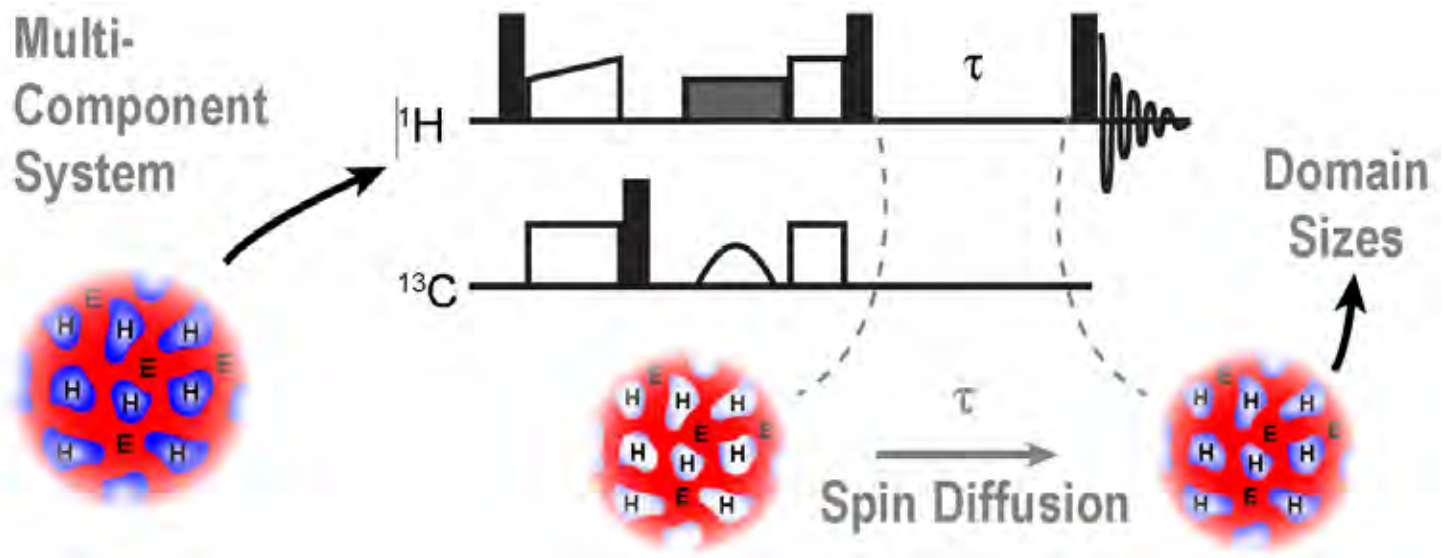
New solid-state NMR methods in controlled release

Staffan Schantz

AstraZeneca


Multi-
Component
System
^{1}H
^{13}C
τ
τ
Spin Diffusion
Domain
Sizes

AstraZeneca R&D

CV-Metabolism

Oncology

Respiratory, Inflammation & Autoimmunity

Infection & Vaccines

Neuroscience

Core Therapy Areas

Opportunity-focused

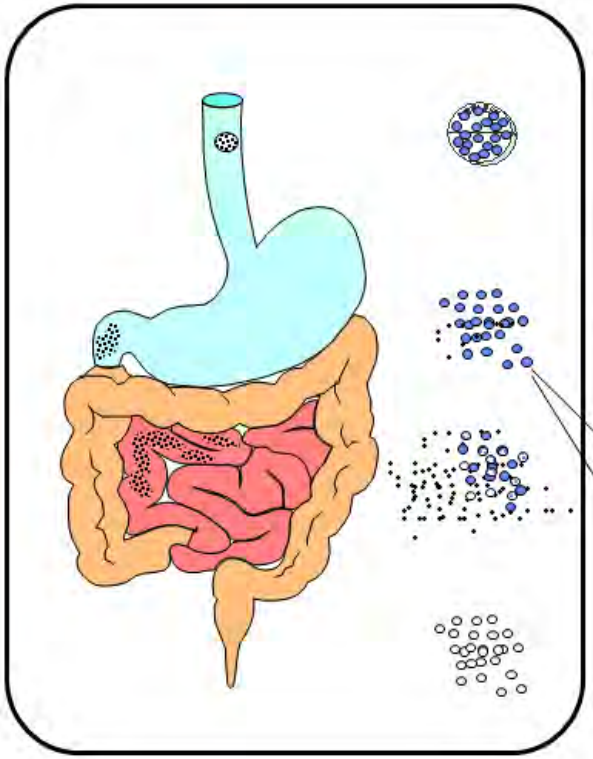
Biologics

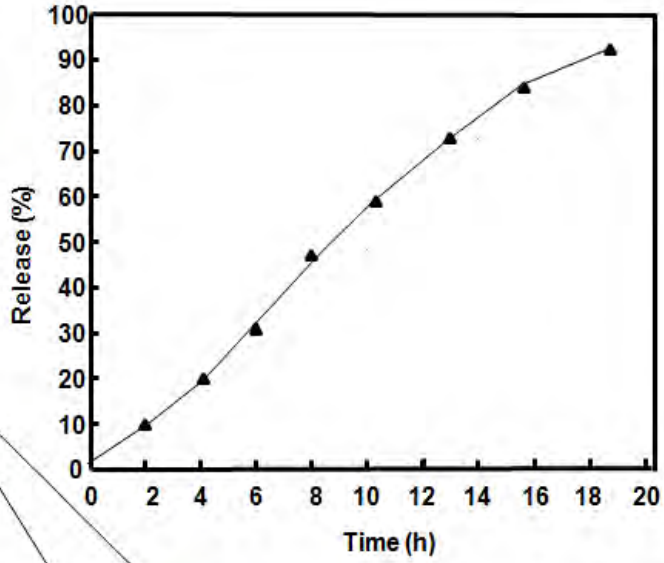
Small Molecules

Immuno - therapies

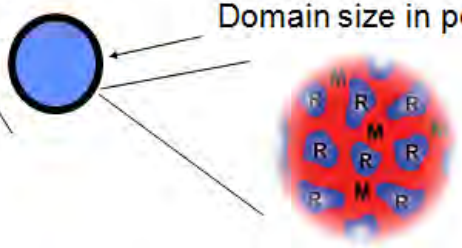
Protein engineering

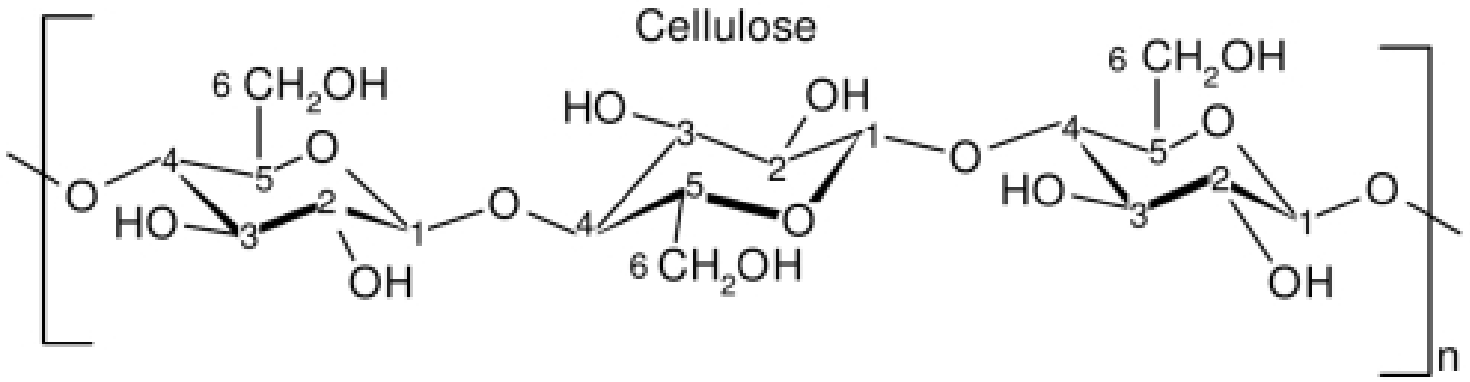
Can we determine domain sizes using NMR?

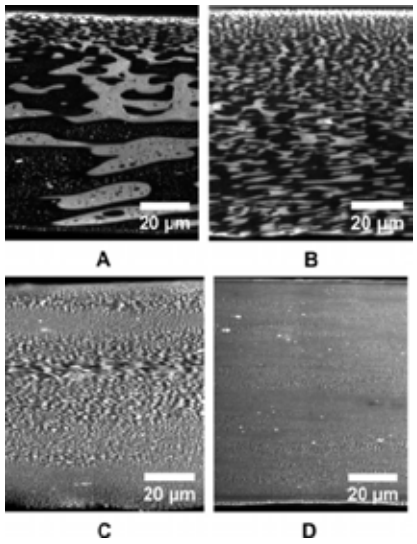


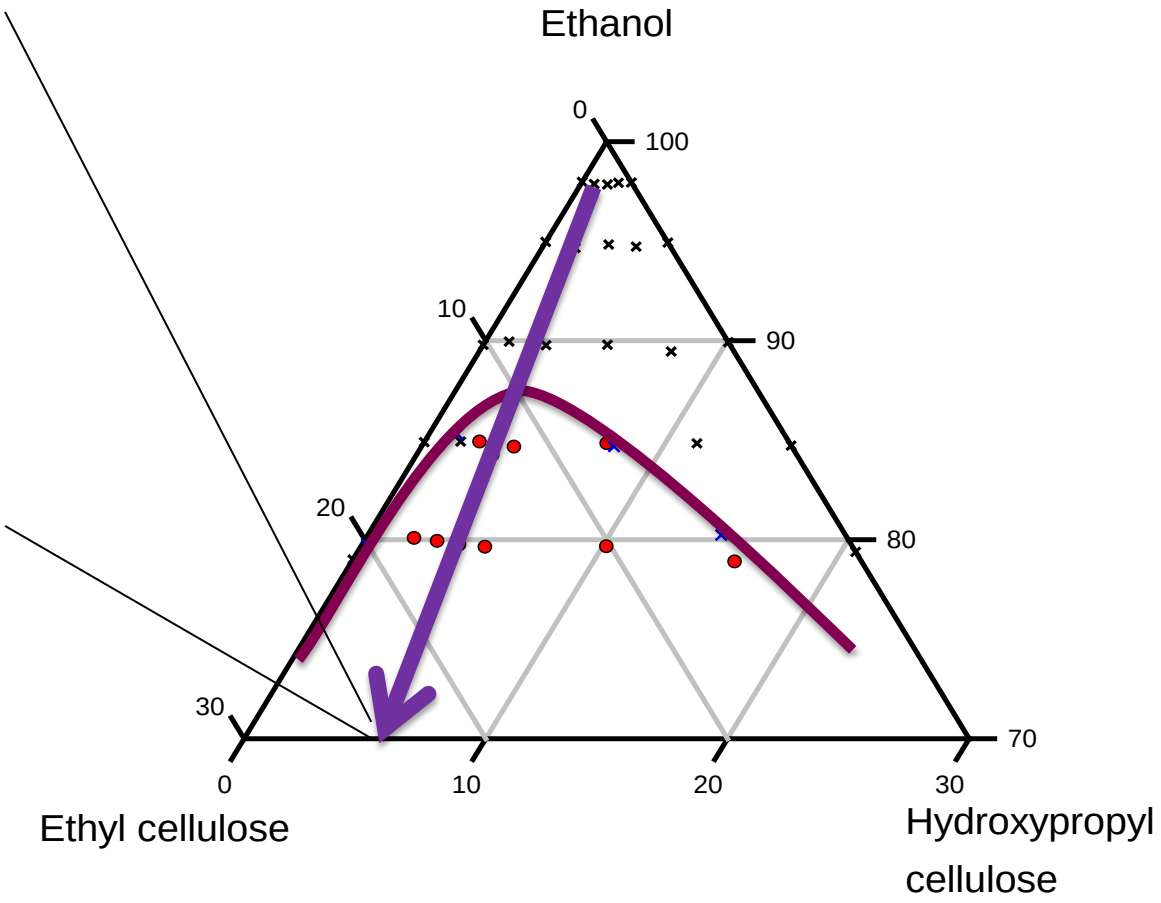


Domain size in polymer coating?




Cellulose
6 CH2OH
HO
OH
O
n

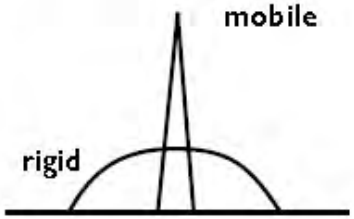

20 µm
20 µm
A
B
20 µm
20 µm
C
D


Ethanol
0
100
10
90
20
80
30
70
0
10
20
30
Ethyl cellulose
Hydroxypropyl
cellulose


BRUKER

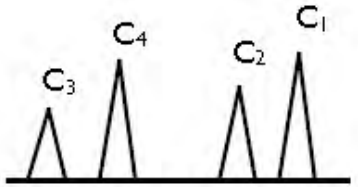
NMR spectra of polymers:

^{1}H



information about mobility

^{13}C



signal for each atom

NMR spectra of polymers:

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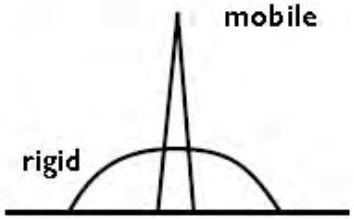

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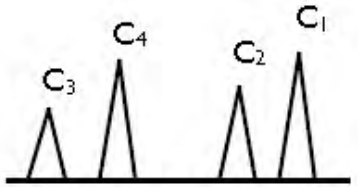
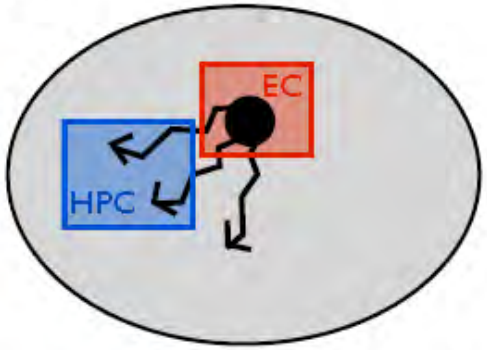
^{13}C



signal for each atom

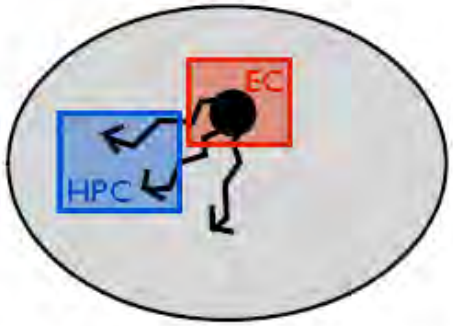
Spin Transport:



Magnetization transfer driven by through-space interactions

"classical"
solid state NMR

Spin Diffusion



"classical"
solid state NMR

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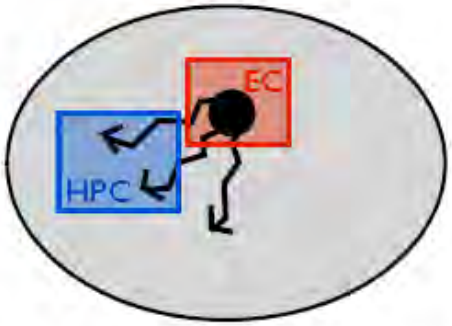
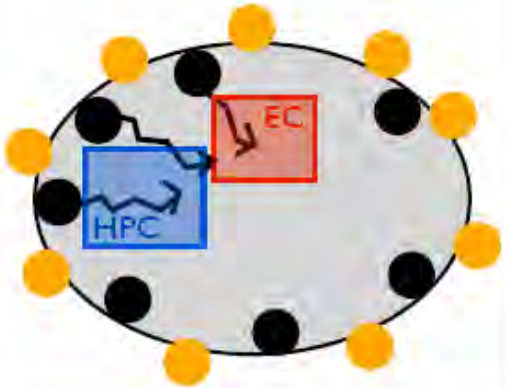


Dynamic Nuclear
Polarization

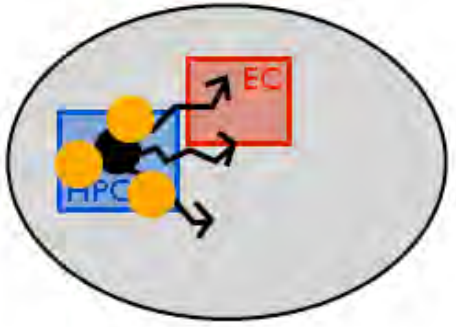
DNP

+ radicals



Paramagnetic Relaxation
Enhancement

PRE



"classical"
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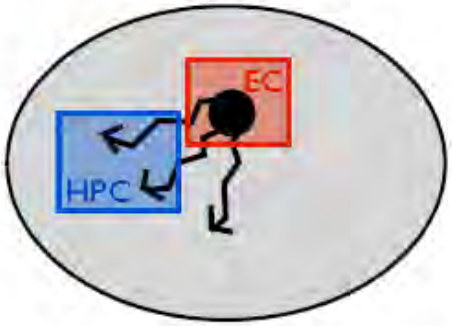

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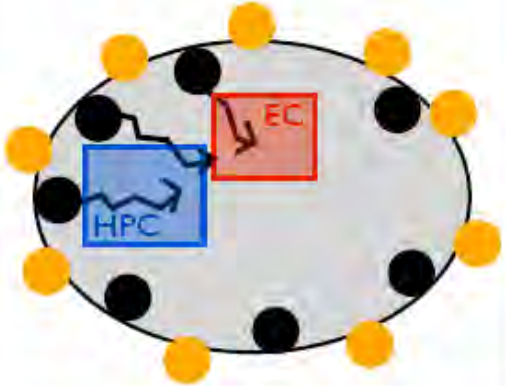

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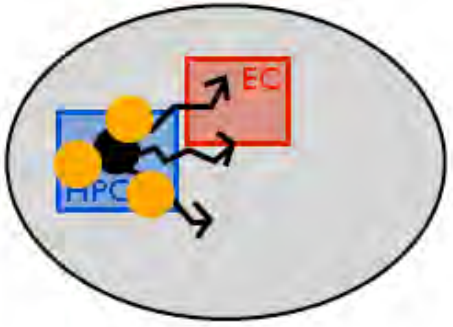
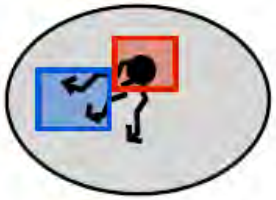


$$\frac{\partial P(r,t)}{\partial t} = D\,\Delta P(r,t) - \frac{P(r,t) - P_0(r)}{T_1(r)}$$

spin lattice relaxation time

monitor polarization *P* (magnetization)
at a position *r*, at a time *t*, as a function of T_1



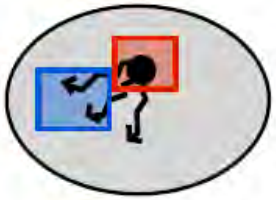
$$\frac{\partial P(r,t)}{\partial t} = D\left(\frac{\partial^2 P(r,t)}{\partial r^2} + \frac{2}{r}\frac{\partial P(r,t)}{\partial r}\right)$$

$$D = D_R \quad \text{for} \quad 0 \le r \le \tfrac{1}{2} d_R$$

$$D = D_M \quad \text{for} \quad \tfrac{1}{2} d_R < r \le \tfrac{1}{2}\left(d_R + d_M\right)$$

D_R , D_M ... diffusion coefficient of the corresponding domain
d_R , d_M ... domain size of the corresponding domain

Simulation of Spin Diffusion Curves:



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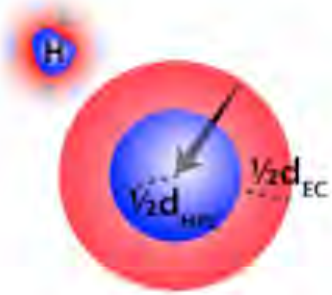
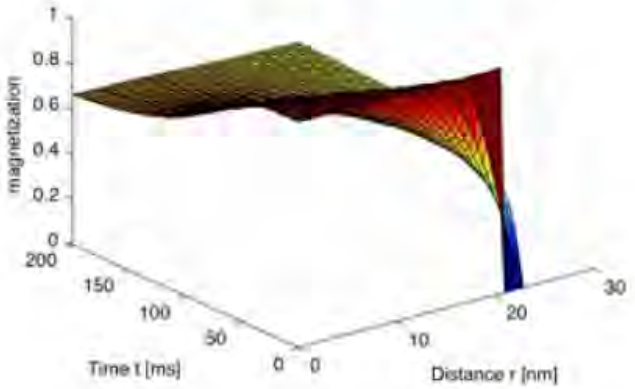
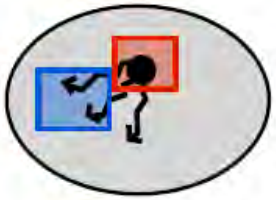


numerical solutions for differential equation:





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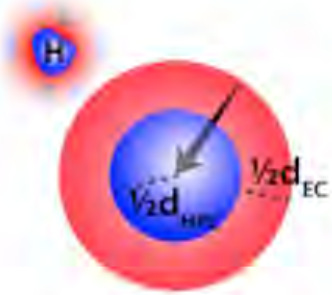

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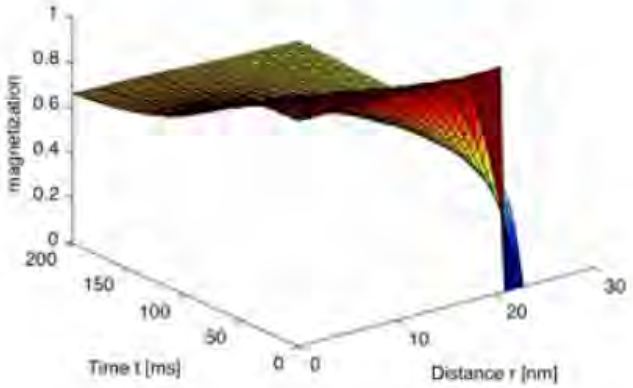
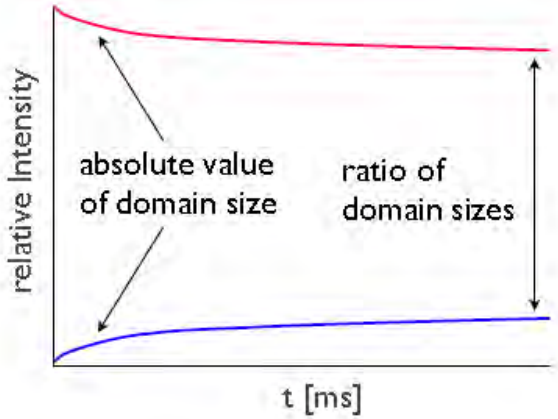
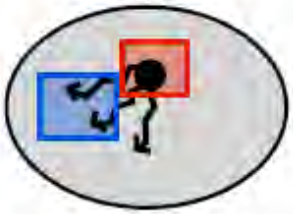


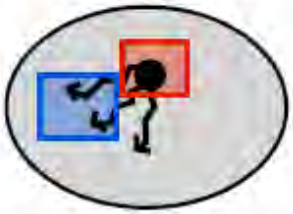




$$\frac{\partial P(r,t)}{\partial t} = D\,\Delta P(r,t) - \frac{P(r,t) - P_0(r)}{T_1(r)}$$

The NMR experiment:

1. select magnetization/signals from only one of the domains



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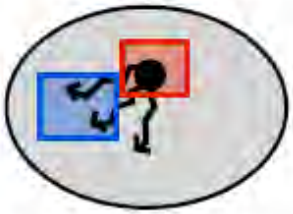

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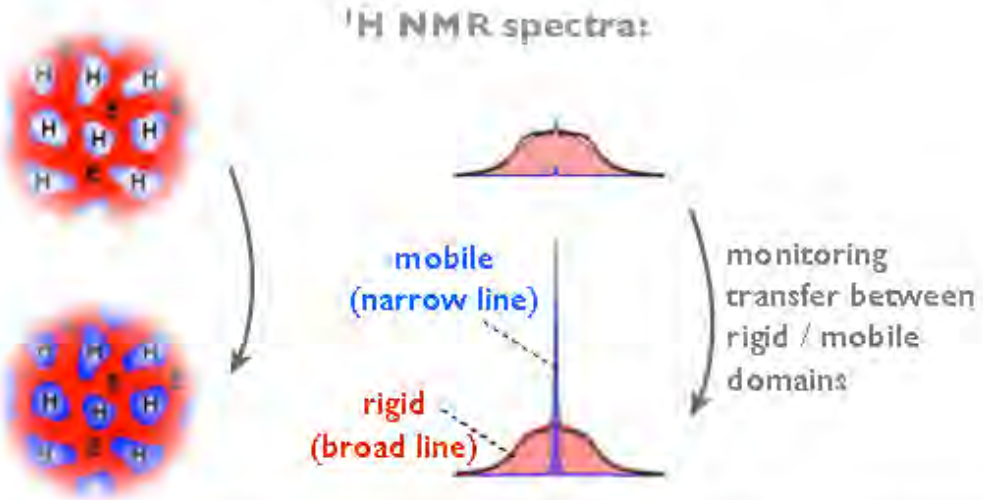

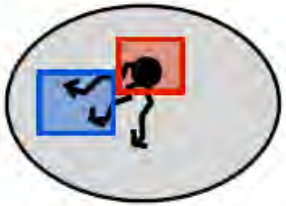

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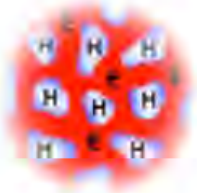
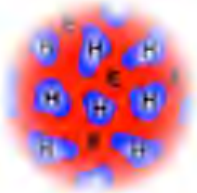
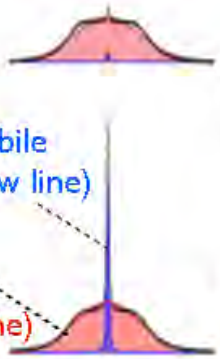


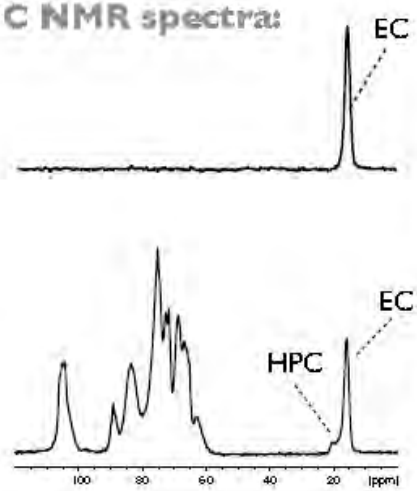


^{1}H NMR spectra:

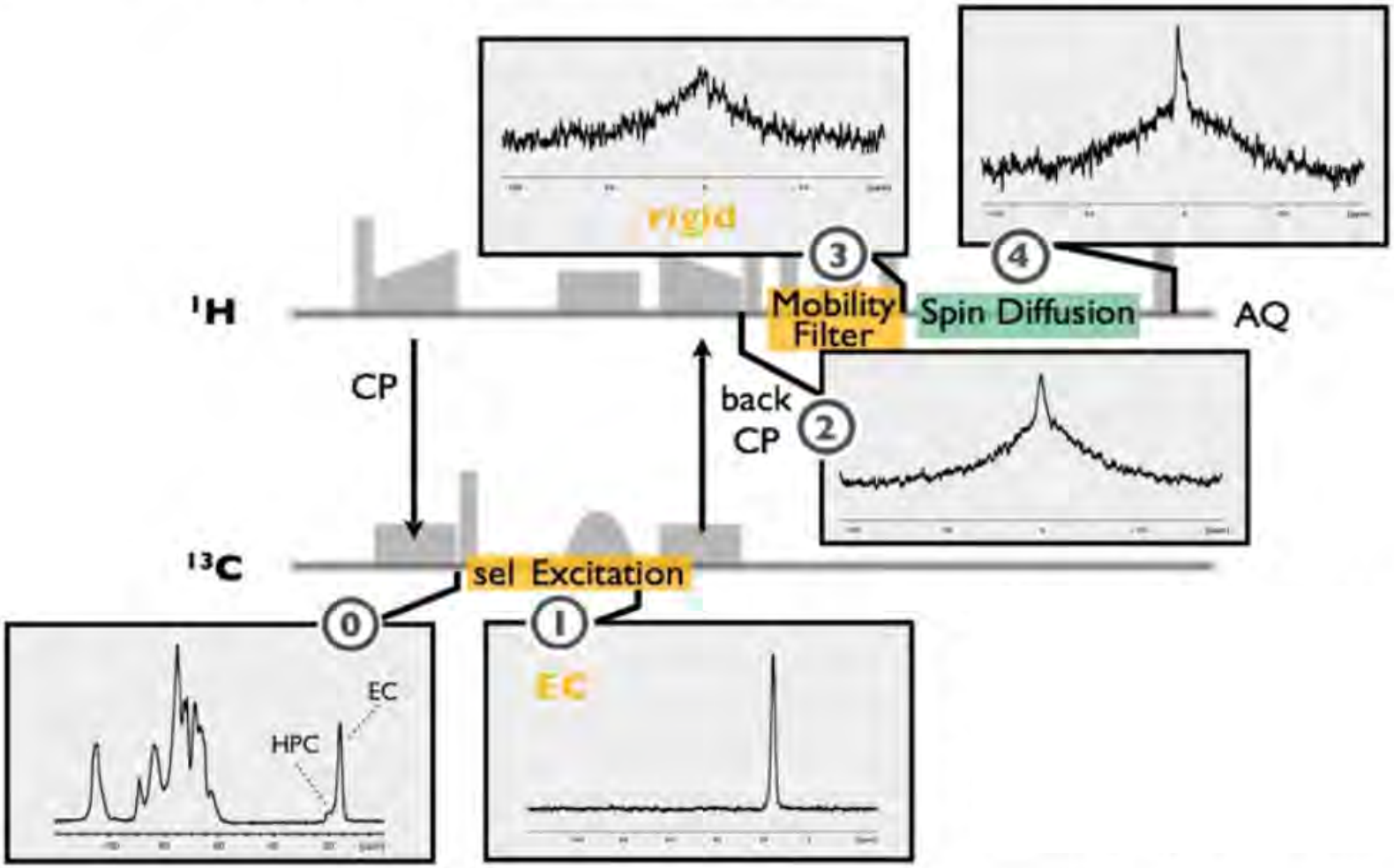


monitoring transfer between rigid / mobile domains

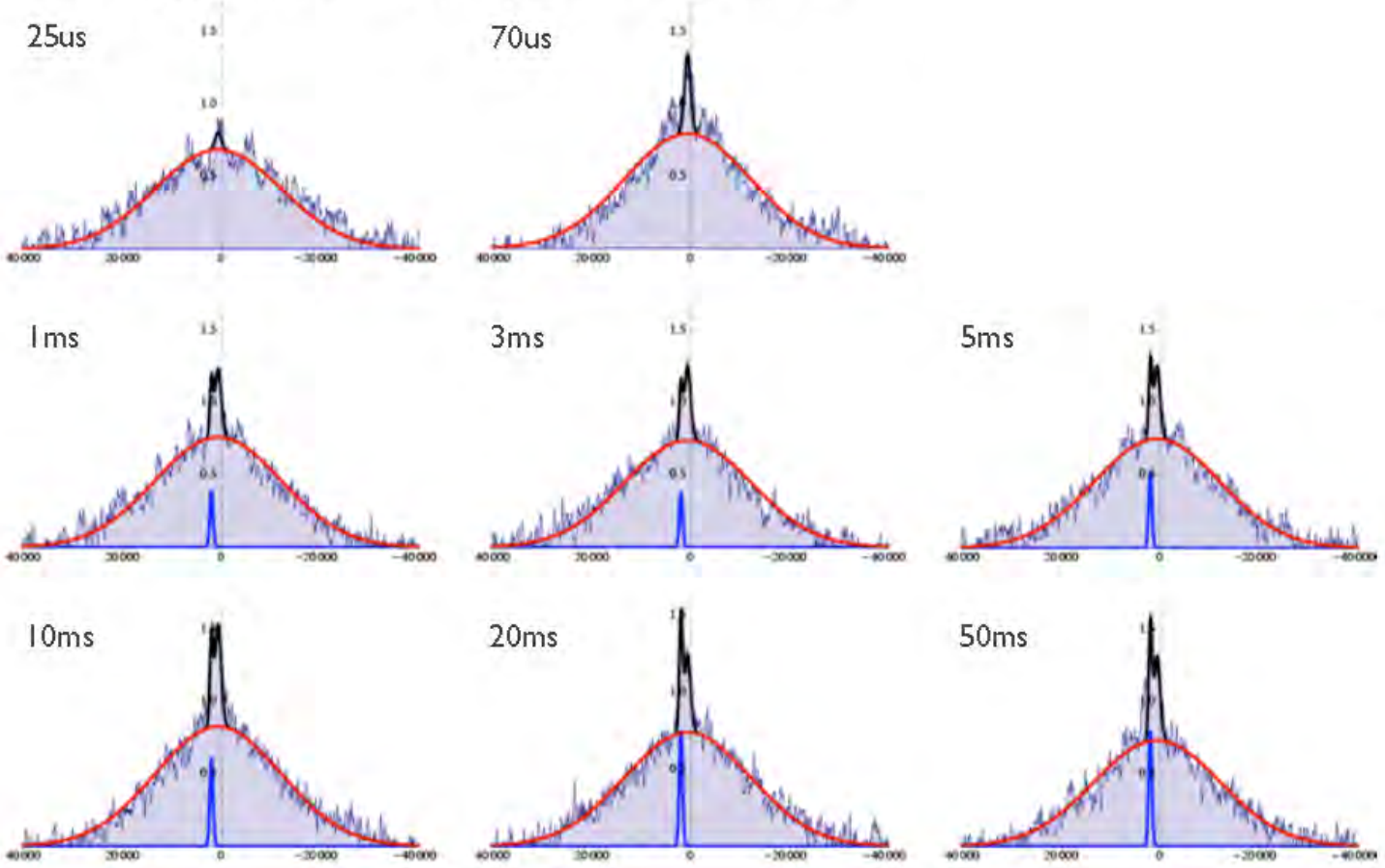
^{13}C NMR spectra:



additional information from 13C NMR to distinguish different components (EC/HPC/MCC) and monitor magnetization transfer between them


rigid
3
4
^{1}H
Mobility Filter
Spin Diffusion
AQ
CP
back CP
2
^{13}C
sel Excitation
0
1
EC
HPC
EC

Obtained signals for different spin diffusion times:



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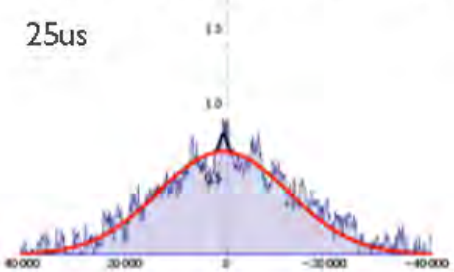
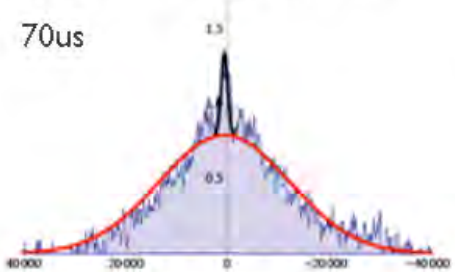
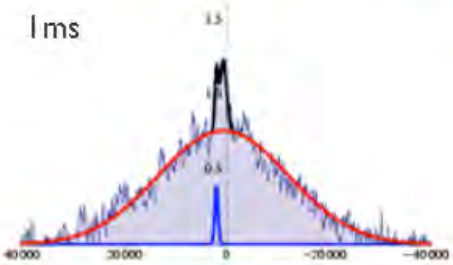
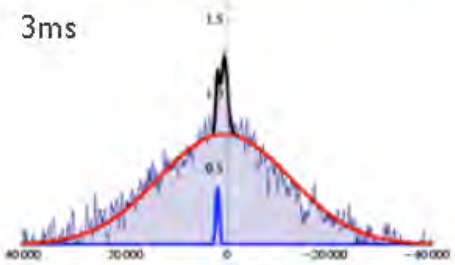
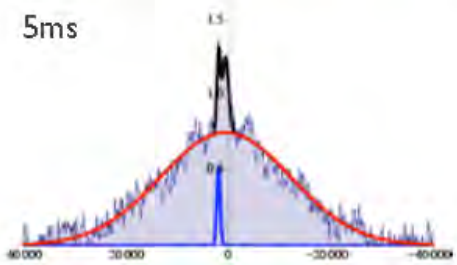
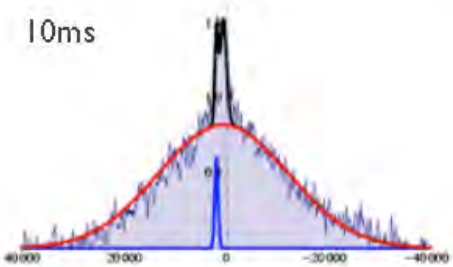


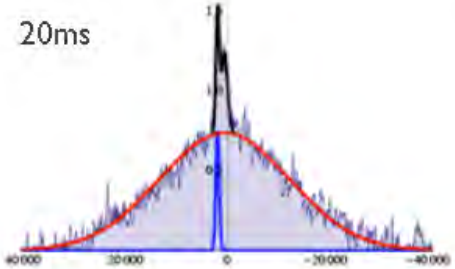


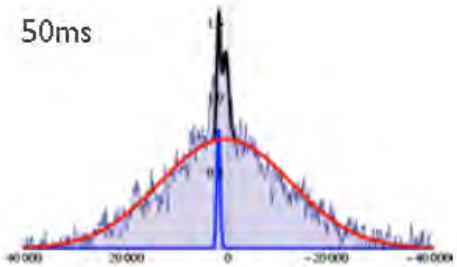


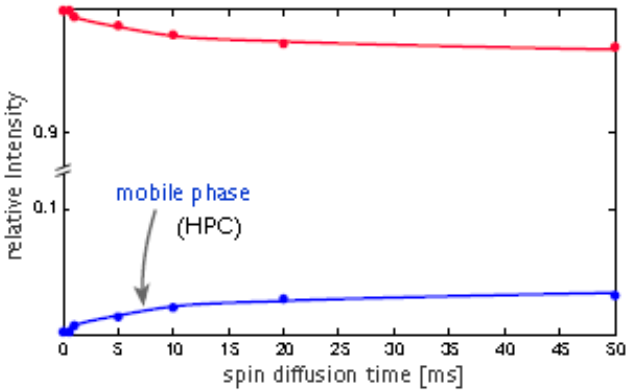












"classical" solid state NMR

Spin Diffusion

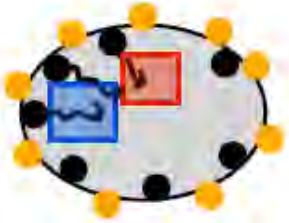
Dynamic Nuclear Polarization

DNP

+ radicals

Paramagnetic Relaxation Enhancement

PRE



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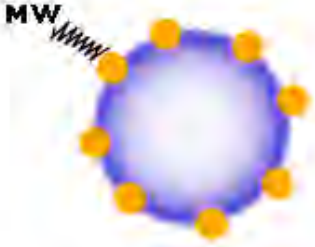
The DNP NMR experiment - particle size measurement:

1. Radicals on surface (+MW) allow us to enhance the polarization on the surface of the sample (and influence the T_1)



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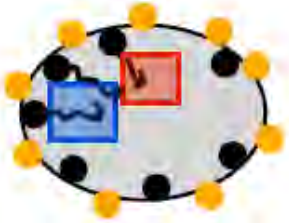
Paramagnetic Relaxation Enhancement

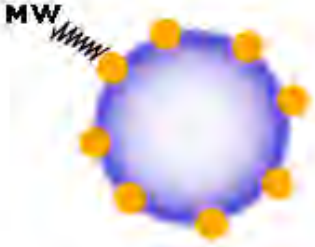
PRE



$$\frac{\partial P(r,t)}{\partial t} = D\,\Delta P(r,t) - \frac{P(r,t) - P_0(r)}{T_1(r)}$$

The DNP NMR experiment - particle size measurement:

1. Radicals on surface (+MW) allow us to enhance the polarization on the surface of the sample (and influence the T_1)



2. NMR experiment to follow transfer of polarization over time

"classical" solid state NMR

Spin Diffusion

Dynamic Nuclear Polarization

DNP

+ radicals

Paramagnetic Relaxation Enhancement

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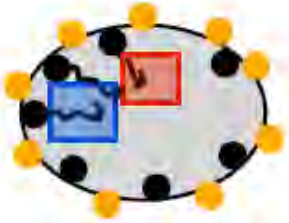

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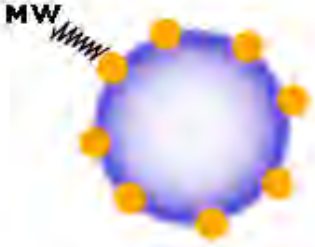

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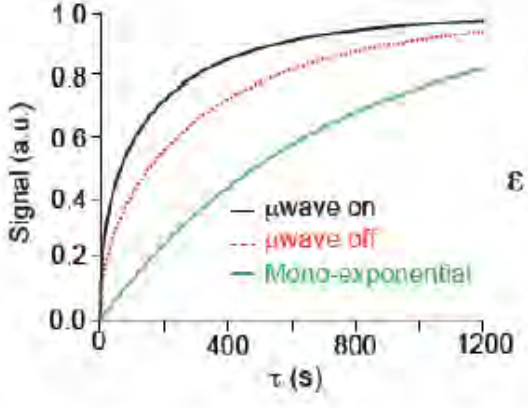

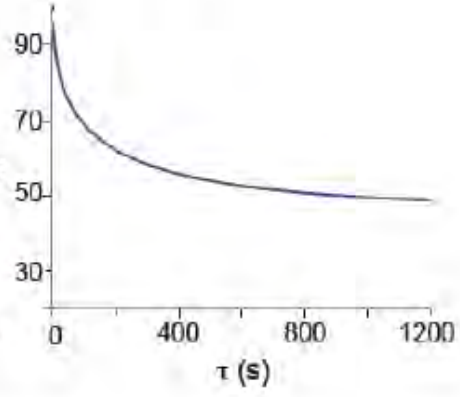

NMR experiment carried out
with the microwave turned on
(DNP, increased polarization on the surface)
and
with the microwave turned off
(no DNP effect)

ratio between intensities of signals on / off
at a certain time τ = Enhancement ε

"classical" solid state NMR

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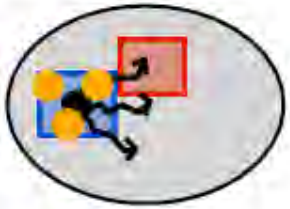

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The PRE NMR experiment:

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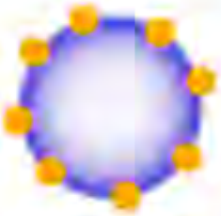

"classical" solid state NMR

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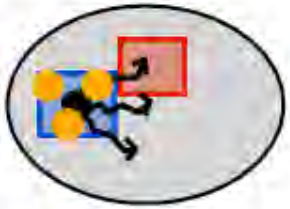

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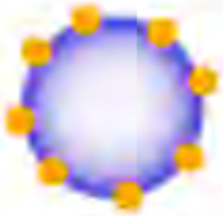

2. acquiring build-up curves to monitor spin diffusion equilibrating introduced imbalance

"classical" solid state NMR

Spin Diffusion

Dynamic Nuclear Polarization

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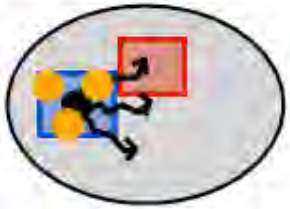

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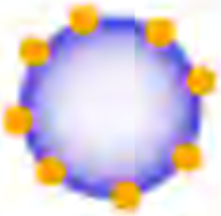

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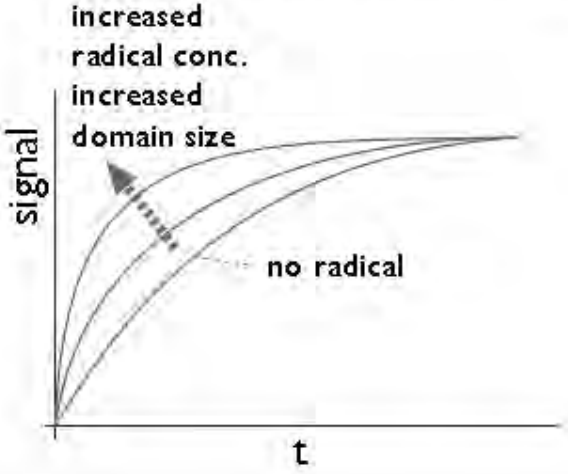
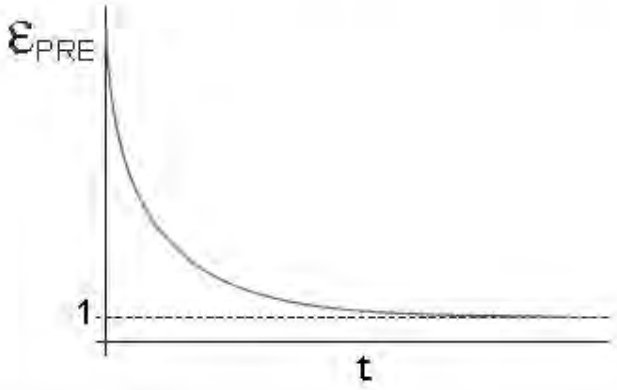


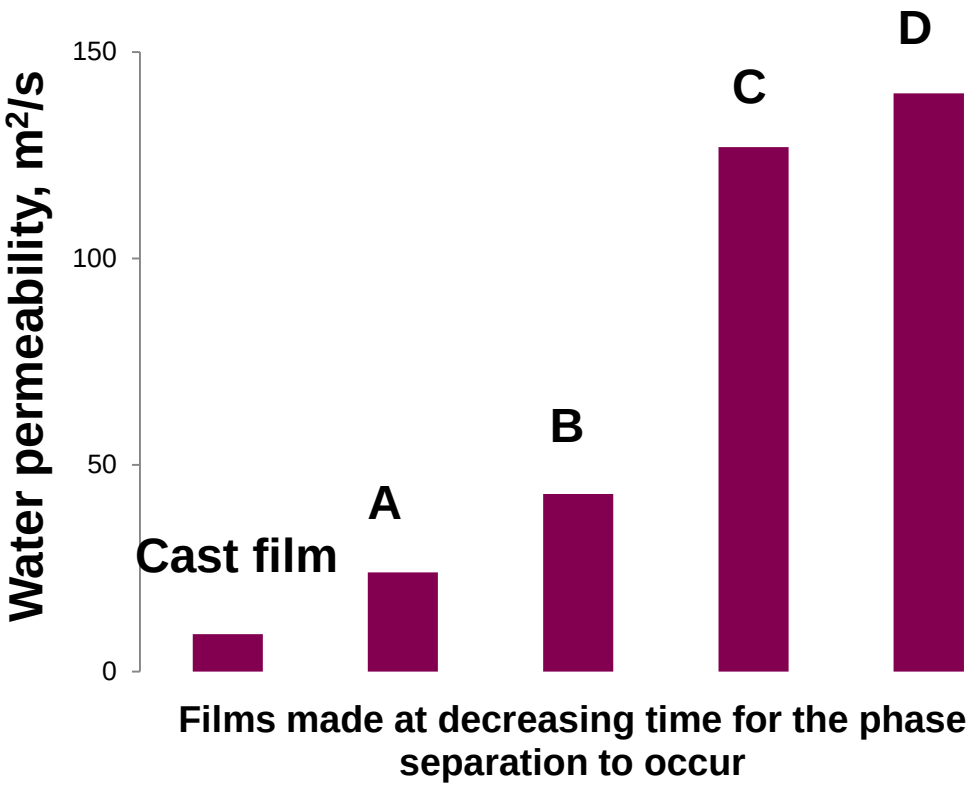


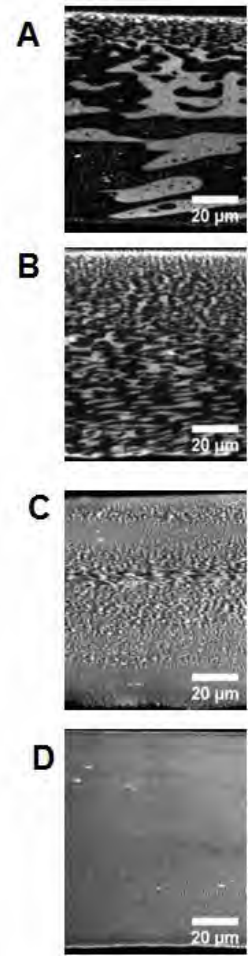
The results are in good agreement with SANS (Marucci et al. 2015).

	CLASSICAL		DNP Method		PRE Method	
	EC/HPC free film	EC/HPC coated p.	EC/HPC free film	EC/HPC coated p.	EC/HPC free film	EC/HPC coated p.
d_{EC}	226 nm	188 nm	200 nm	140 nm	280 nm	120 nm
d_{HPC}	456 nm	380 nm	405 nm	280 nm	570 nm	246 nm

	EC/HPC free film (slow drying)	EC/HPC free film (intermediate drying)	EC/HPC free film (fast drying)	EC/HPC/MCC coated pellets	EC/HPC/API coated pellets
Domain size HPC^c [nm]	294	216	154	156	134
Domain size EC^c [nm]	145	107	76	86	66

Faster film formation kinetics give smaller domains with higher connectivity (Marucci 2013).





Thanks to…

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Dr Aaron Rossini

Dr Sara Richardson

Prof Lyndon Emsley