Water and Protein Folding

http://www.ffn.ub.es/gfranzese

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Christoff Dellago
Hans Hermann
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H. Eugene Stanley*
Kevin Stokely
Elena Strekalova
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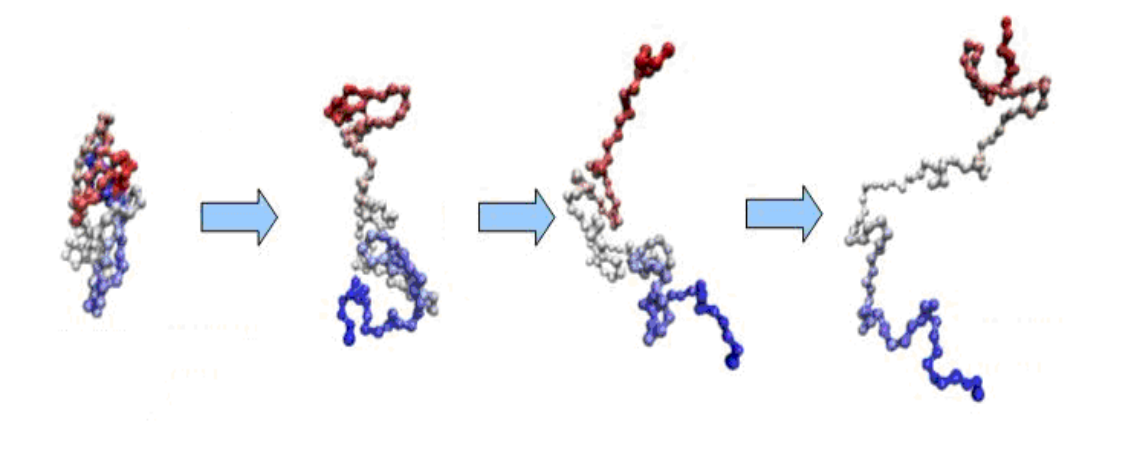
Limei Xu*

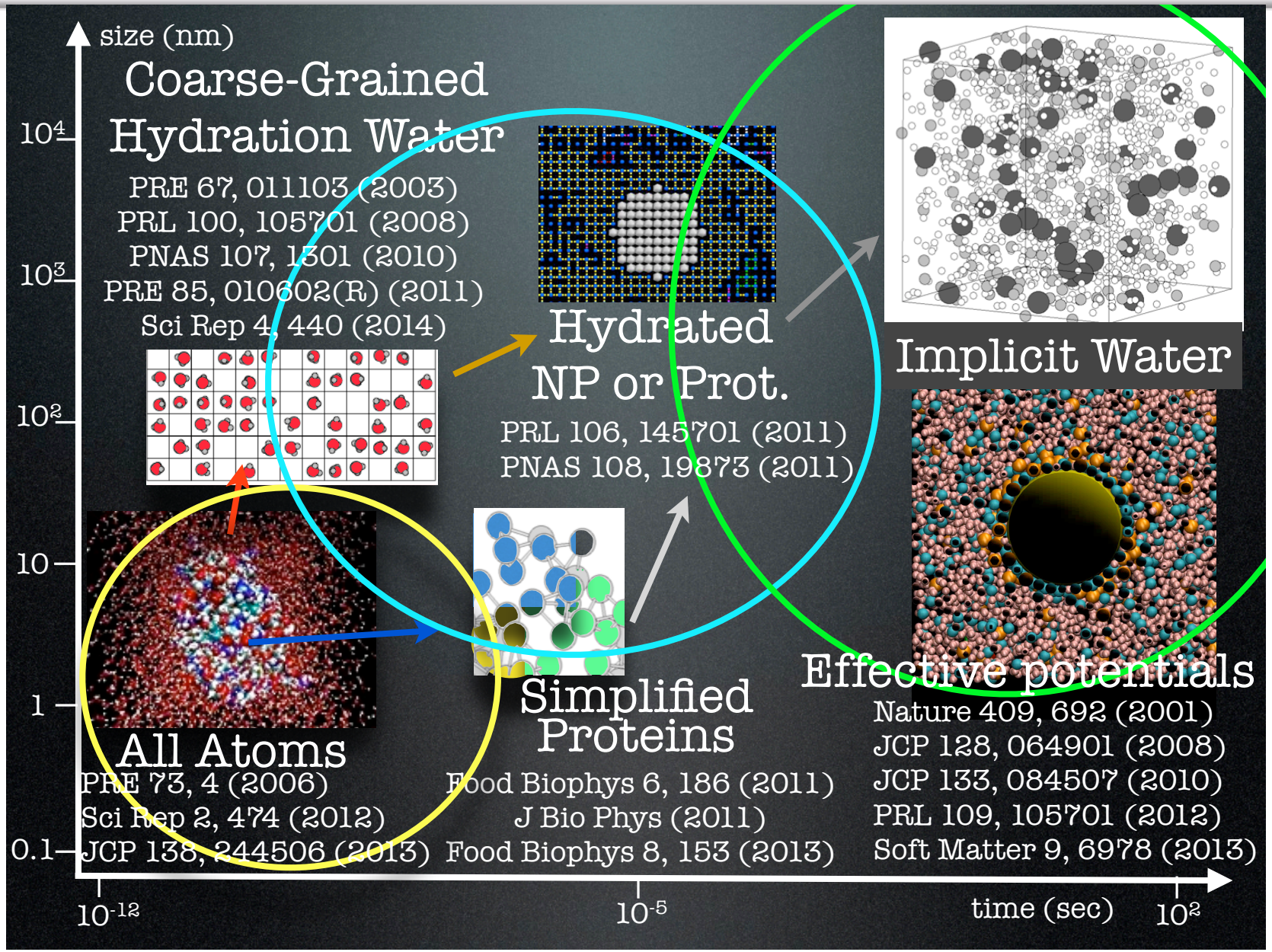
UNIVERSITAT DE BARCELONA

Protein Denaturation



- Stop of the biological function
- Change of optical properties
- Change of solubility
- Diseases (Alzheimer, Parkinson, Huntington, "Mad cow" BSE, Creutzfeldt-Jakob, ... allergies ...)

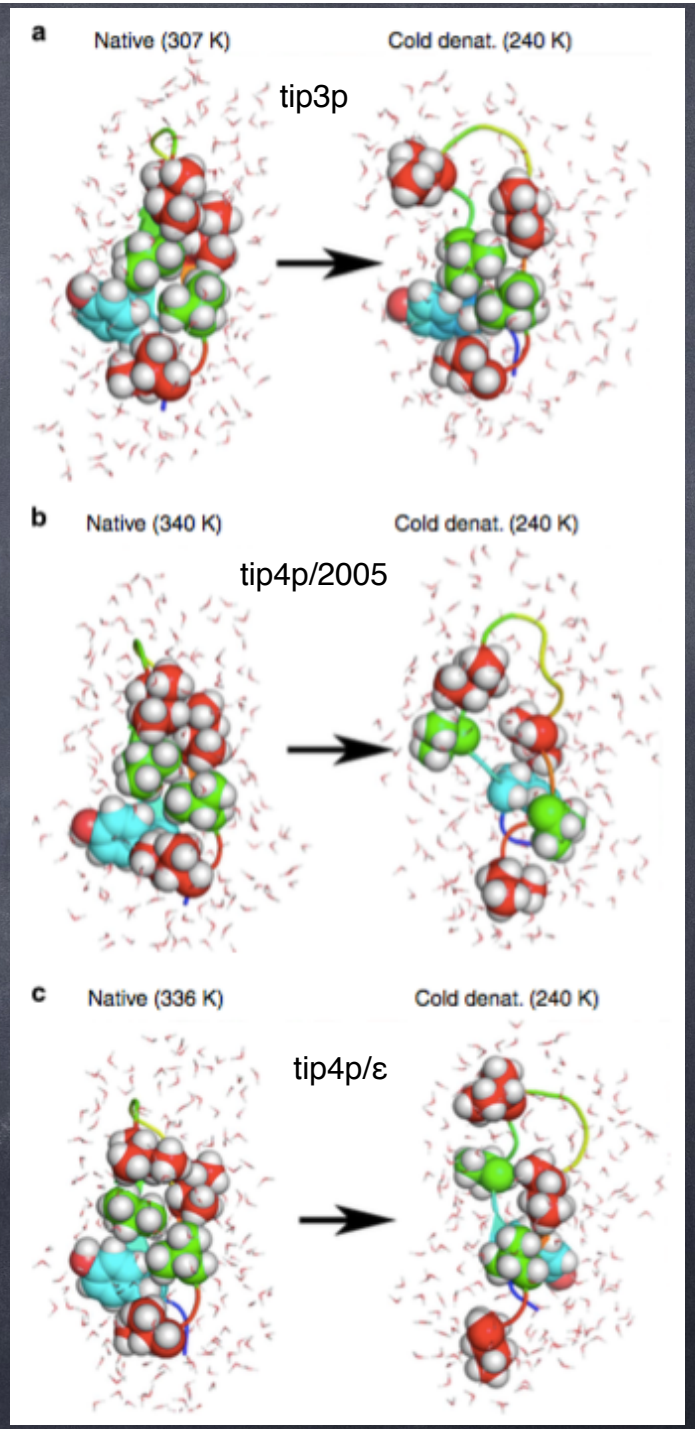
Our approach: Multi-scale modeling



Why multiscale approach?

Fully atomistic: very computationally expensive!

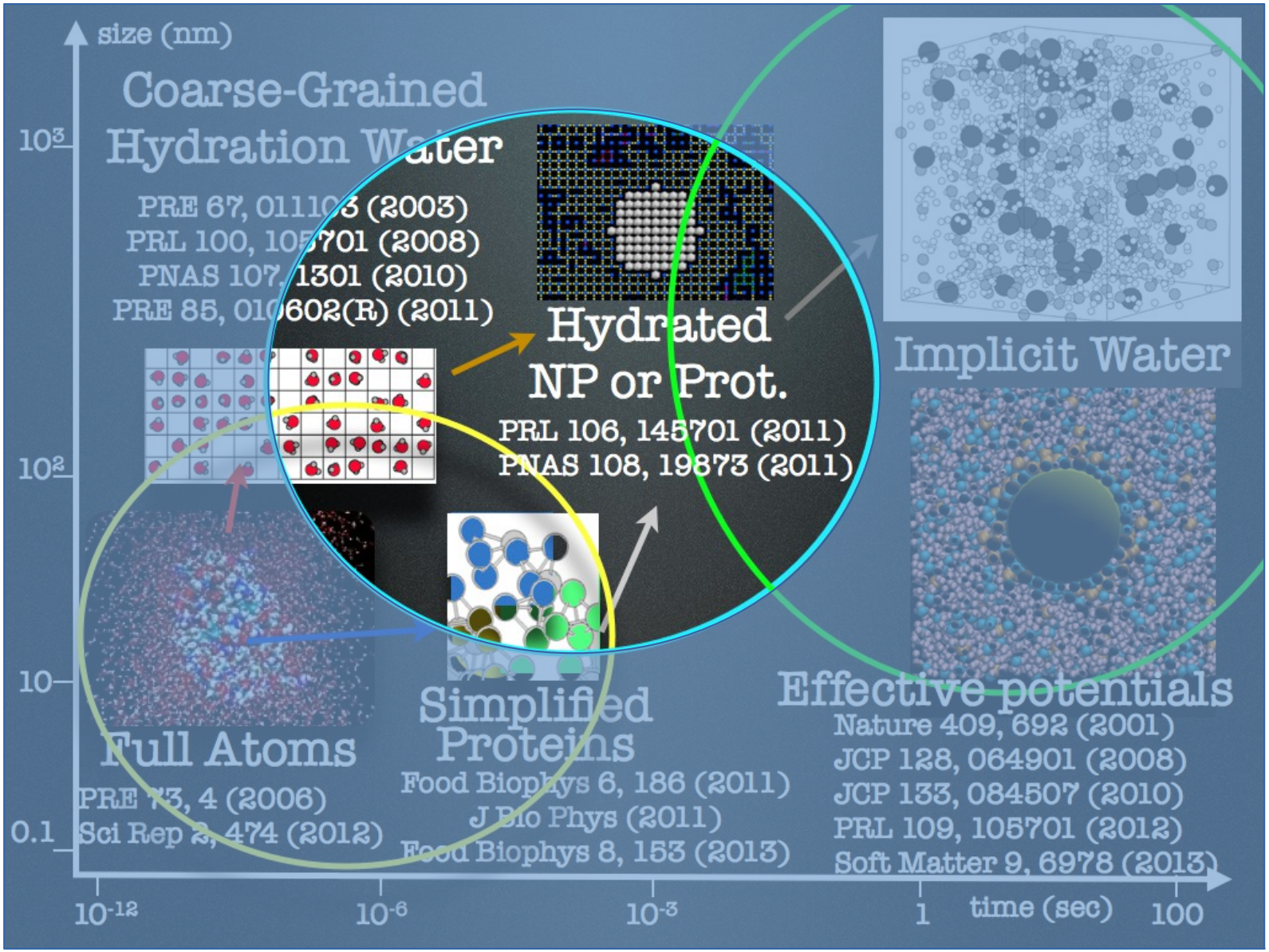
- 2577 water molecules for (only) 16 residues protein (β-hairpin)
- 2μs-long simulations x 70 replicas (140μs)
- results "indicative of possible cold denaturation" ...
- denatured state depends on water model
- ...



Yang, C. et al. Nat. Commun. 5:5773 (2014)

Set up of the stage

Multi-scale approach: Hydrated Proteins & Coarse-grain water



THE NEED OF A COOPERATIVE MANY-BODY MODEL

Nature Vol. 282 29 November 1979 459

Cooperative effects in simulated water

P. Barnes, J. L. Finney, J. D. Nicholas & J. E. Quinn
Department of Crystallography, Birkbeck College, University of London, Malet Street, London WC1, UK

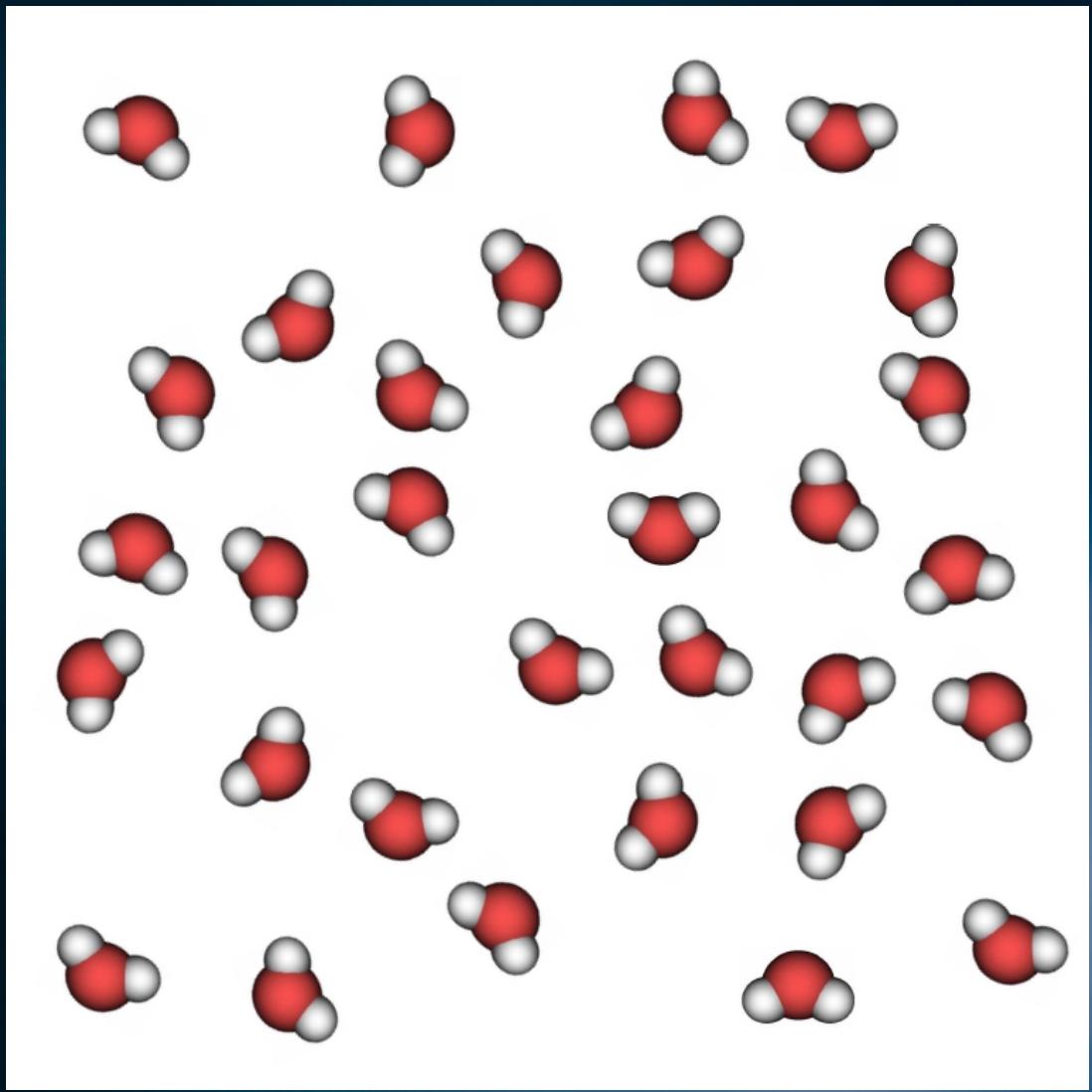
Computer simulation calculations on liquid water, aqueous solutions and biological interfaces have been made almost universally assuming pair-additive interactions. Experimental and theoretical evidence implies this is a serious oversimplification. The development and testing of a different approach is reviewed in which many-body forces are specifically taken into account through molecular

e.g., quantum calculations show that hydrogen bonds (HB) energy in trimers and tetramers is 20-30% stronger than in dimers

Conclusions

It is necessary to abandon the use of pair potentials for aqueous systems. Although a parametrised effective pair potential

Many-body model for water



Franzese, Marqués, Stanley PRE (2003)

Kumar, Franzese, Stanley, PRL (2008)

Strekalova, Mazza, Stanley, Franzese PRL (2011)

Mazza, Stokely, Pagnotta, Bruni, Stanley, Franzese PNAS (2012)

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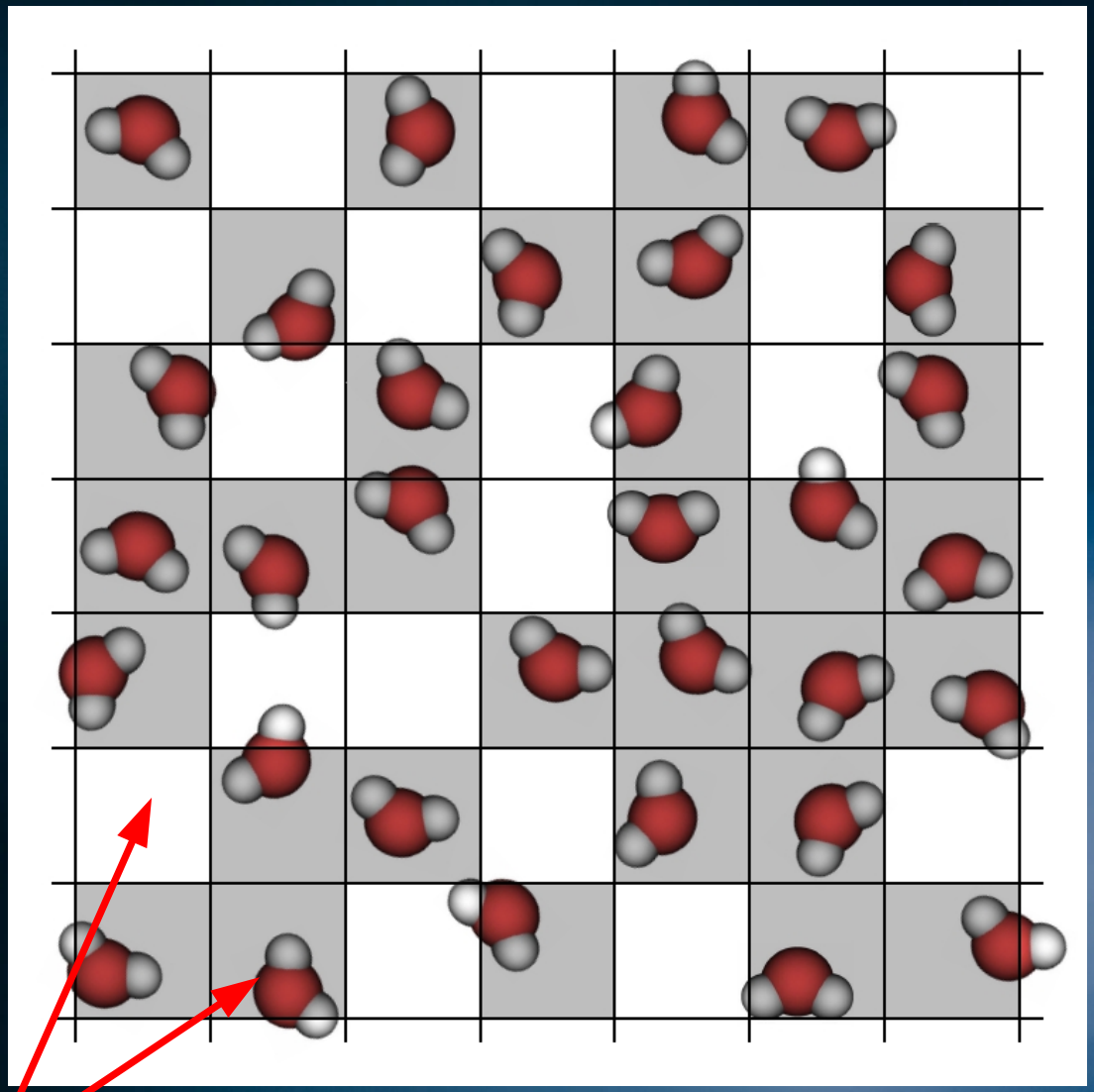

We introduce a density field *n(x,y)*

Franzese, Marqués, Stanley PRE (2003)

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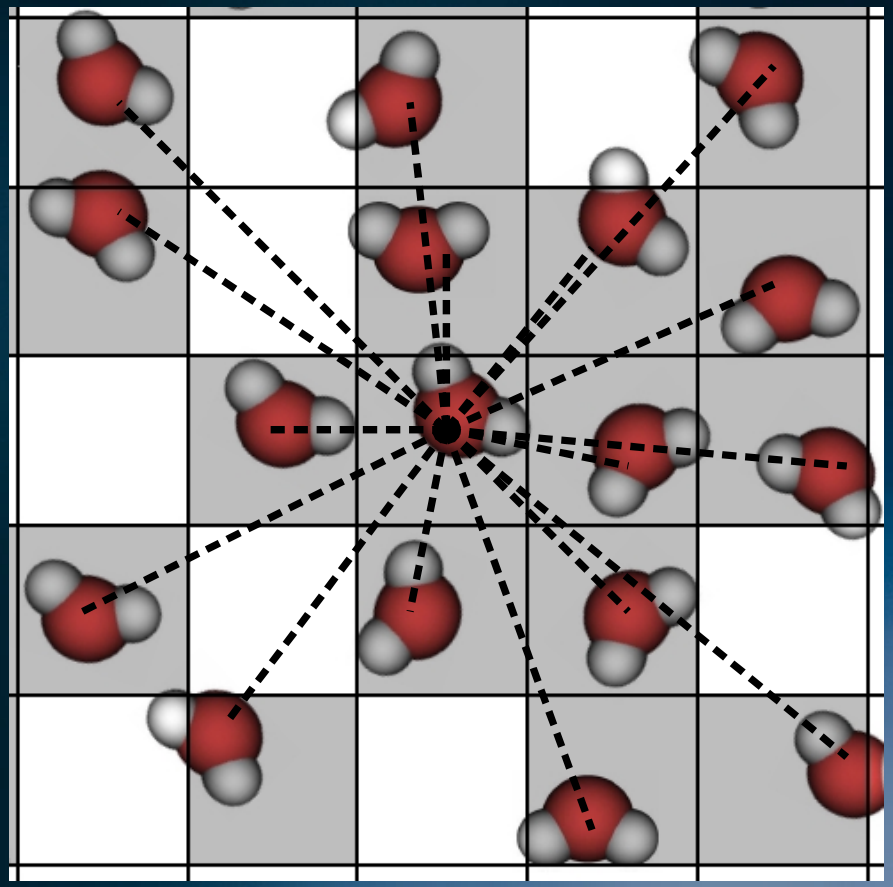
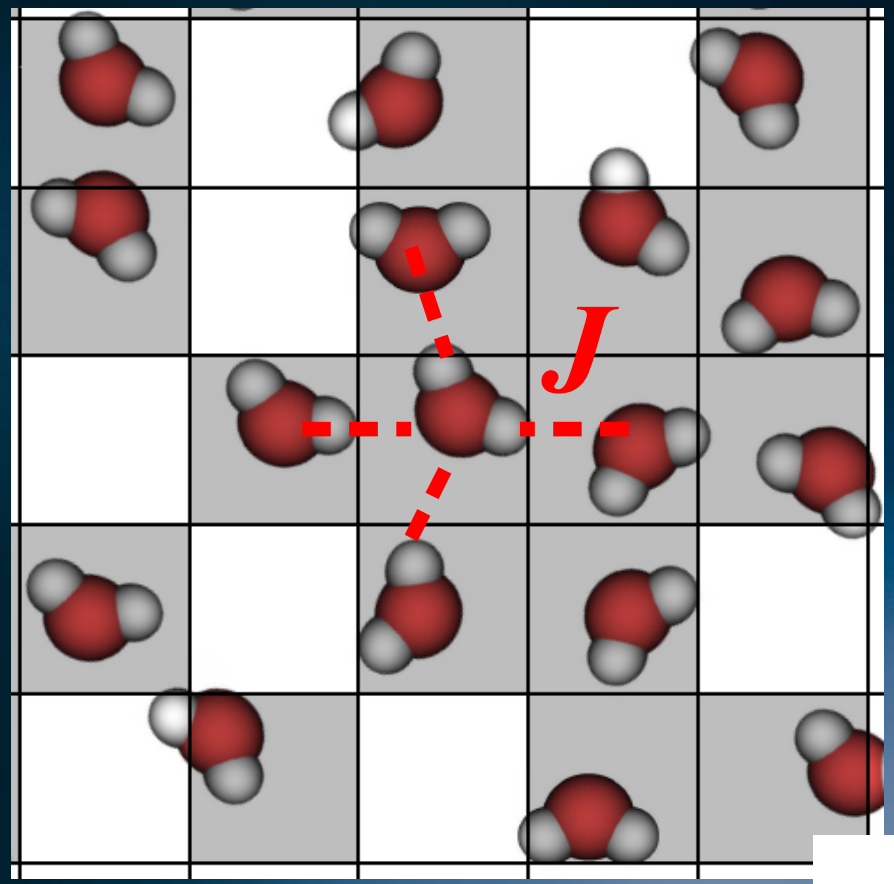


vdW interaction

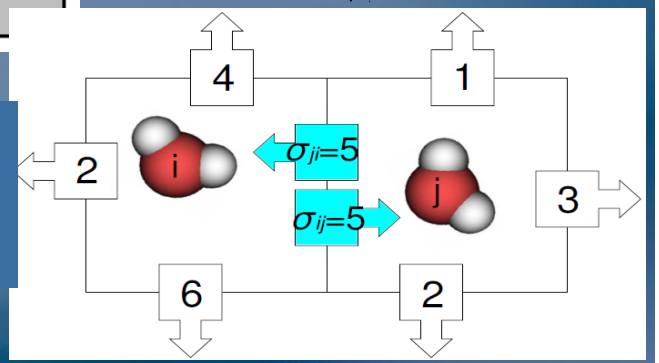
$$E = U(r)$$

Many-body model for water

Directional and covalent component of the hydrogen bond



The state of a water molecule is described introducing 4 bonding variables



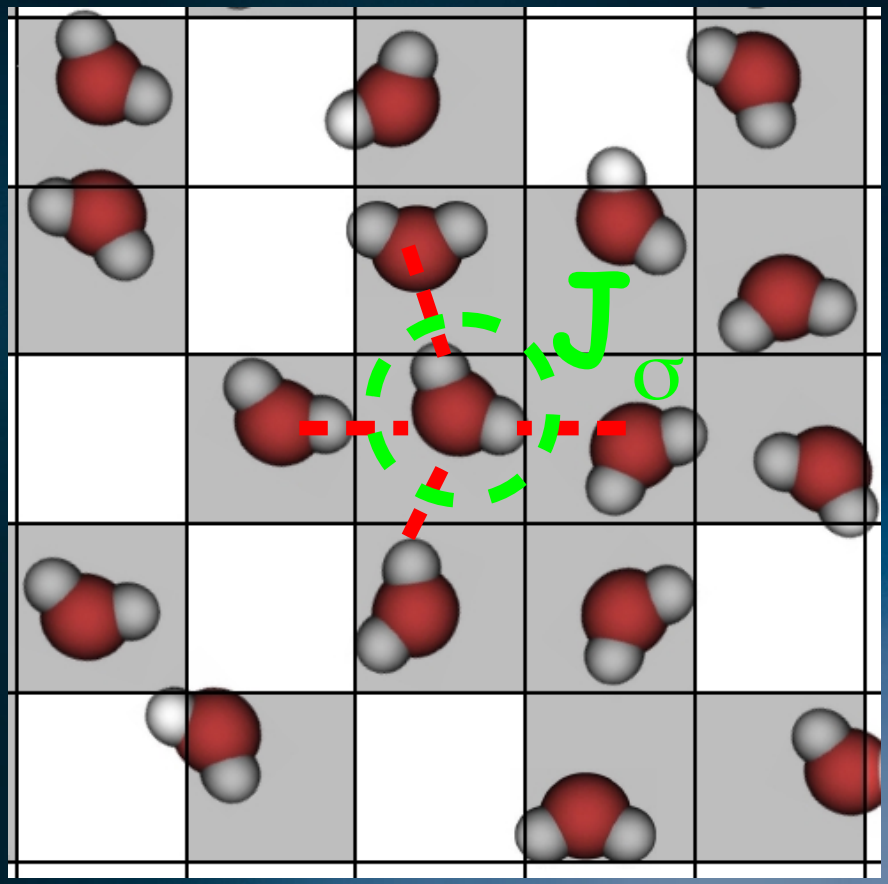
$$E = U(r) - J\,N_{HB}$$

cfr. Sastry et al. PRE (1996)

Many-body model for water

1st shell (five-body) interaction

Coopertivity (Quantum effect)

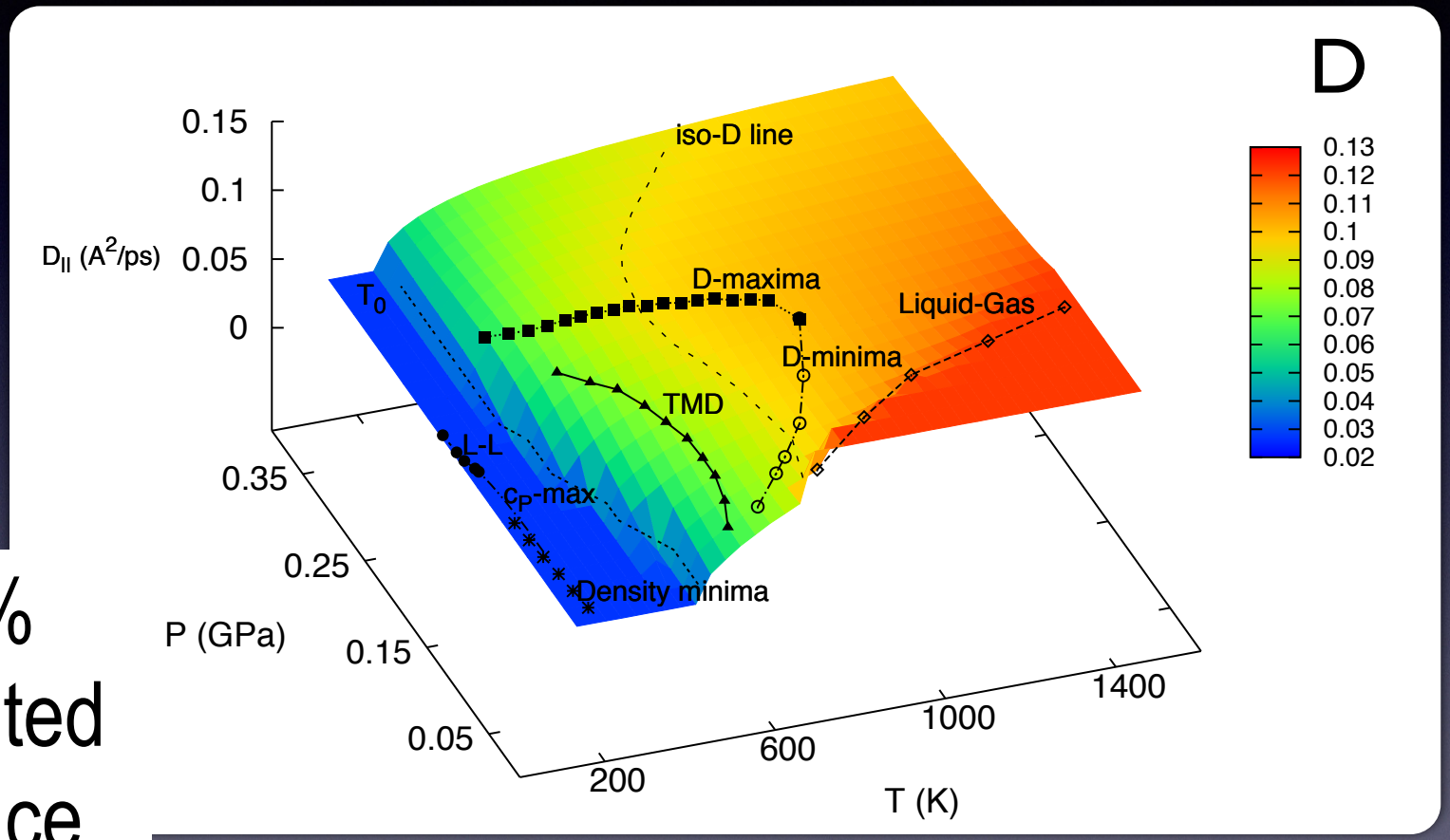


$$E = U(r) - J\,N_{HB} - J_{\sigma}\,N_{\sigma}$$

$$V = N v_0 + N_{HB}\,v_{HB}$$

The phase diagram of the Many-Body water model

Phase diagram and Anomalies of a hydration monolayer



75% hydrated surface

F. de los Santos & G. Franzese J. Phys. Chem B 115, 14311 (2011)
G. Franzese, et al. JPCM 14, 2201 (2002); PRE 67, 011103 (2003);
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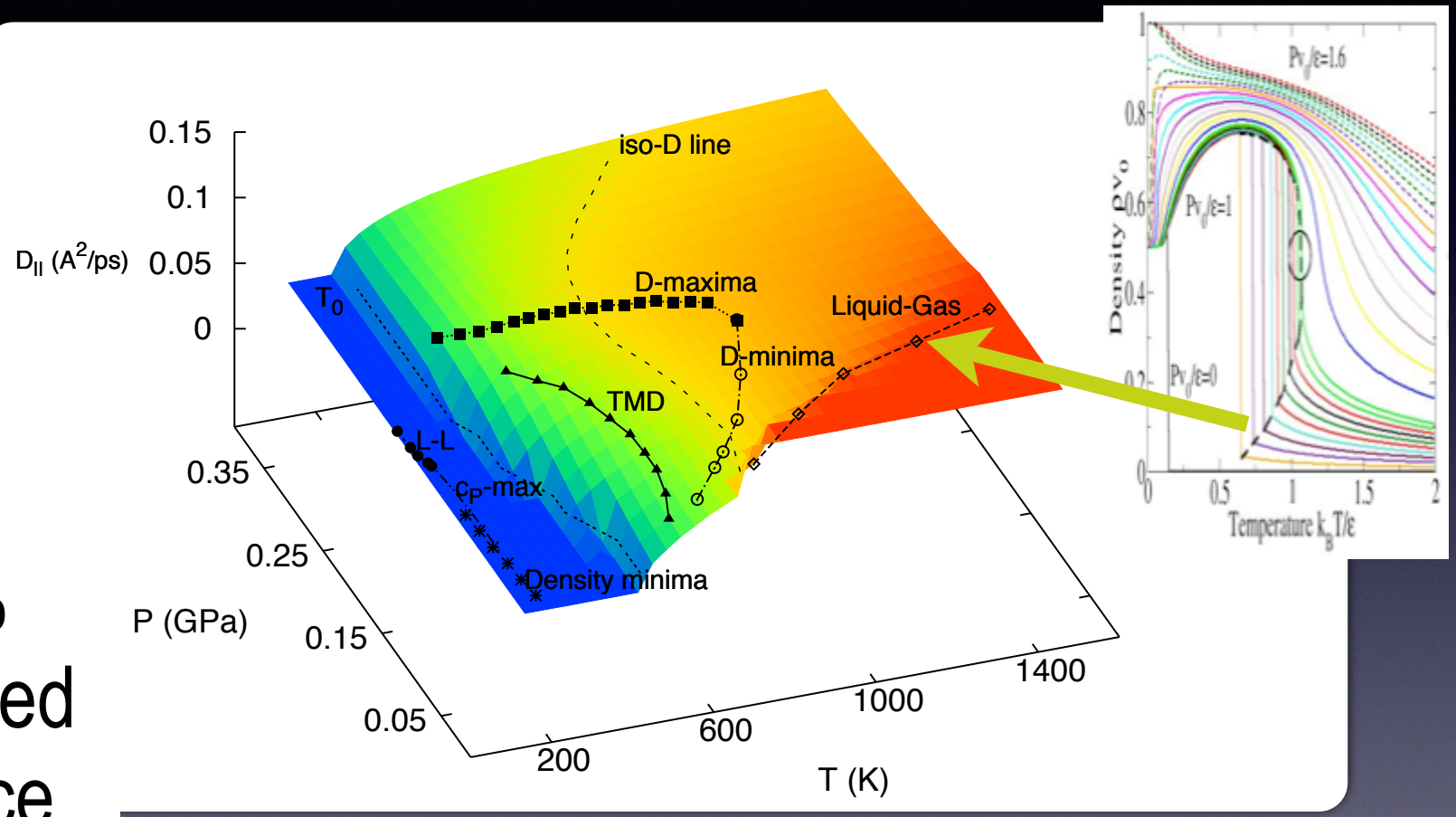

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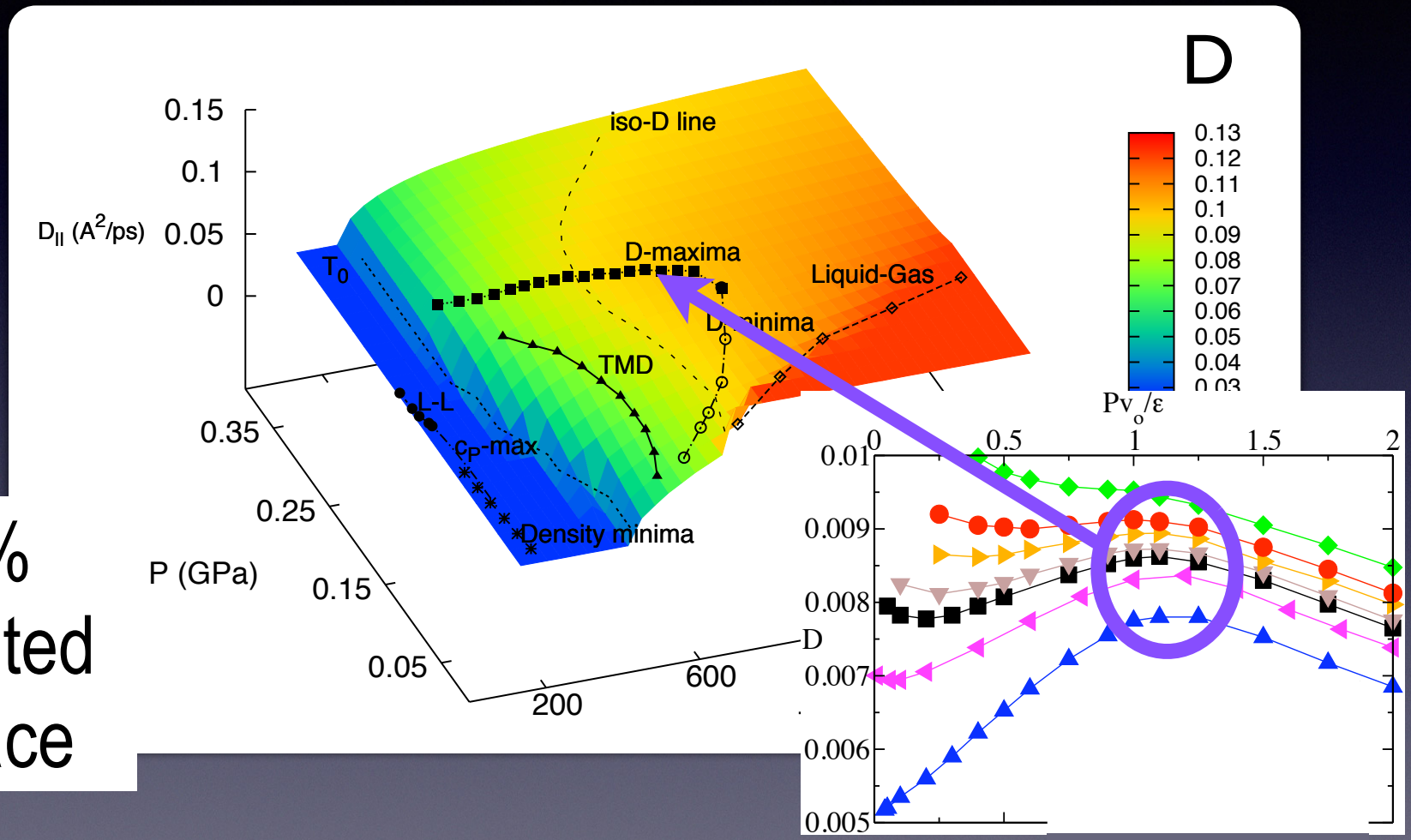

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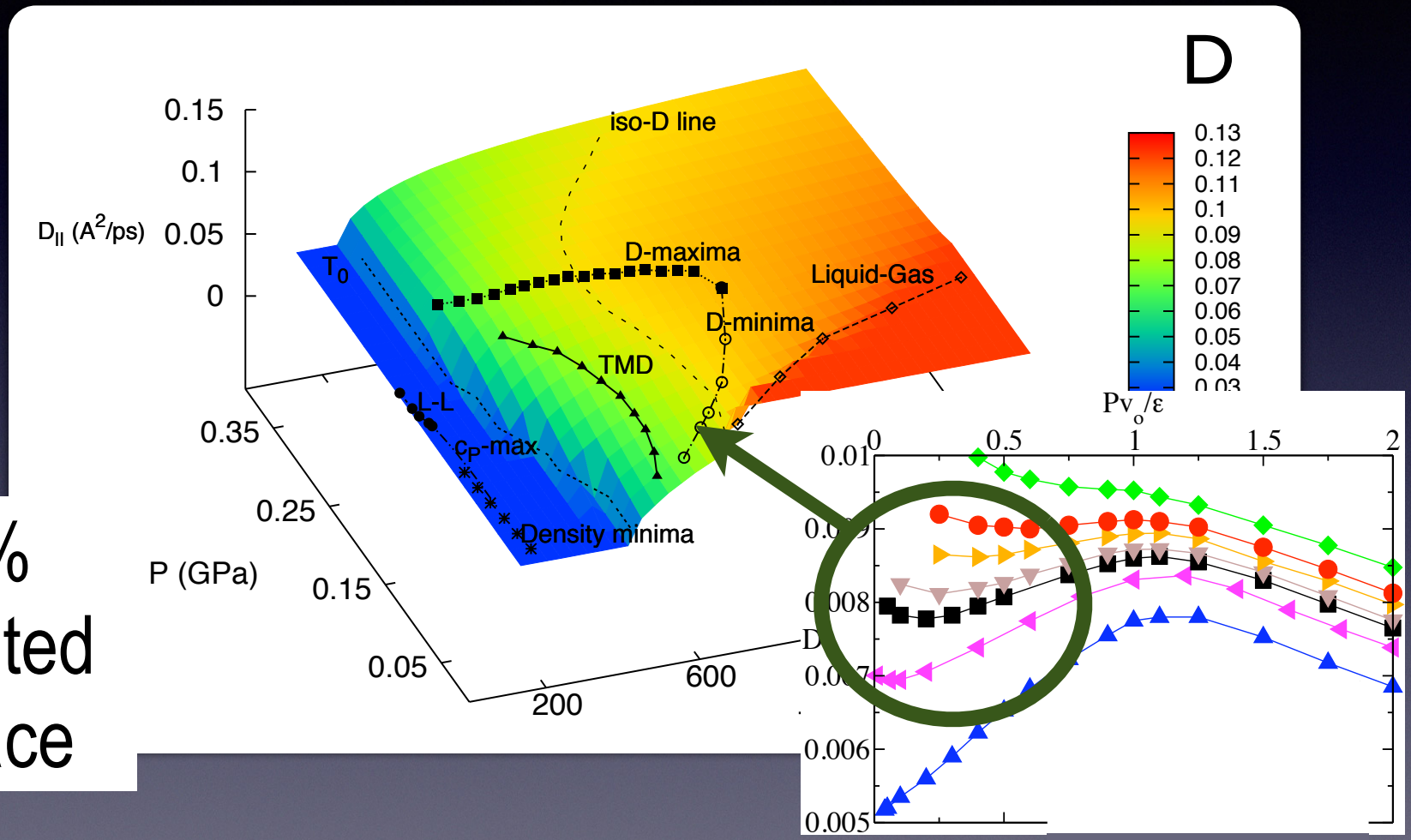

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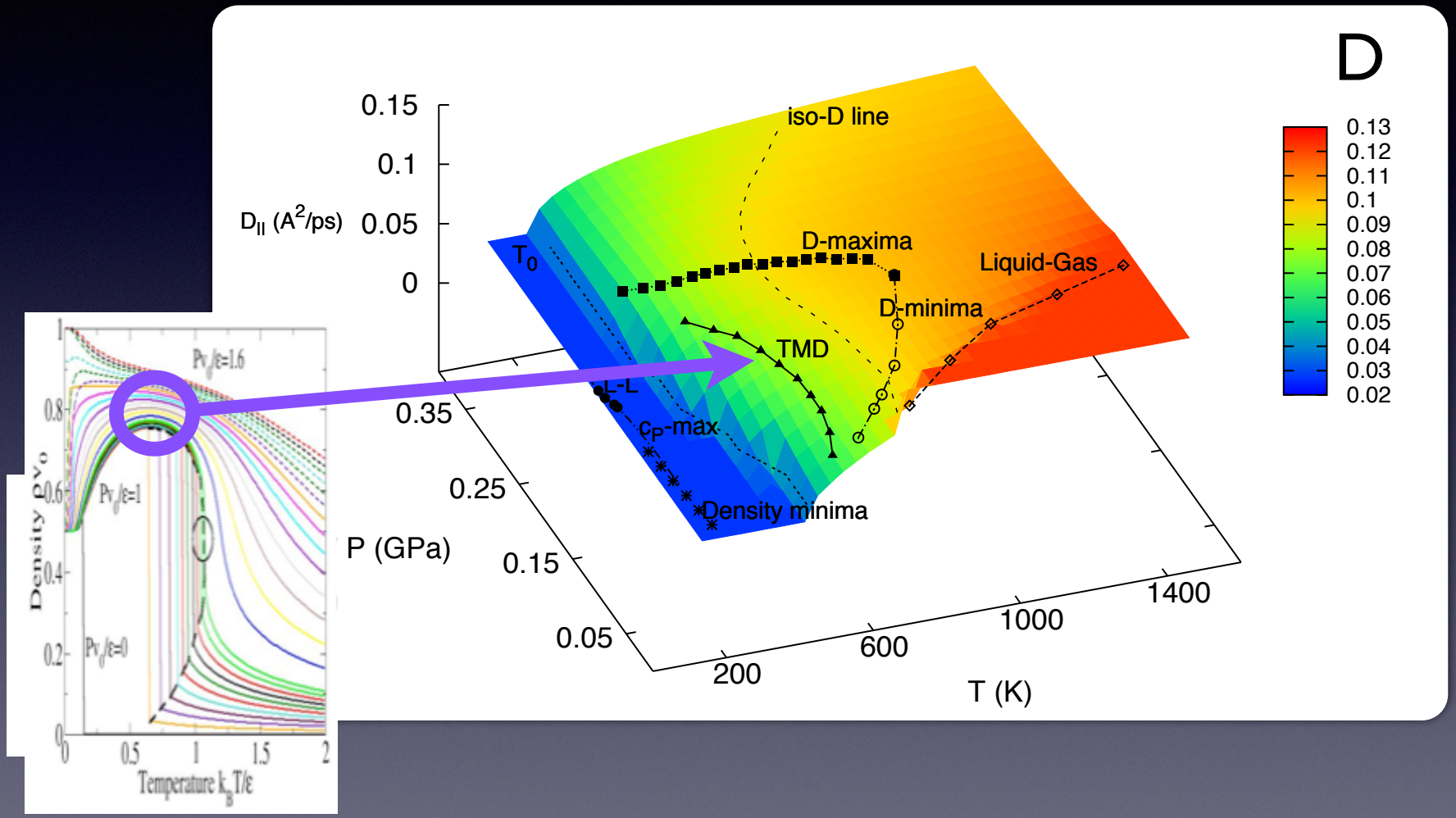

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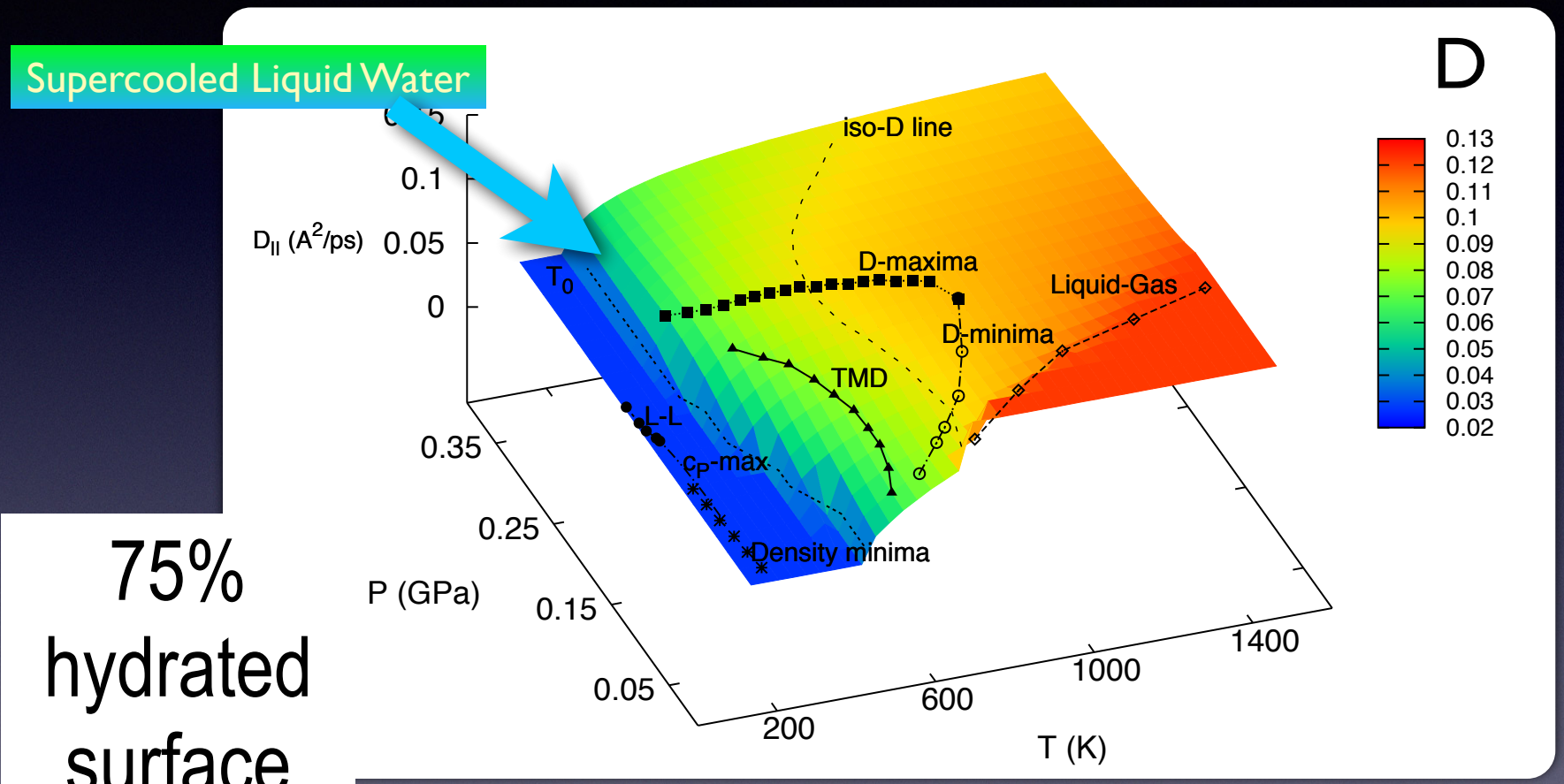

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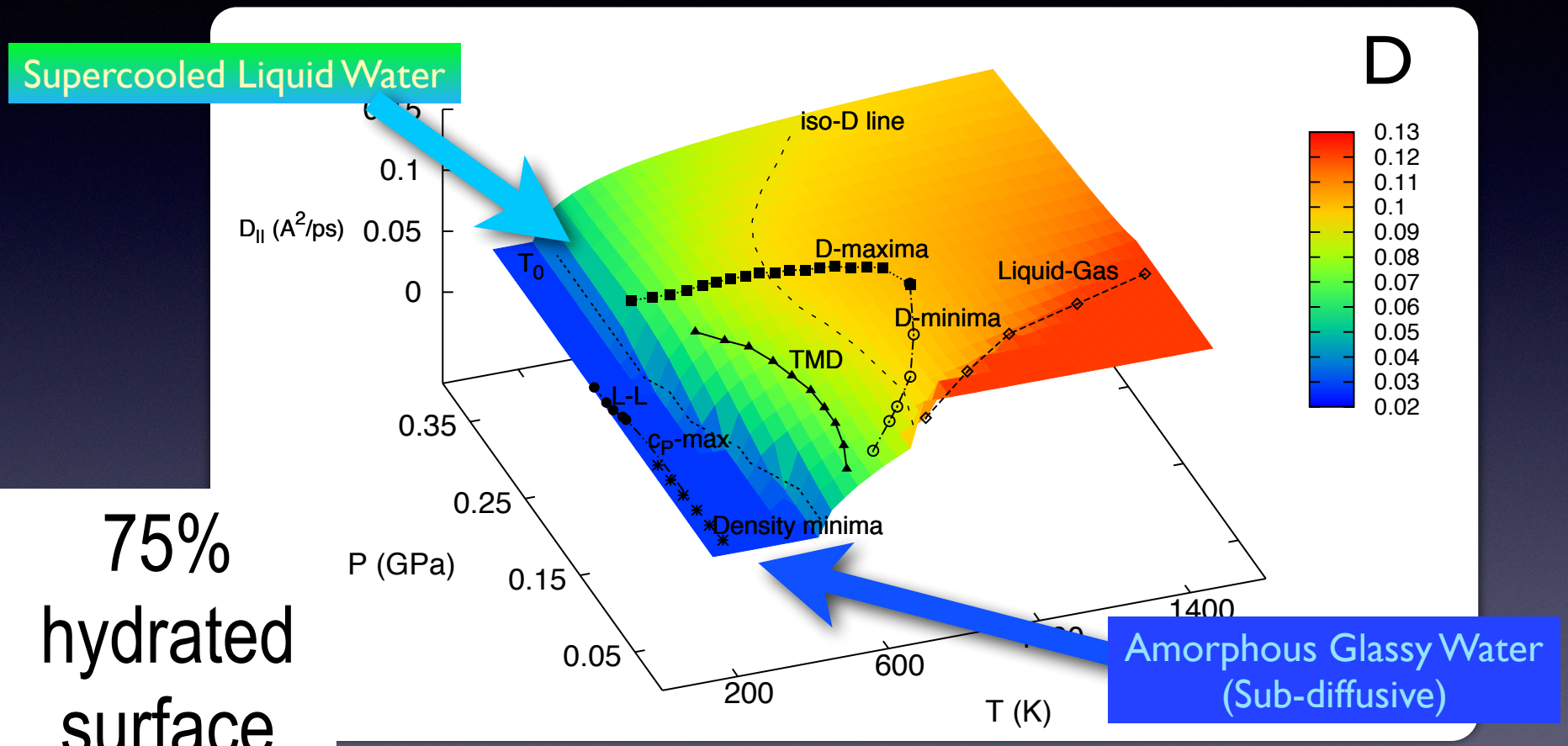

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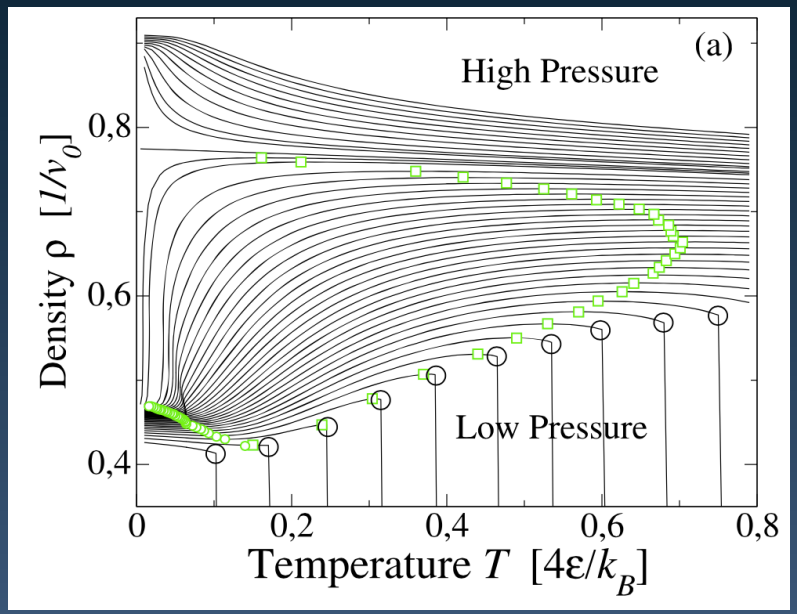
Exploring the Phase Diagram



Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).

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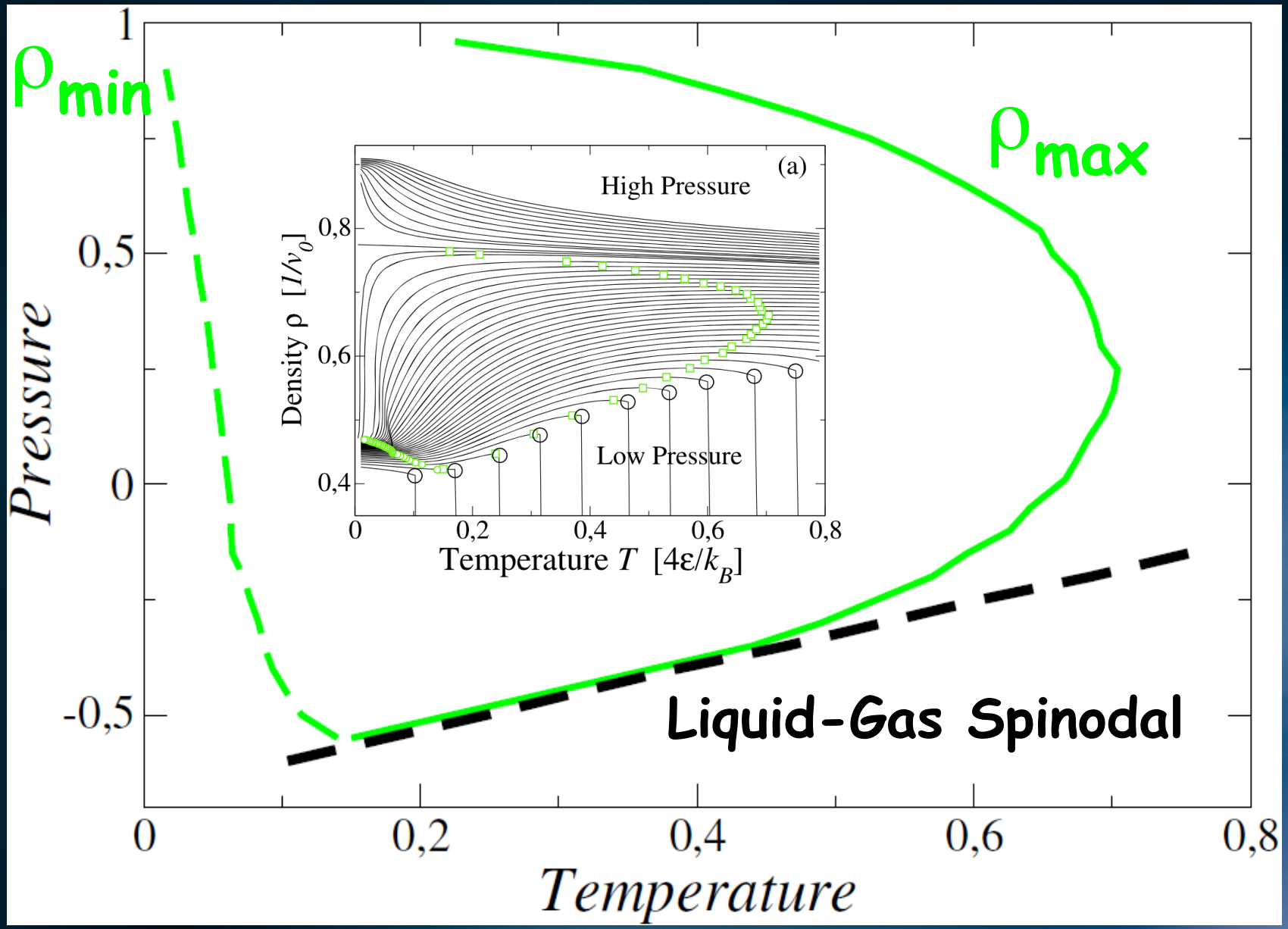
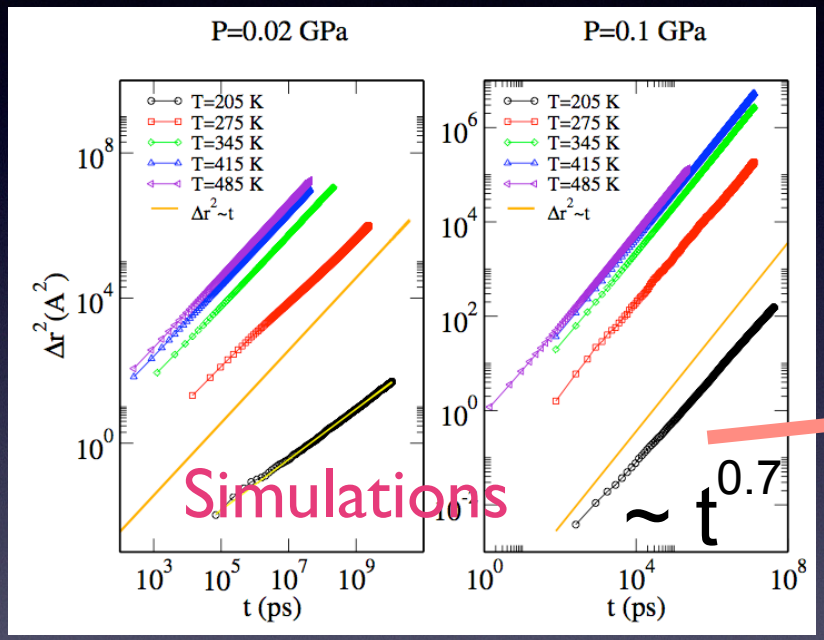
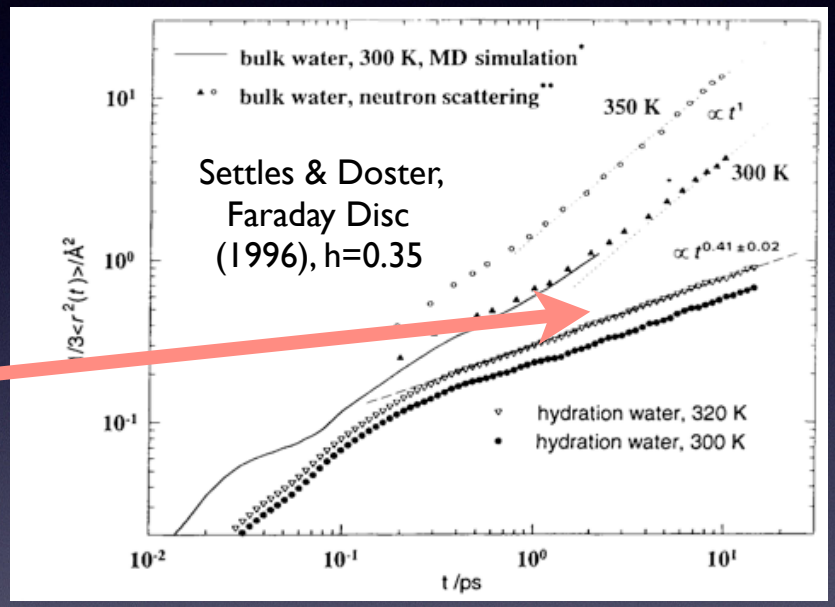


Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).

Sub-diffusion and Glassy dynamics

Comparison with experiments for hydrated Myoglobin at low hydration (h=0.35): Subdiffusion at 320K and below





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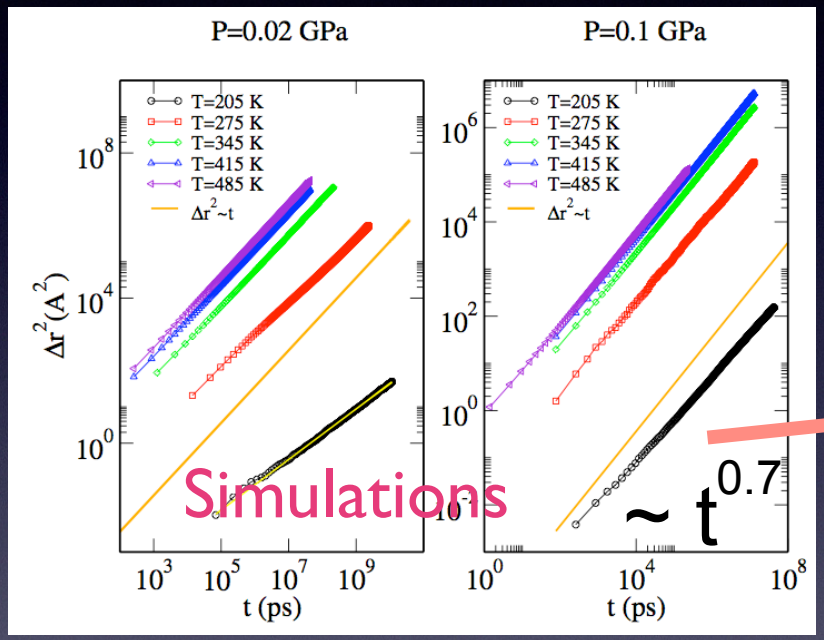
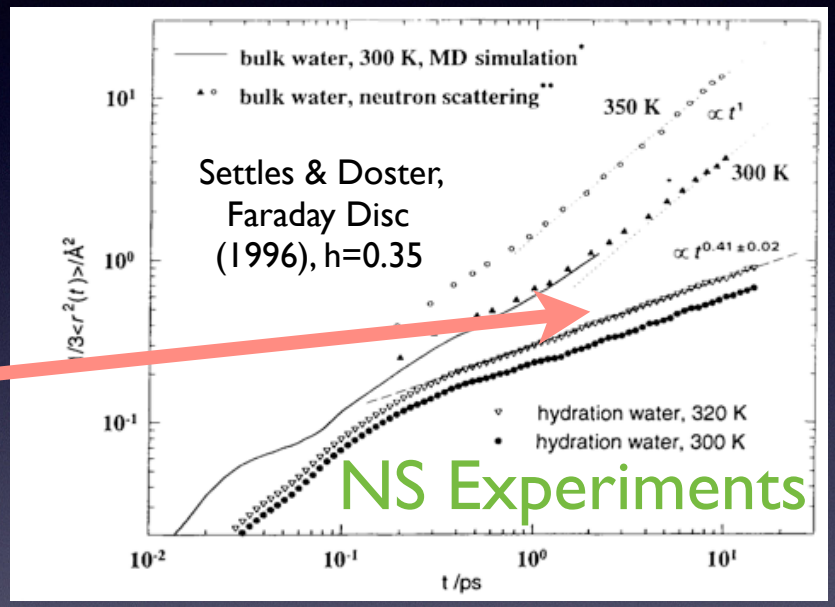




Result: Subdiffusion is not a consequence of heterogeneity in water-surface interaction,
but results from increasing H-bonds correlation

F. de los Santos & G. F., J.Phys. Chem B 115, 14311 (2011)

Glassy Dynamics at low T (< TminD < TMD)

G.Franzese and F. de los Santos J. Phys. Cond Mat. 21, 504107 (2009)

$P = 1\epsilon/v_0$

>P(C)

$T = 0.05\epsilon/k_B$

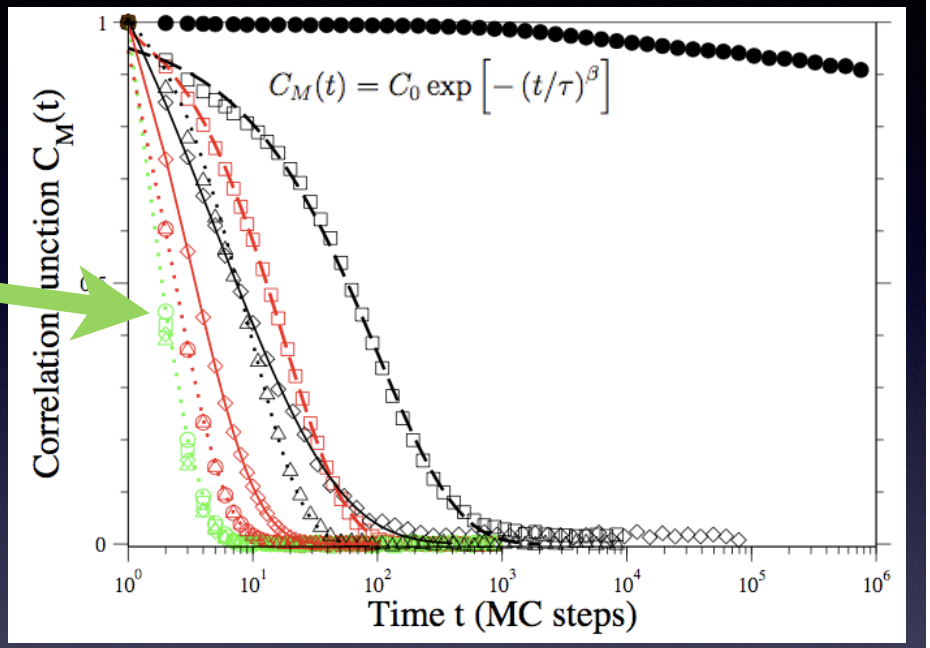
<T(C)

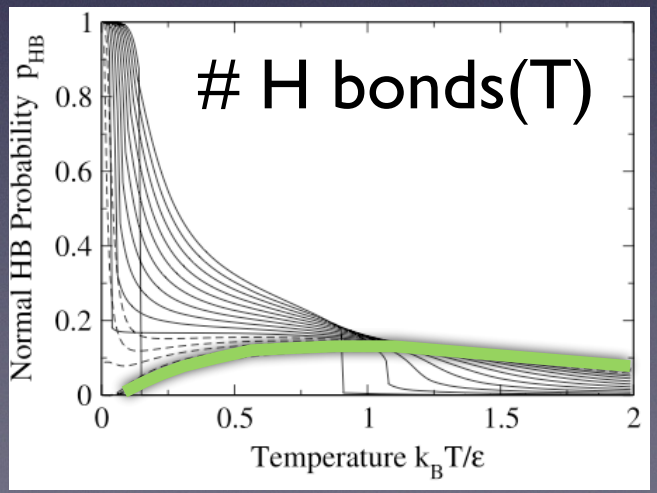
$T = 0.1\epsilon/k_B$,

>T(C)

$T = 0.4\epsilon/k_B$

≈T(MD)





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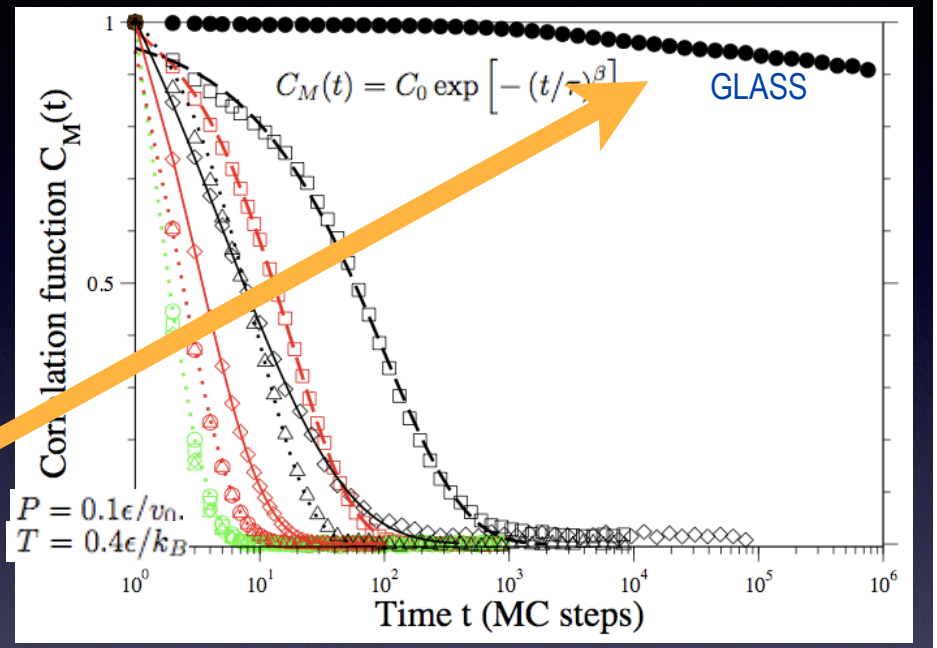

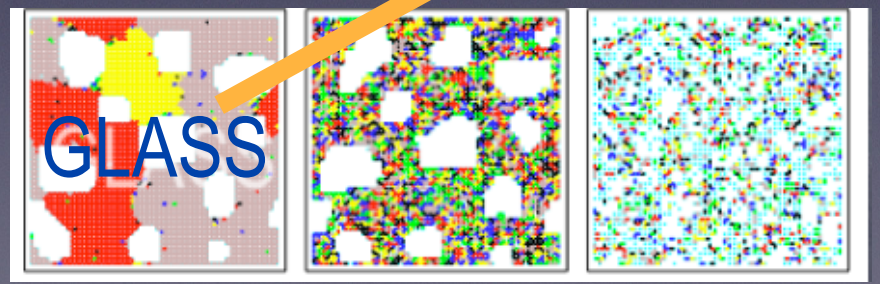

$P = 0.1\epsilon/v_0$,

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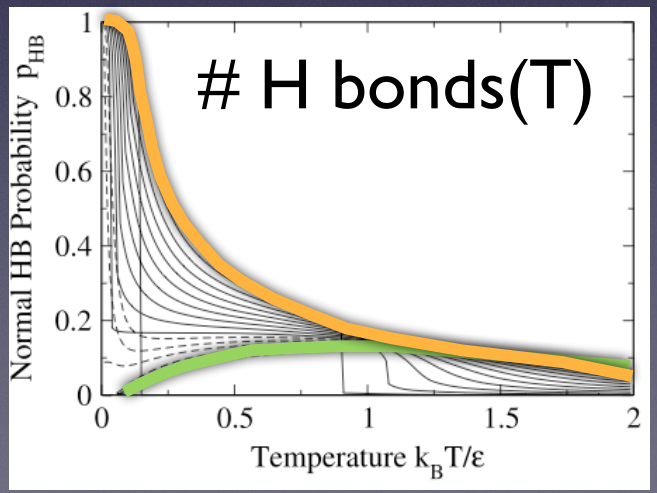

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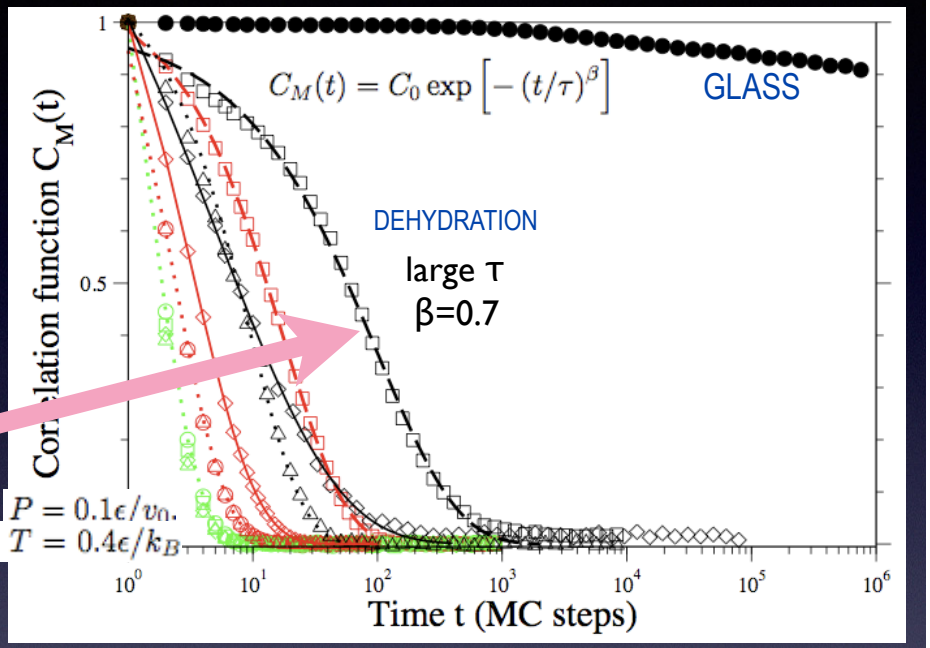

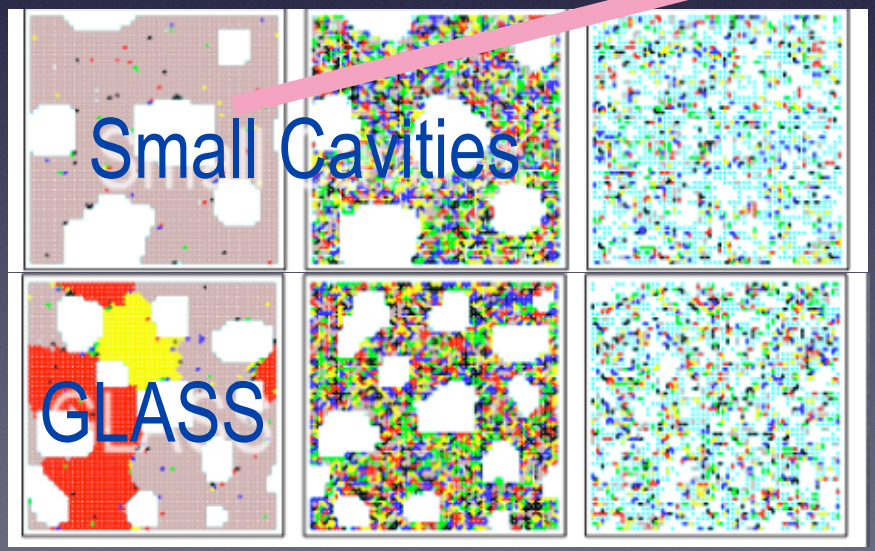

$P = 0.4\epsilon/v_0$

<P(C)

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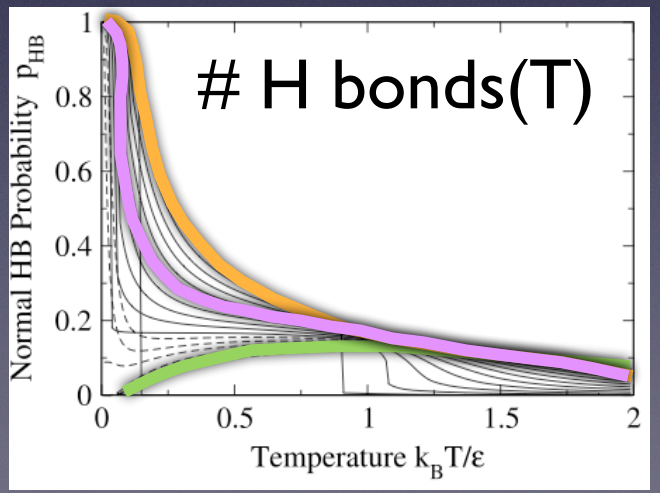

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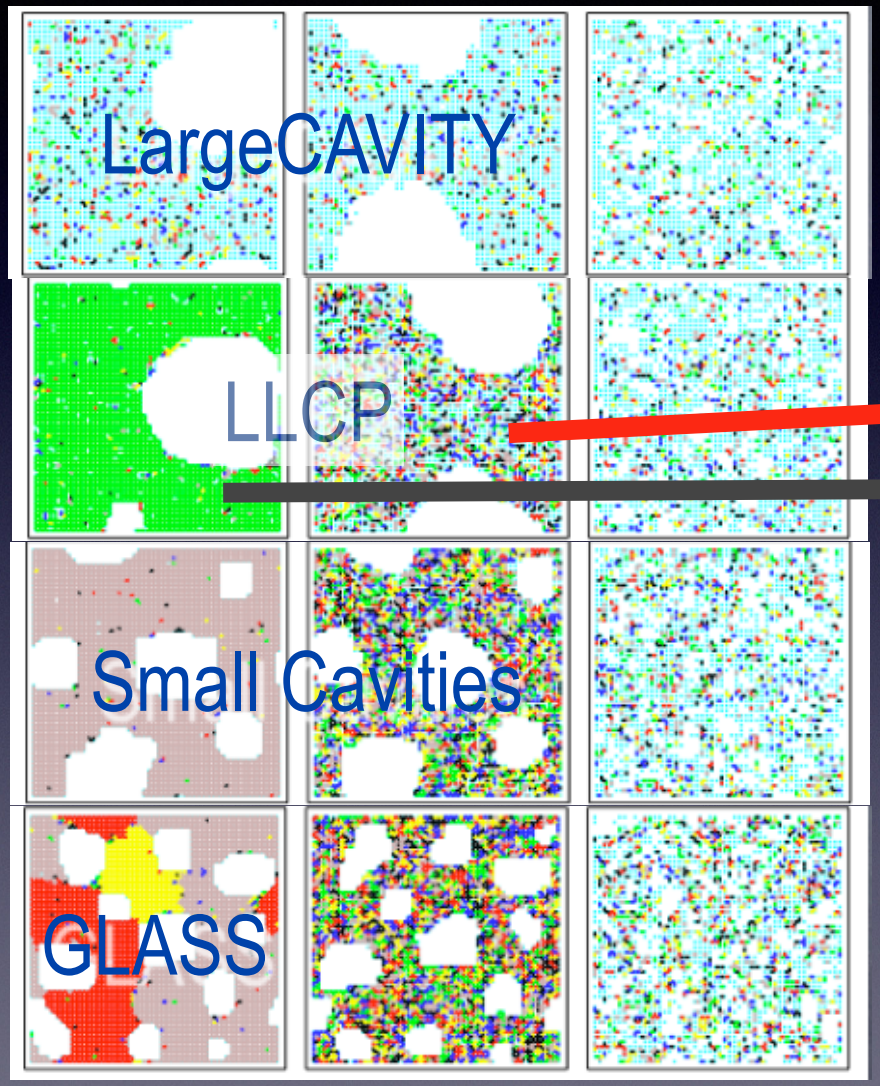
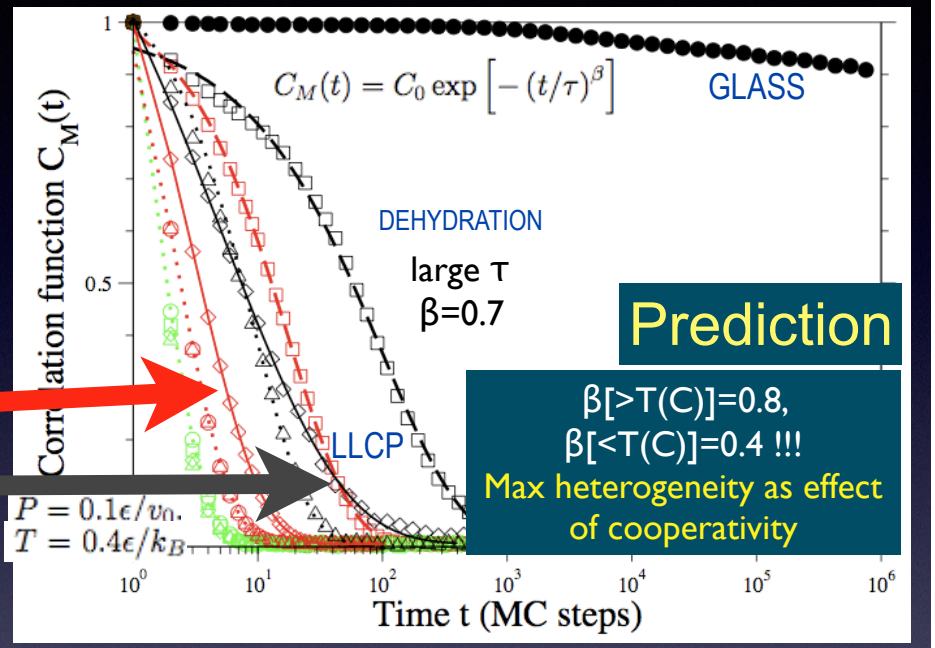
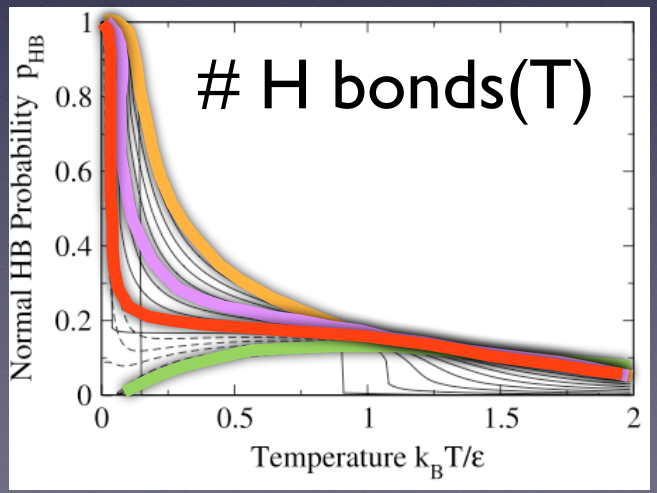
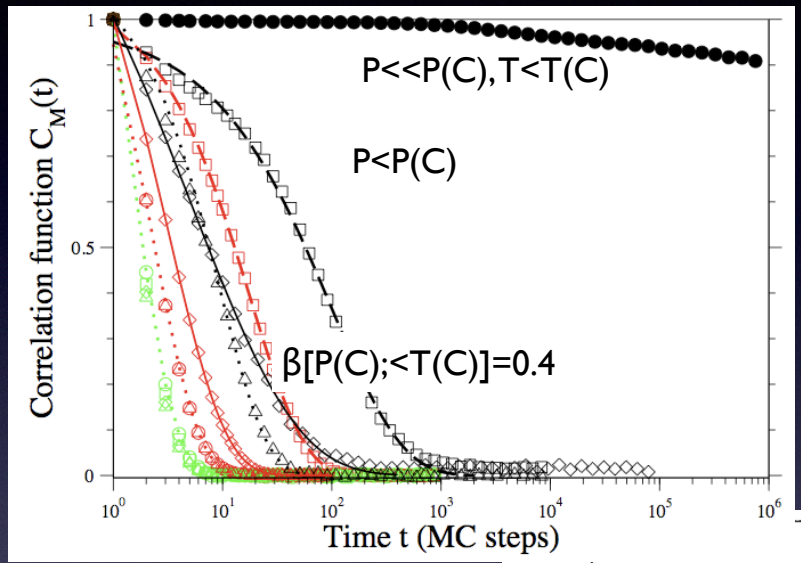
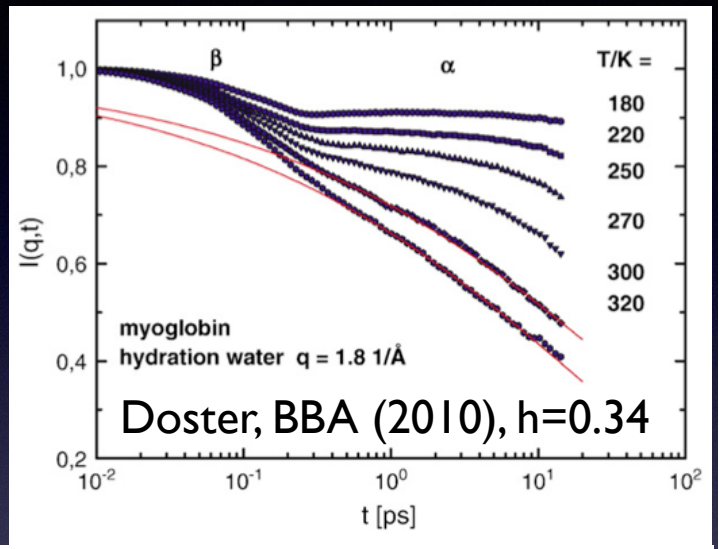






Comparison with experiments: Myoglobin at low hydration (h=0.35):





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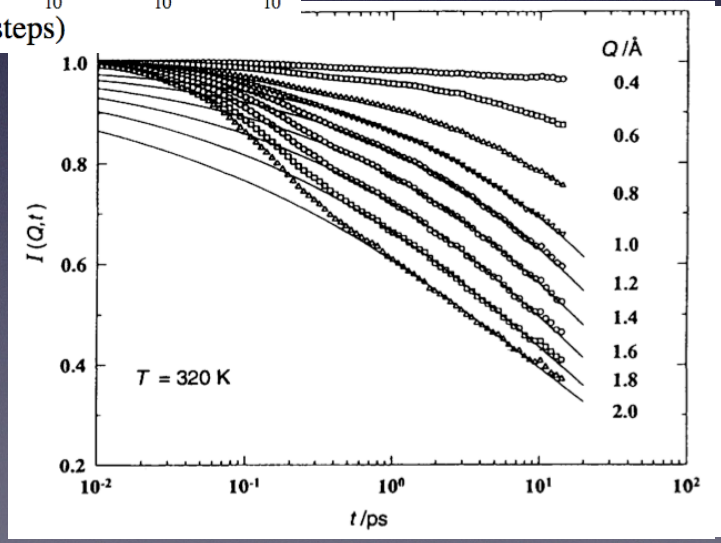

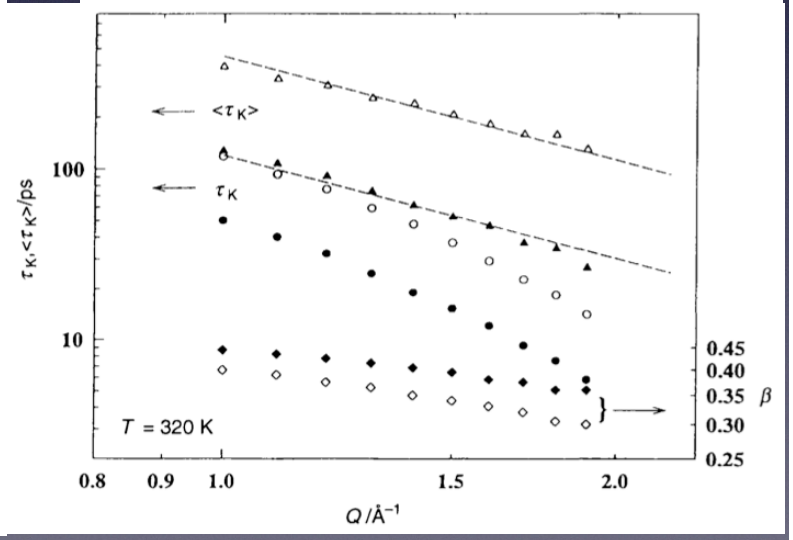

Settles & Doster, Faraday Disc (1996), h=0.35

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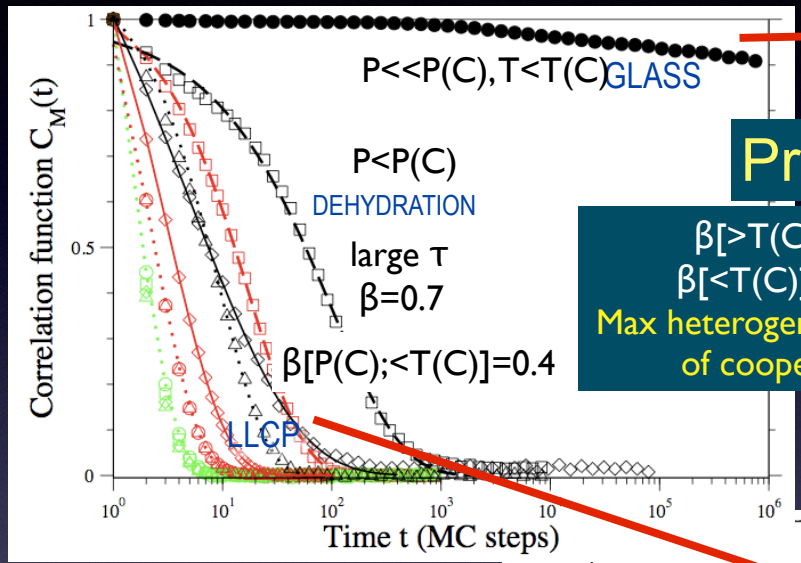
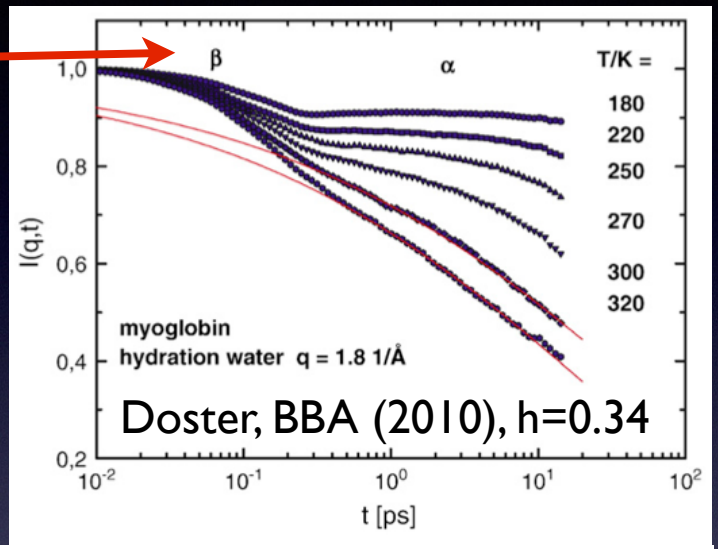


Prediction

β[>T(C)]=0.8,
β[<T(C)]=0.4 !!!
Max heterogeneity as effect of cooperativity



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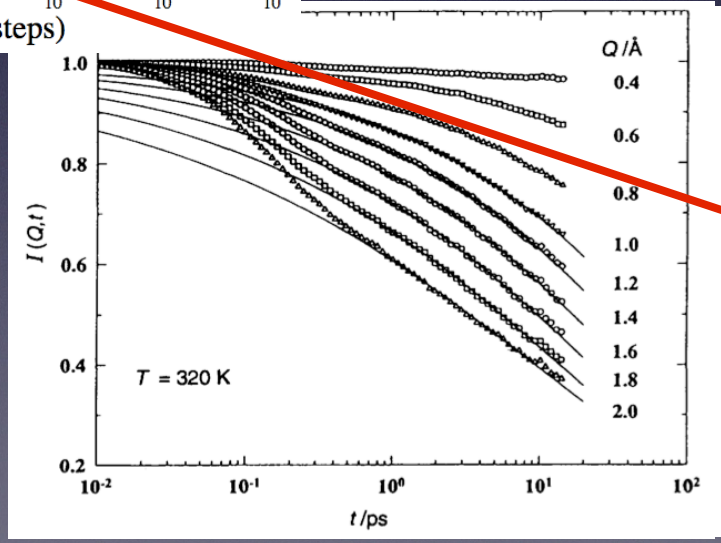
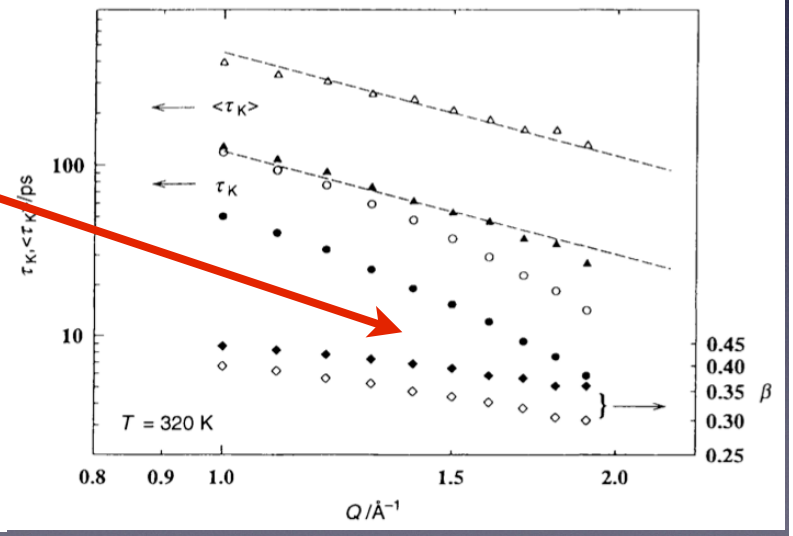
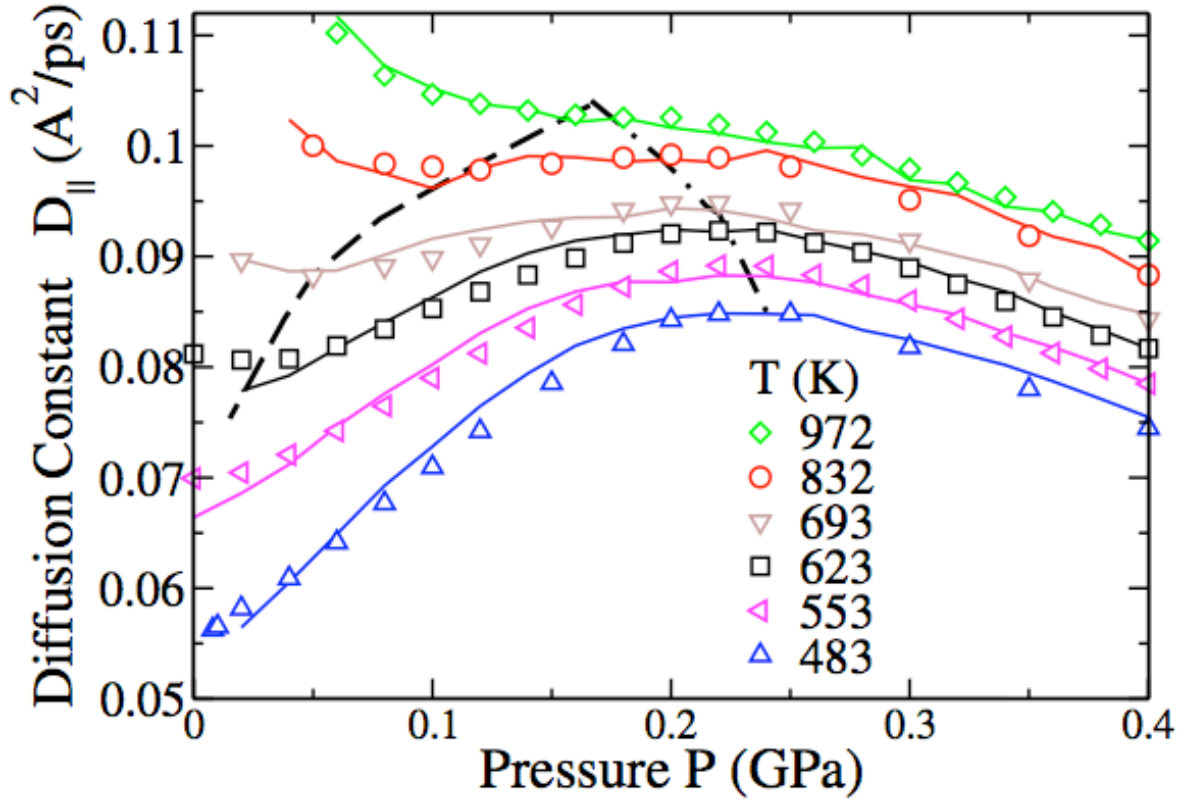


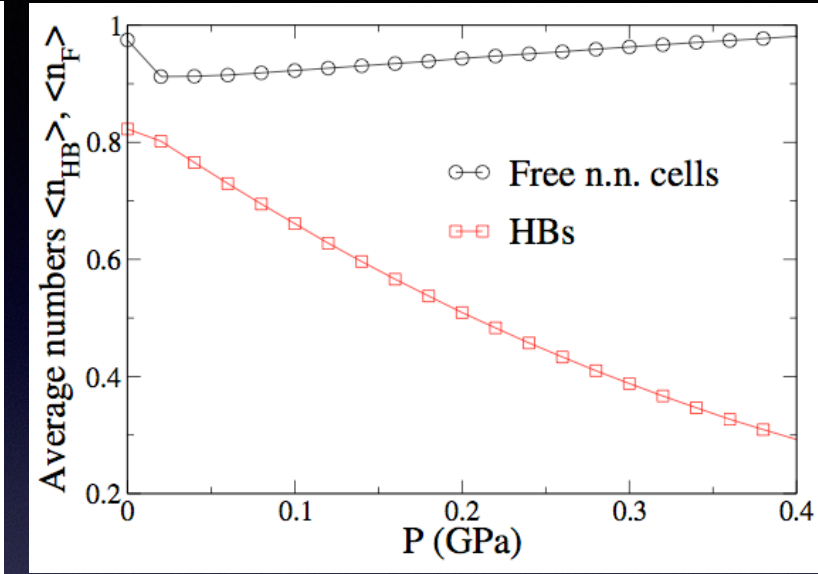


Settles & Doster, Faraday Disc (1996), h=0.35

Diffusion Anomaly and *1nm* Cooperative Rearranging Regions

At high T: Diffusion maxima and minima





Average N_{HB}/molecule

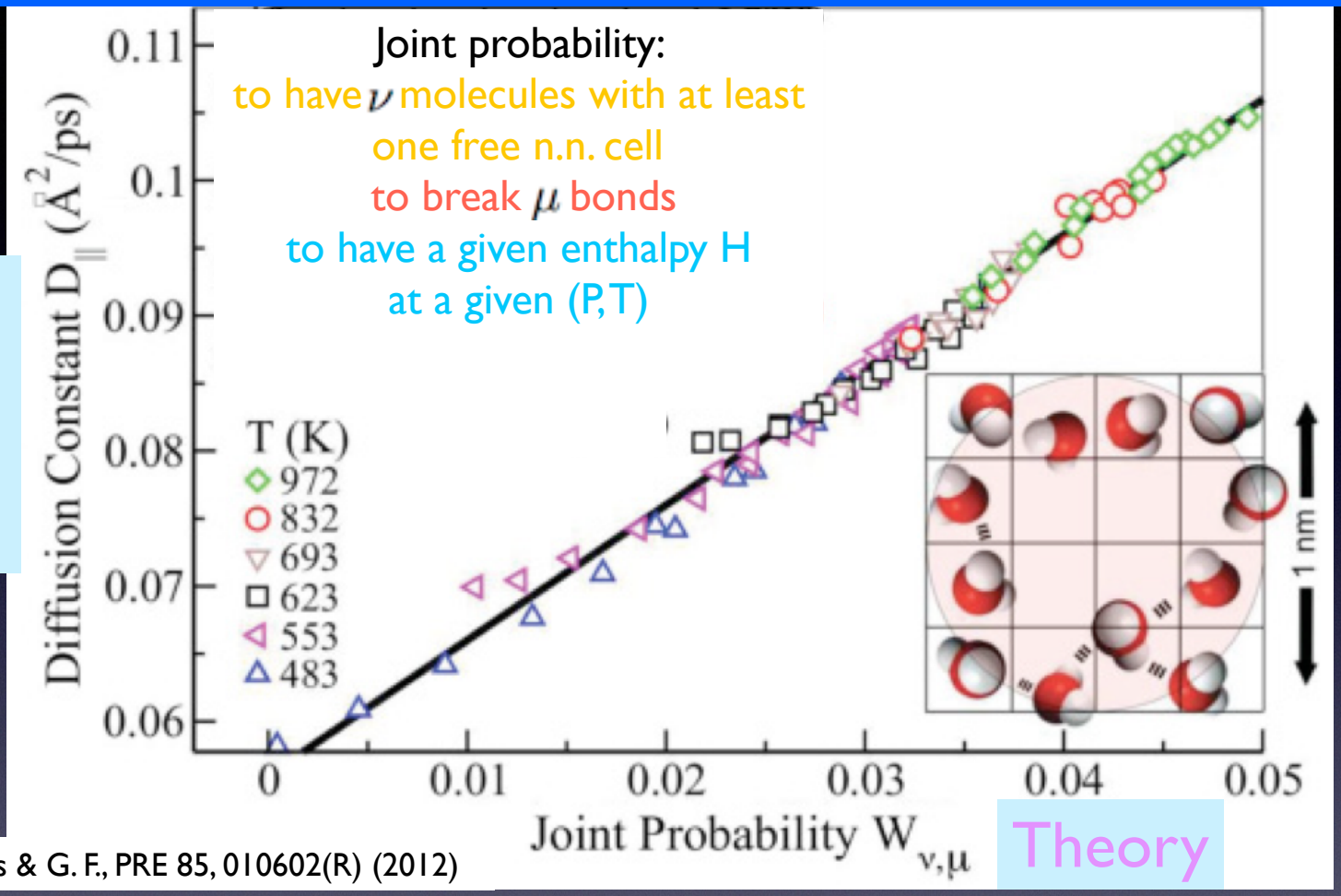
Average
(free volume)/molecule

$0.1\ A^2/ps = 10^{-5} cm^2/s$

are both monotonic!!

F. de los Santos & G. F., PRE 85, 010602(R) (2012)

Theoretical explanation



F. de los Santos & G. F., PRE 85, 010602(R) (2012)

Anomalous Diffusion results from competition between H-bonds breaking and free-volume in Cooperative Rearranging Regions (CRRs).

The model predicts CRRs of *1nm* size

Experiments show change in diffusion for confinement below *1nm* !!

Relevant for water filtration/purification

The effect of Cooperativity

Tuning the Cooperativity strenght

PNAS

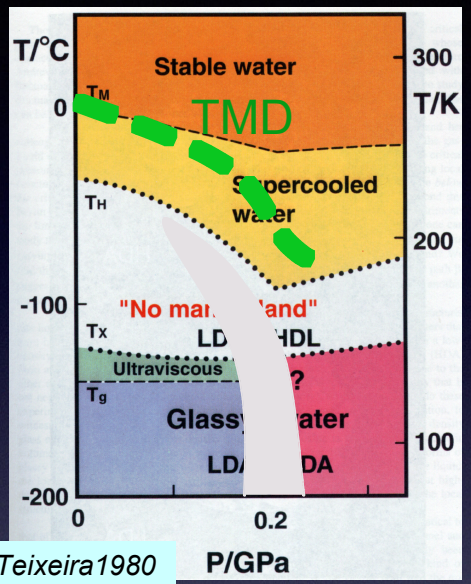
Effect of hydrogen bond cooperativity on the behavior of water

Kevin Stokely[a,1], Marco G. Mazza[a2], H. Eugene Stanley[a], and Giancarlo Franzese[b]

PNAS | **January 26, 2010** | vol. 107 | no. 4 | **1301–1306**

Tuning the Cooperativity strenght

Singularity-Free



Stanley & Teixeira1980
Sastry et al. 1996

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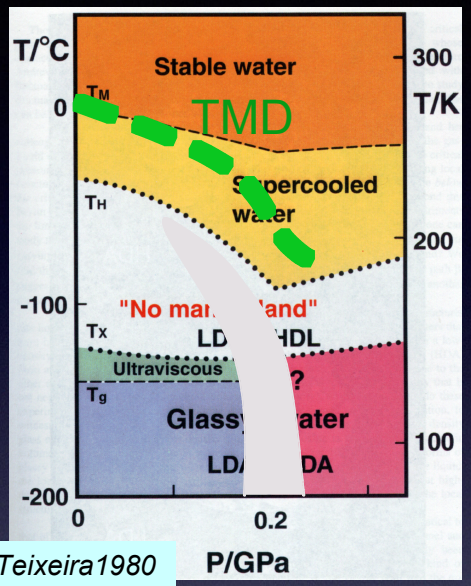
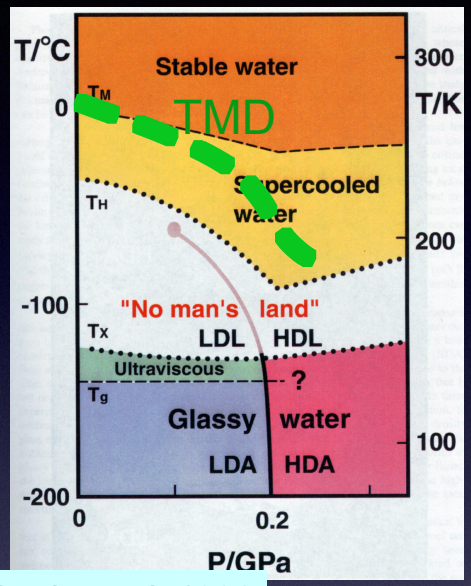
PNAS | January 26, 2010 | vol. 107 | no. 4 | 1301–1306

Tuning the Cooperativity strenght

Singularity-Free → Liquid-liquid Crit. Point



Stanley & Teixeira1980
Sastry et al. 1996



Poole et al. 1992

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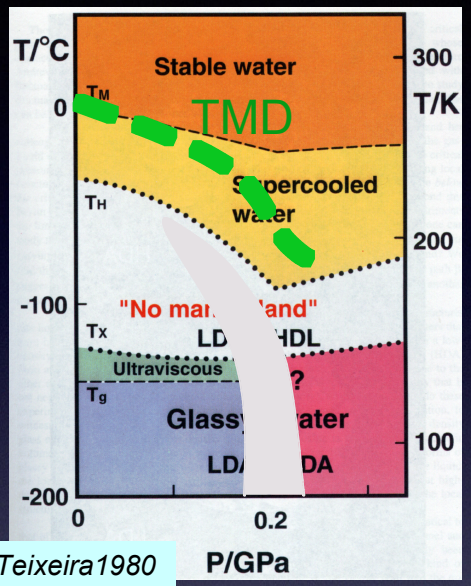
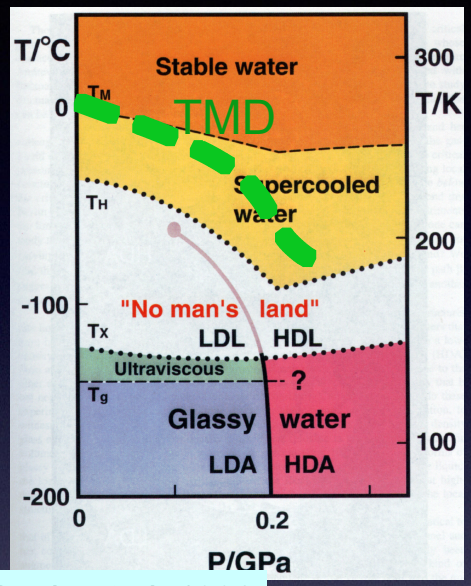
Tuning the Cooperativity strenght

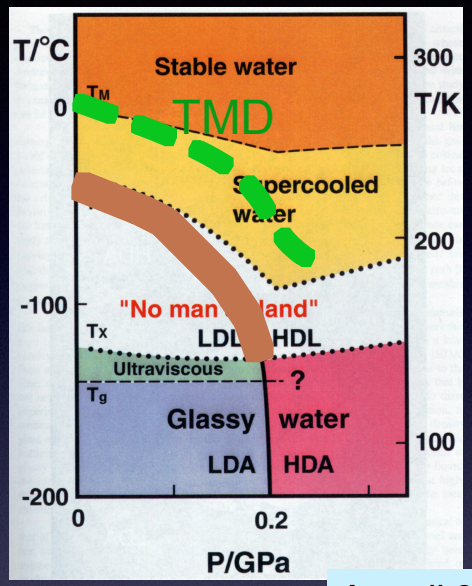
Singularity-Free → Liquid-liquid Crit. Point → Crit. Point-Free



Stanley & Teixeira1980
Sastry et al. 1996



Poole et al. 1992



Angell 2008

ALL THE SCENARIOS FROM THE SAME MECHANISM

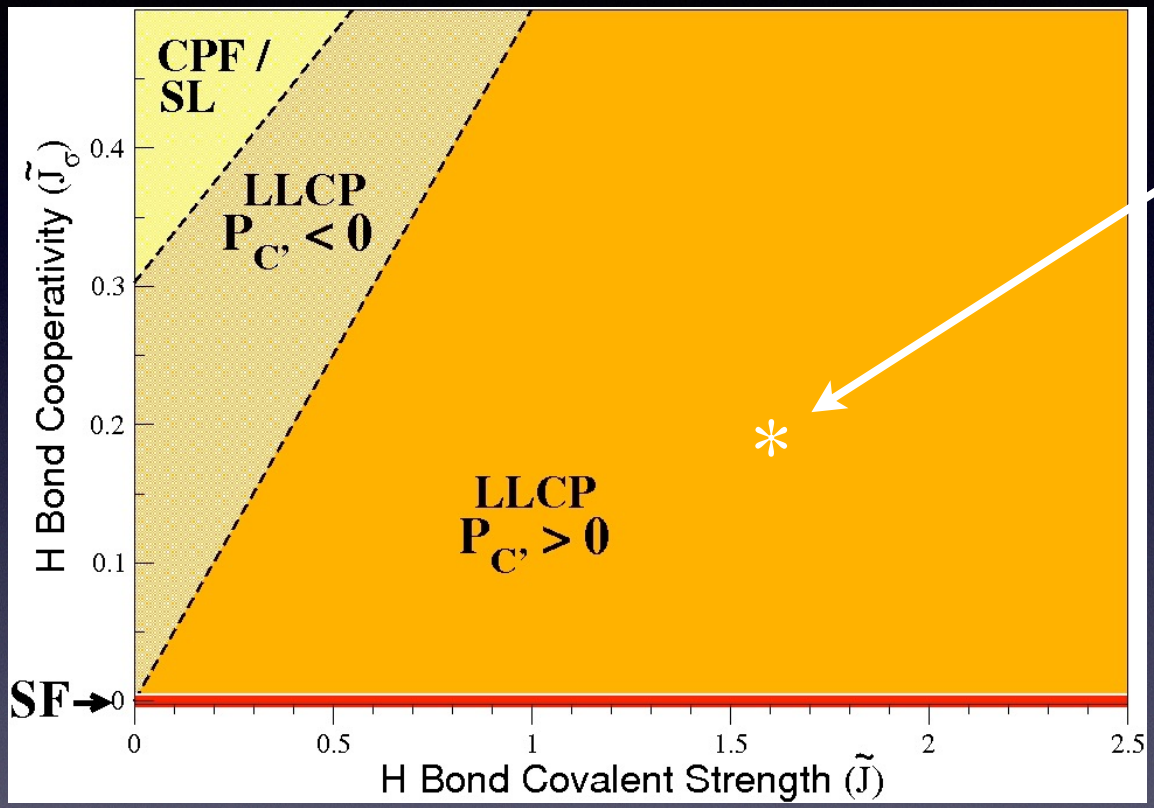
PNAS

Effect of hydrogen bond cooperativity on the behavior of water

Kevin Stokely[a,1], Marco G. Mazza[a2], H. Eugene Stanley[a], and Giancarlo Franzese[b]

PNAS | January 26, 2010 | vol. 107 | no. 4 | 1301–1306

Parameters from Experiments lead to Liquid-Liquid Critical Point (LLCP)



From Experiments:
from Ih - liq. => $J\sigma \approx 1$ kJ/mol
$4\varepsilon \approx 5.5$ kJ/mol ($J\sigma/4\varepsilon \approx 0.2$)
$E_{HB}(\varepsilon, J, J\sigma) \approx 5.8$ kJ/mol
=> $J \approx$ 6-12 kJ/mol ($J/4\varepsilon \approx 1.1$-2)

LLCP predicted
in a region inaccessible
in experiments so far

PNAS

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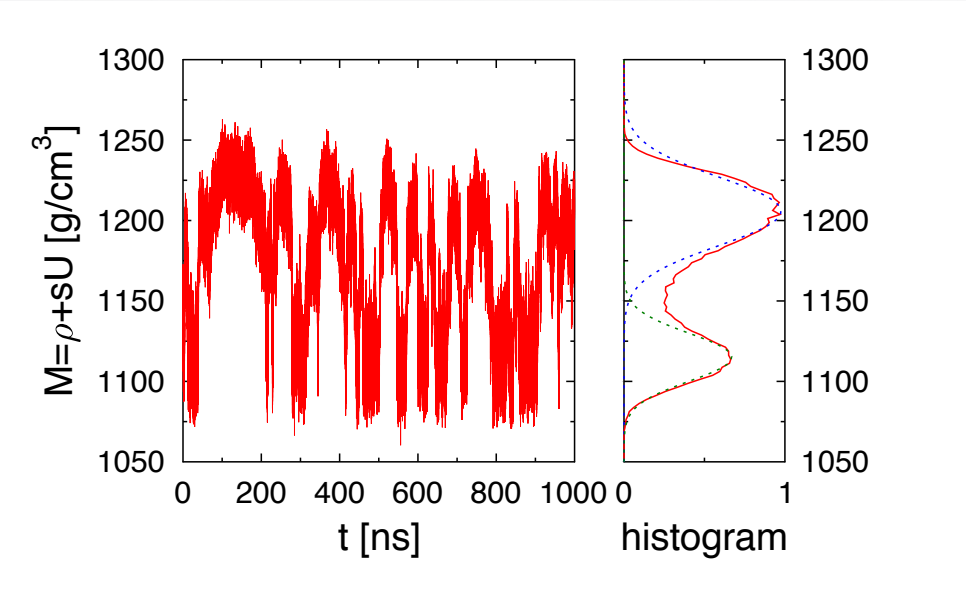
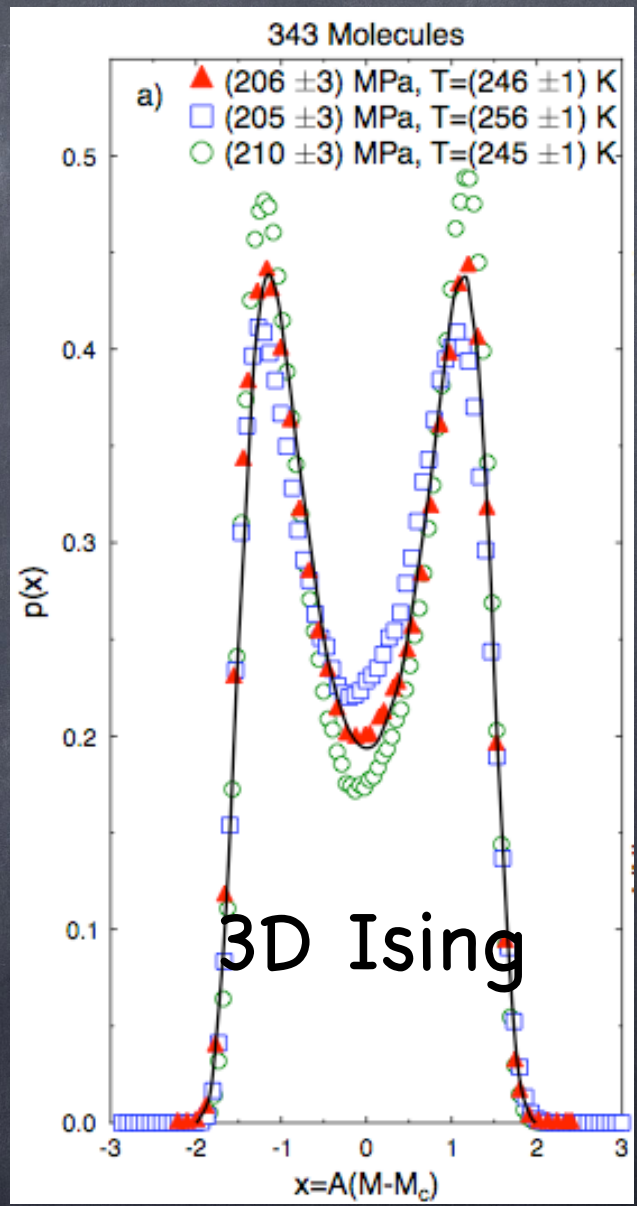
PNAS | January 26, 2010 | vol. 107 | no. 4 | 1301–1306

LLCP Accessible in Simulations of ST2 water model



Order parameter: combination of density and energy

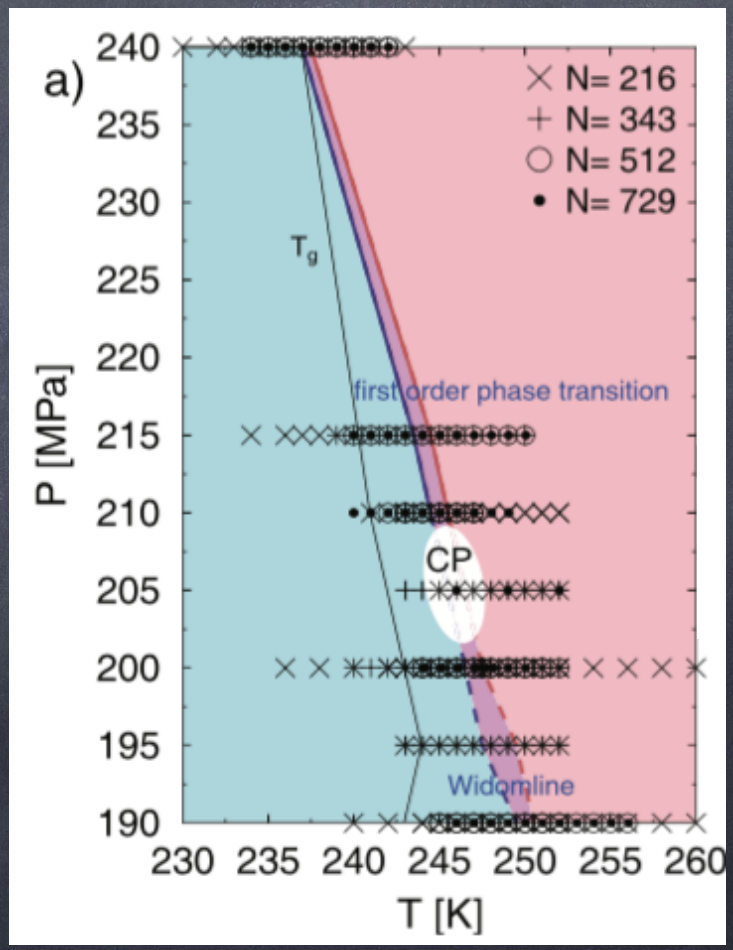
T.A. Kesselring, G. Franzese, S.V. Buldryev, H.J. Herrmann, and H.E. Stanley, Sci. Rep. 2, 474 (2012)



at approx. 0.2 GPa and 246 K

Problem with simulations of atomistic water models

- The LLCP is very close to Tg (difficult to equilibrate)
- very slow equilibration on approaching LLCP from 1-phase region (where the Widom line should be)



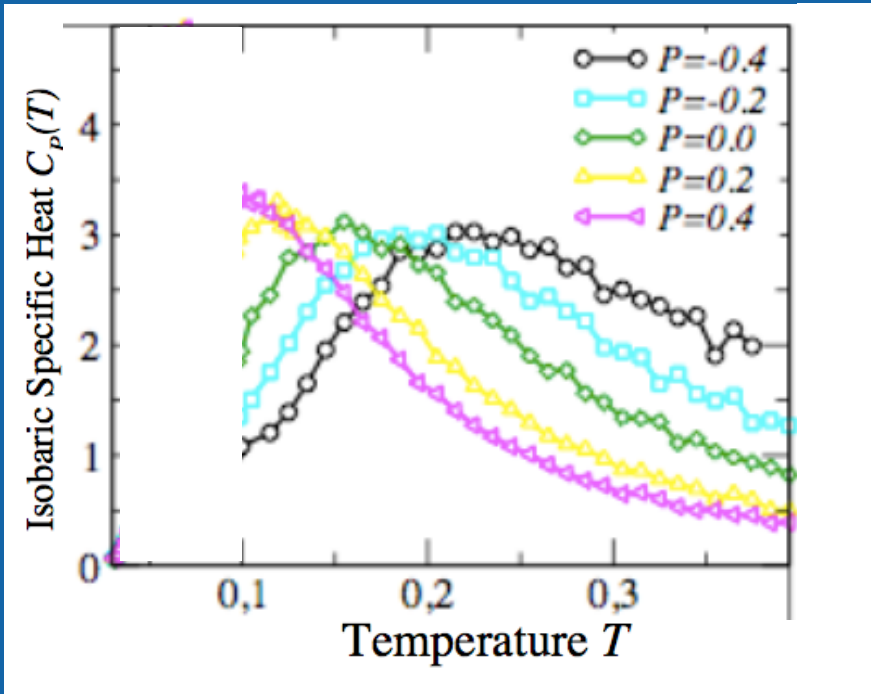
T.A. Kesselring, G. Franzese, S.V. Buldryev, H.J. Herrmann, and H.E. Stanley, Sci. Rep. 2, 474 (2012)

Response function maxima: Weak and Strong

Mazza, Stokely, Stanley, Franzese
J. Chem. Phys. 137, 204502 (2012)

MAXIMA IN RESPONSE FUNCTIONS

Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).



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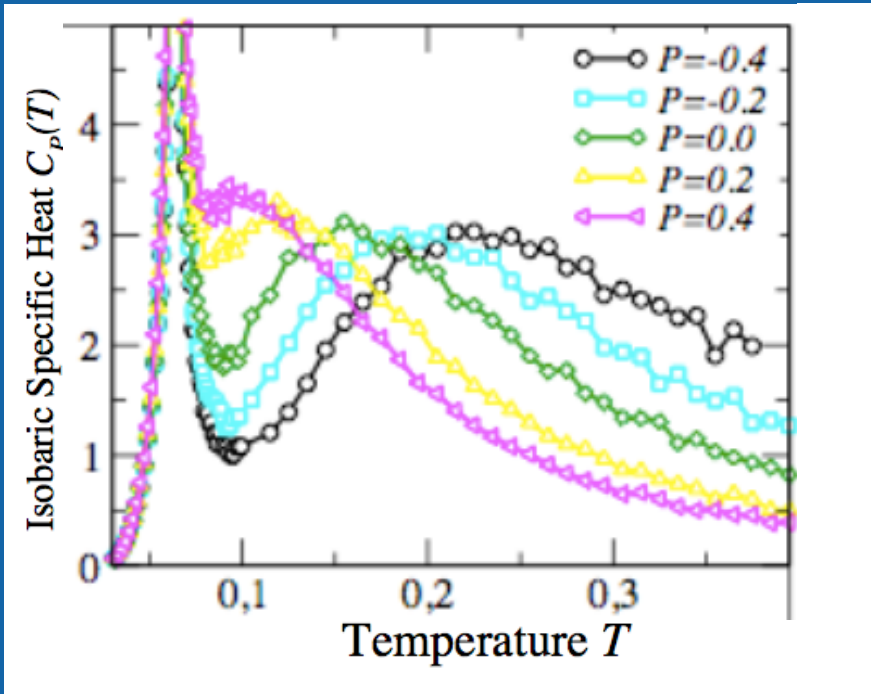

TWO MAXIMA IN RESPONSE FUNCTIONS

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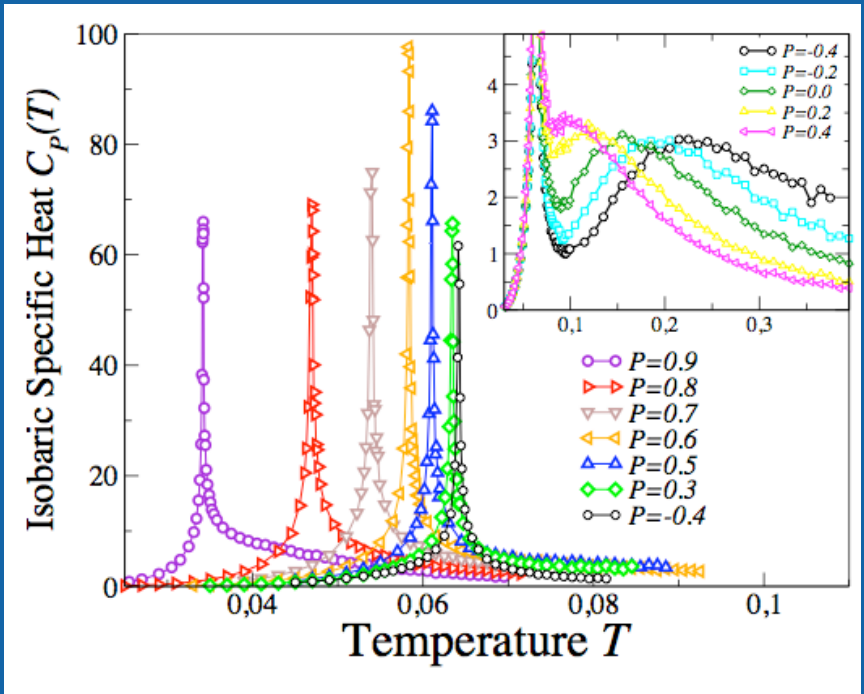

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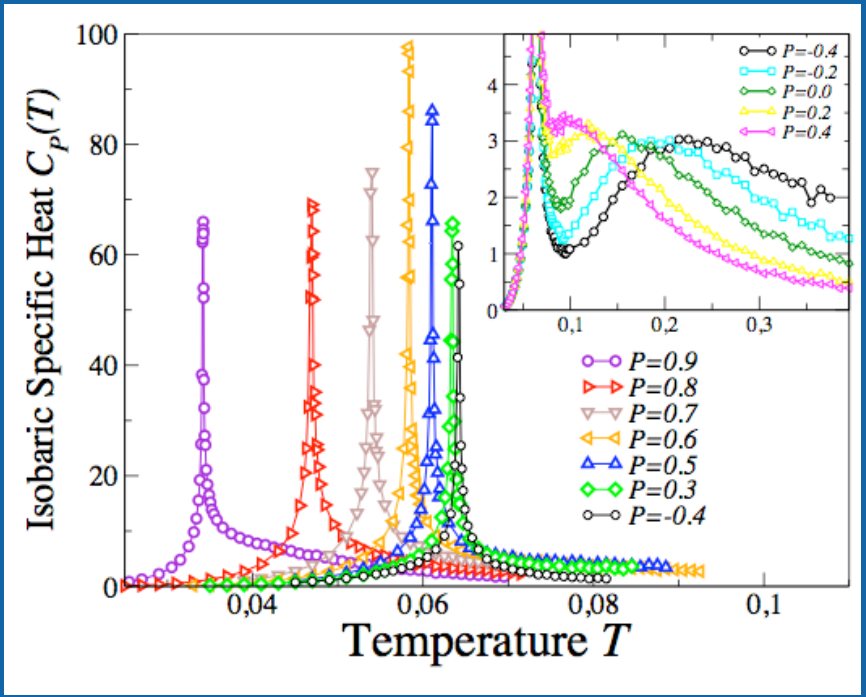

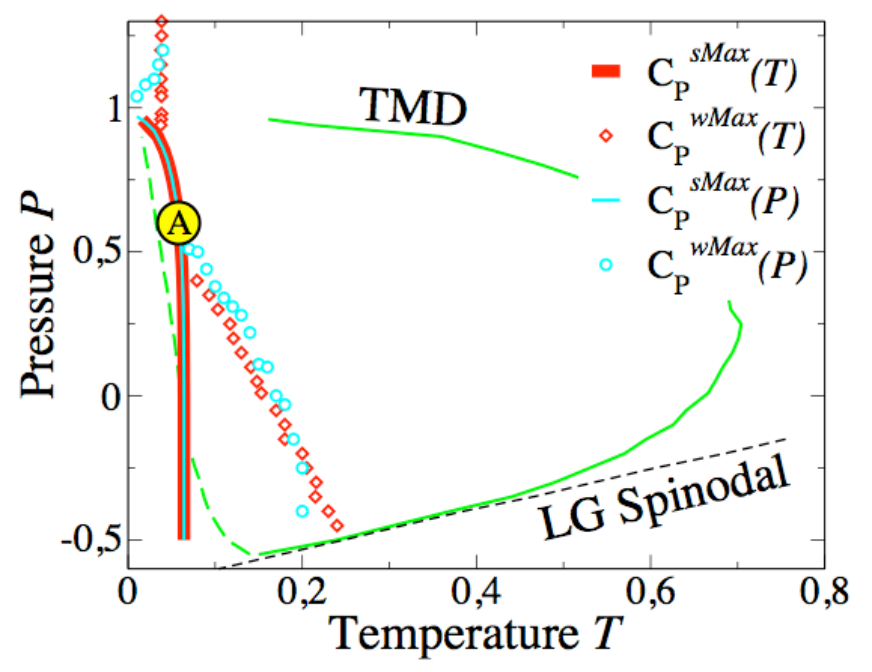

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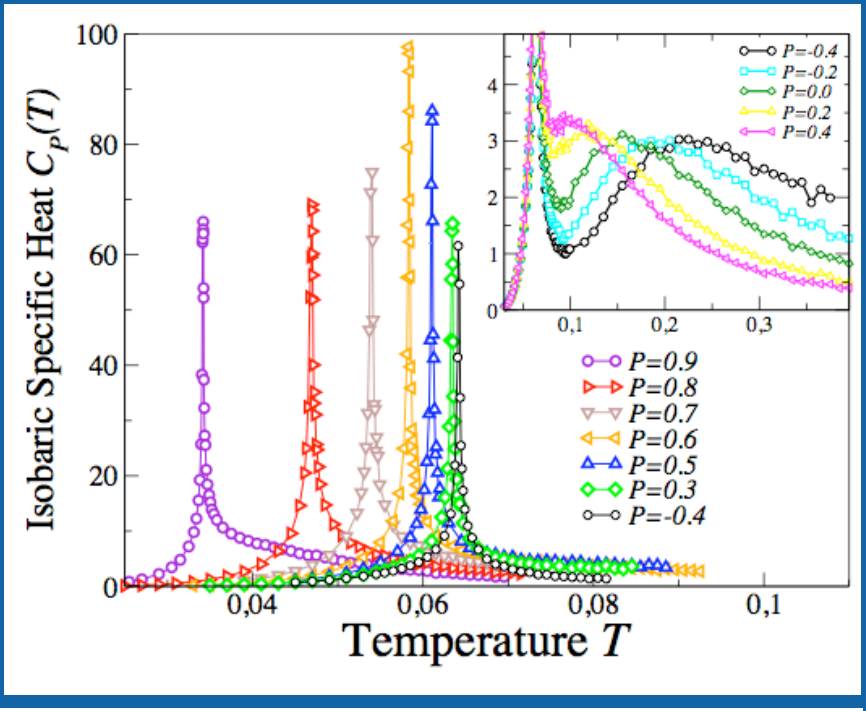

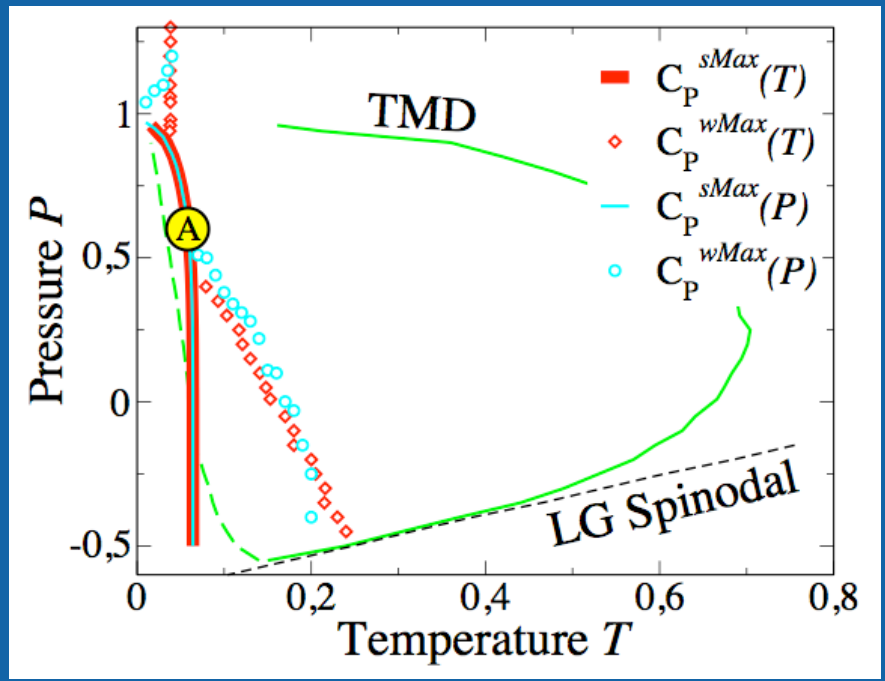

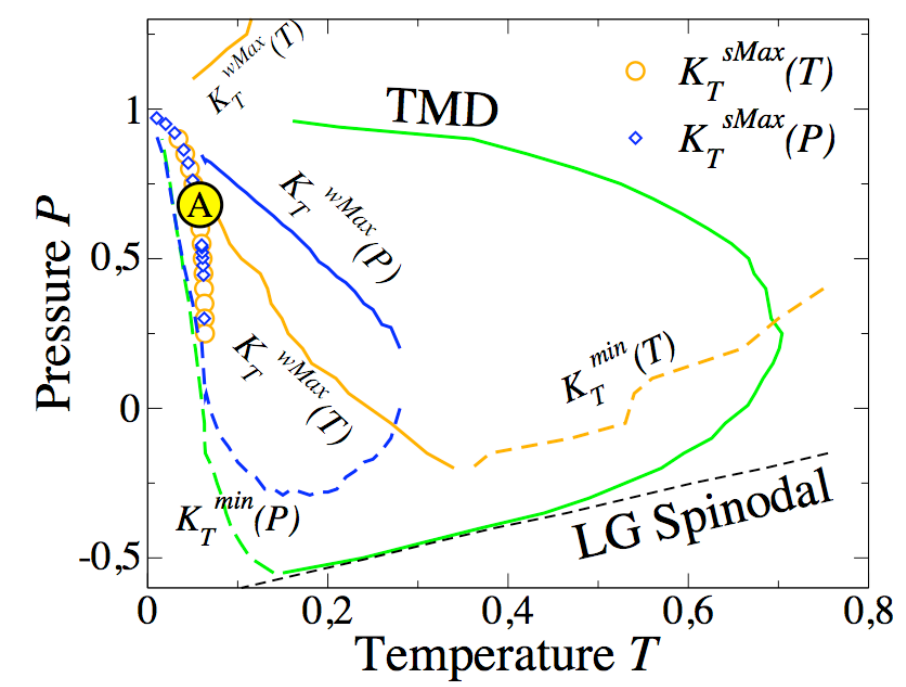

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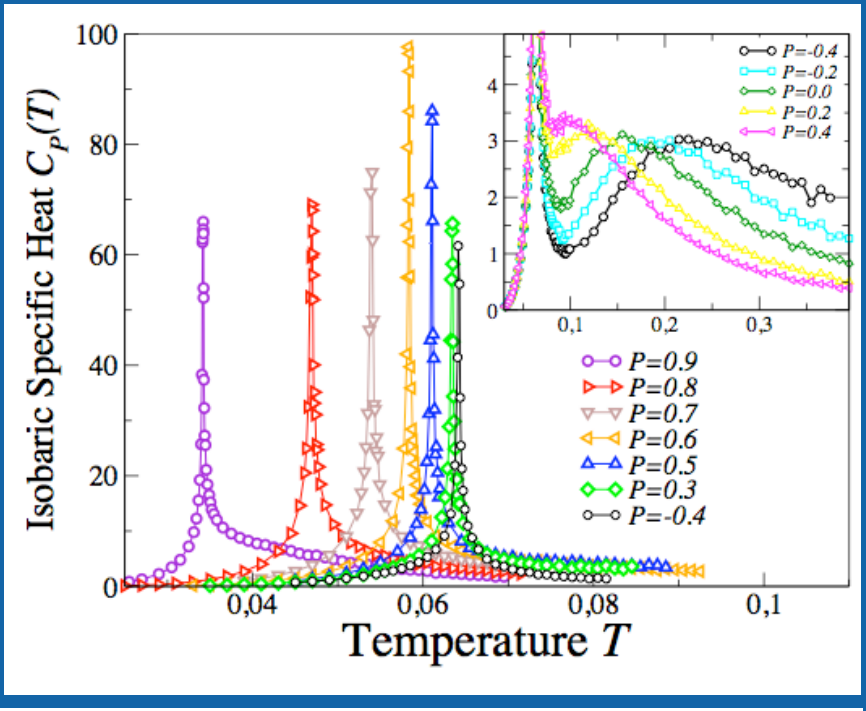
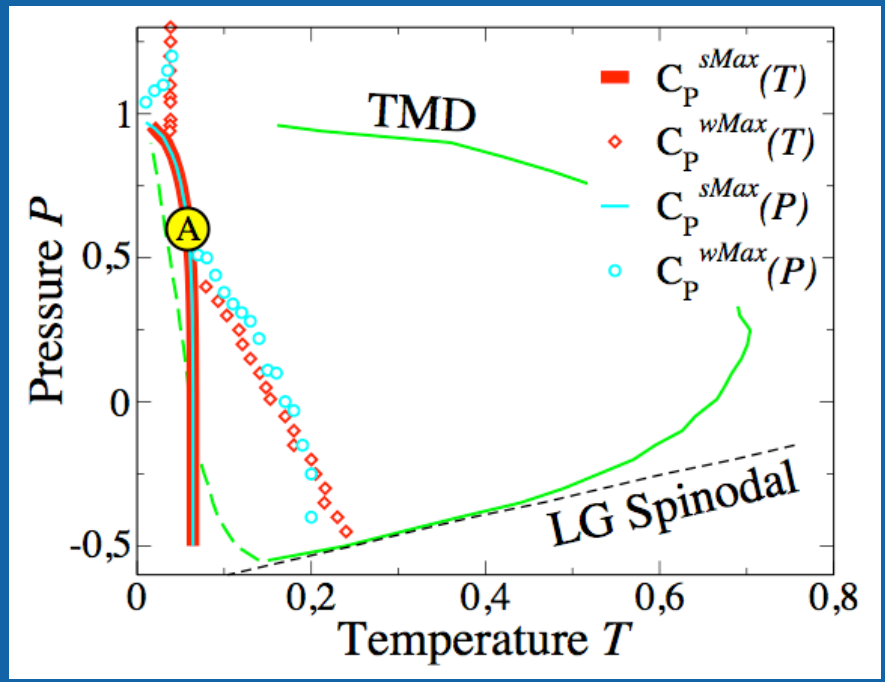
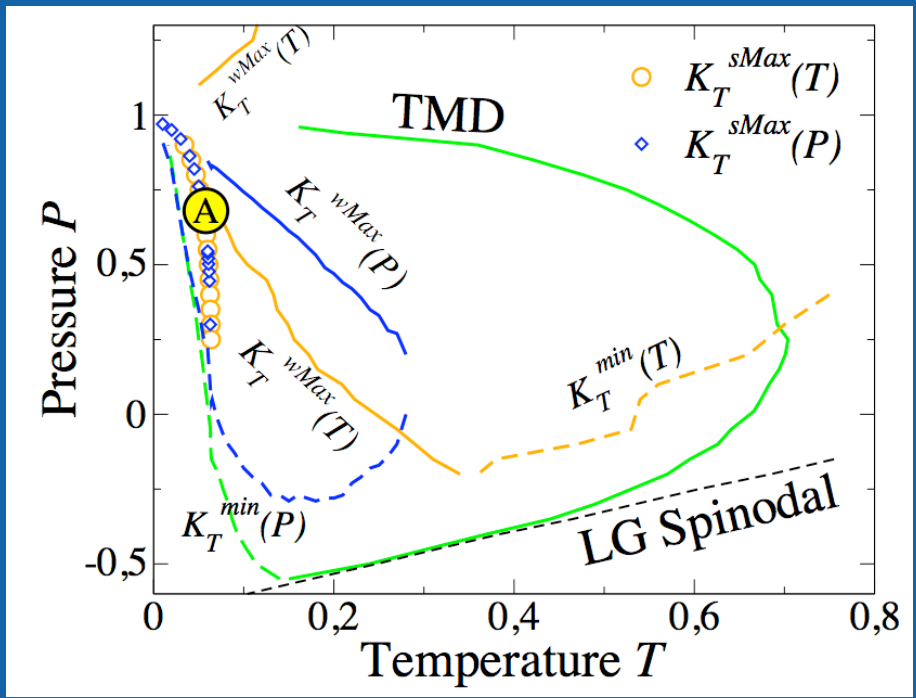
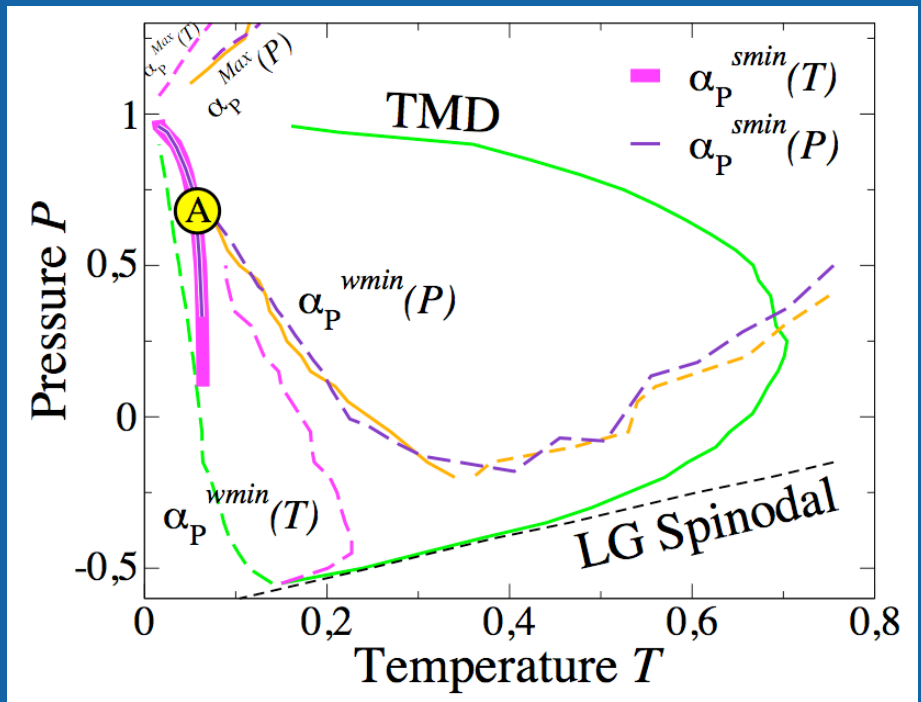


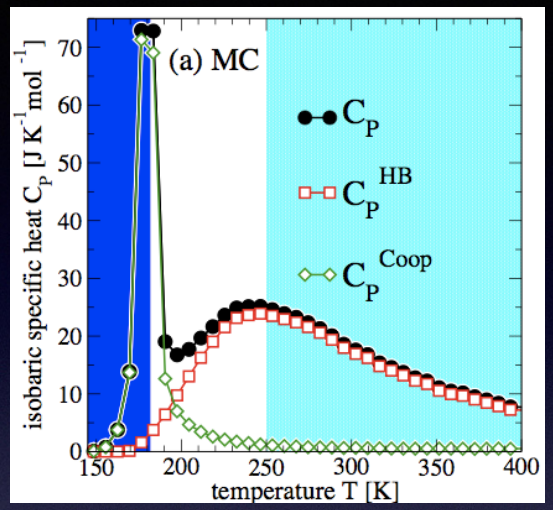






2 Structural changes !!

Simul./Theo.: 2 Max in Cp
T≈180 K
T≈250 K



higher T: at the largest increase of N_{HB}
lower T: at the largest increase of tetrahedrally oriented HBs
= WIDOM LINE

Mazza, Stokely, Pagnotta, Bruni, Stanley, Franzese
PNAS 108, 19873 (2011)

Mazza, Stokely, Stanley, Franzese
J. Chem. Phys. 137, 204502 (2012)

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lower T: at the largest increase of tetrahedrally oriented HBs
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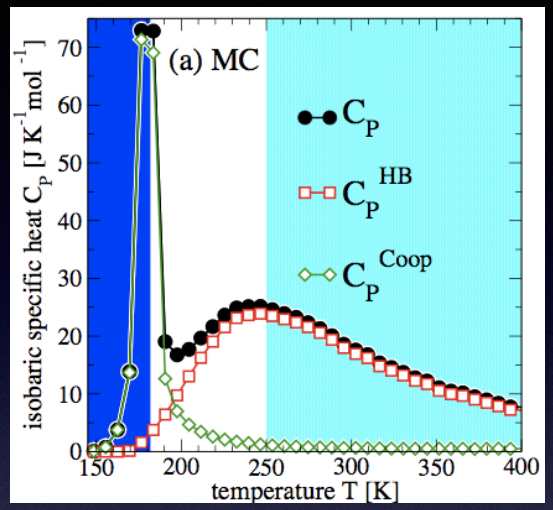

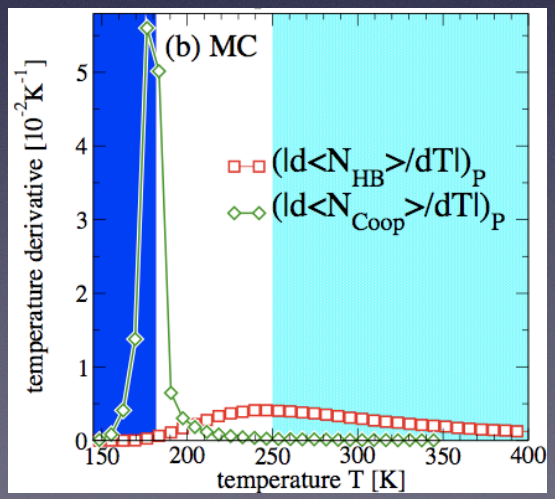

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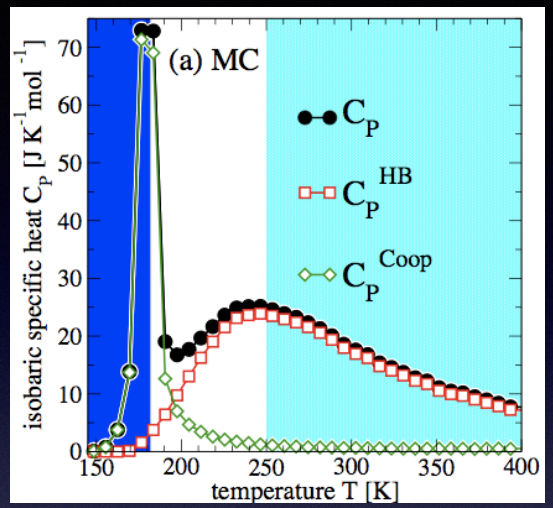

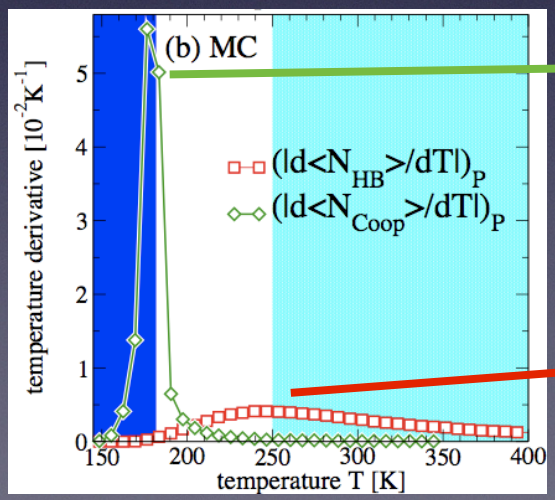

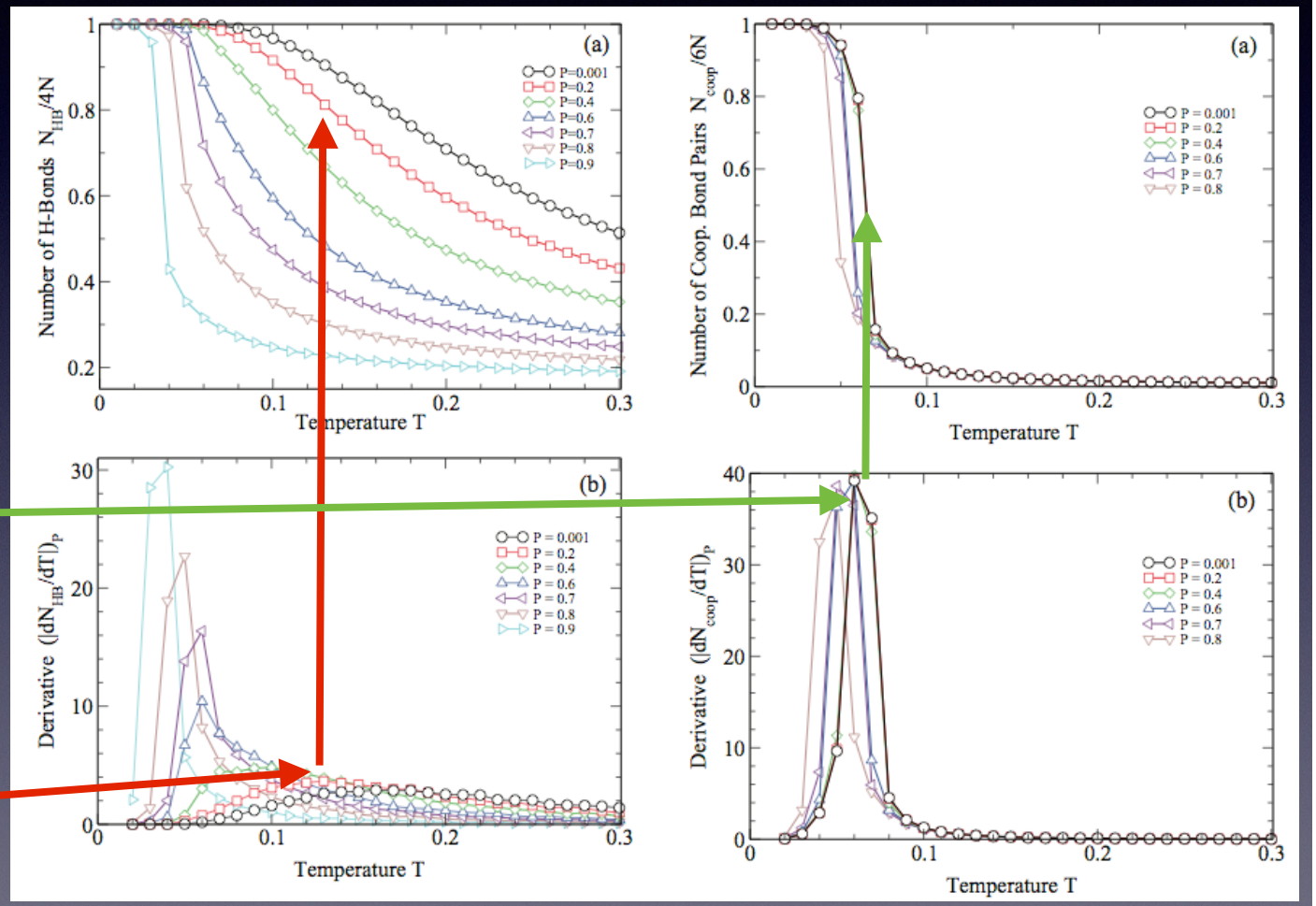

Mazza, Stokely, Pagnotta, Bruni, Stanley, Franzese
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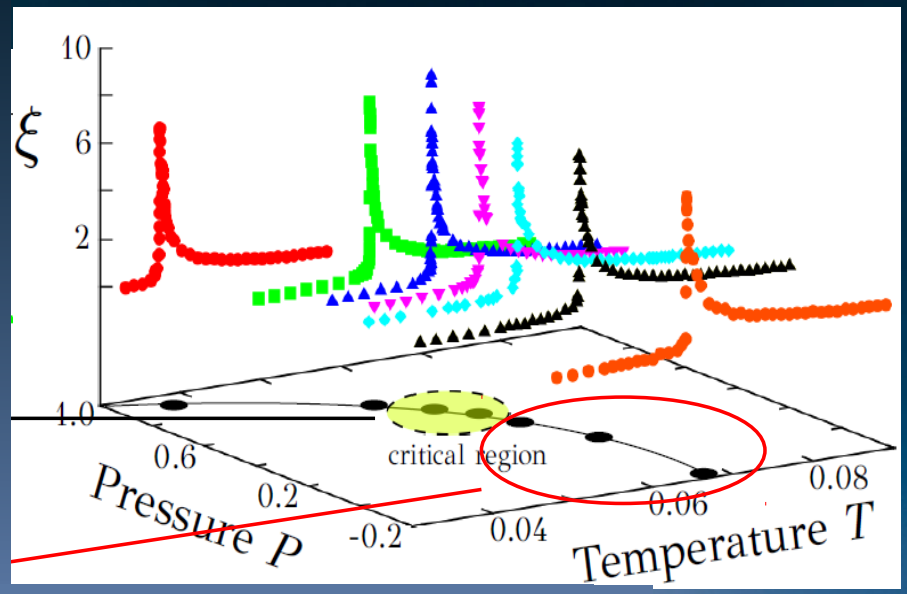
Mazza, Stokely, Stanley, Franzese
J. Chem. Phys. 137, 204502 (2012)

Where is the Widom line?

(Locus of maxima of correlation length)

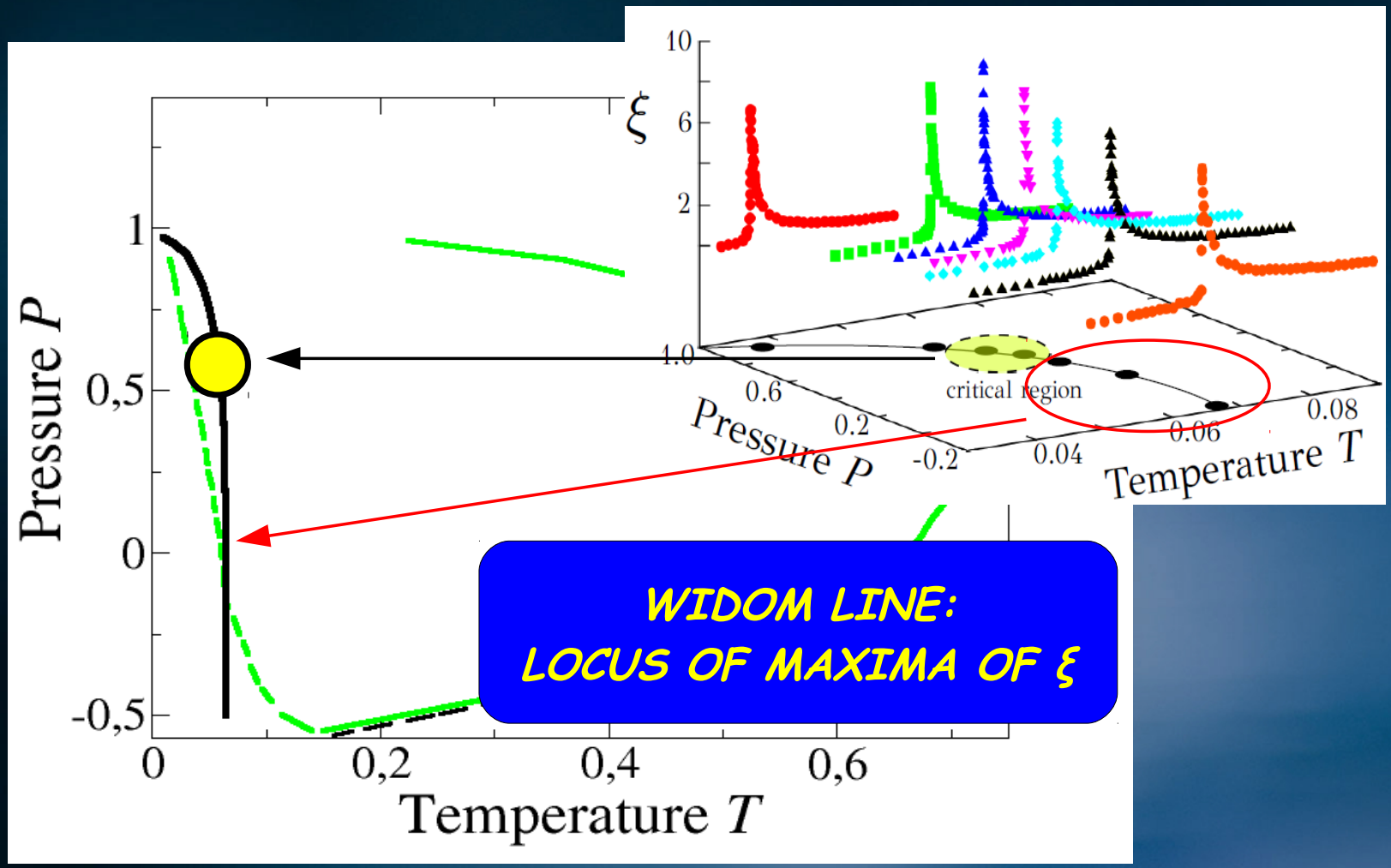
Correlation Length and Widom Line



WIDOM LINE:
LOCUS OF MAXIMA OF ξ

Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).

Correlation Length and Widom Line



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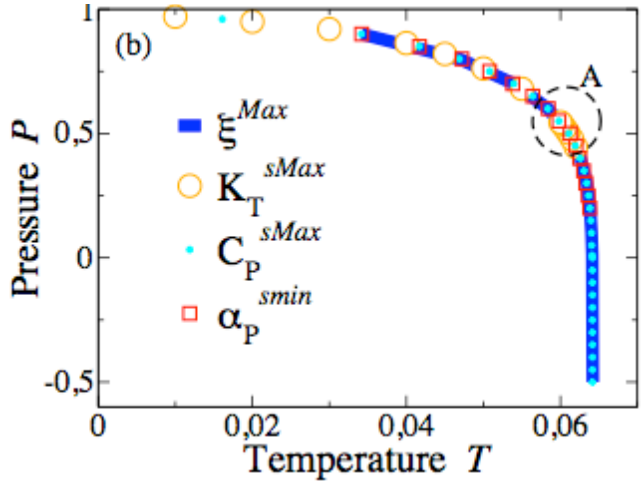
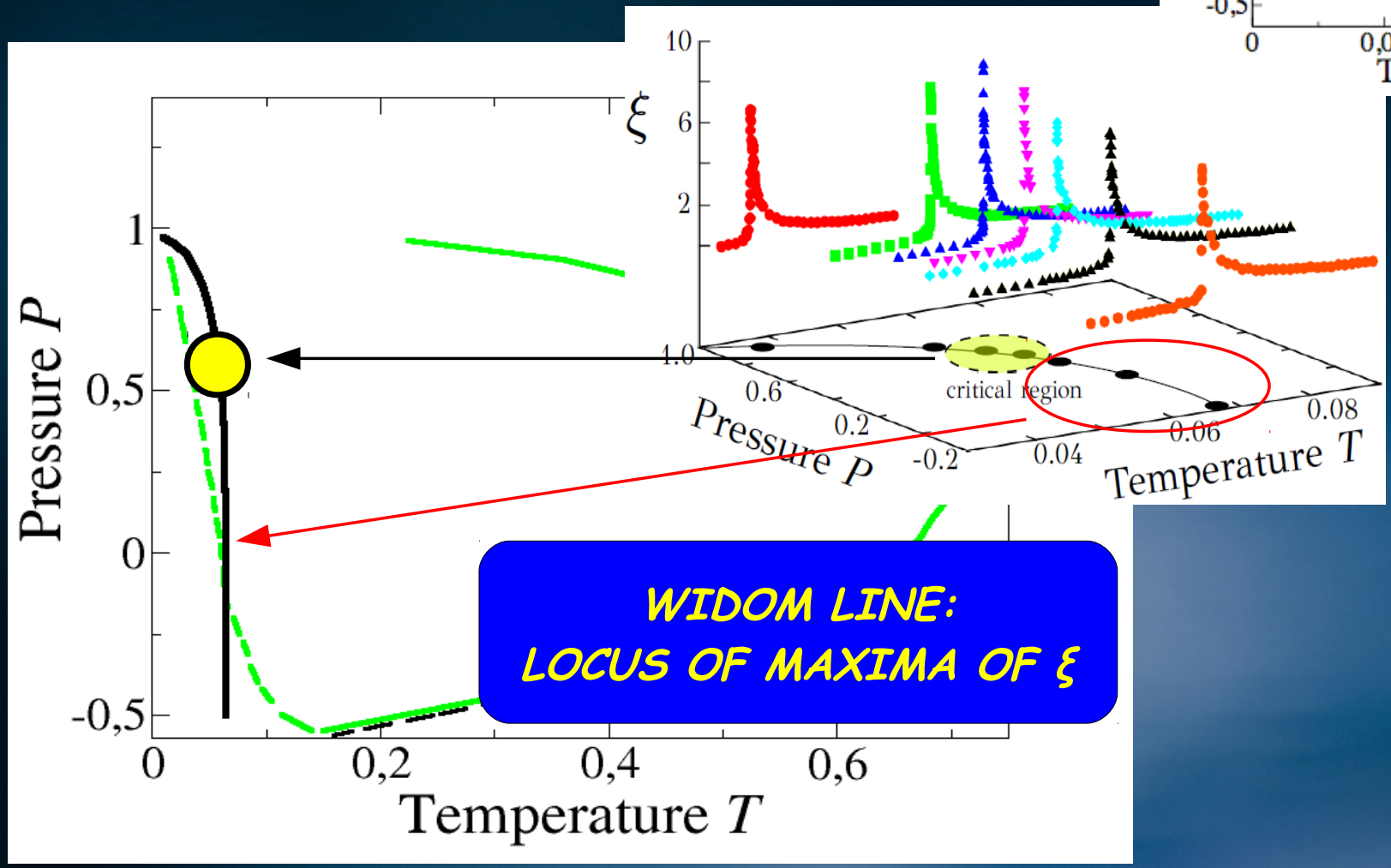
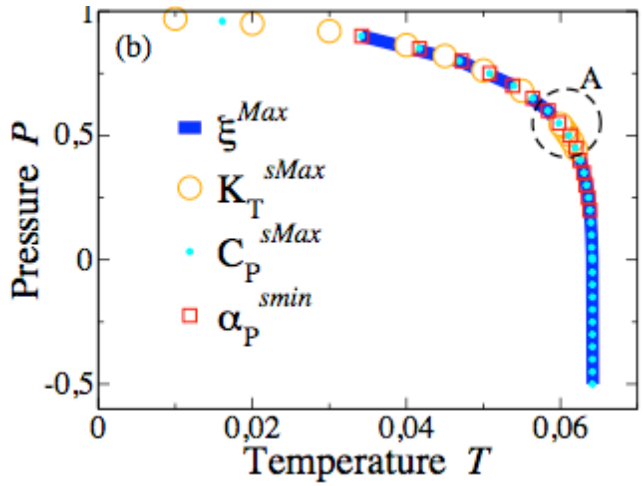
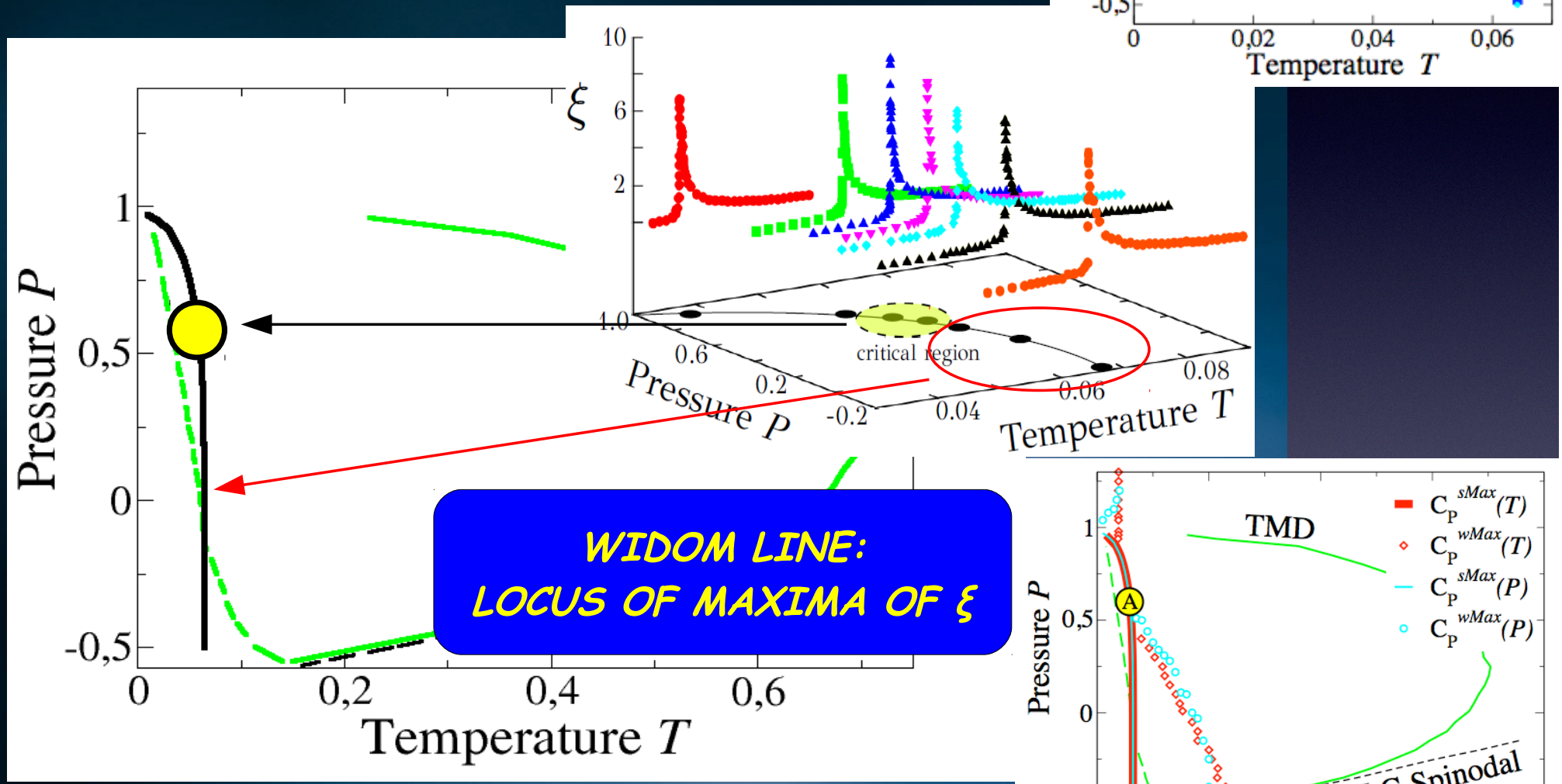


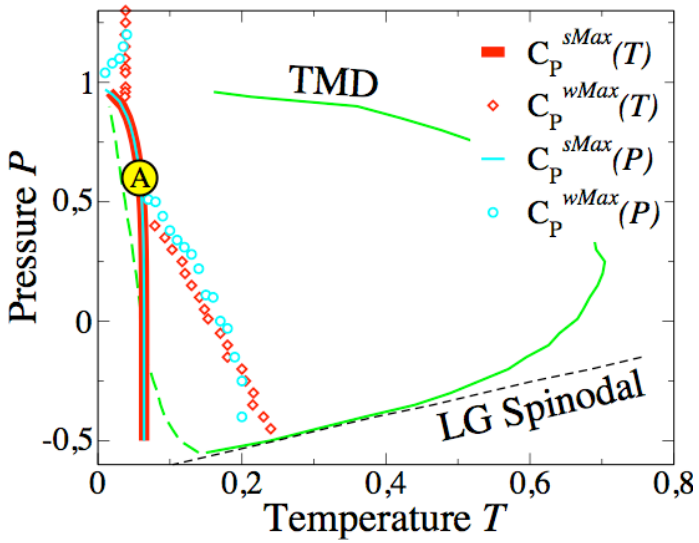


Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).

Correlation Length and Widom Line



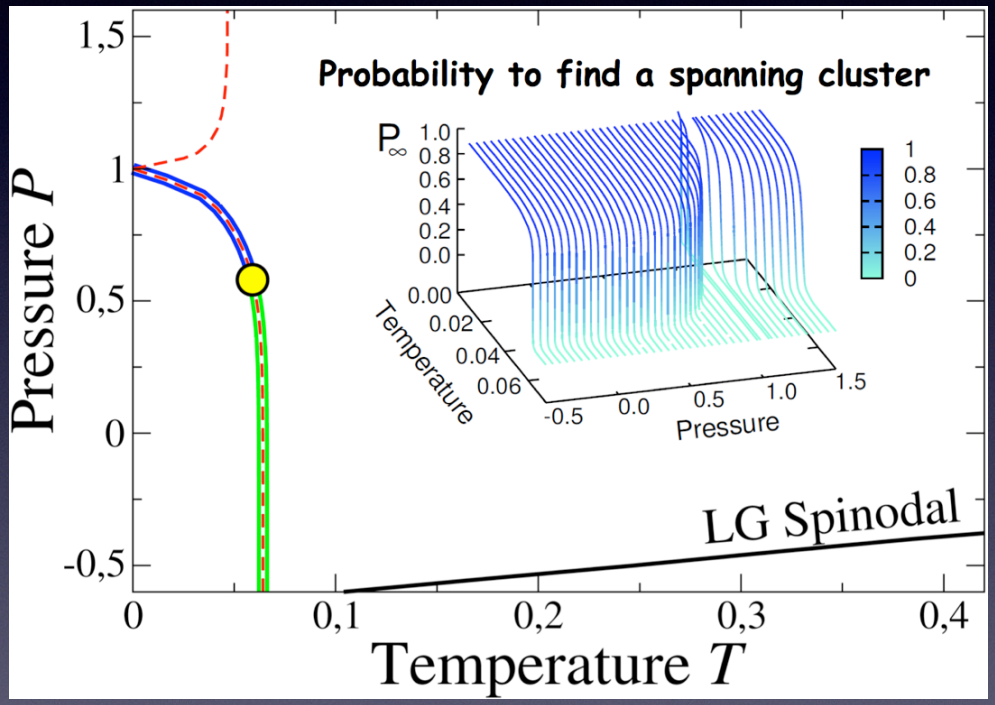


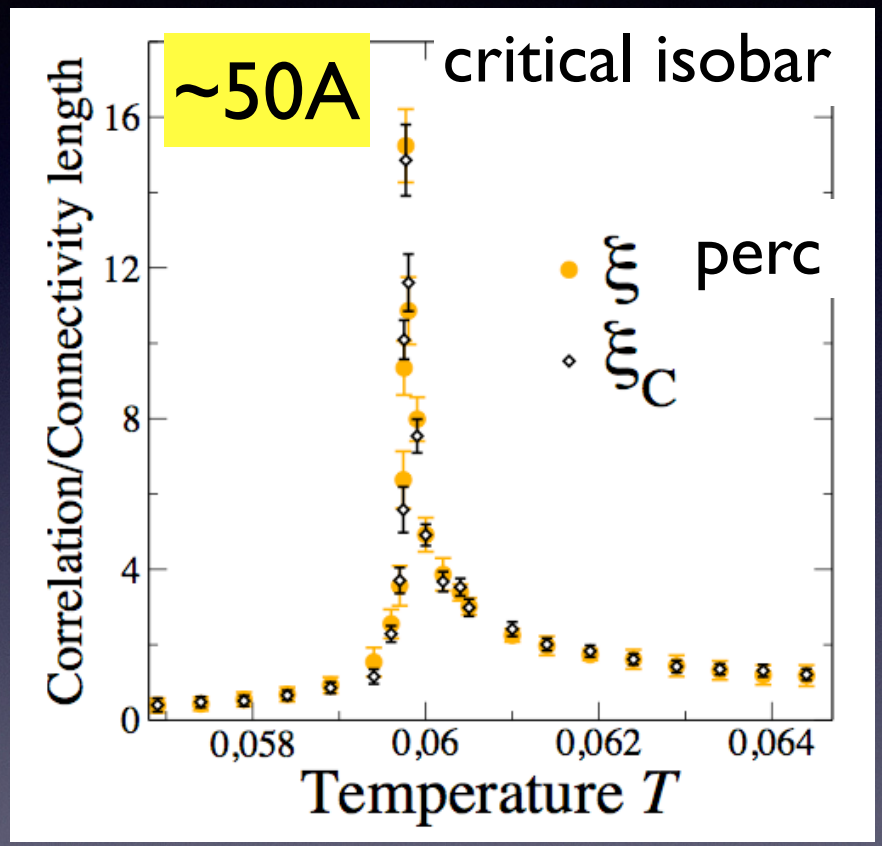


Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).

The Widom line has much larger slope than predicted from atomistic models

atomistic models stop at "weak maxima" line(s)

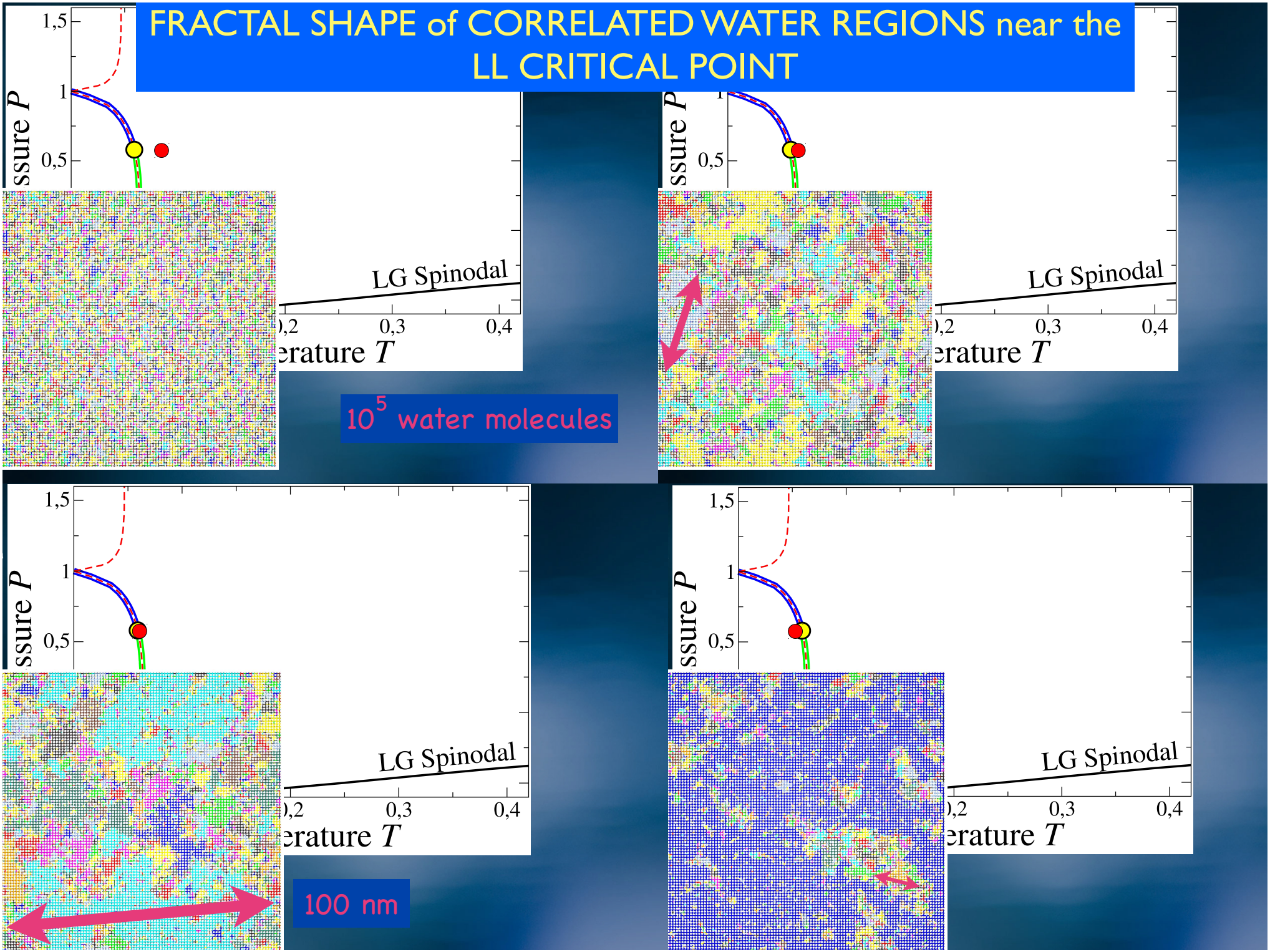




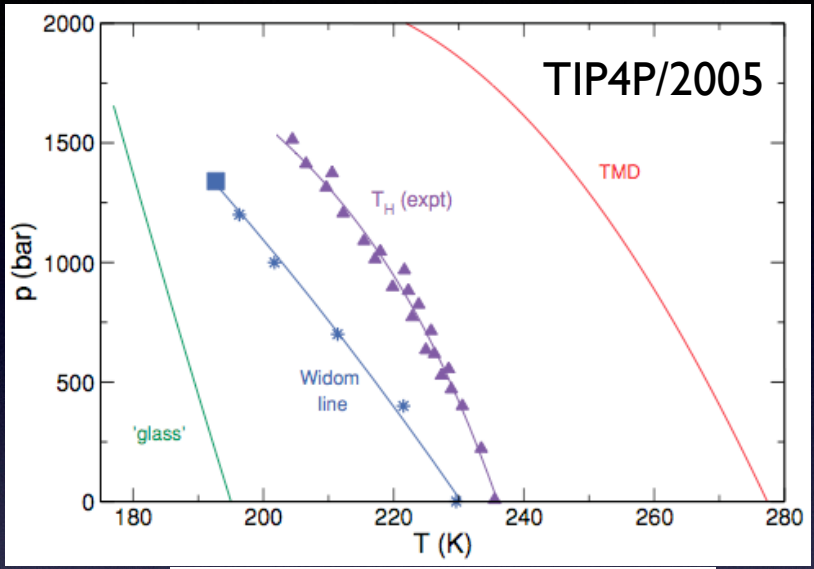
Correlated-bond Percolation
at the liquid-liquid critical point
Widom line = Kertész line

Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).

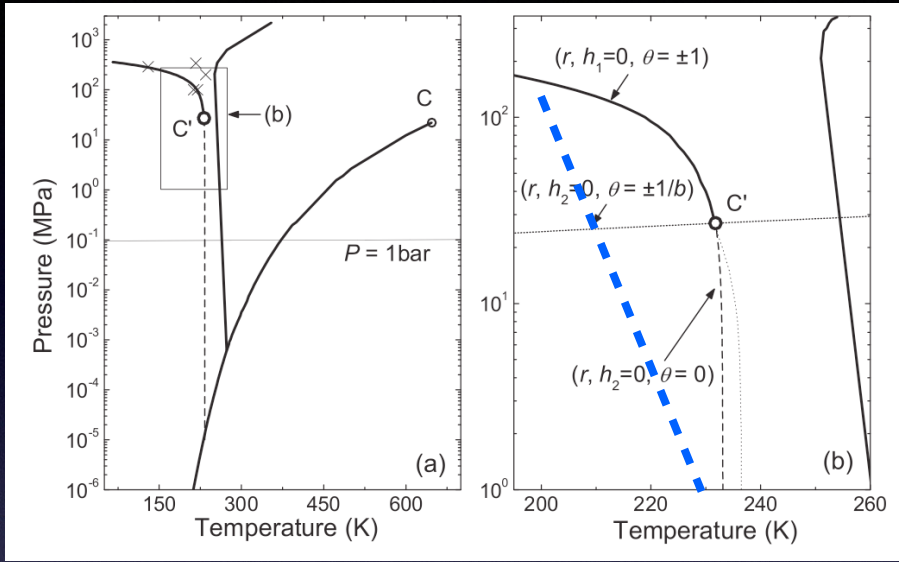
FRACTAL SHAPE of CORRELATED WATER REGIONS near the LL CRITICAL POINT



Widom line consistent with fitting from experiments,
Weak Cp Max line consistent with "Widom line" from simulations



Abascal and Vega JCP (2010)



Fuentevilla and Anisimov PRL (2006)

Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).

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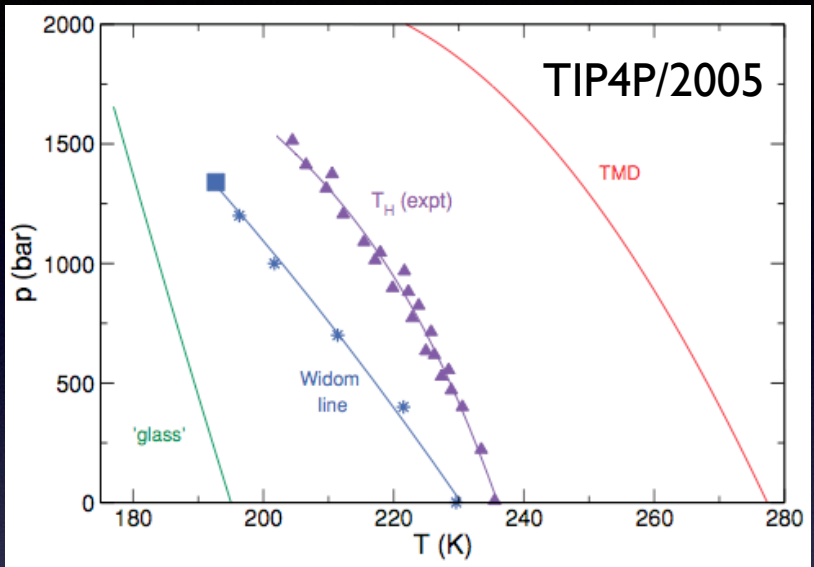

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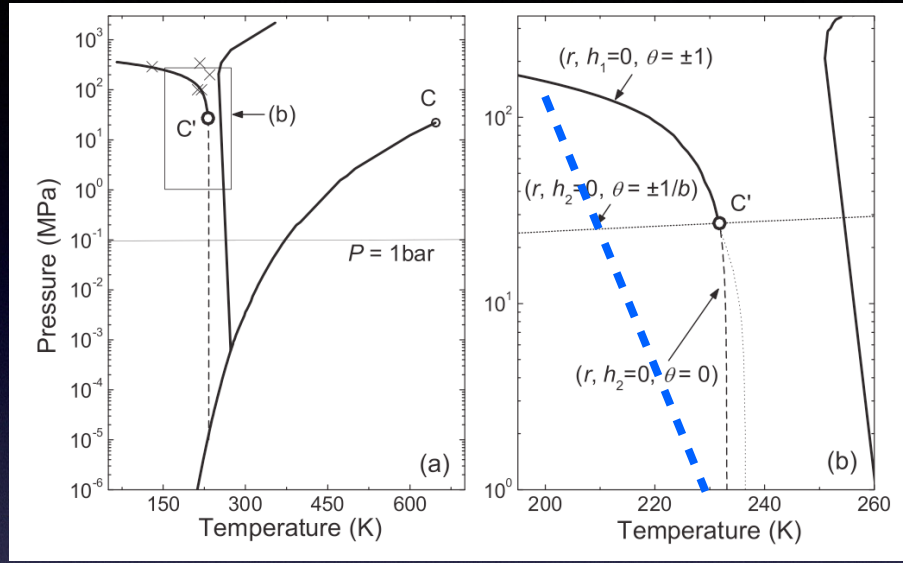
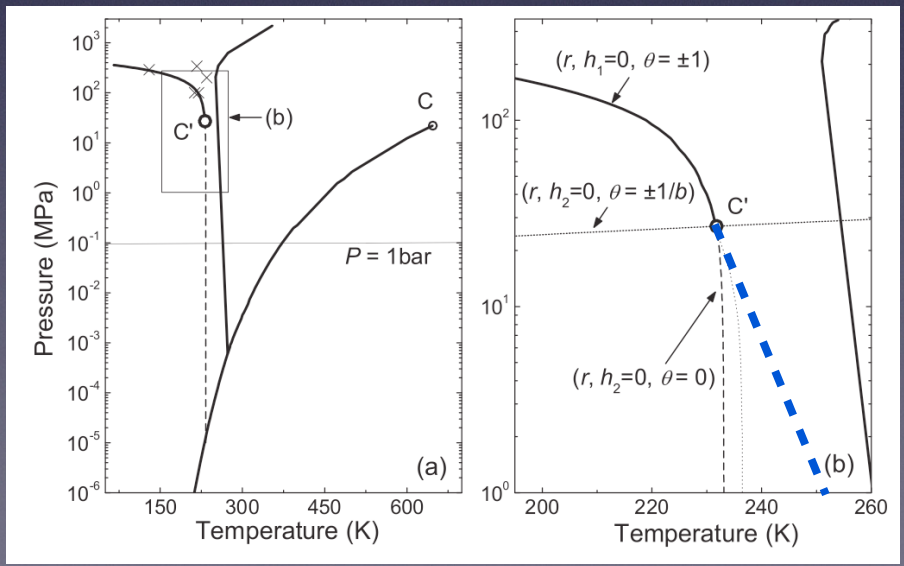
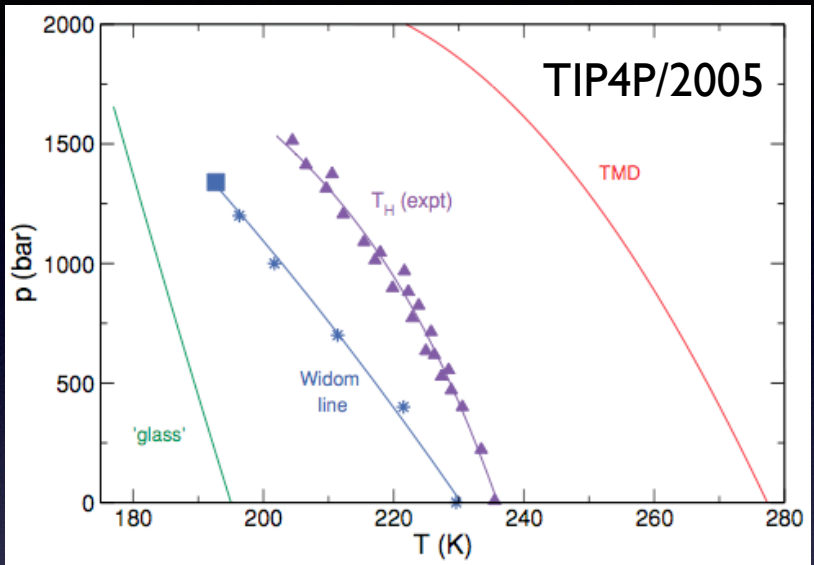


Fuentevilla and Anisimov PRL (2006)

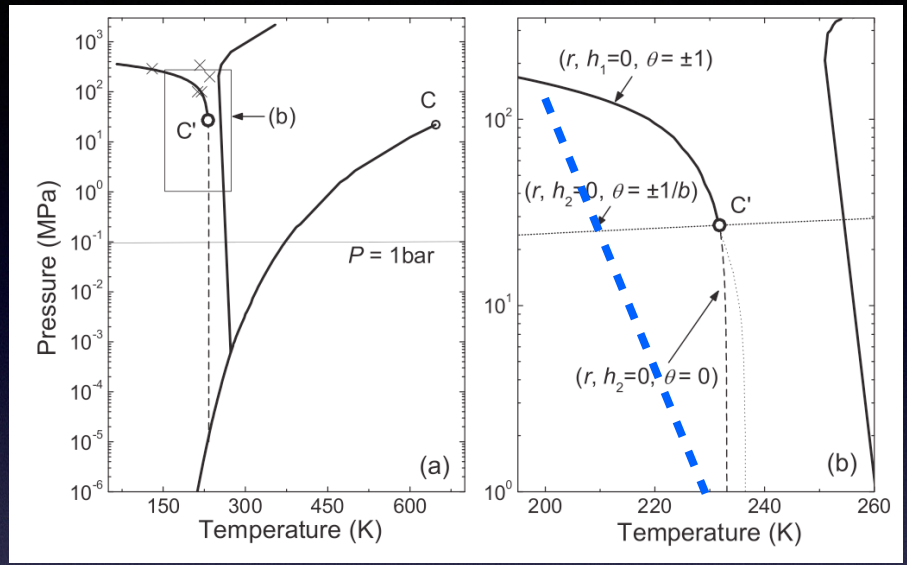


Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).

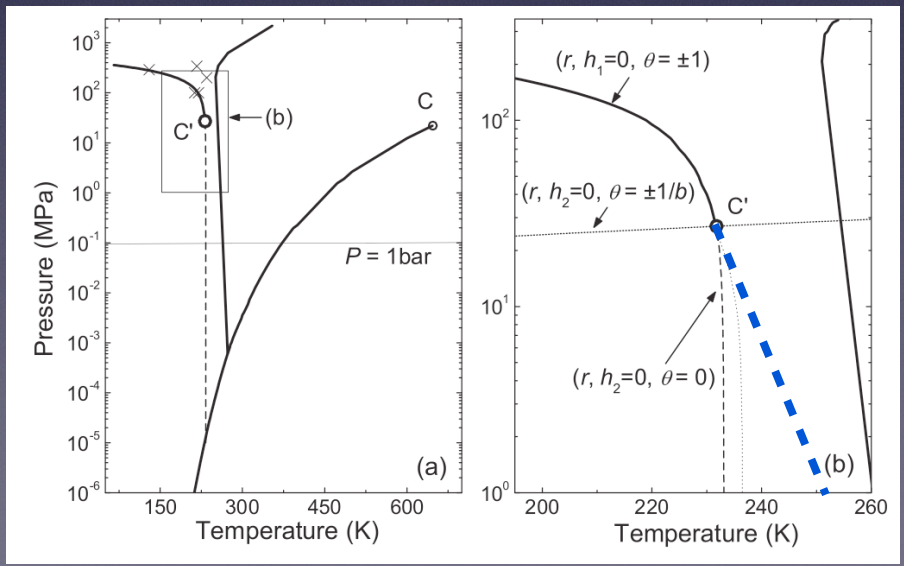
Widom line consistent with fitting from experiments,
Weak Cp Max line consistent with "Widom line" from simulations

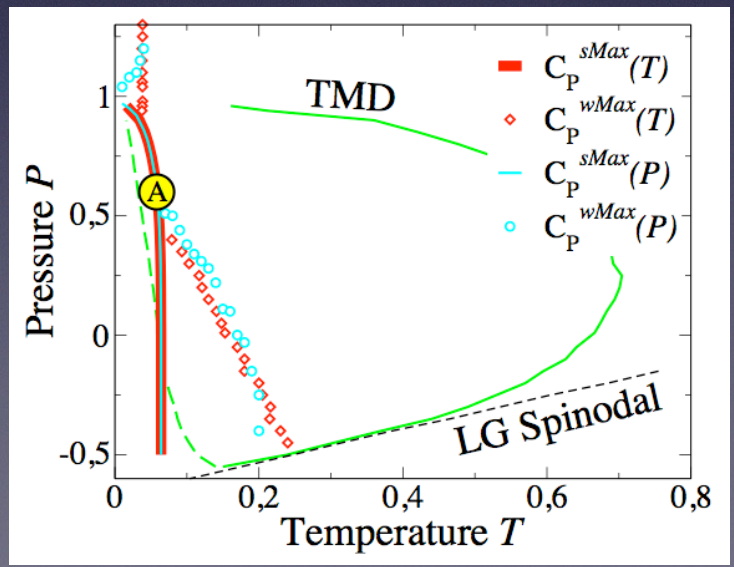


Abascal and Vega JCP (2010)

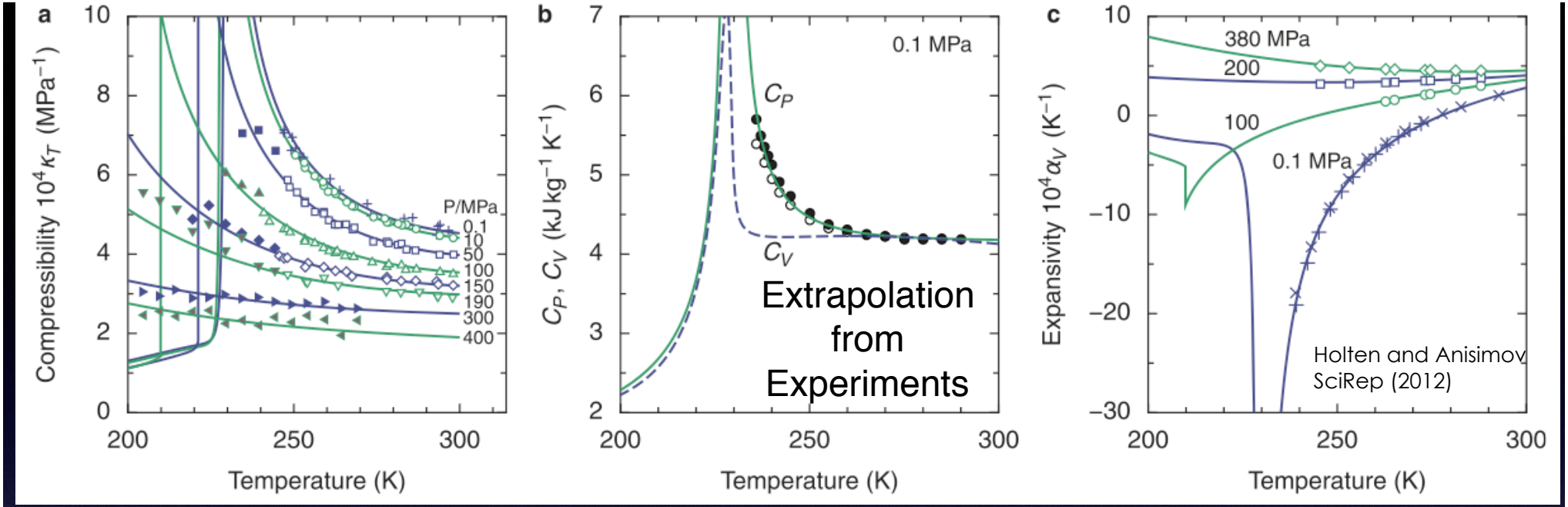


Fuentevilla and Anisimov PRL (2006)

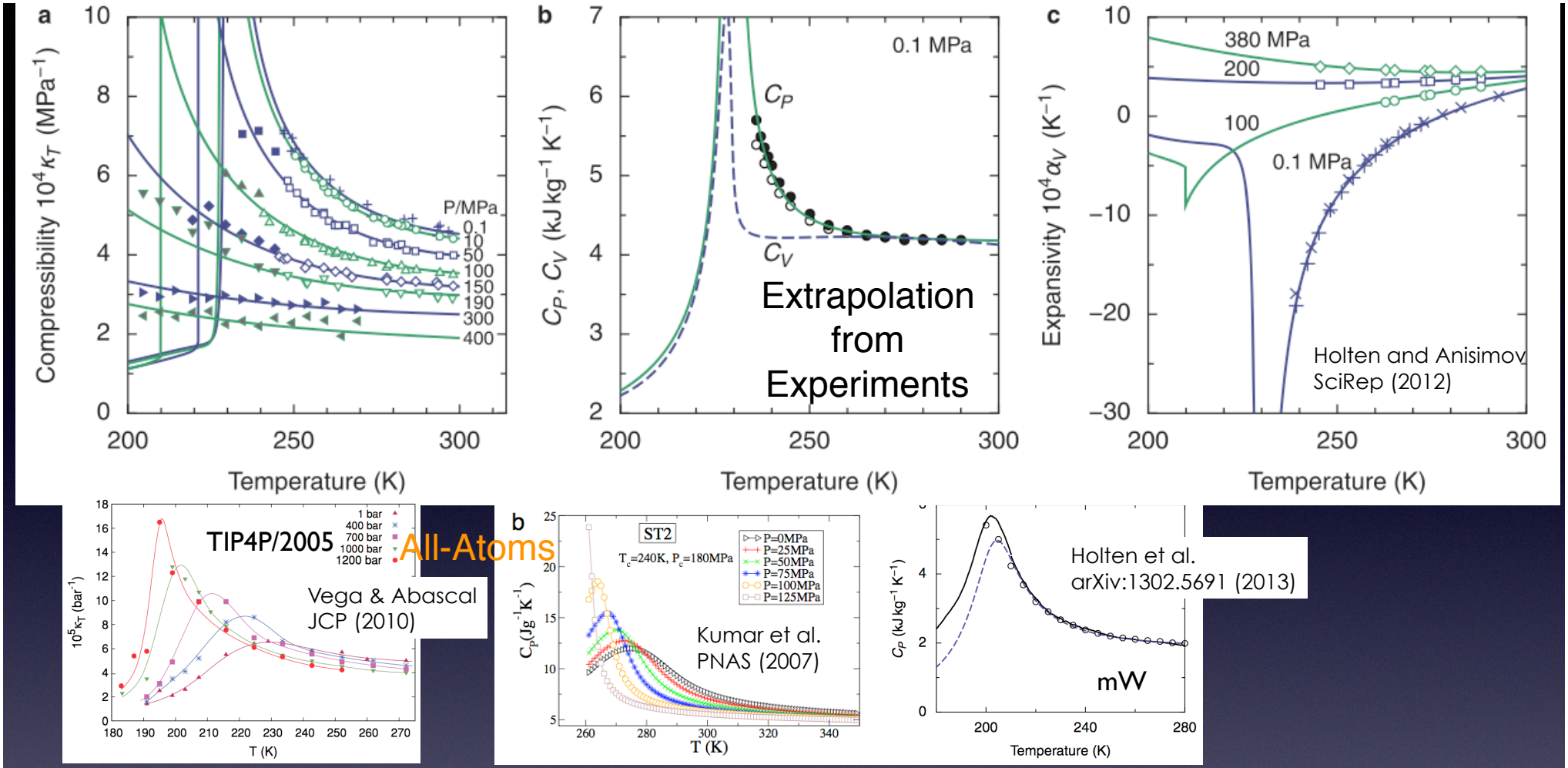




Valentino Bianco & G.F., Scientific Reports 4, 4440 (2014).


a
Compressibility $10^4 \kappa_T$ (MPa^{-1})
P/MPa
0.1
10
50
100
150
190
300
400
Temperature (K)
b
C_P, C_V (kJ kg^{-1} K^{-1})
0.1 MPa
C_P
C_V
Extrapolation from Experiments
Temperature (K)
c
Expansivity $10^4 \alpha_V$ (K^{-1})
380 MPa
200
100
0.1 MPa
Holten and Anisimov SciRep (2012)
Temperature (K)

TIP4P/2005


a
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P/MPa
0.1
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0.1 MPa
C_P
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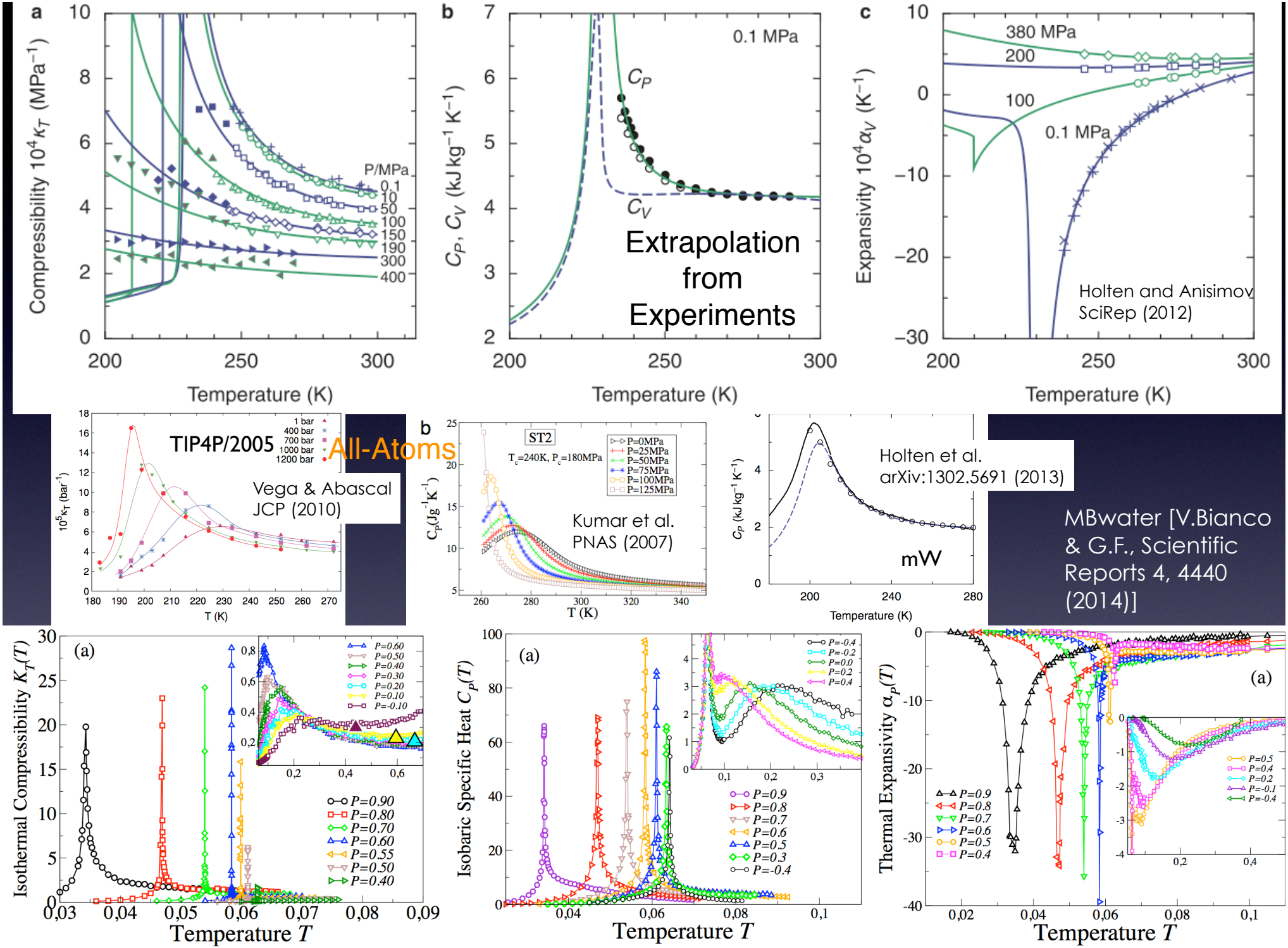
380 MPa
200
100
0.1 MPa
Holten and Anisimov SciRep (2012)
Temperature (K)

TIP4P/2005
All-Atoms
1 bar
400 bar
700 bar
1000 bar
1200 bar
$10^5 \kappa_T$ (bar^{-1})
T (K)
Vega & Abascal JCP (2010)

b
ST2
T_c=240K, P_c=180MPa
P=0MPa
P=25MPa
P=50MPa
P=75MPa
P=100MPa
P=125MPa
C_p(Jg^{-1}K^{-1})
T (K)
Kumar et al. PNAS (2007)

Holten et al. arXiv:1302.5691 (2013)
C_P (kJ kg^{-1} K^{-1})
mW
Temperature (K)


a
Compressibility $10^4 \kappa_T$ (MPa^{-1})
P/MPa
0.1
10
50
100
150
190
300
400
Temperature (K)
b
C_P, C_V (kJ kg^{-1} K^{-1})
0.1 MPa
C_P
C_V
Extrapolation from Experiments
Temperature (K)
c
Expansivity $10^4 \alpha_V$ (K^{-1})
380 MPa
200
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TIP4P/2005
All-Atoms
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400 bar
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1000 bar
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$10^5 \kappa_T$ (bar^{-1})
Vega & Abascal JCP (2010)
T (K)
b
ST2
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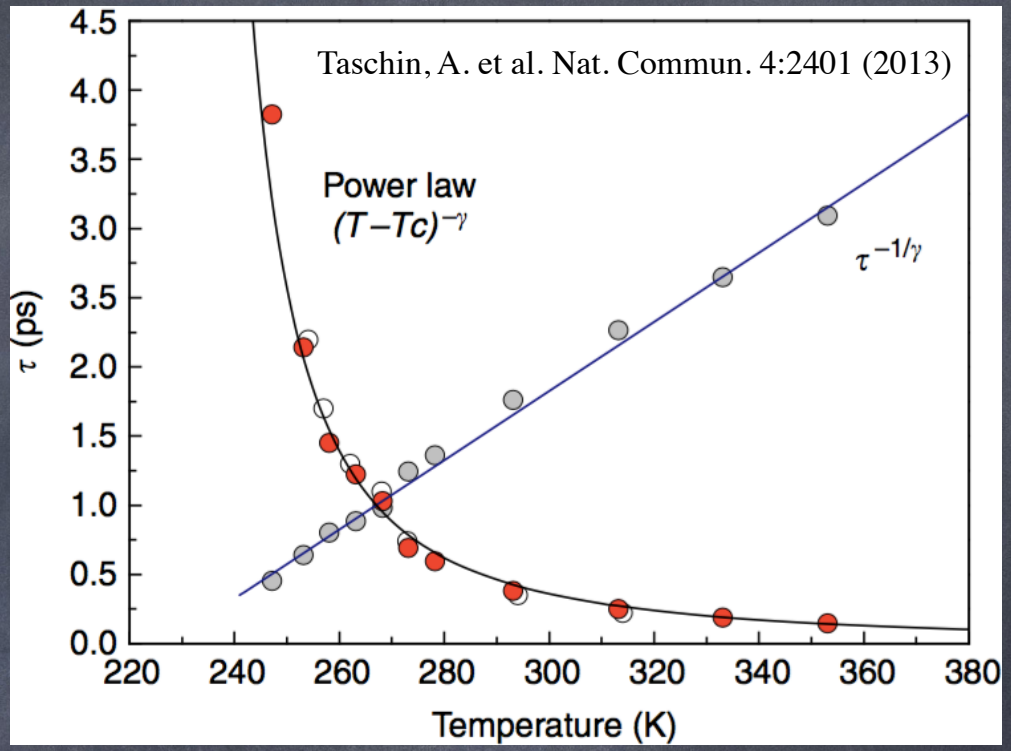
P=125MPa
C_p(Jg^{-1}K^{-1})
Kumar et al. PNAS (2007)
T (K)
C_P (kJ kg^{-1} K^{-1})
Holten et al. arXiv:1302.5691 (2013)
mW
Temperature (K)
MBwater [V.Bianco & G.F., Scientific Reports 4, 4440 (2014)]
(a)
Isothermal Compressibility $K_T(T)$
P=0.60
P=0.50
P=0.40
P=0.30
P=0.20
P=0.10
P=-0.10
P=0.90
P=0.80
P=0.70
P=0.60
P=0.55
P=0.50
P=0.40
Temperature T
(a)
Isobaric Specific Heat $C_P(T)$
P=-0.4
P=-0.2
P=0.0
P=0.2
P=0.4
P=0.9
P=0.8
P=0.7
P=0.6
P=0.5
P=0.3
P=-0.4
Temperature T
(a)
Thermal Expansivity $\alpha_P(T)$
P=0.9
P=0.8
P=0.7
P=0.6
P=0.5
P=0.4
P=0.5
P=0.4
P=0.2
P=-0.1
P=-0.4
Temperature T

Experimental evidences?

- optical Kerr effect (OKE) on vibrational dynamics at P=1 atm
- structural correlation time τ Large increase (divergence) for T—> Tc=227 K
- 227 K ~ Tc of LLCP at P >> 1atm ==> Widom line P-independent



X

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