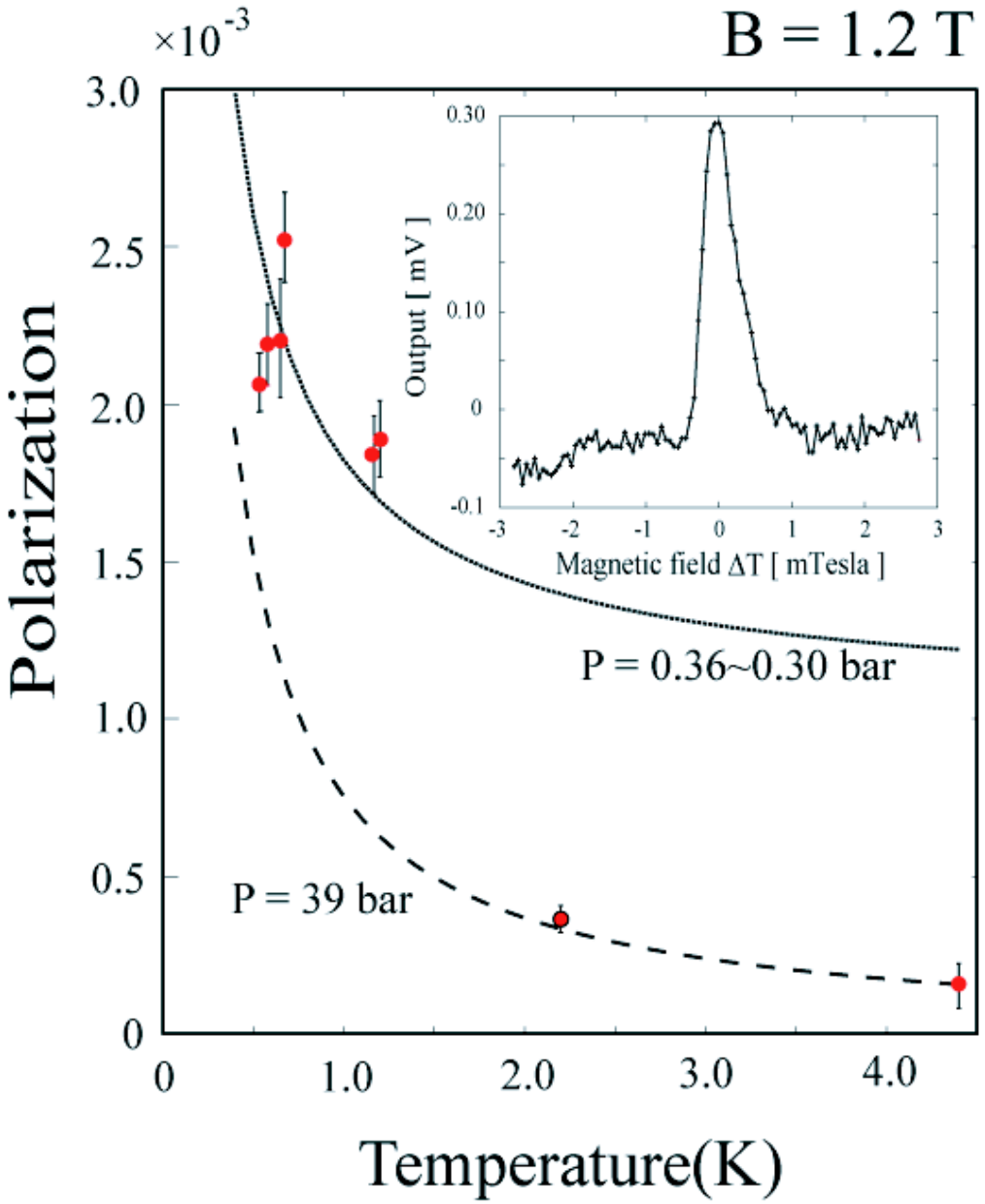

Winmostar3D V1.66 winmos_temp.gld Winmostar
File View Help
FTBA
^{12}C
^{19}F
^{14}N
15:21
2015/09/11

3. Present status of the development

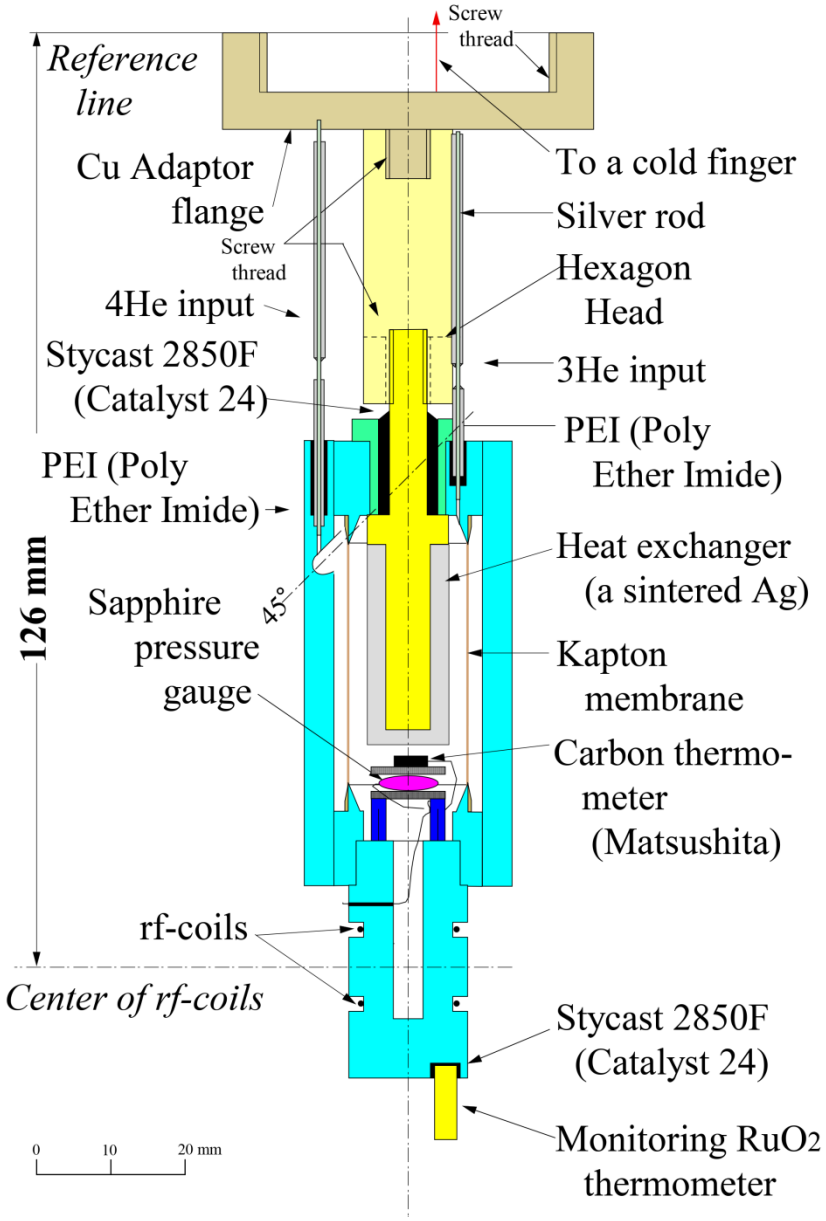
Brute force method


Pomeranchuk cell for test experiment
High purity Cu cold finger
Adapter ①
Ruthenium Oxide Thermometer
1. Lid of 4He cell (Cu)
4He cell
2. Cu cylinder
Evacuation hole
3. Basal plate
of 4He chamber (Cu)
4. Piston
(Metal or Insulator)
5. Lid of 3He cell (Cu)
6. Poly carbonate
3He cell
Center line of NMR coil
Trench for NMR coil
Ruthenium Oxide Thermometer
7. Be-Cu capacitance
thermometer
Reference line
4He input/output
Bellows
Phosphor bronze
No 28(OD:28.5, ID:19.0)
Bellows
Phosphor bronze
No.19(OD:19.0, ID:12.5)
SUS(Nonmagnetic) Capillary tube
0.5 ϕ
3He input/output
28
98

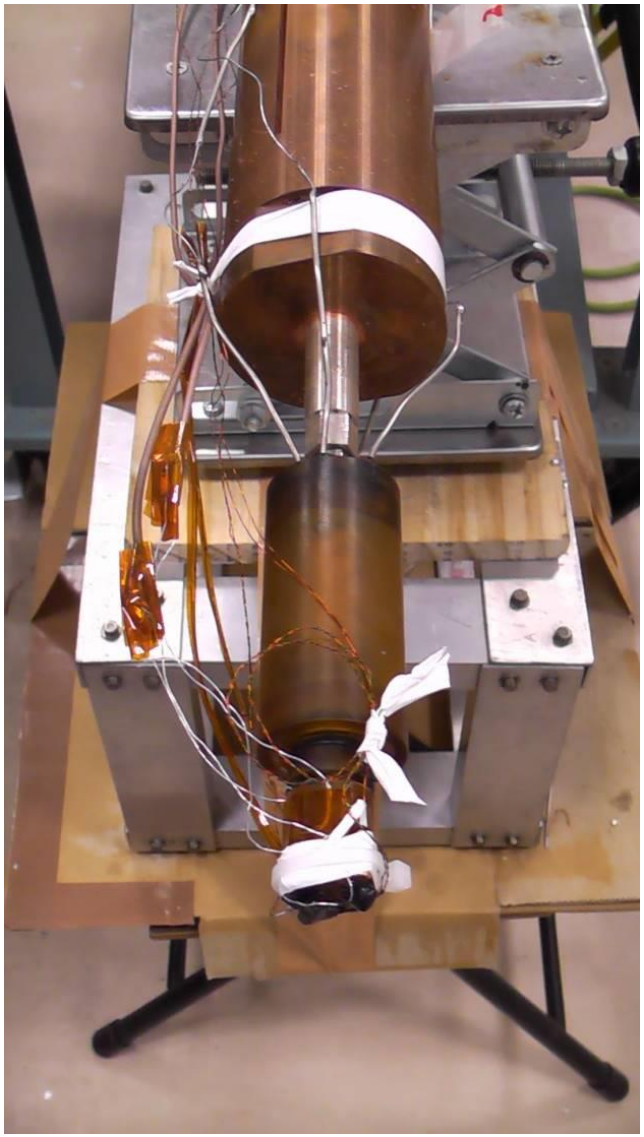
The first observation of NMR signals

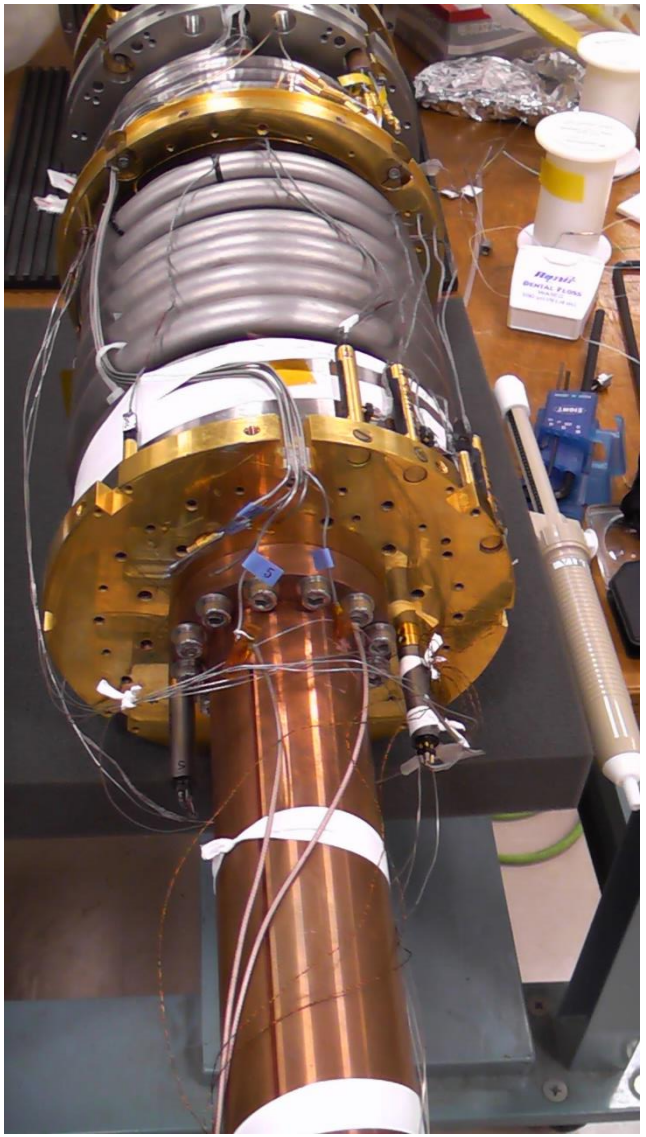


Adding Return Lines for ^{3}He and ^{4}He gas handling system



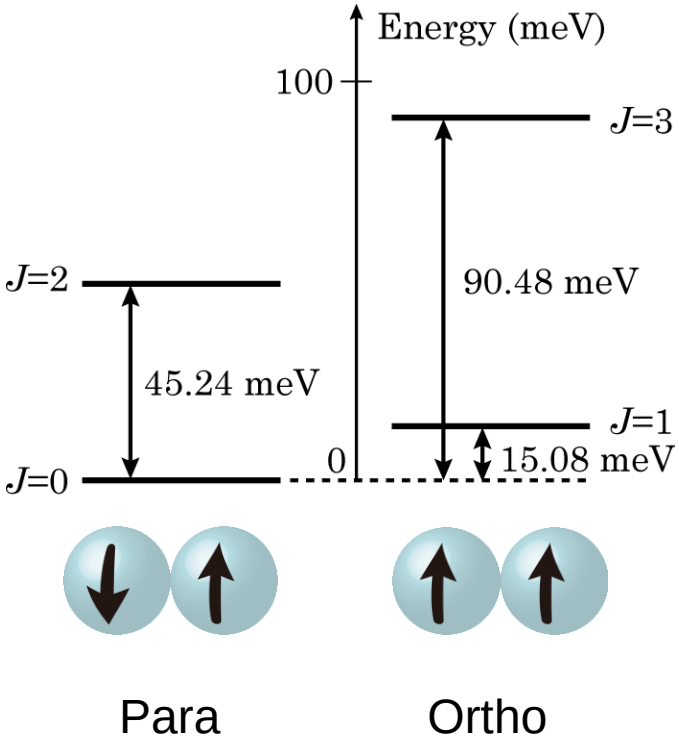
Installation of Pomeranchuk Cell to the Dilution Cryogenic System

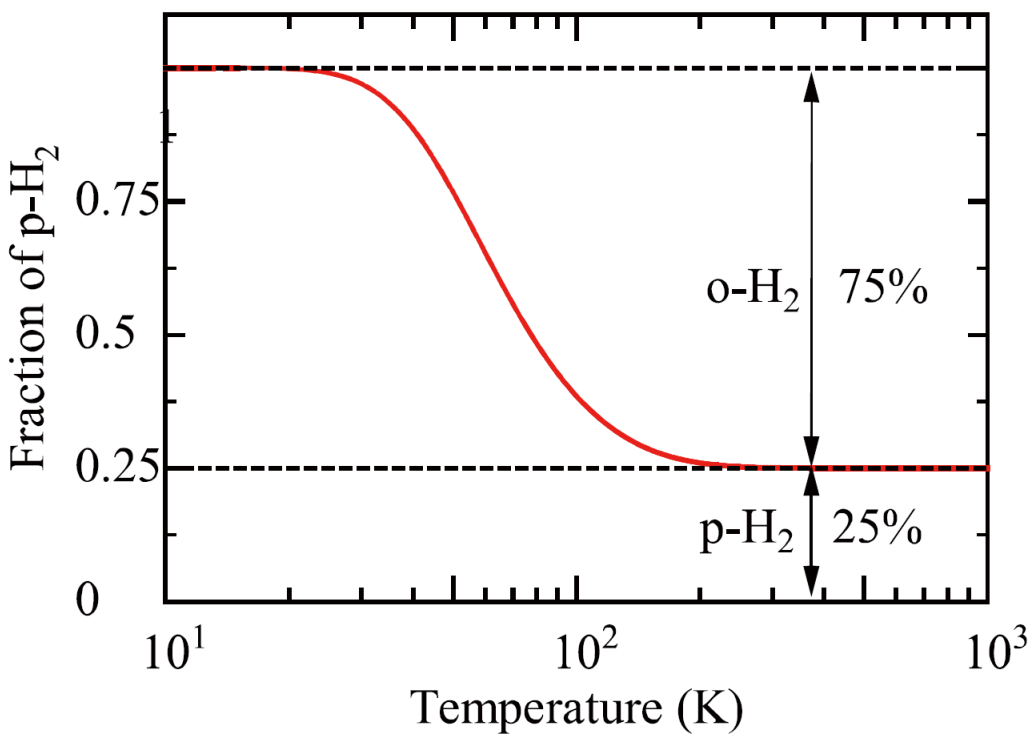




PHIP

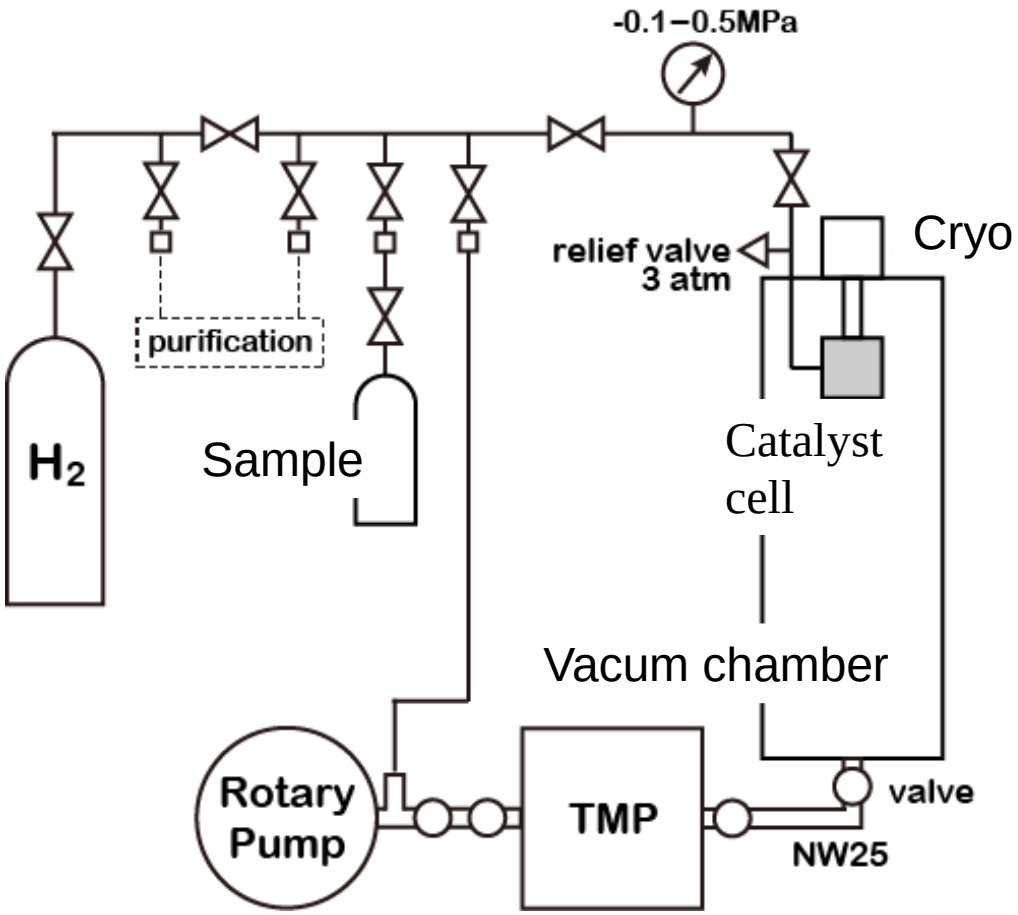
Production of parahydrogen



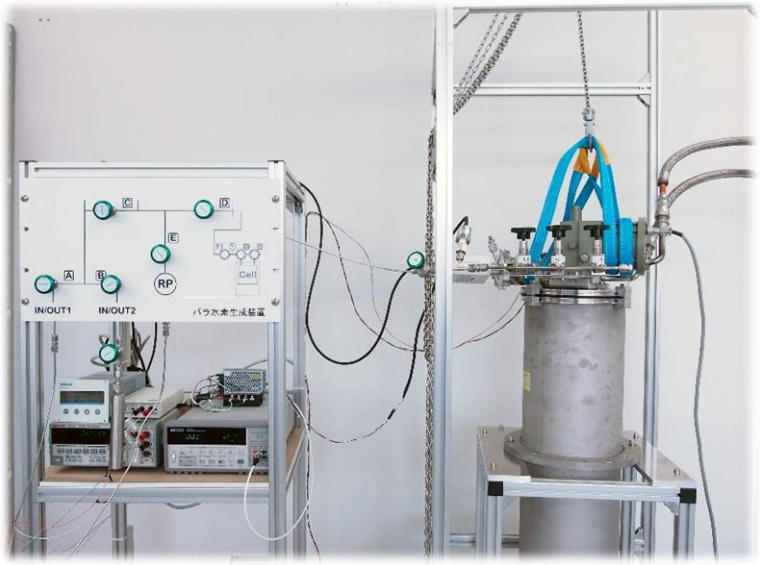


Equipment for production of Para-Hydrogen

Wakayama Med. University Group



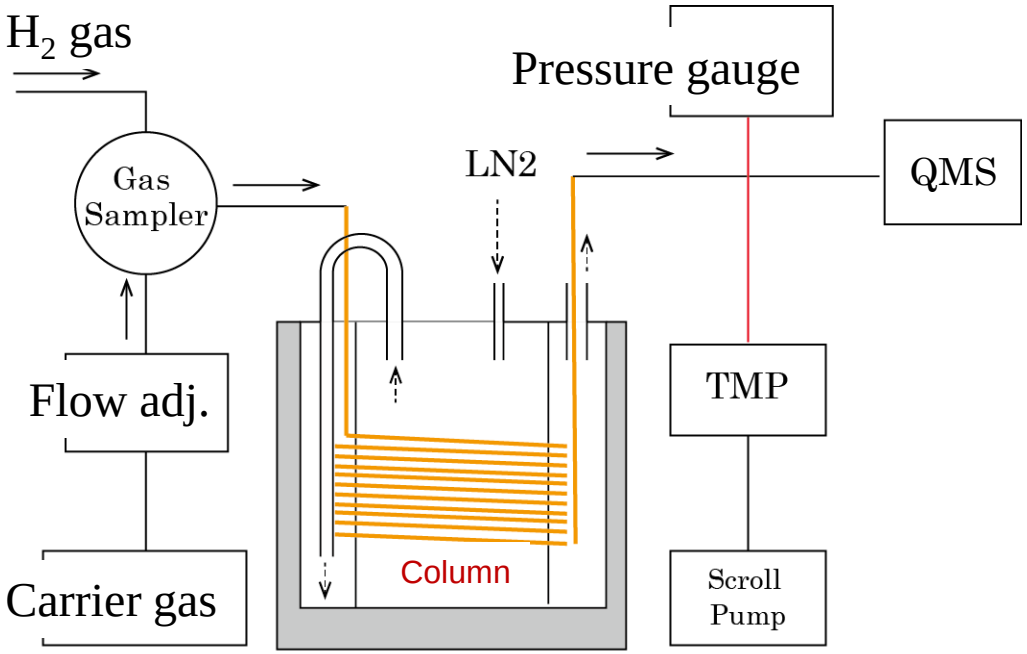
Temp : 22K
Pressure : 0.3 – 1 atm
Catalyst : FeO(OH) Sigma Aldrich

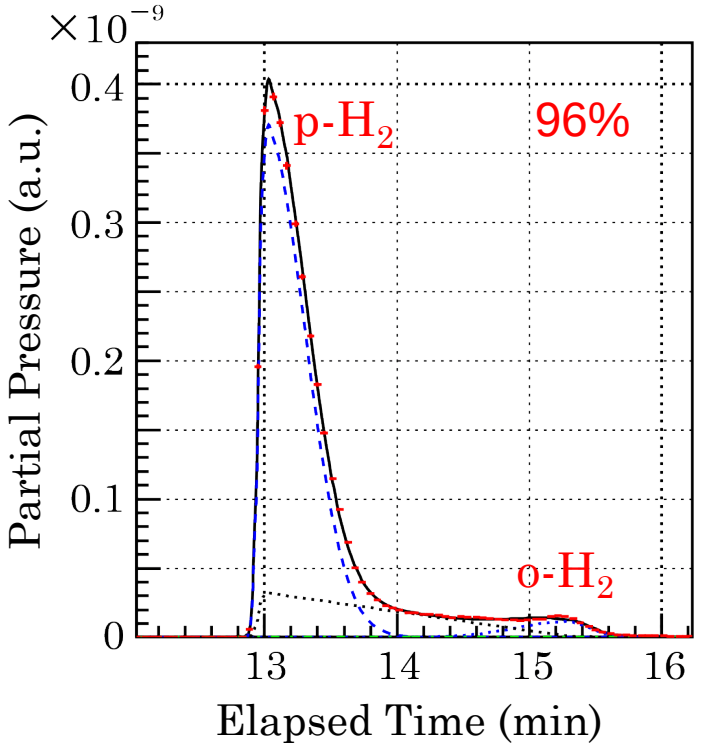


Gas Handling Cryo+Catalyst cell

Gas Chromatography

T. Ohta *et al.*, Nucl. Instr. and Meth. A 640 (2011) 241.





Carrier gas：He
Flow rate：1.0ml/min
Temp：110-120K
Column：Varian CP Molesive 5A

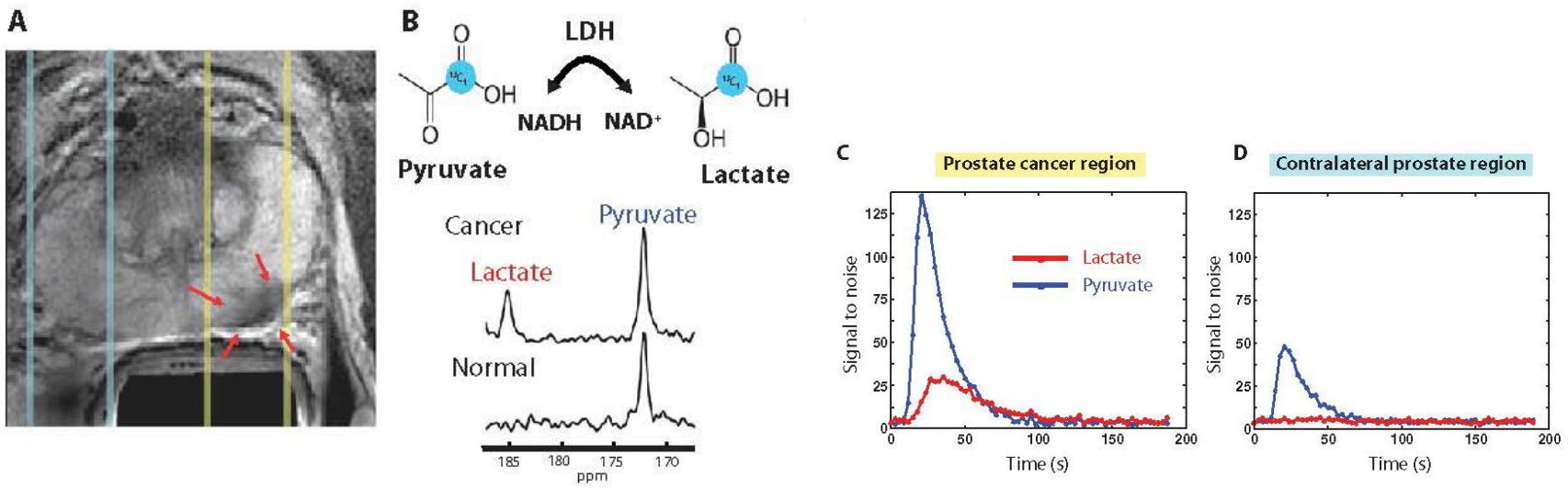
4. Conclusion and future prospect

- **Conclusion**
  1. **Experiments on the hyperpolarization with either brute force method or PHIP are almost ready to get started after many many preliminary failures.**
  2. **On the PHIP, the success seriously depends on whether lone pairs of the amin base can be usable or not.**
  3. **Even if the PHIP may not be successful, the brute force method applied to the PFC will hopefully be promising.**
- **Future Prospect**
  1. **A novel way to the cancer diagnostics using hyperpolarized ^{13}C by the brute force method**
  2. **Can the hyperpolarized ^{3}He be replaced with the hyper-polarized PFC? If so, we will be completely free from expensive ^{3}He.**

Note that the hyperpolarization was created by the DNP as Prof. Ardenkjear-Lansen mentioned.

Prostate Cancer: **Science Translation Medicine,** University of California, San Francisco 2013

1-^{13}C labeled Pyruvate → Lactate (…ate = salt of acid)



If the brute force method is applied, almost similar result would hopefully obtained.

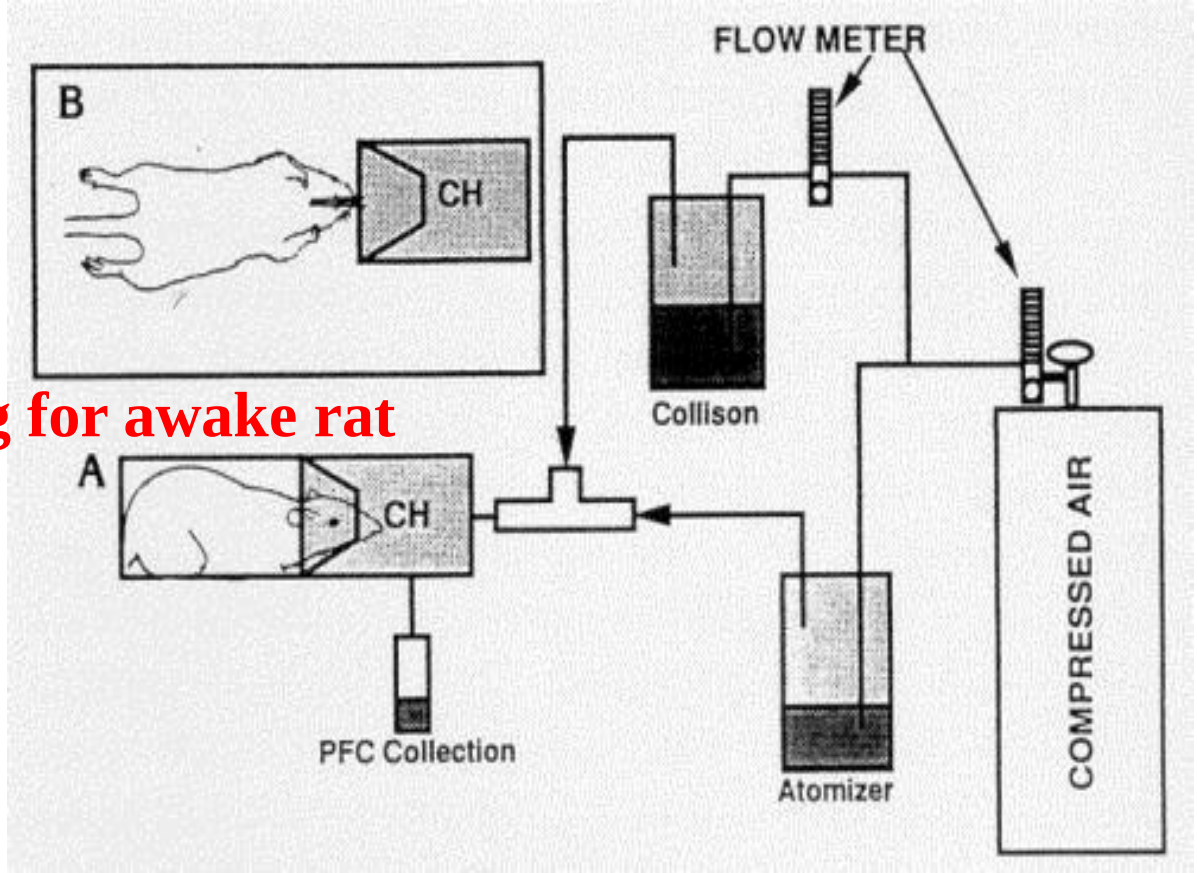
A more important aspect is that the sample polarization would be kept for long time since no free radical is used, which support the transport of the sample needing long time.

This is substantial advantage compared with the PET with the radioisotope ^{18}F labeled glucose.

Cicinati group reported in Investigative Radiology (1997) that the lung image for rats by using PFC aerosols were successfully obtained.

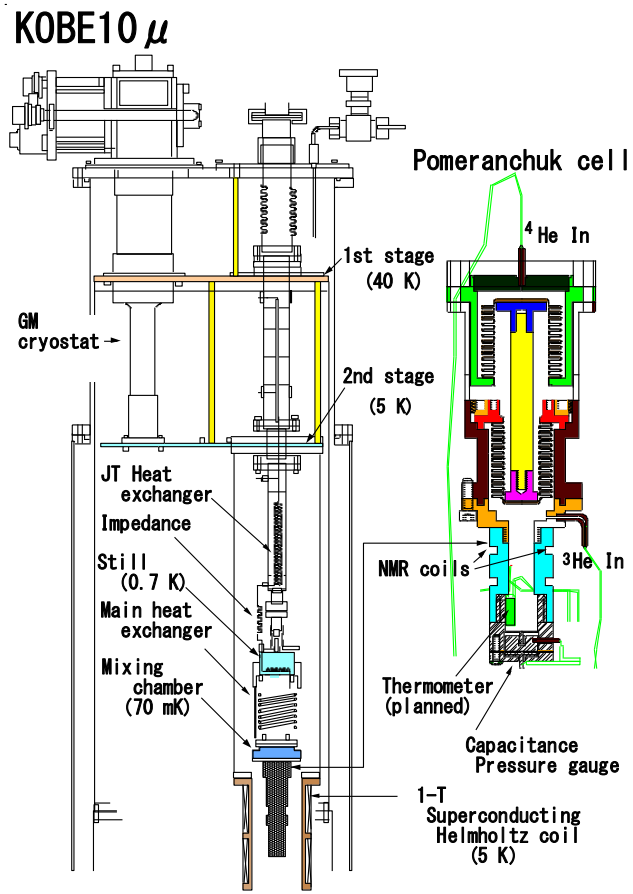
Tracheotomy tube for anesthetized rat

Free breathing for awake rat



Introduction of Cryofree dilution refrigerator

KOBE10μ
(Cryofree dilution refrigerator)



Characteristic

- GM cryostat for 5 K
- No 1K pot is used.
- JT heat exchanger for 1 K
- Q ~ 10 mW at 100 mK
- T_{min} ~70 mK

Festina Lente

(Make haste slowly)

The first Roman emperor Augustus and one of our colleagues, Prof. Emeritus Frossati (Kamerlingh Onnes Institute, Leiden, the Netherlands) loved this proverb.