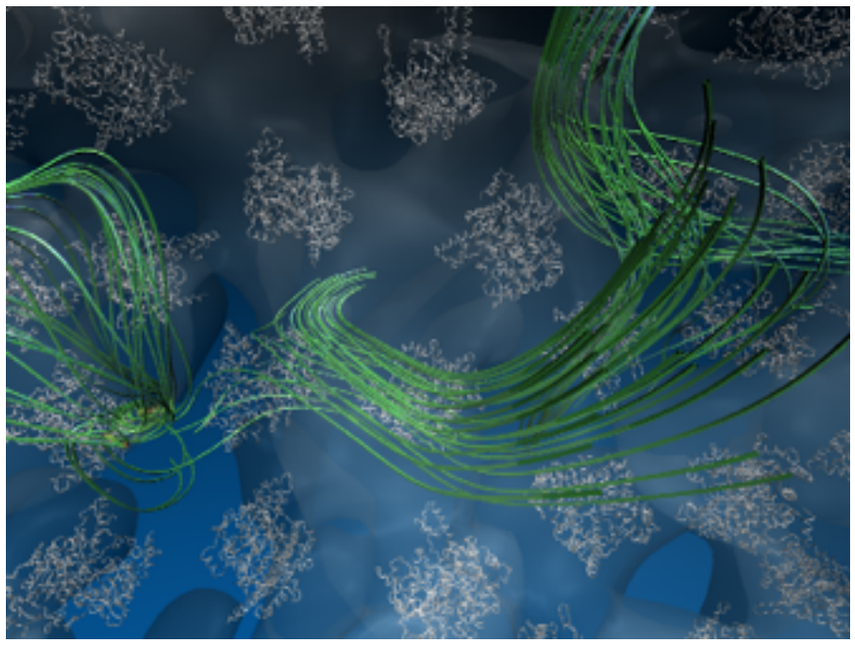
GRC.water.2016

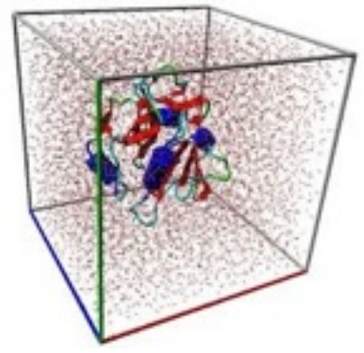
Proteins in cell

modelling cell-like environments...



F.Sterpone
LBT/UPR9080
IBPC,CNRS,Paris

Proteins in silico



Parallel
SuperComputing

DE Shaw
Anton Computer

GPU

years

PME / RESPA

70’s | 80’s | 90’s | 00’s

McCammon,Gelin, Karplus
Nature (1977)

BPTI in vacuum

9 ps

Levitt&Sharon Pnas (1988)

BPTI in water

210 ps

10….100 ns

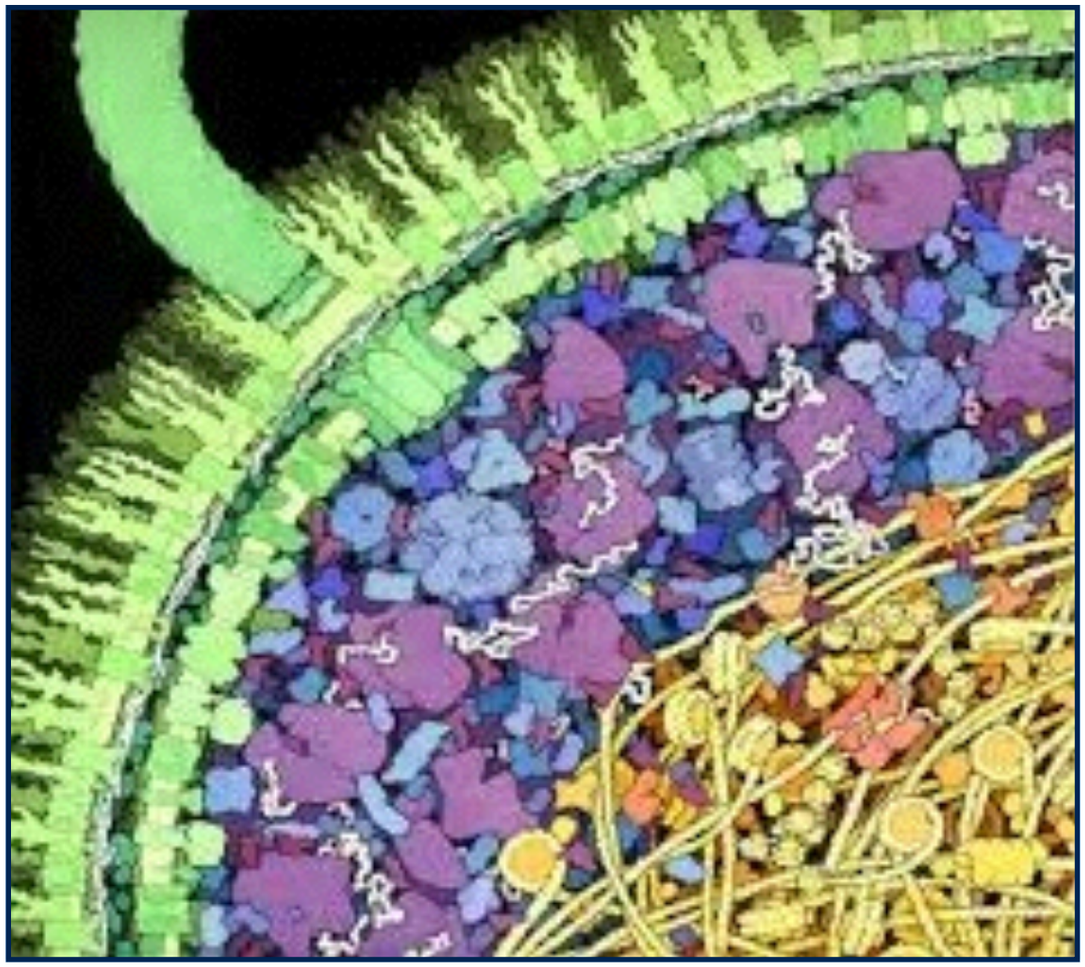
µs-ms

MD mainly confined to a single protein in solution or in membrane!

Proteins in the Cell

Ellis, Trends in Biochemical Sci (2001)

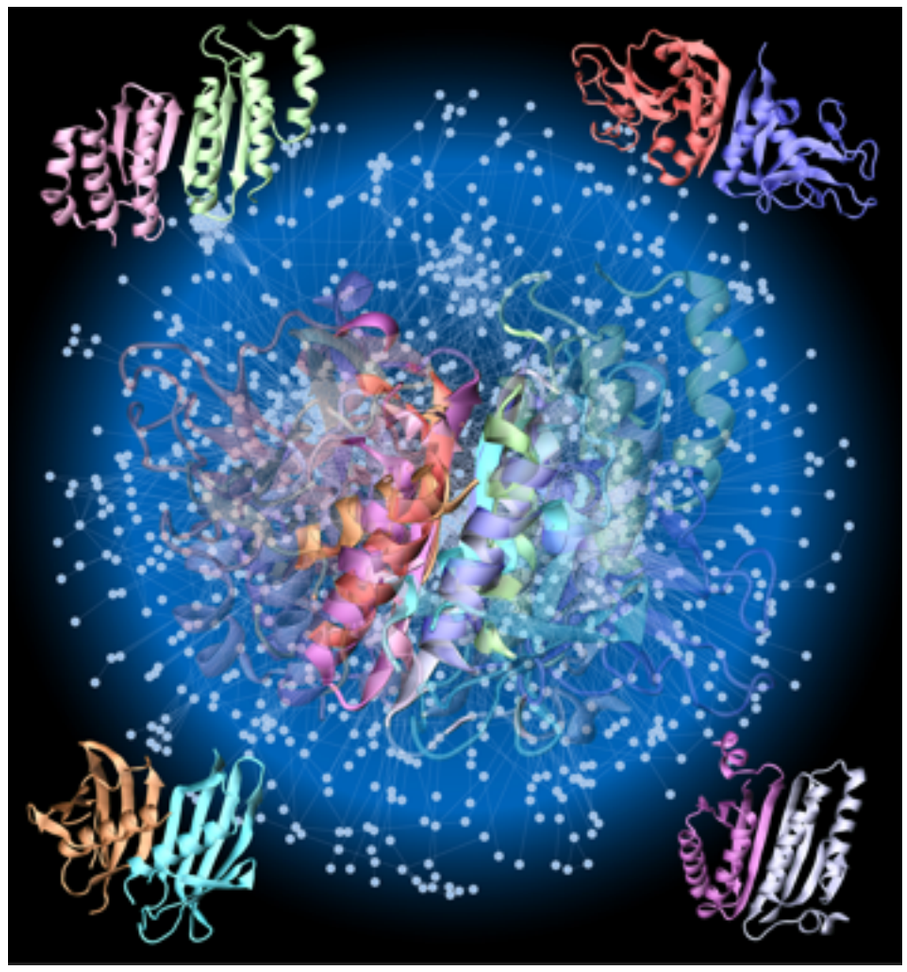
model of E. coli



Goodsell, Scripps, California, US

… some keywords

heterogenous distributions
trafficking
functional cascades
network of interactions



… composition

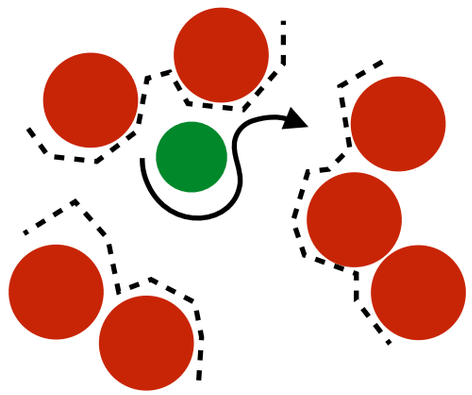
water 70 % in mass
macromolecules ~30 %
ions < 1%

Protein diffusion in cells

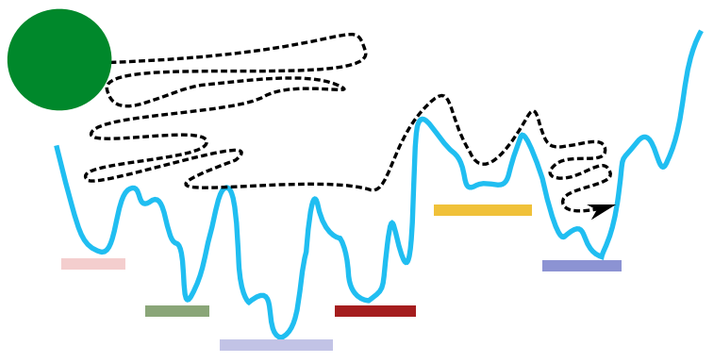
Dix, Verkman, Ann Rev Biophys (2008)

crowding effects on mobility

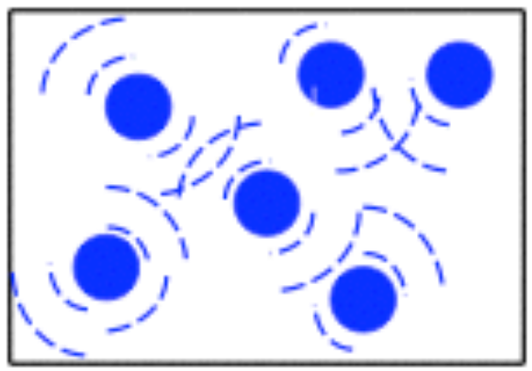
geometric disorder



distribution of times for jumping

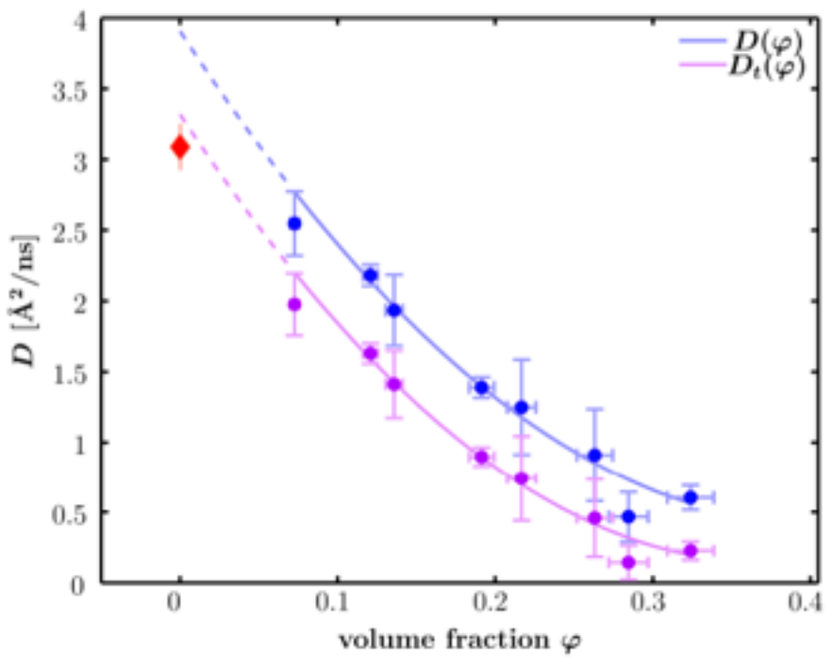


solvent mediated interactions

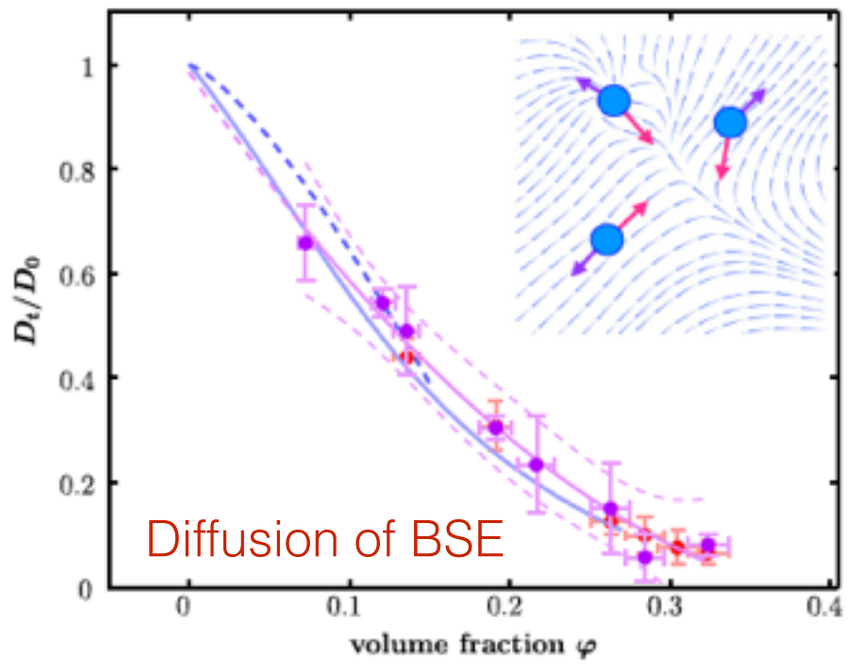


e.g. Neutron Scattering timescale nanoseconds

slowdown is due to solvent-mediated interactions



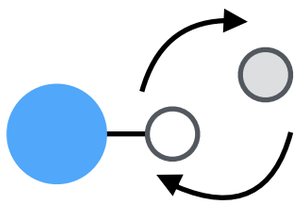
slowdown by crowding



Roosen-Runge et al. PNAS (2011)

Stability under crowding

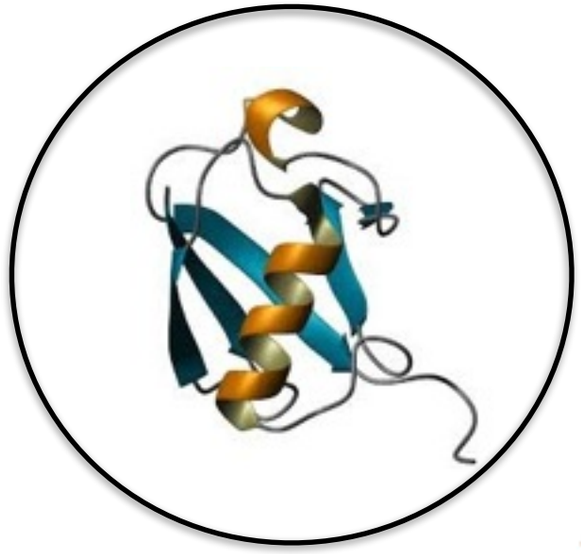
Wang et al, JACS (2012)



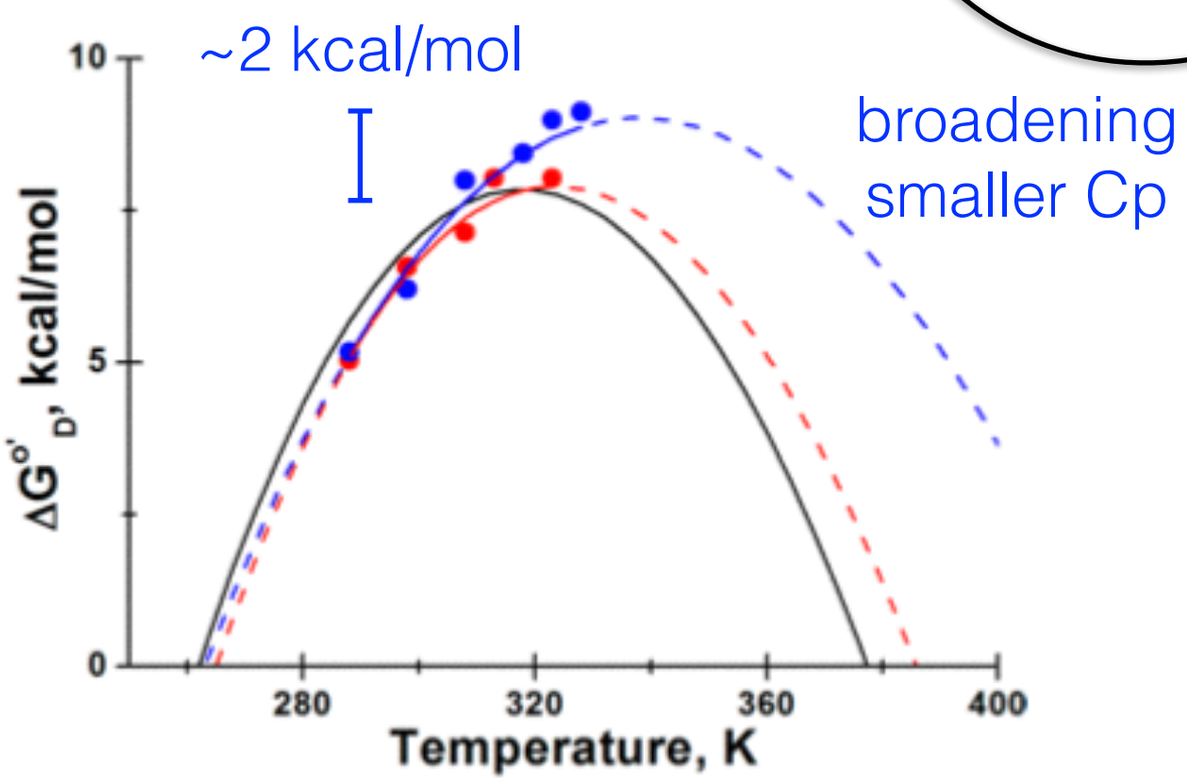
H/D exchange

<f>/<u>

Stability of ubiquitin

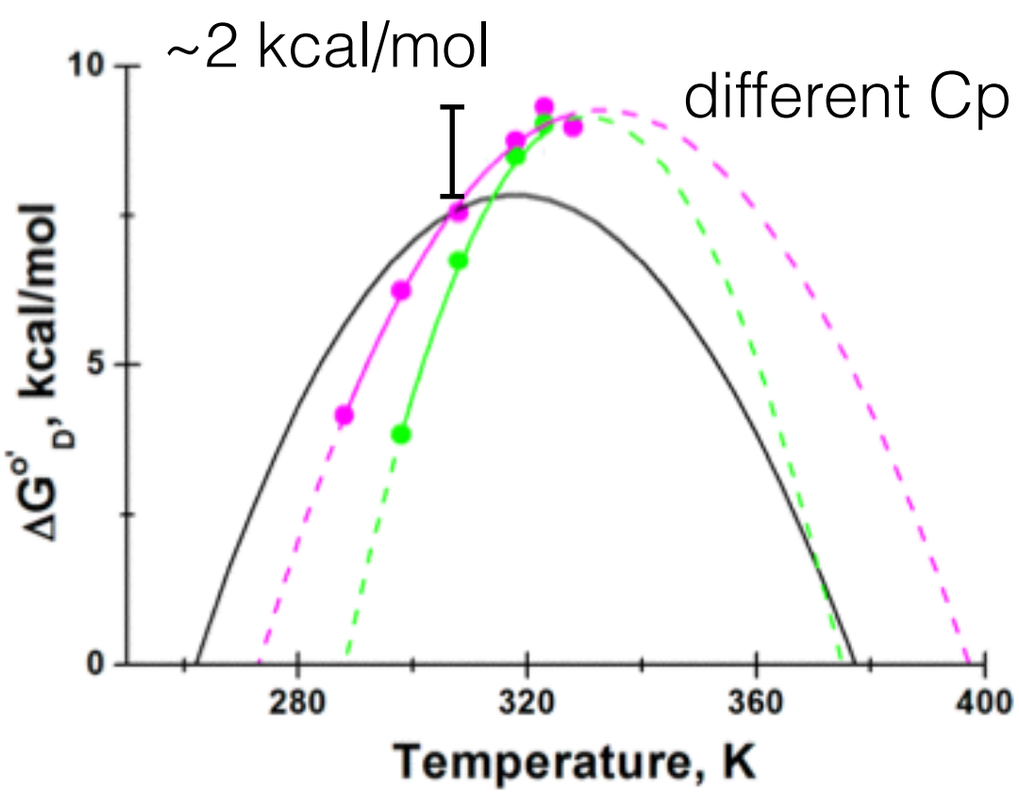


- Ficoll 100 g/L
- PVP 100 g/L



Crowding by polymers

- lysozyme 100 g/L
- BSA 100 g/L



Crowding by proteins

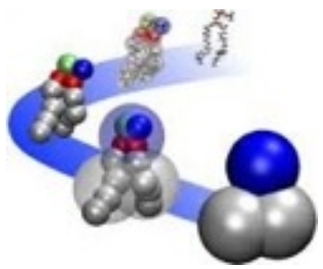
Toward simulations of cell-like environments

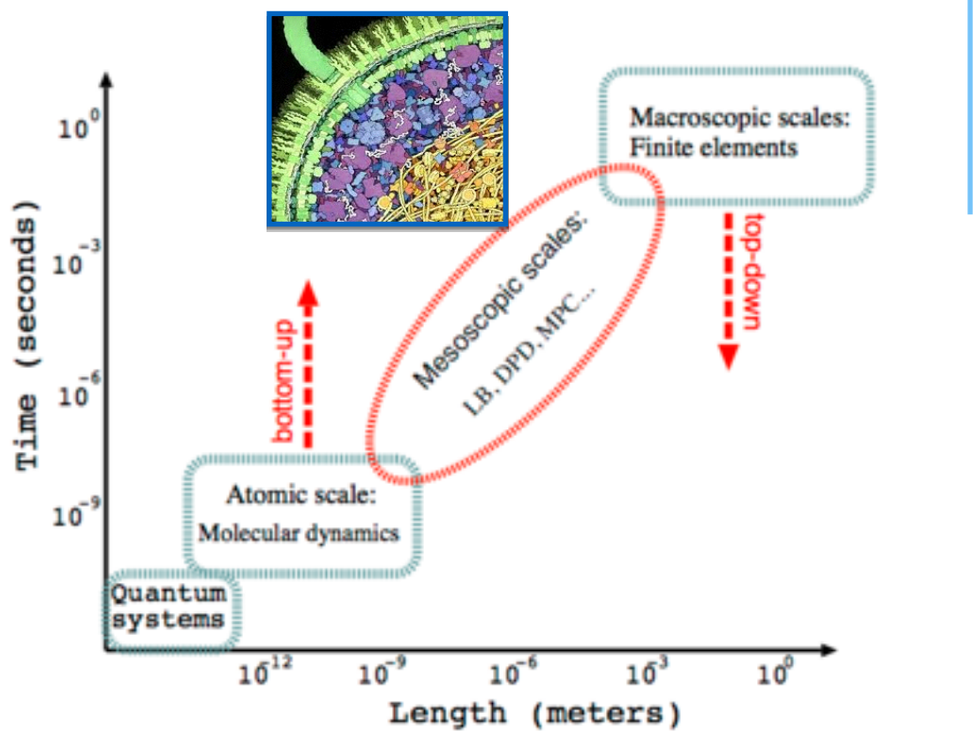
All atom approach: too challenging

1000 proteins in solution at φ~30%

~90,000,000 particles

Implicit solvent coarse-grained: good





but solvent mediated interactions ?

Brownian Dynamics + Hydrodynamics Interactions (Oseen / Rotne-Prager-Yamakawa)

poor scalability with size!

diffusion/folding	Ermak&McCammon JCP(1978) Frembgen-Kesner&Elcock JCTC (2009) Mikhailov&Kapral PNAS (2015) Lipska et al JCP (2016)
molecular motor	Goldtvik et al JPC (2016)
aggregation	Ando&Skolnick BJ (2013)

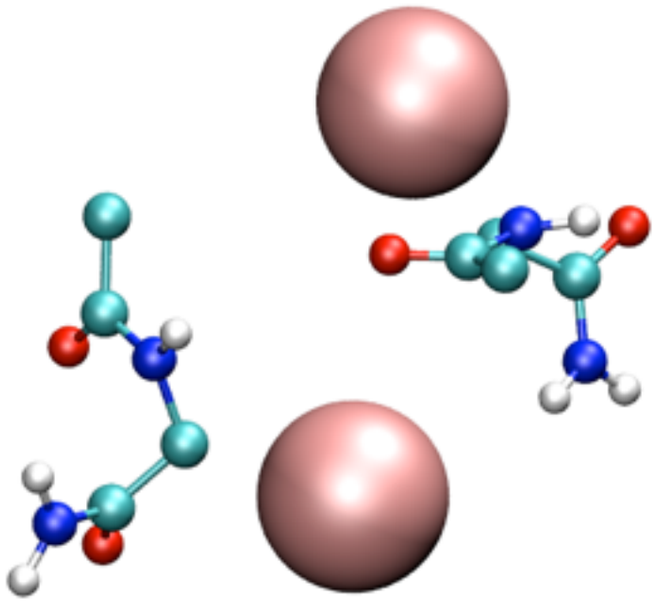
MD + Multiple Particle Collision

	Malevanets&Kapral, JCP(1999)
mobility/catalysis	Schfield et al, JCP(2012)

MD + Lattice Boltzmann accounting kinetics of solvent ← excellent scalability with size!

colloid/polymers	Ahlrichs&Dunweg, JCP(1999) Limbach, CPC(2006)

The coarse-grained model OPEP



Chebaro et al, JPCB(2102),**FS** et al. JNCS(2014),**FS** et al, ChemSocRev(2014)

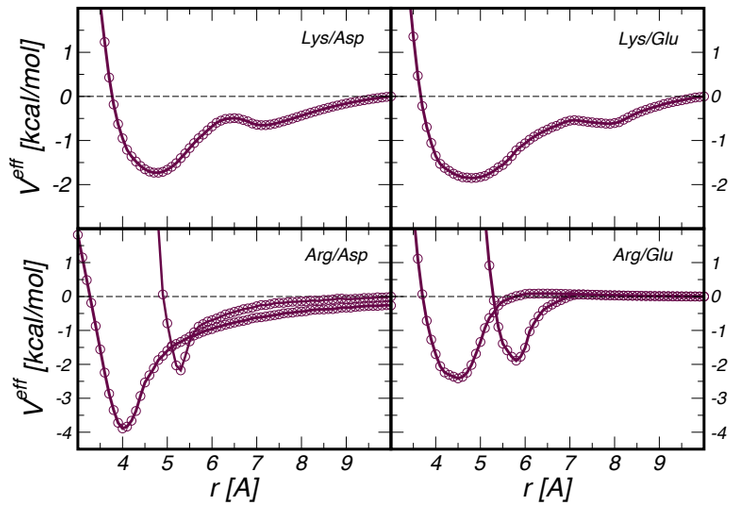
Optimized **P**otential for **E**fficient protein structure **P**rediction

back-bone atomistic resolution
Side-chain 1 bead

water and electrostatic free

cooperative term for HBs
ad hoc potential for ion-pairs

Ion-Pair Potentials



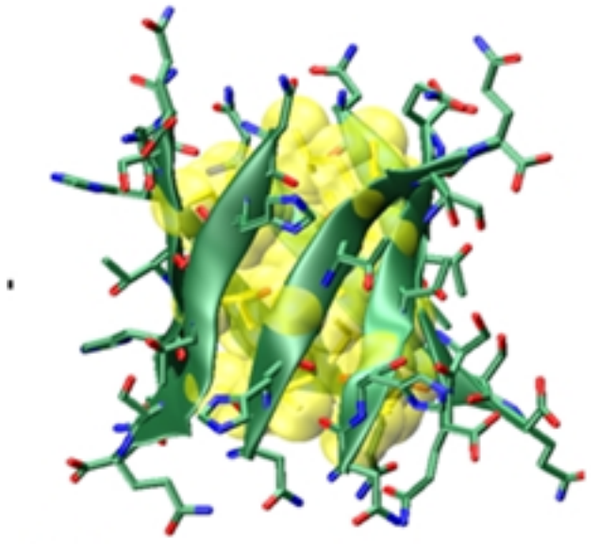
Techniques / Applications

Molecular Dynamics, Monte Carlo

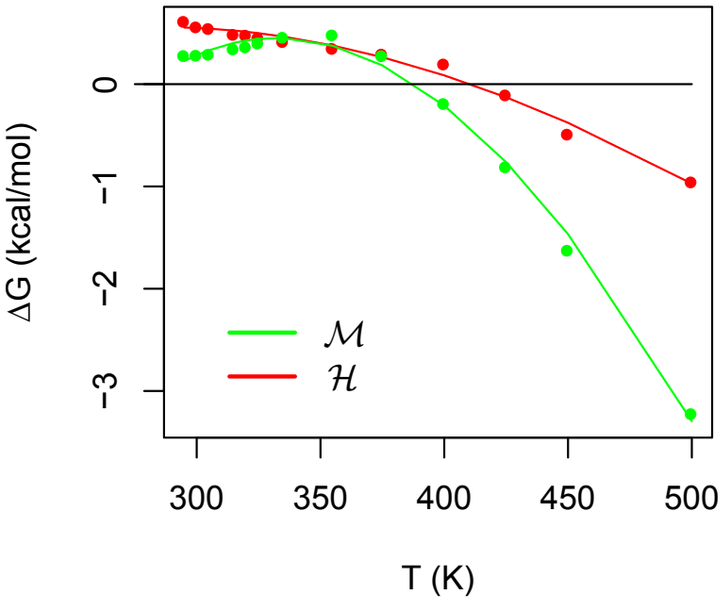
REMD, Simulated Tempering,
Metadynamics

Folding/Unfolding,
Amyloid aggregation

Amyloid oligomer structures



Different stability for mesophilic/thermophilic proteins



A solute in fluid

coupling MD and LB

FS et al Chem Soc Rev (2014), **FS** et al. JCTC (2013), **FS** et al. JCTC (2015), MK,PD,**FS** JNCS **(2015)**

fluid → molecule

$$\mathbf{F}_{drag,i} = -m\gamma(\mathbf{v}_i - \mathbf{u}_i)$$

interpolation

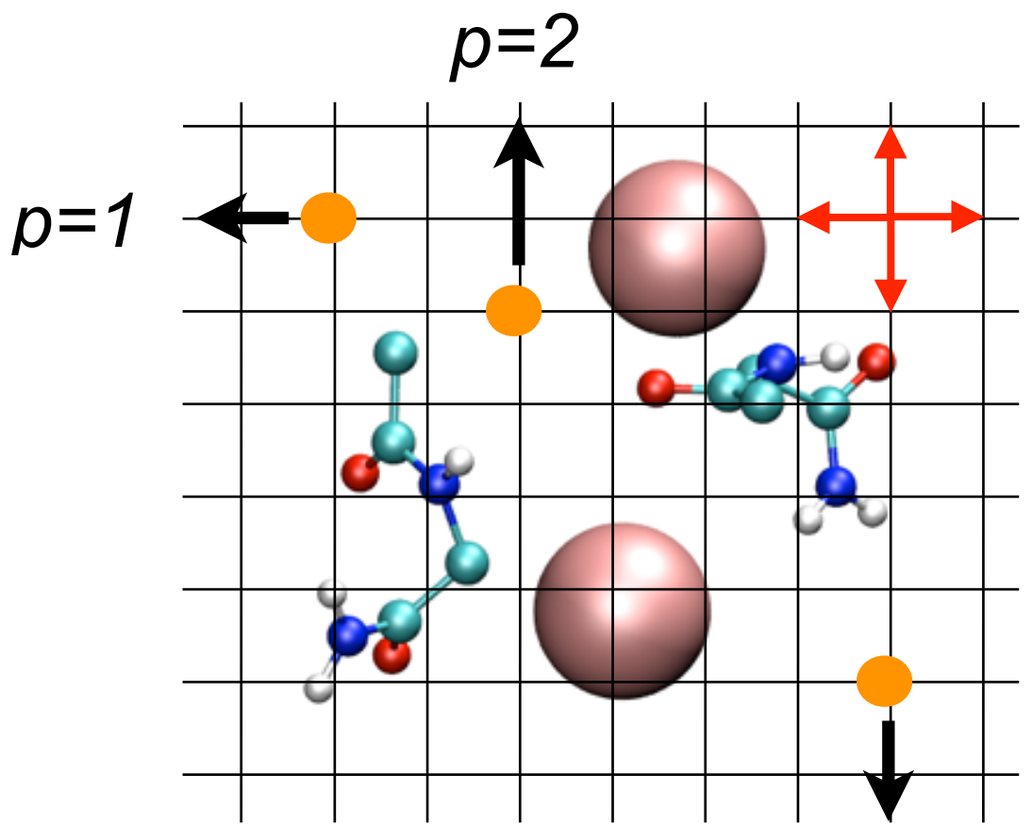
extrapolation on grid

Molecular Particle i

molecule → fluid

$$S_p(\mathbf{x},t) = \omega_p \sum_i [\mathbf{F}_{drag,i} + \mathbf{F}_{r,i}] \cdot \mathbf{c_p}/c_s^2$$

mesh *random force*



Lattice Boltzmann Particle

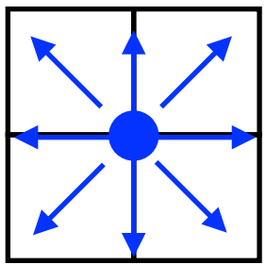
Discrete velocity (cp)

$f_p(\mathbf{x},t)$ Velocity distribution along *pth* direction

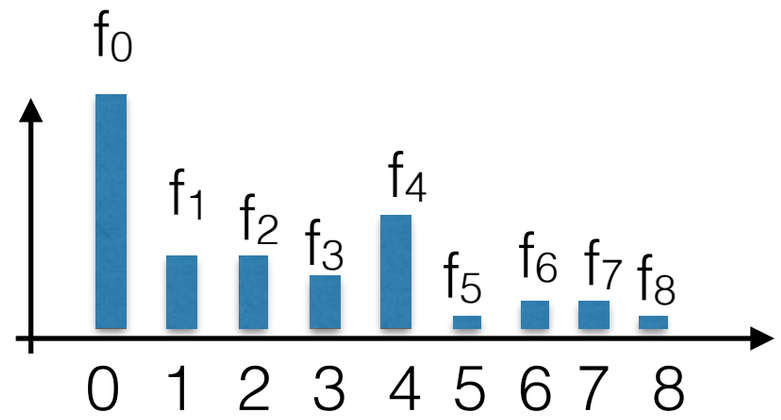
$$\mathbf{u}(\mathbf{x},t) = 1/\rho \sum_p f_p \mathbf{c_p}$$

A solute in fluid

coupling MD and LB



ie 2 dimensional lattice D2Q9



streaming BGK collision

$$f_p(x + c_p\Delta t, t + \Delta t) = f_p(x,t) - \omega\Delta t(f_p - f_p^{eq})(x,t) + S_p\Delta t$$

Solute feedback

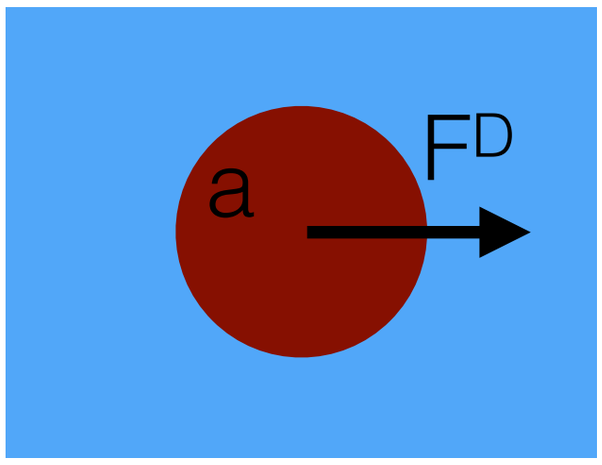
+ noise

➡ Relaxation Time $\omega \sim 1/\nu$ ν = Fluid Kinematic Viscosity

Water 0.1 - 0.166 [Å^2 / fs]

➡ Solute/Fluid coupling microscopic friction γ used as independent parameter

Hynes,Kapral,Weinber, JCP(1978)



$$F^D = -\gamma(v - u)$$
$$\gamma = 6\pi\eta a$$

Macroscopic Stokes Law relates γ and η

A solute in fluid

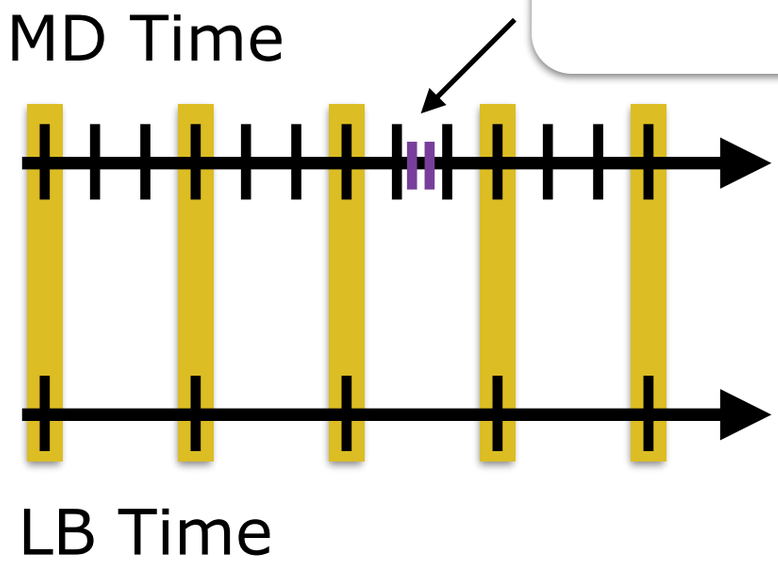
Multi-scaling

MD Time |||

multi-timestep

intra-

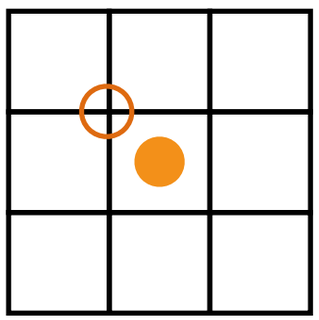
inter-



LB Time and MD Time

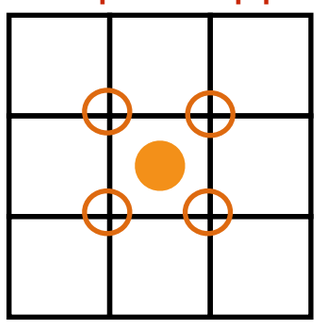
Grid Interpolation

Nearest Point



cheap

Multiple support



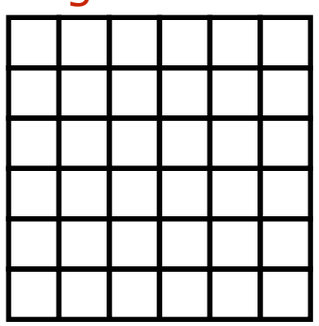
expensive

lattice

particle

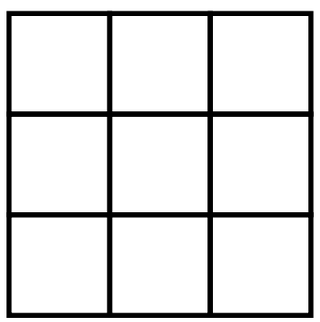
Grid Resolution

High Res



expensive

Low Res



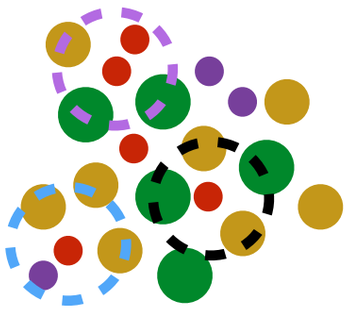
cheap

CPU Time $\sim N_g^3$

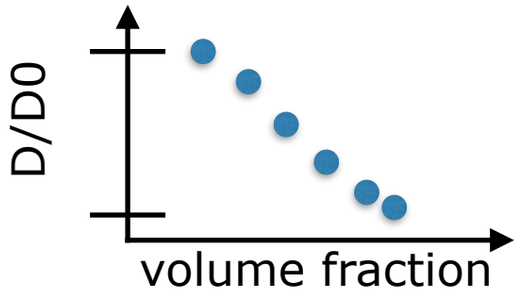
A solute in fluid

toward the cell

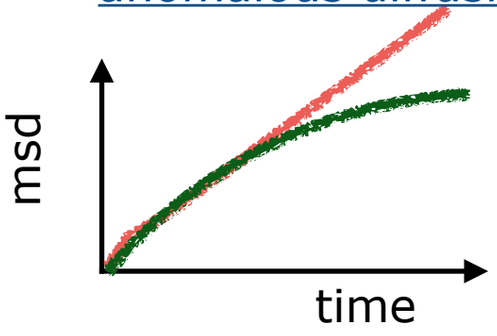
Diffusion/Stability



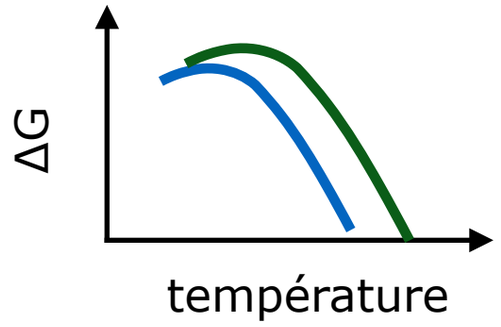
slowdown



anomalous diffusion

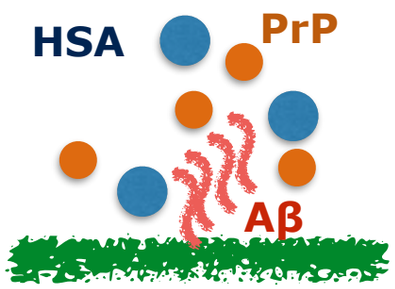


packing/specific interactions



P. Derreumaux (LBT), experiments G. Pielak (Univ North Caroline)

Aggregation Amyloid



Problems

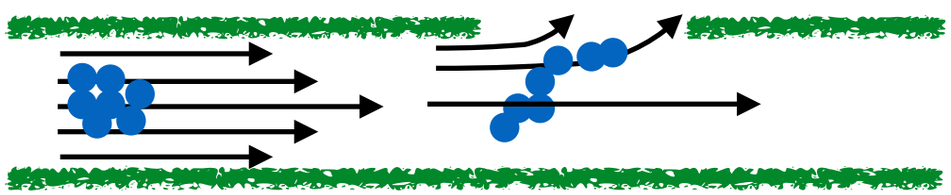
crowding and aggregation, co-receptor, membrane

CG model for lipids

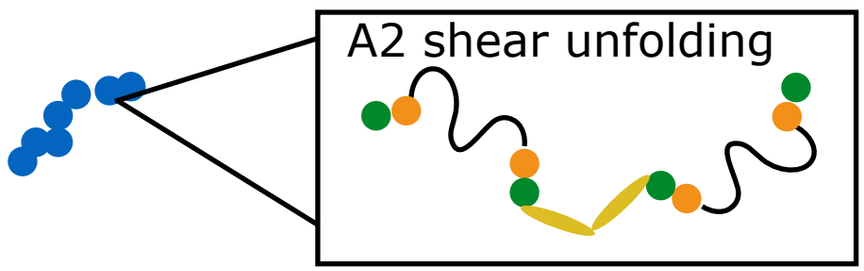
P. Derreumaux (LBT), experiments U. Rezai (INSERM)

Shear-Flow effect

vassel injuries



VWF (multimeric protein) senses shear-flow (vassel injuries)

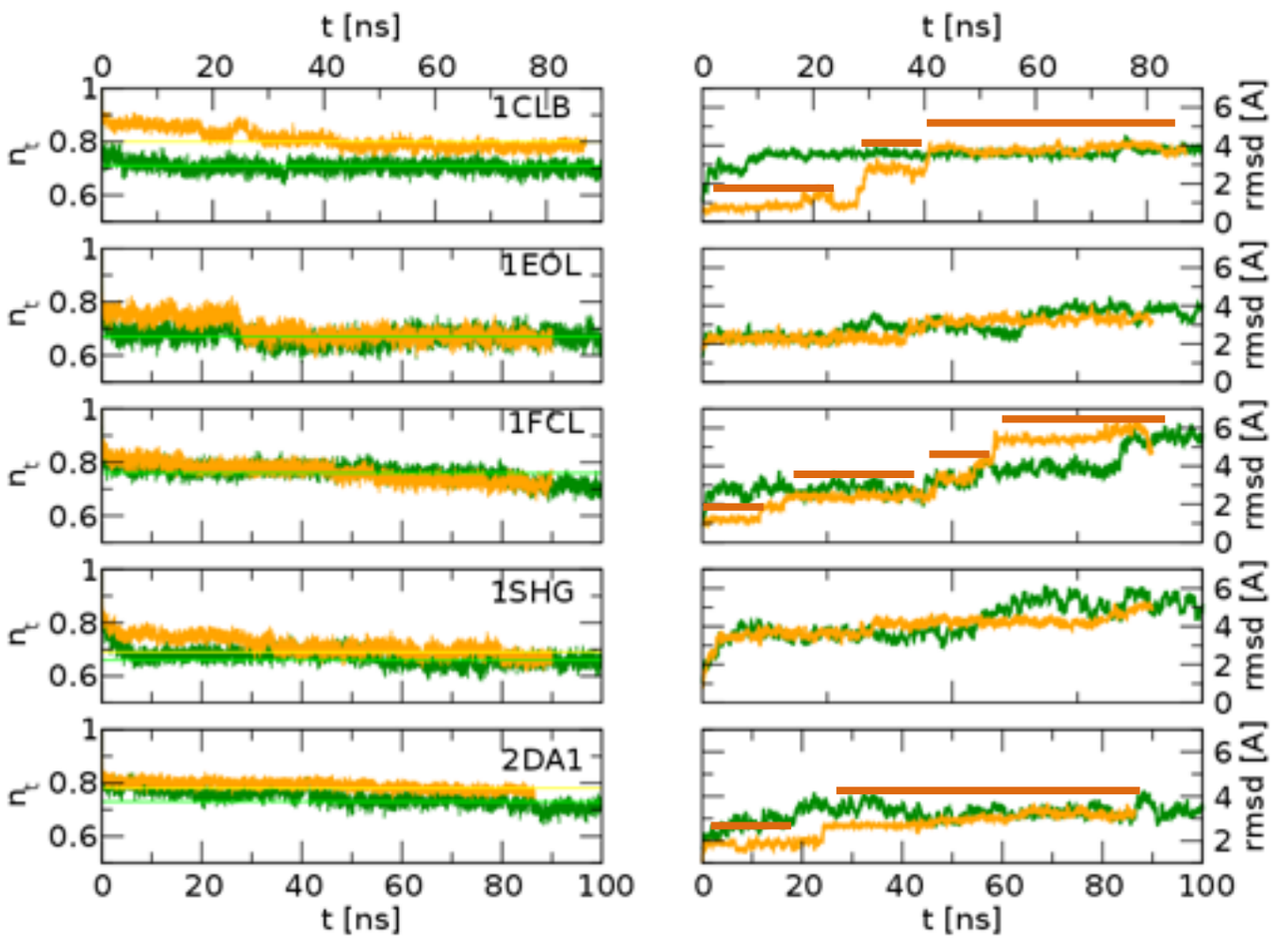


Muphy/OPEP: Protein Stability

FS et al. JCTC (2015)

1CLB 1E0L 1FCL 1SHG 2DA1

Hydrodynamics Langevin



Same Stability in Langevin Dynamics and with Hydrodynamics

RMSD [A]

1CLB	3.7
1E0L	3.4
1FCL	5.5
1SHG	5.3
2DA1	3.3

when RMSD is high
arrangement of secondary structures, only minor instabilities

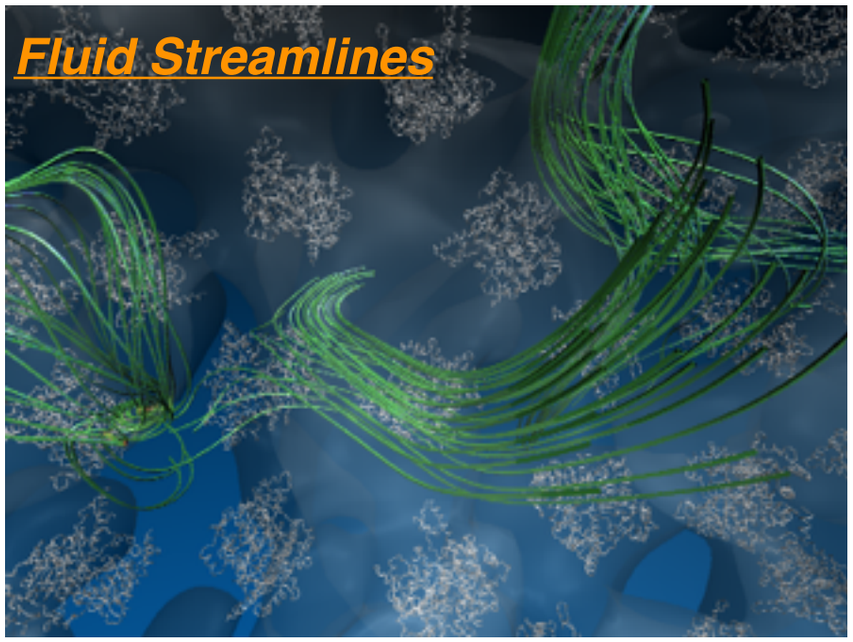
Hydrodynamics:: longer living states

Muphy/OPEP: Protein diffusion

Protein mobility in "cell"

Massive simulation

FS et al ChemSocRev (2014)



Simulations

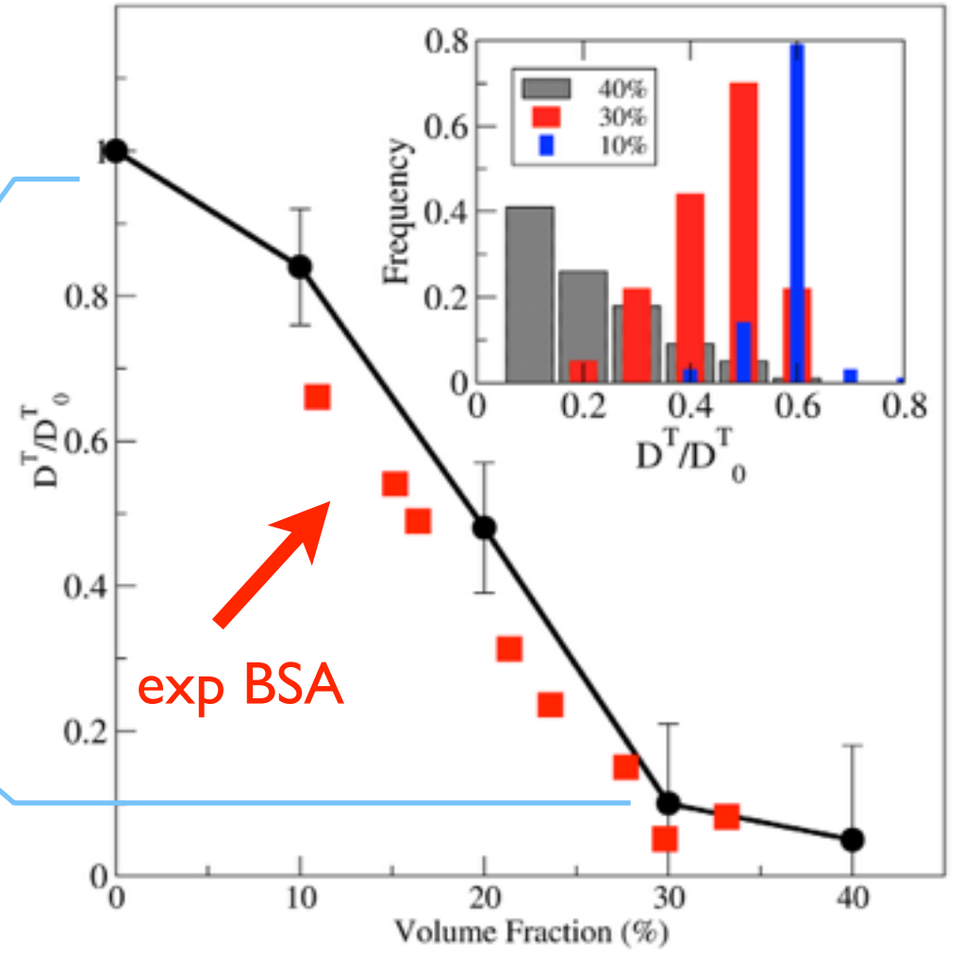
17576 Rat 1 yeast proteins (*S. Pombe*)
Rat 1= 4013 CG particles
17756 GPU Titan Supercomputer (Oak Ridge)
for **Gordon Bell Prize 2013 (SuperComputing)**

Simulation time ~30 ns

Authors

Bernaschi / Bisson / Fatica / Melchionna

Crowding Φ=30%
Diffusion slowdown D/D0~1/10



*Roosen-Runge et al. PNAS(2011)

Muphy/OPEP: Protein diffusion

Chiricotto, Derreumaux, **FS,** Melchionna**,** Philos.Tran.(2016)

Protein mobility in "cell"

Elastic Network for Proteins

Simulations

70 CI2 protein
CI2= 331 CG particles
Elastic Network (EN) or protein

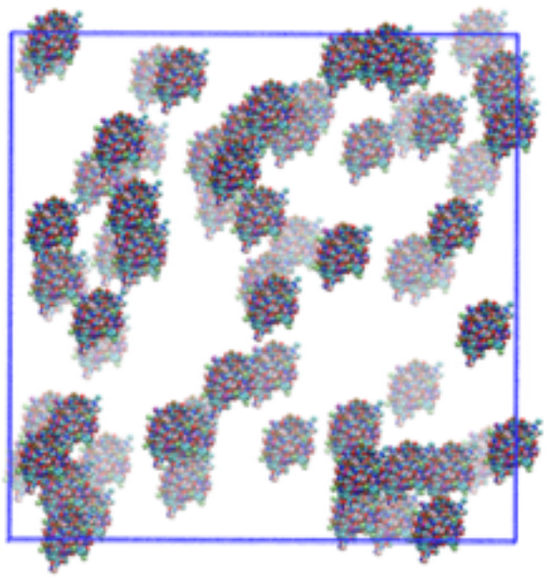
Box L=135, 145, 160, 180, 250 A.

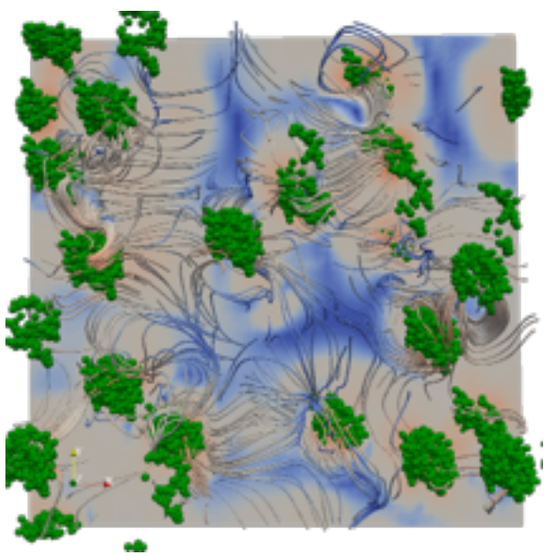
Simulation time 0.5 μs

D0~14 A^2/ns (*exp 15 A^2/ns)

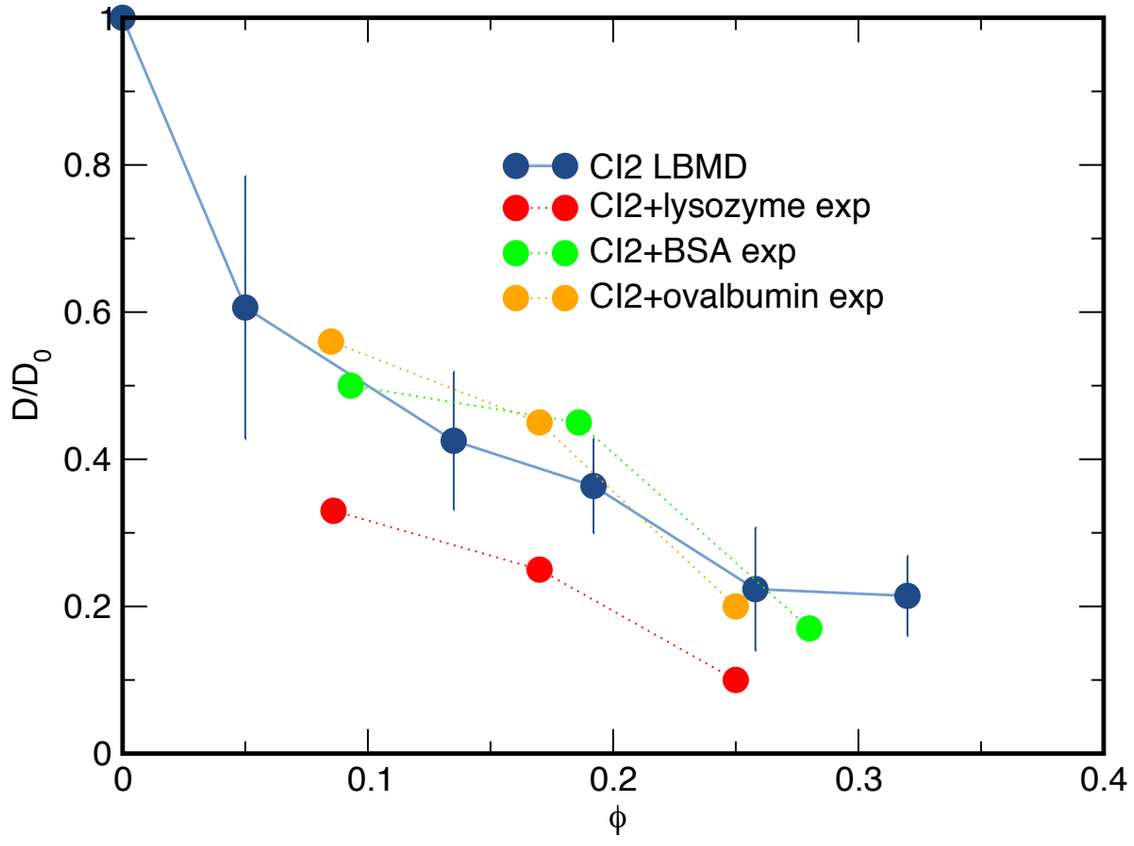
EN cheap&good
possibility to modulate flexibility
time scale up to μs

€ affordable $
64 < cores < 512





Fluid Streamlines

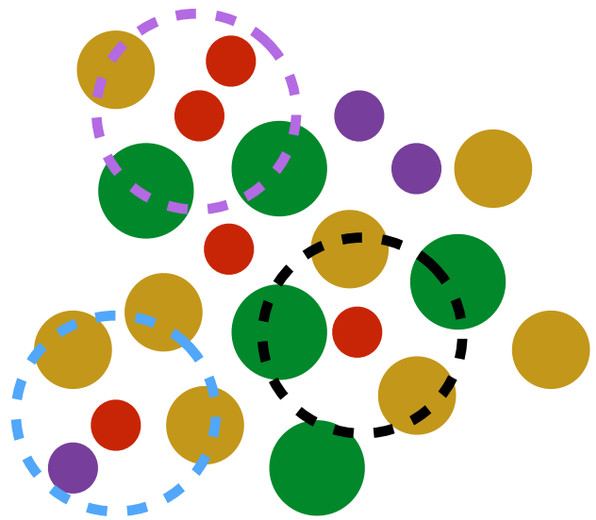


*Wang, Li, Pielak JACS (2010)

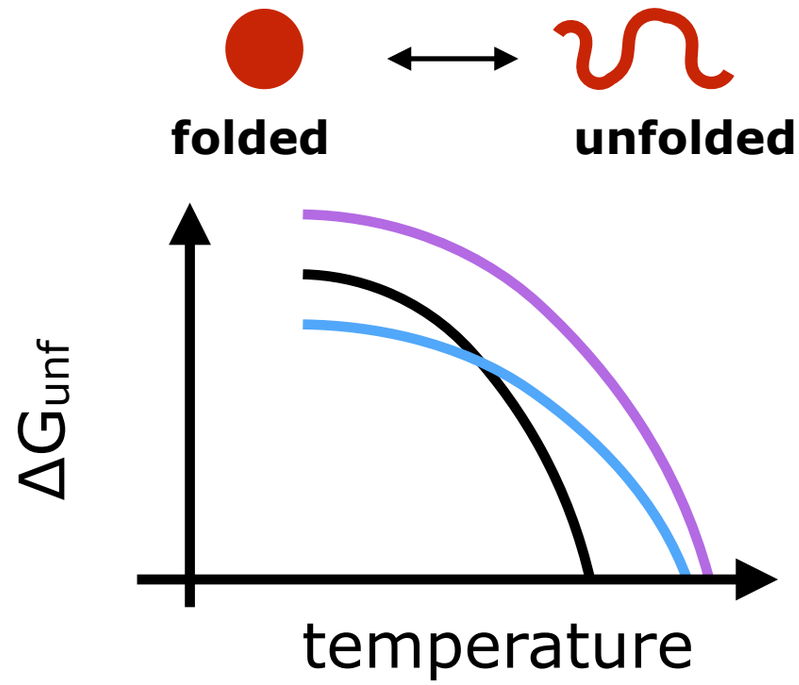
Muphy/OPEP: Back-map…

Protein mobility in "cell"

Shake, sample, and back-map



LBMD:: sampling local packing



Enhanced Sampling :: stability curves

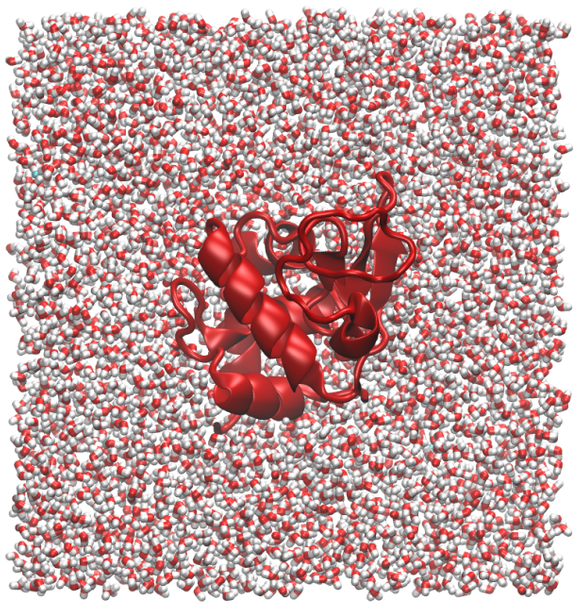
@CG level or all-atoms (back-map)

Muphy/OPEP: Back-map…

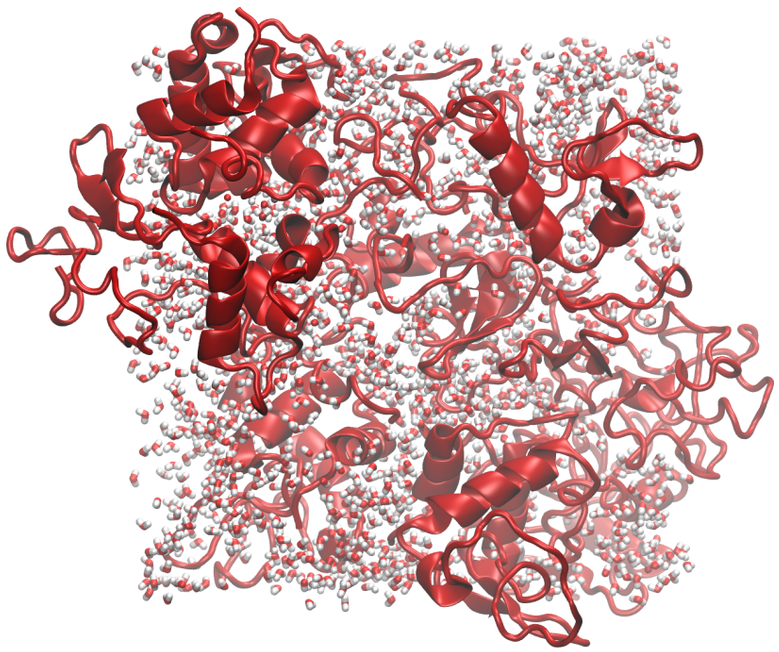
Protein mobility in "cell"

lysozyme in powder + REST2

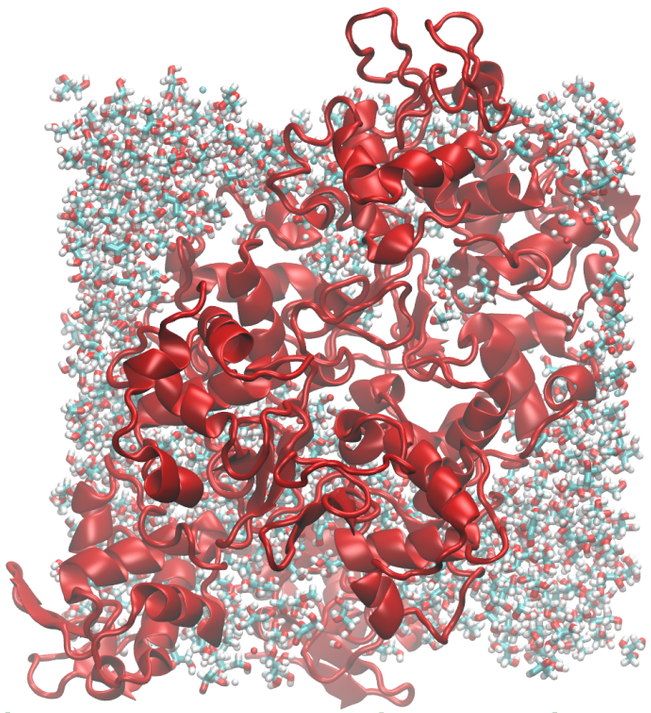
Katava et al in preparation



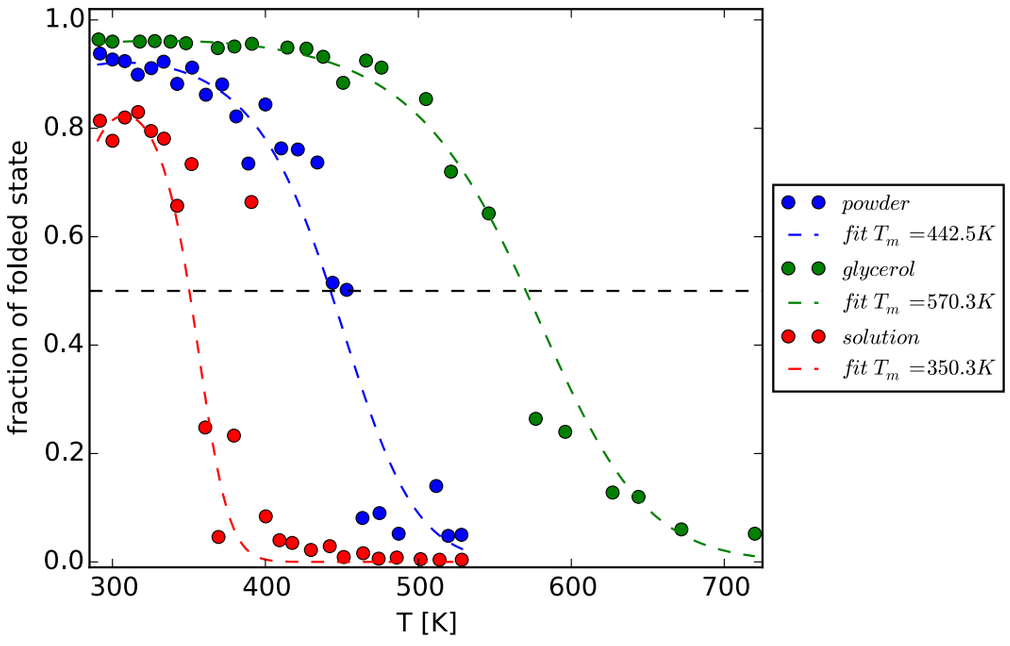
lysozyme in H2O



lysozyme powder + H20 (h=0.3)



lysozyme powder + glycerol (h=0.3)



REST2 to sample f/u

thermal response via corresponding state principle

experimental trend reproduced

Stirnemann&**FS**, JCTC (2015)

Muphy/OPEP: amyloid aggregation

FS et al. JCTC (2015)

Hydrodynamics speeds up peptides aggregation

Simulations

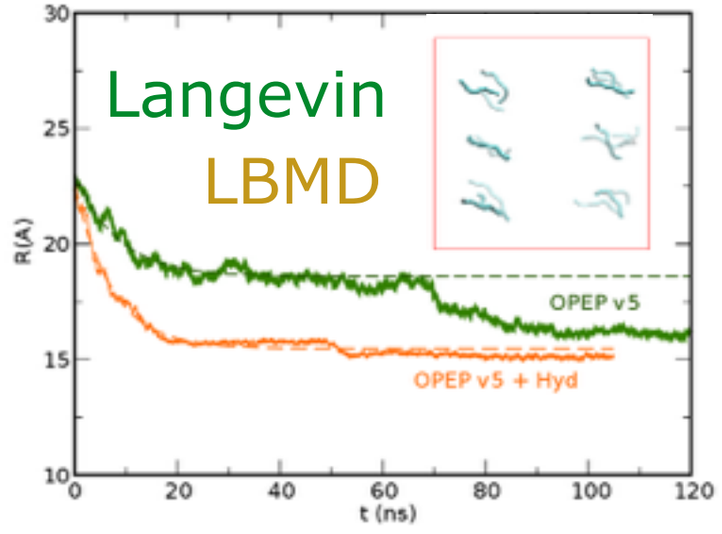
18 monomers $A\beta_{16\text{-}22}$

KLVFFAE

CH3-CO and NH2 terminal

Cubic box 65 Å

c=100 mM



Two-step mechanism

Speed up of both collapses (45%)

Hydrodynamics

enhance diffusivity of proteins

Frembgen-Kesner&Elcock JCTC (2009)

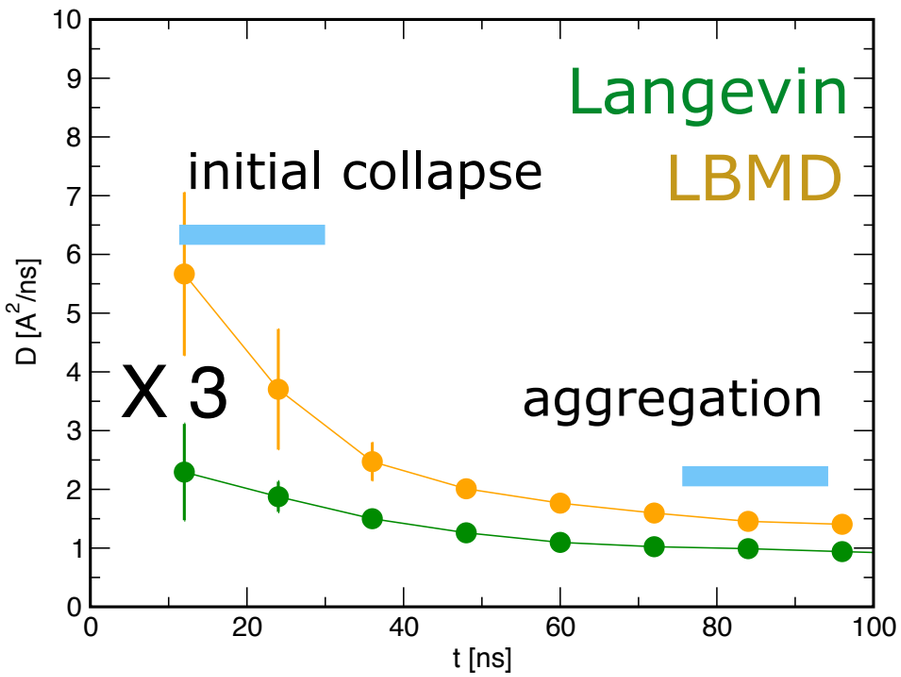
enhance aggregation of lipids

Ando&Skolnick BJ (2013)

enhance folding kinetics

Cieplak&Niewieczerza JCP (2009)

$A\beta_{16\text{-}22}$ ~23 A^2/ns (dilute solution)



HI enhance diffusivity

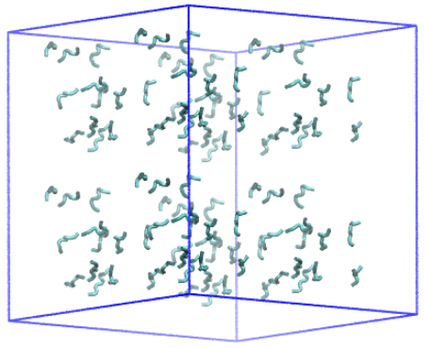
Muphy/OPEP: amyloid aggregation

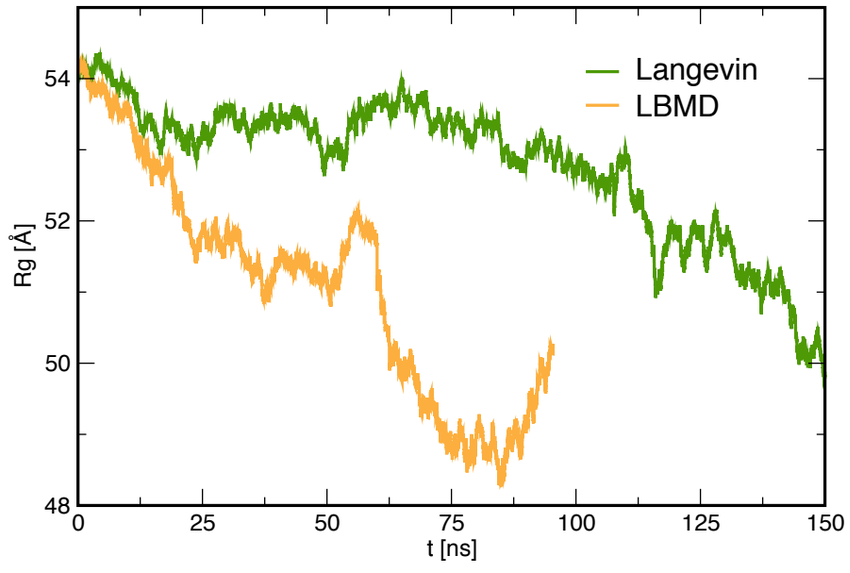
Aβ aggregation toward big systems

100 monomer Aβ(16-22) Chiricotto, et al JCP(2016)

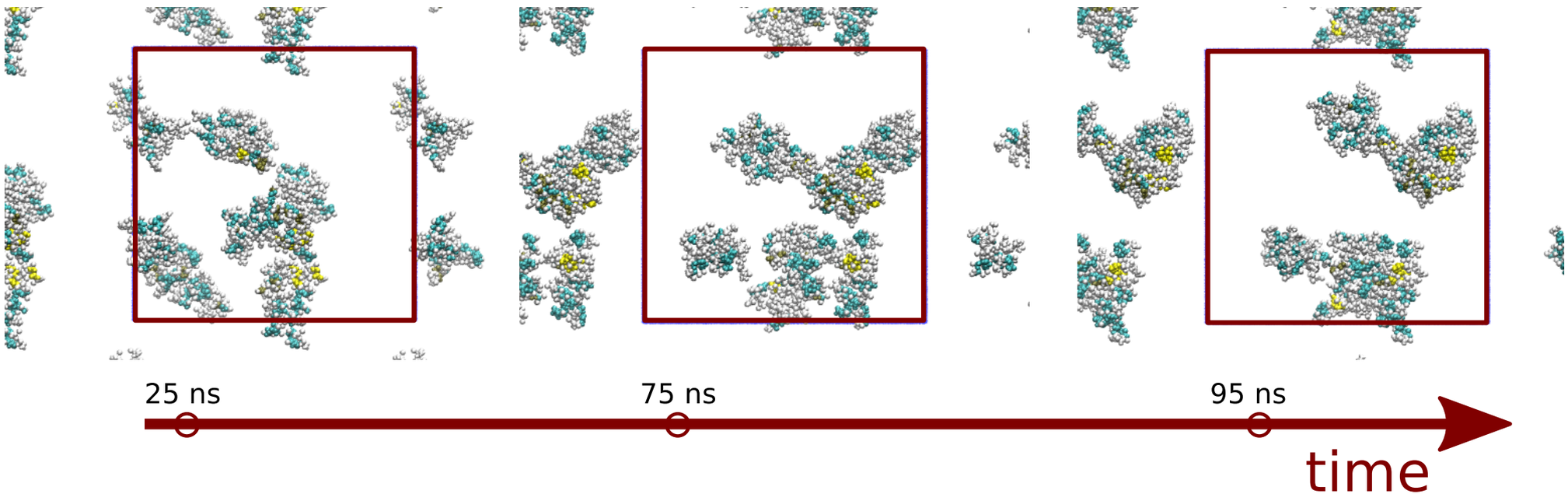
Simulation

100 monomer Aβ(16-22)
all atoms equivalent 300k
L=150 Å
c~50 mM





HI speed up aggregation



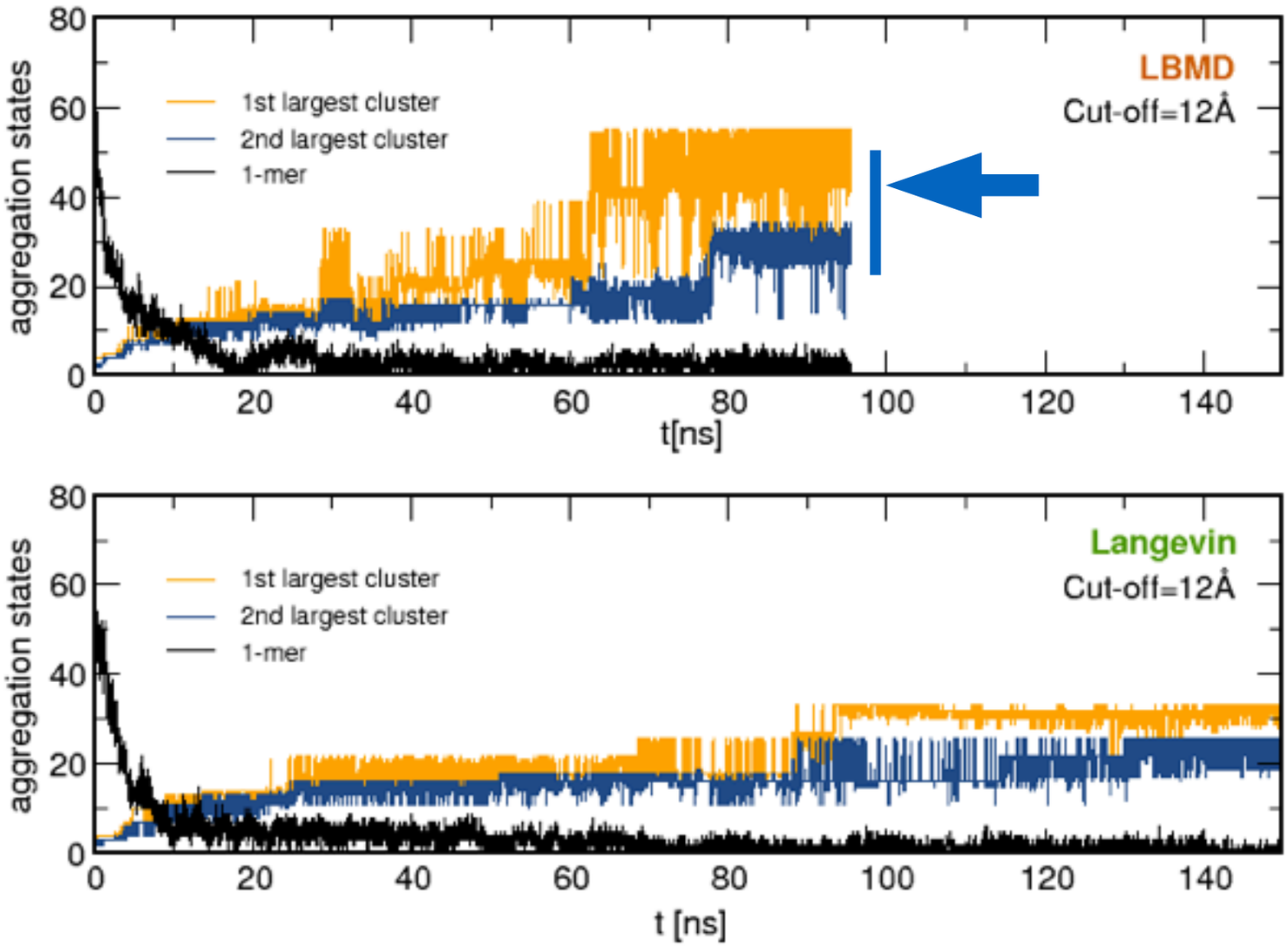
Muphy/OPEP: amyloid aggregation

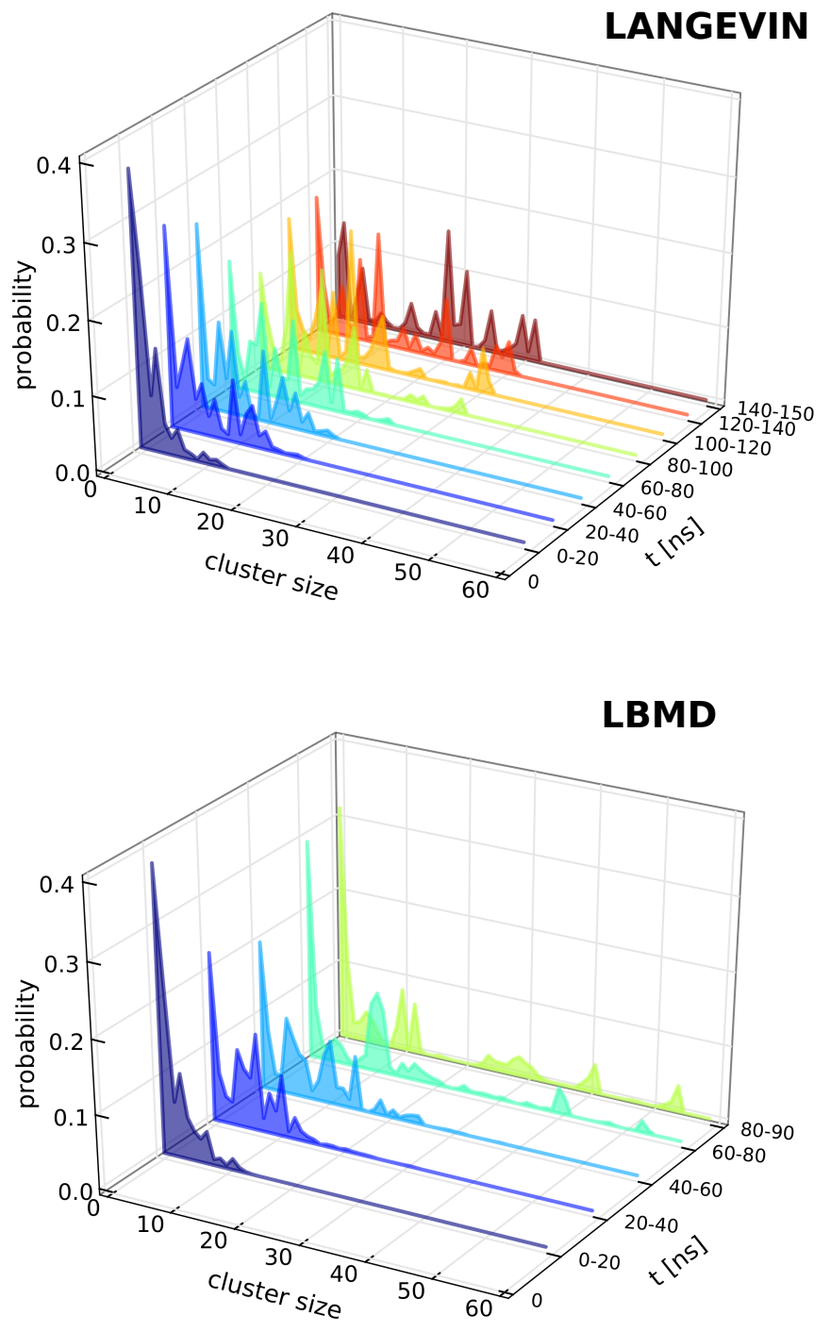
Aβ aggregation toward big systems

100 monomer Aβ(16-22)

Chiricotto, et al JCP(2016)

HI enhance cluster formation and exchange





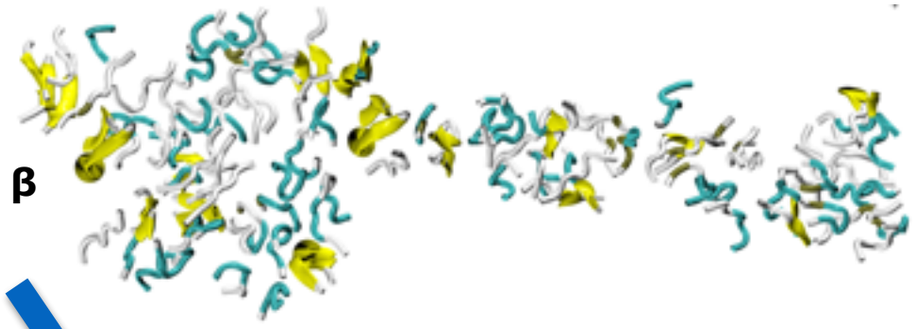
Muphy/OPEP: amyloid aggregation

Aβ aggregation toward big systems

extending simulation time
lower resolution LB

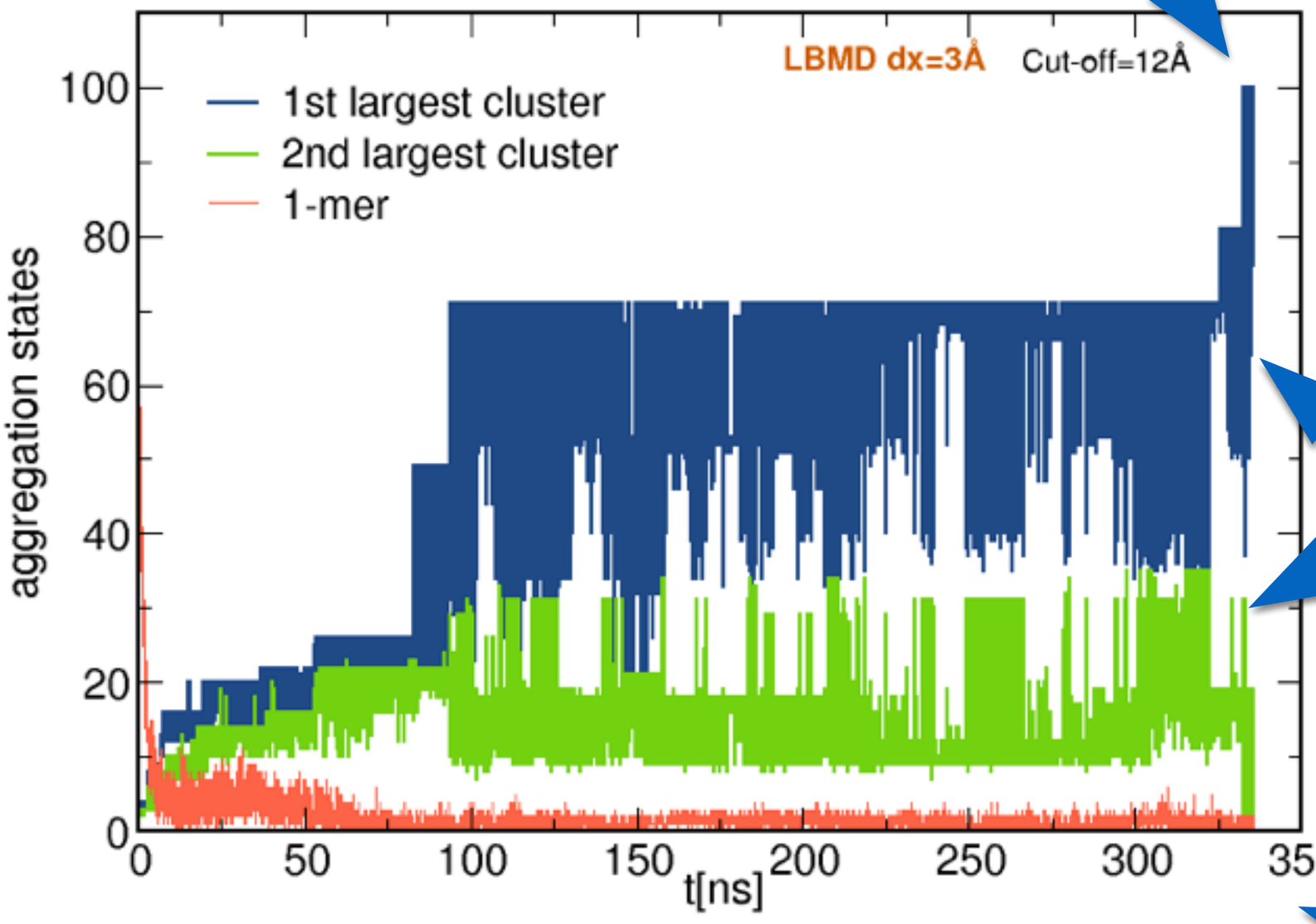
100 monomer Aβ(16-22)

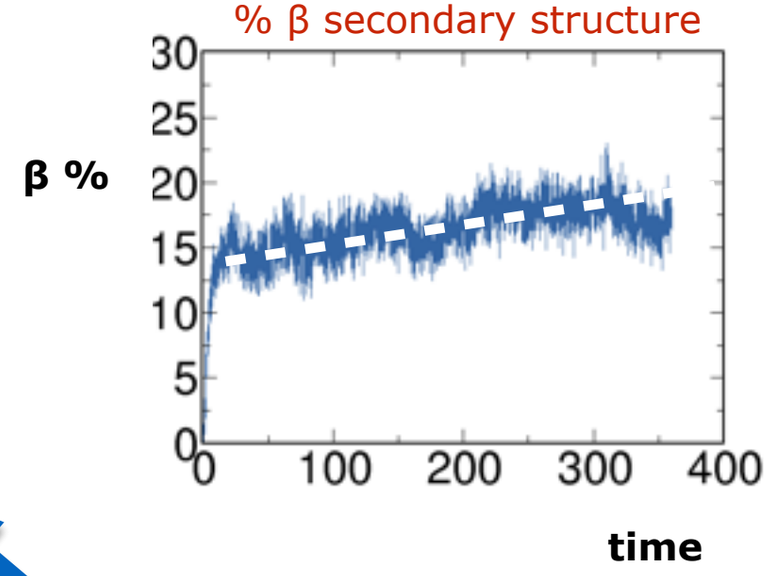
Chiricotto, et al JCP(2016)



17 % β

Aggregation Completed!





fusion of largest and second largest clusters

timescale ~300/400 ns

Muphy/OPEP: amyloid aggregation

Aβ aggregation
toward big systems

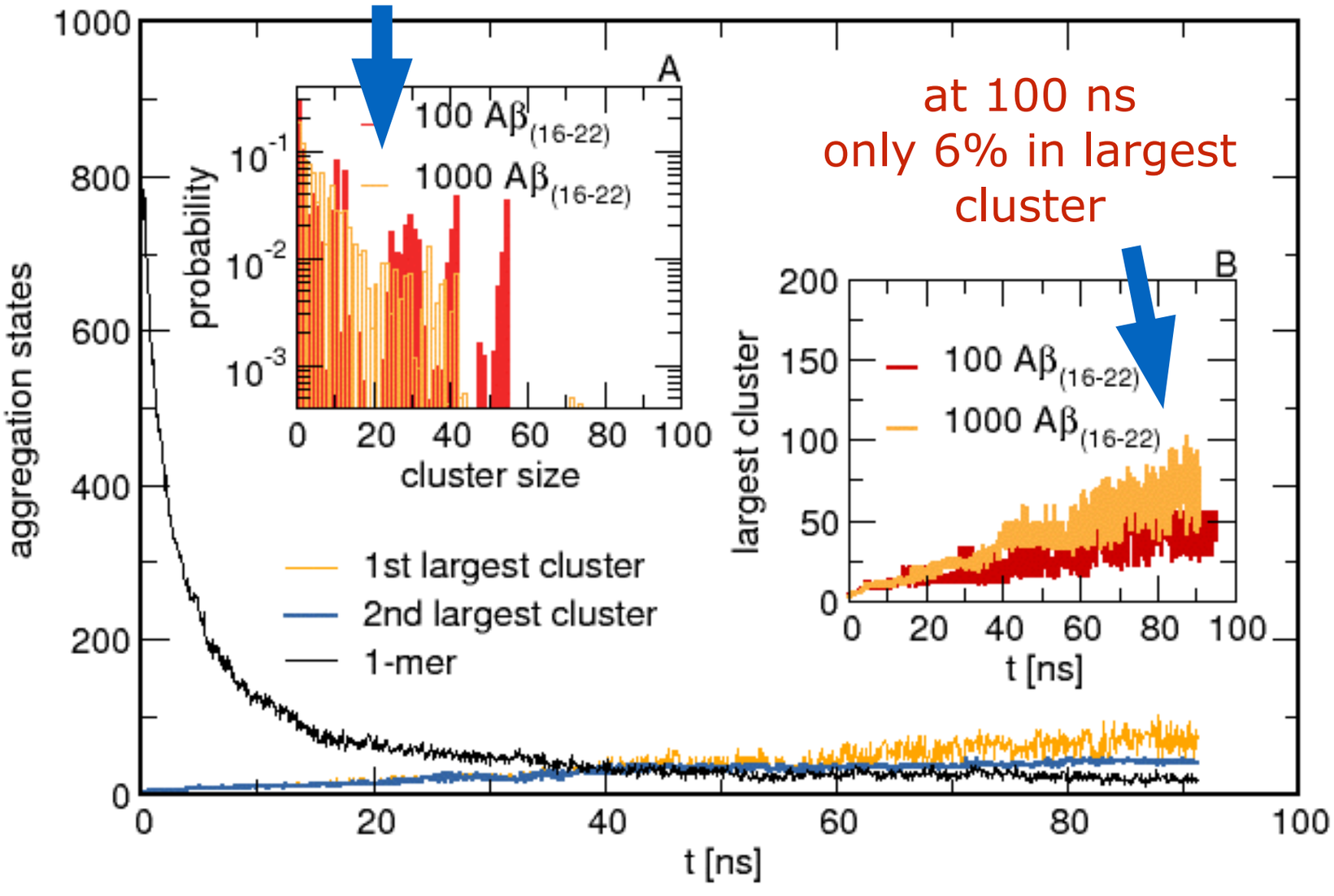
1000 monomer Aβ(16-22)

Chiricotto, et al JCP(2016)

Intermediate sizes highly populated

<u>Simulation</u>

1000 monomer Aβ(16-22)
all atoms equivalent 2,4Mio
L=300 Å
c=55 mM



at 100 ns
only 6% in largest
cluster

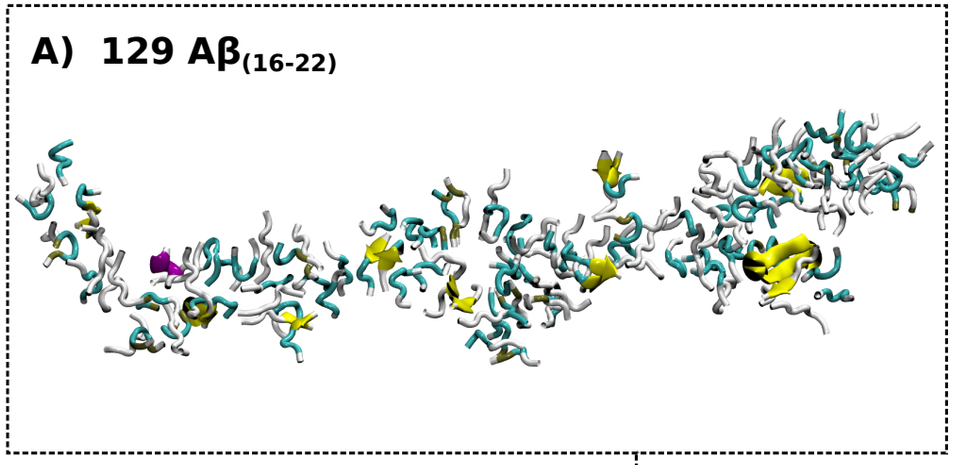
Comparing 100 Aβ and 1000 Aβ

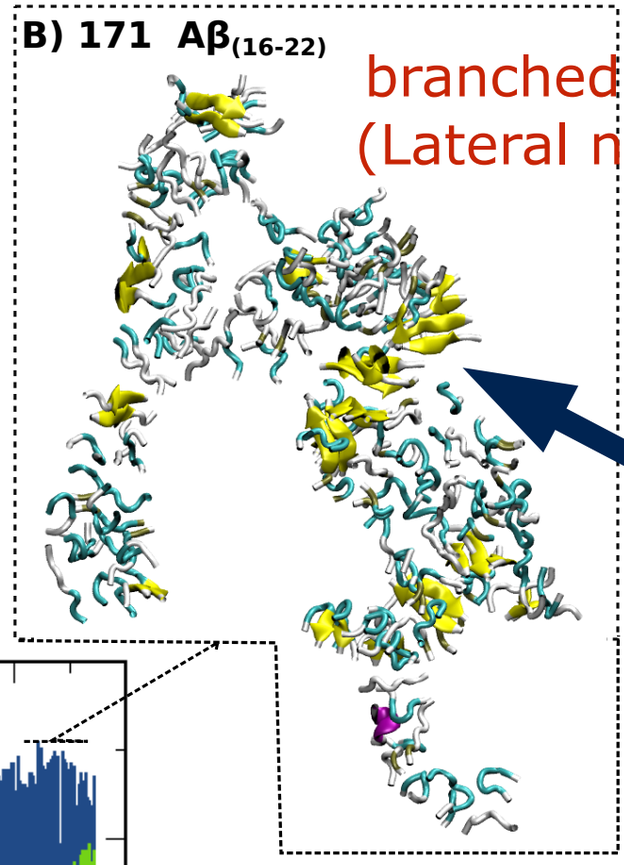
Muphy/OPEP: amyloid aggregation

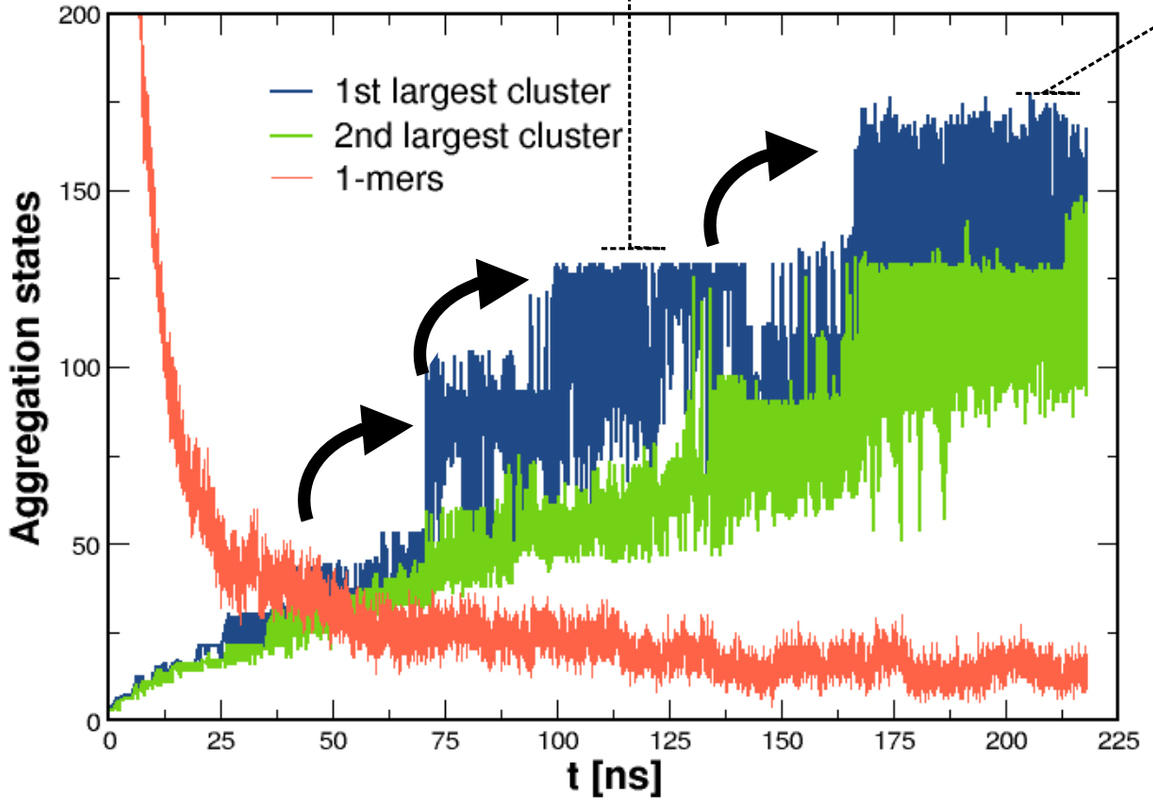
Aβ aggregation toward big systems

extending simulation time
lower resolution LB

1000 monomer Aβ(16-22) Chiricotto, et al JCP(2016)

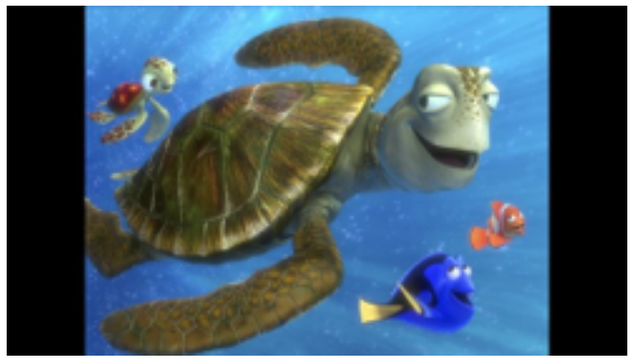






inclusion of oligomers

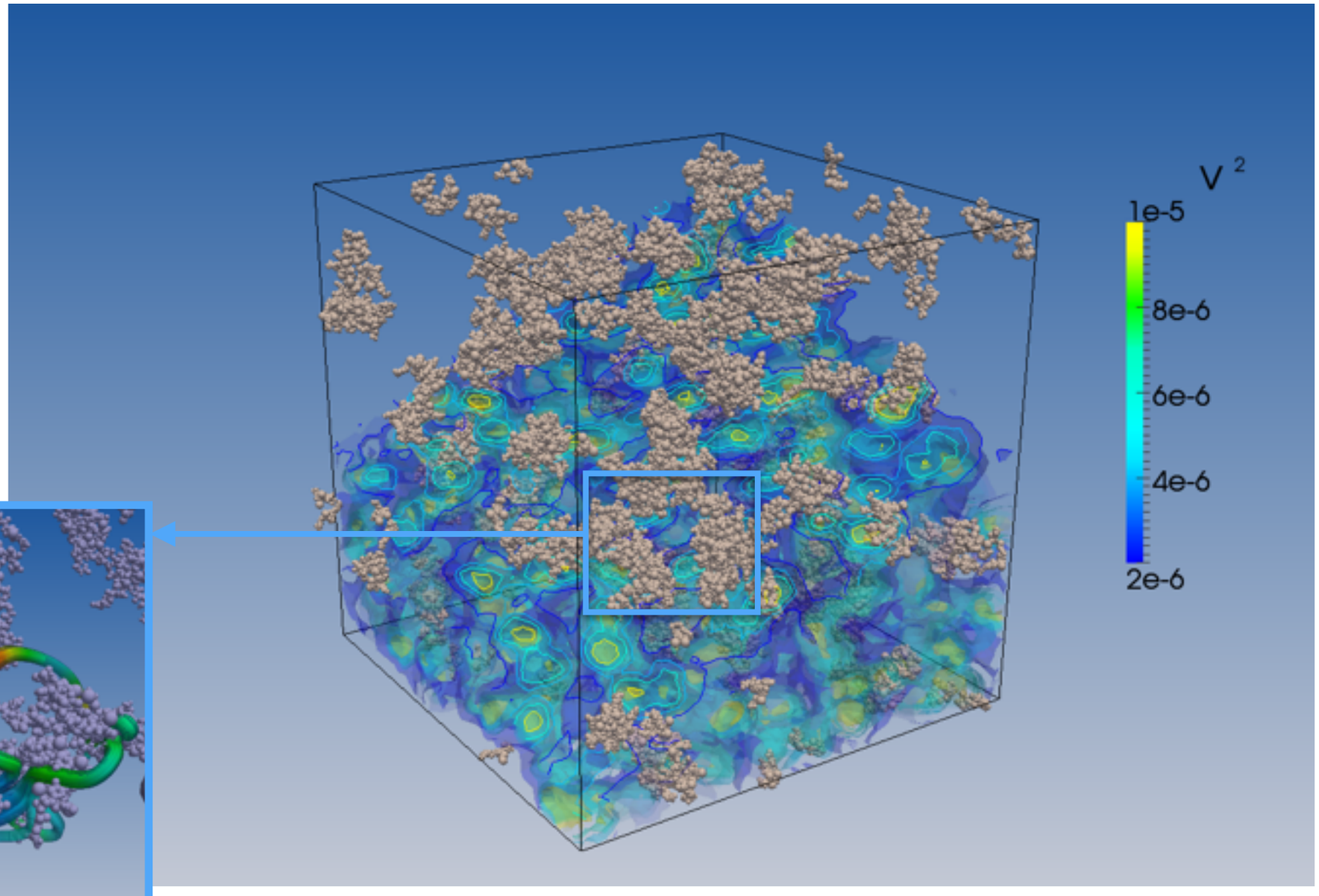
at 250 ns two leading aggregates (~30% of the system)



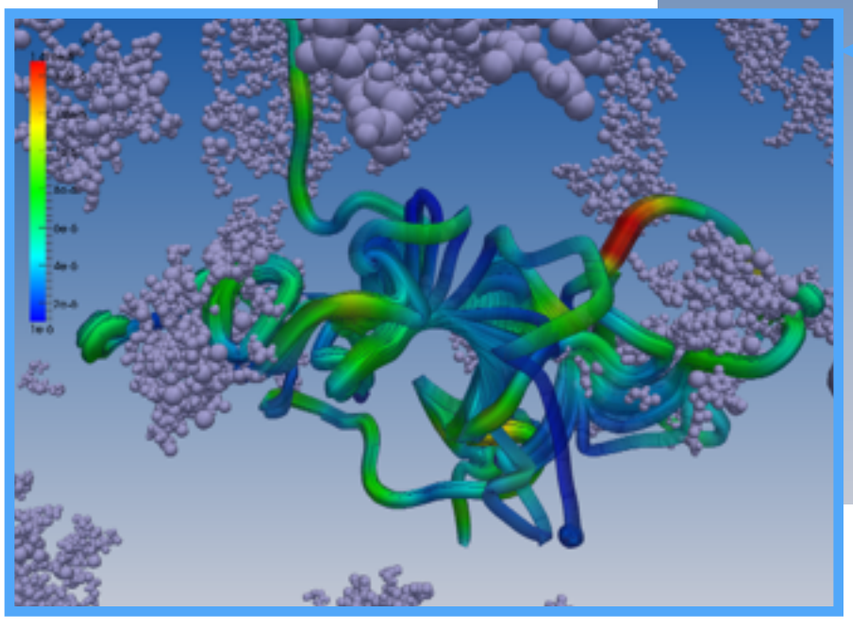
Muphy/OPEP: amyloid aggregation

1000 monomer Aβ(16-22)

Fluid iso-kinetic surfaces

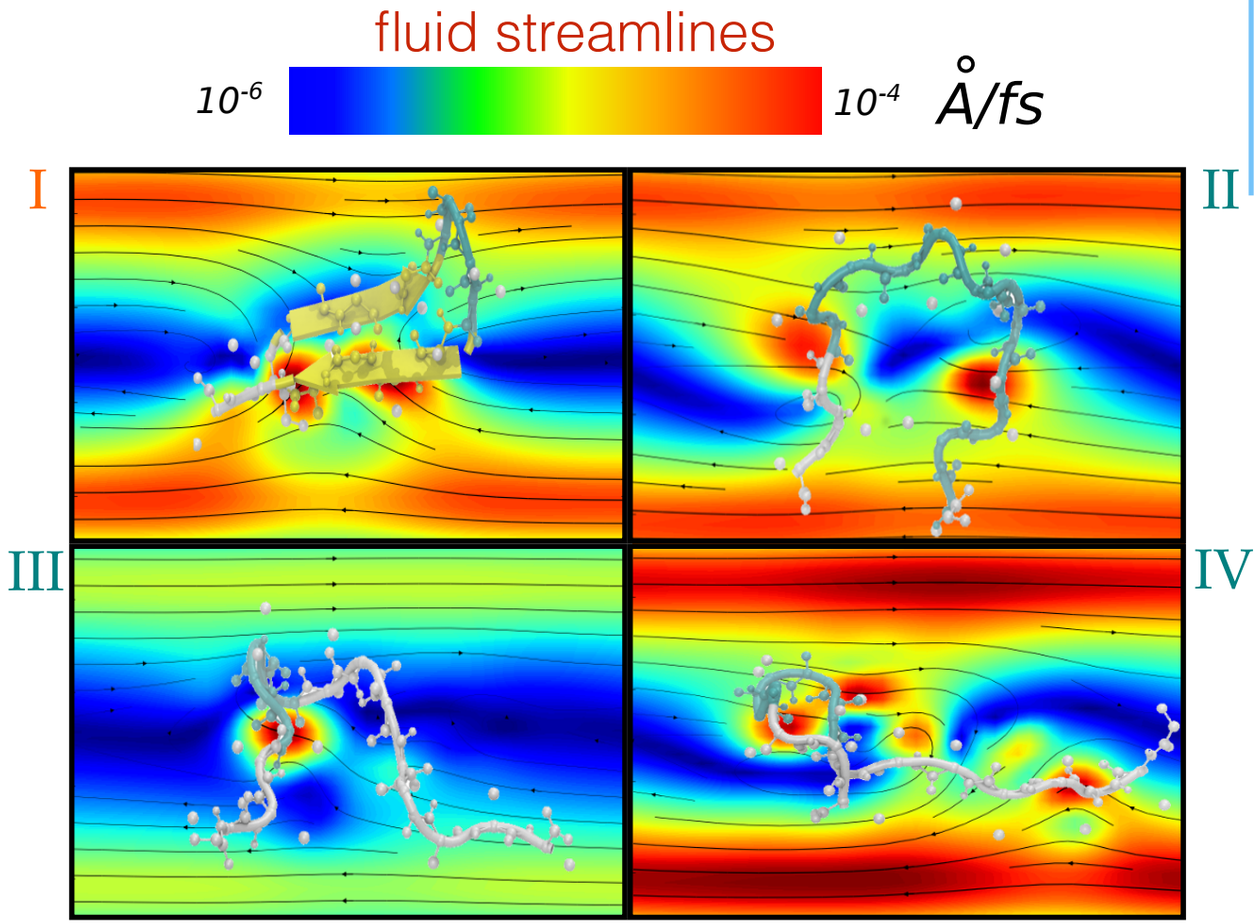


Local fluid streamlines



Muphy/OPEP: Shear

Protein unfolding in shear flow



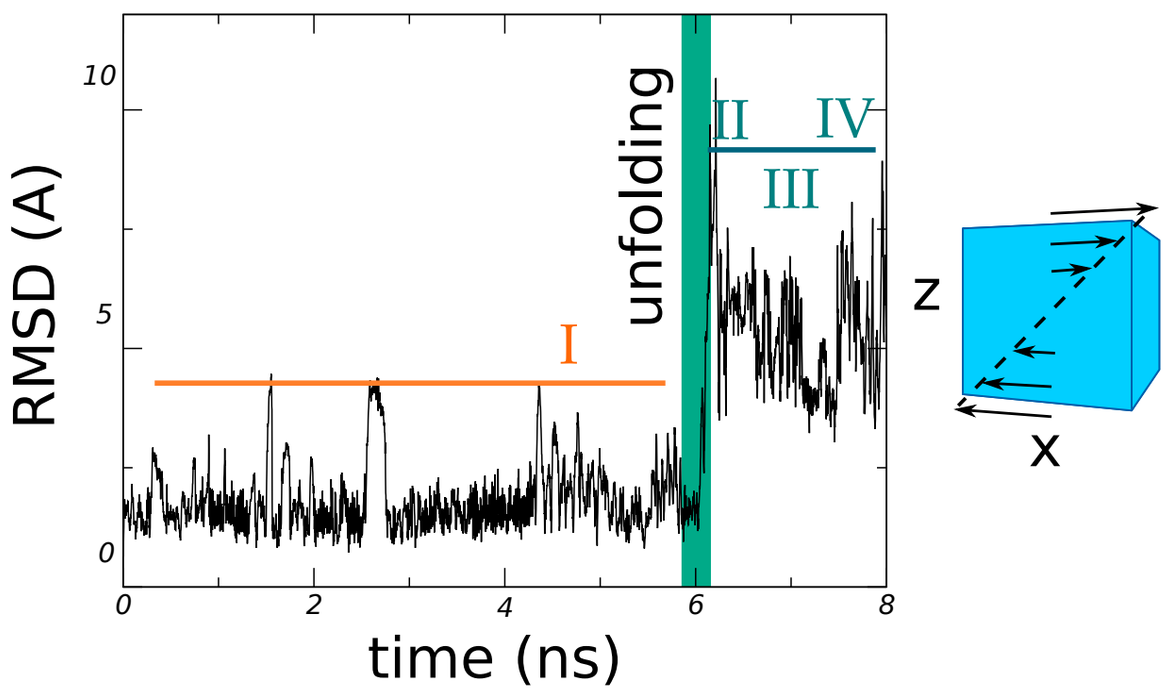
Simulations

β-hairpin (GB1, fragment 41-56)
Box 50x50x50 Å
Shear Rate 10^{10} s^{-1}

SHEAR
a route to probe mechanical stability

OPEN QUESTION
do proteins unfold under shear?

Protein unfolds!
but at very high shear rate (*)



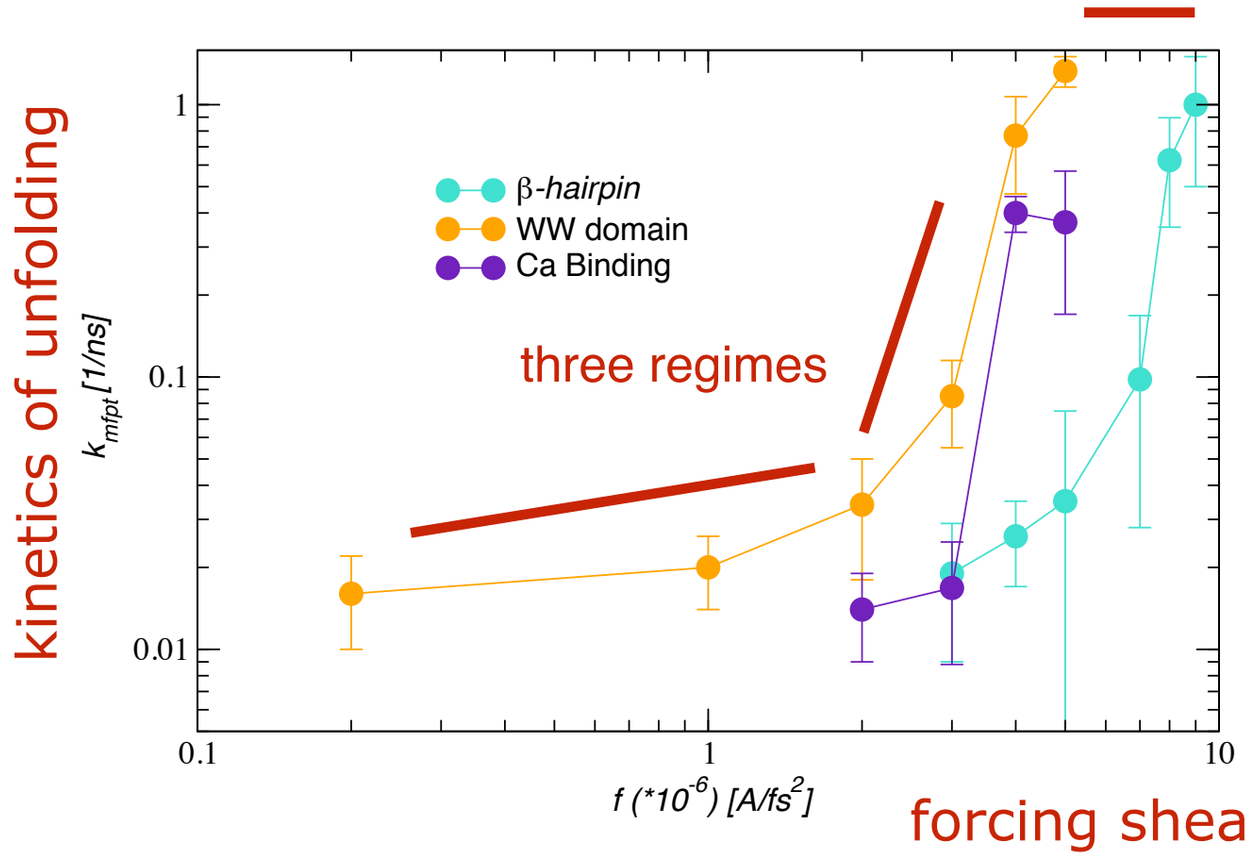
ChemSocRev (2014), * Jaspe&Hagen Biophys J (2006)

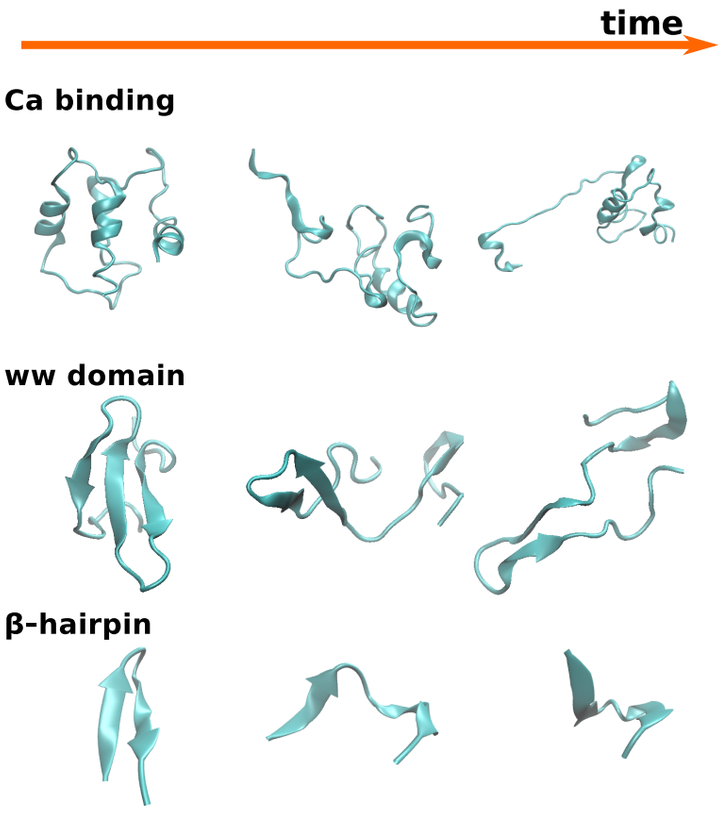
Muphy/OPEP: Shear

Protein unfolding in shear flow

Mechanical weakness

…where unfolding starts
…. to be compare to
…..T and Force unfolding





3 α helices

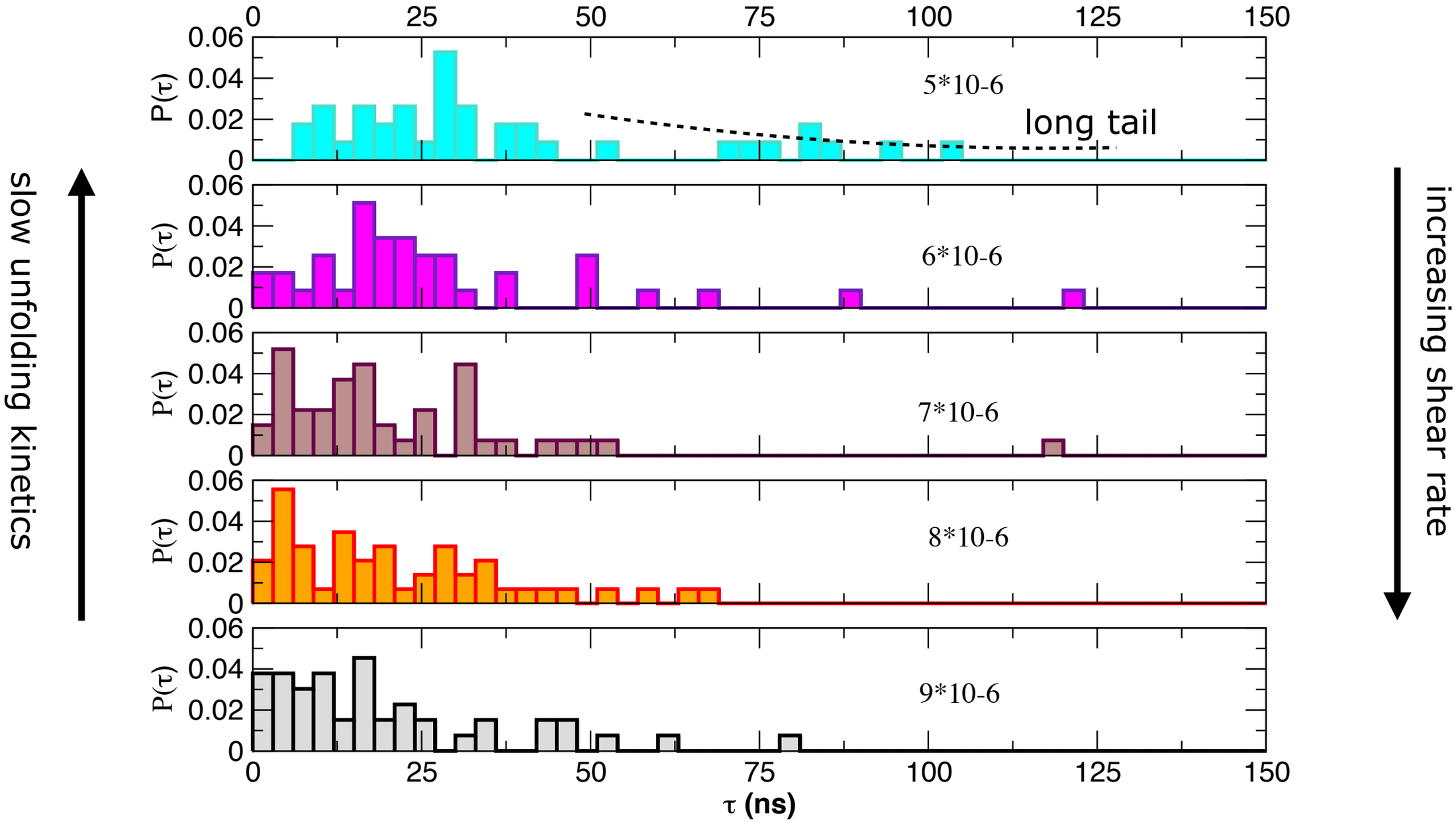
β sheets

β hairpin

Muphy/OPEP: Shear

Protein unfolding in shear flow

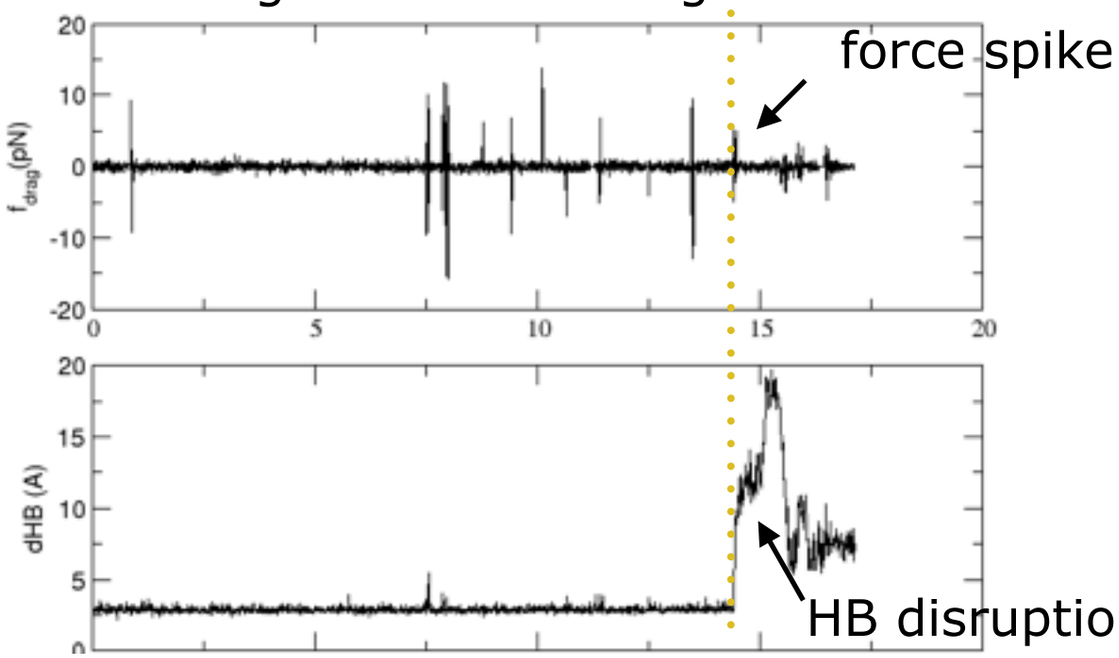
distribution of unfolding time for **β-hairpin**

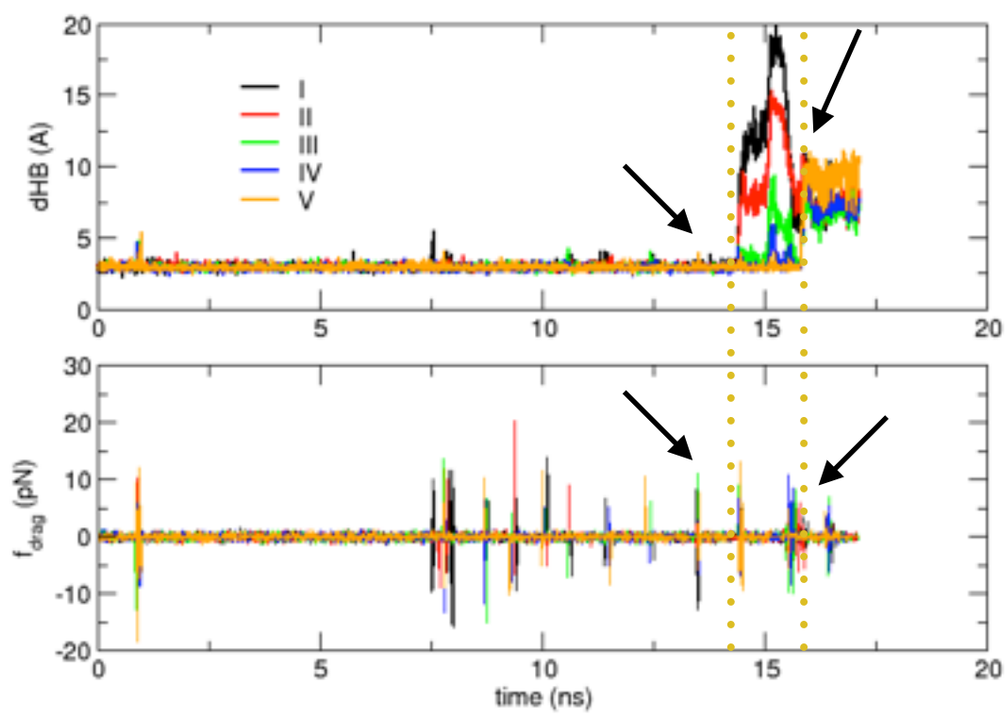


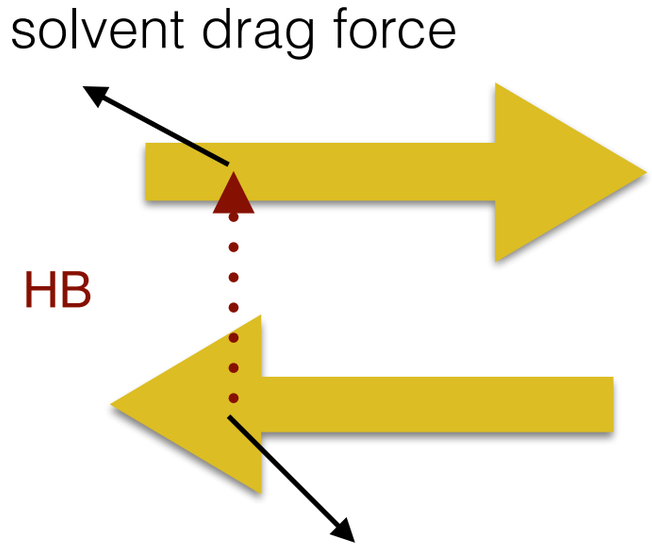
Muphy/OPEP: Shear

Protein unfolding in shear flow

reaction coordinate only sporadically aligned with shear gradient







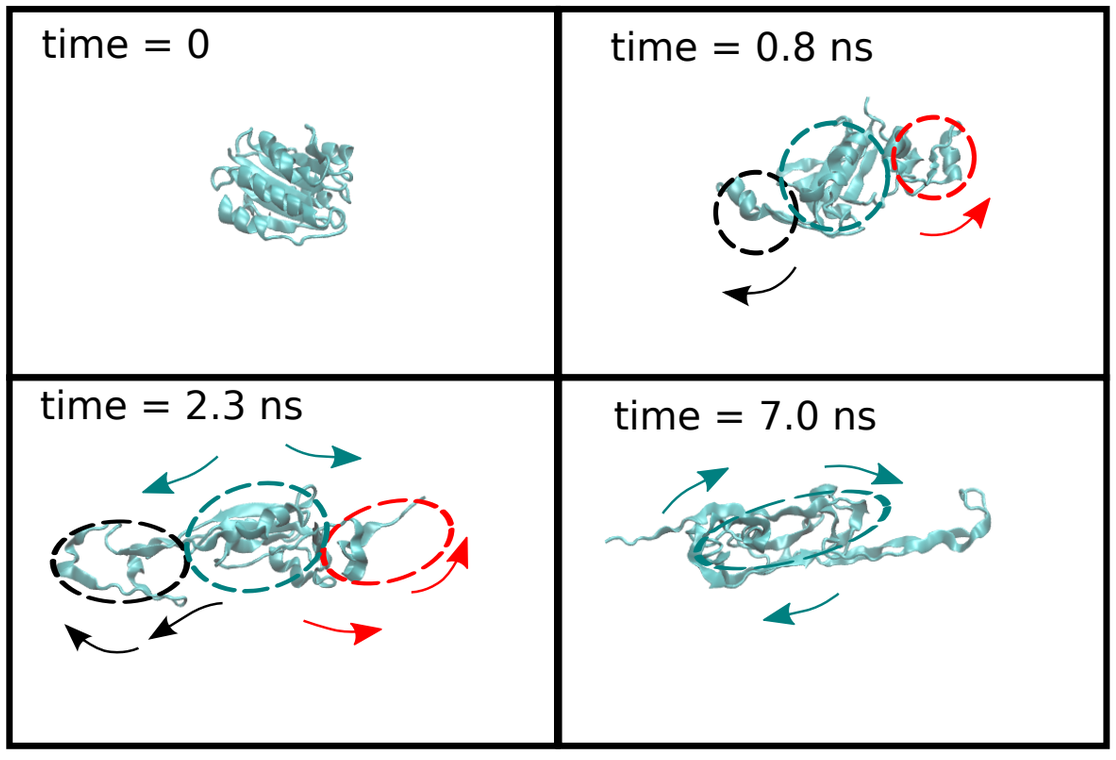
f_{drag}=force on HB_{donor} - $HB_{acceptor}$ projected on HB direction

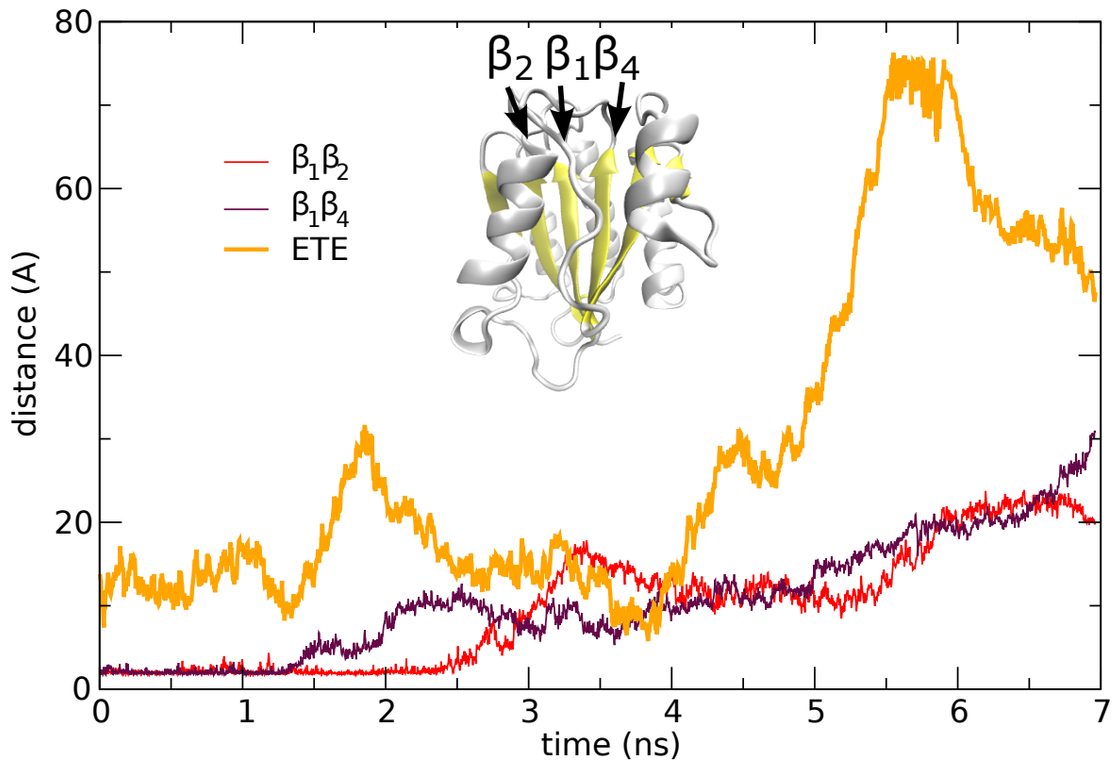
HBs break at different times as effect of different spikes

Muphy/OPEP: Shear

Protein unfolding in shear flow

test on large domain **A2 VWF**





unfolding steps:

1. separation peripheral domains
2. crack of hydrophobic cores (3 β-sheets)

Crowding in silico

Kesner&Elcock Biophys Rev (2013)

years

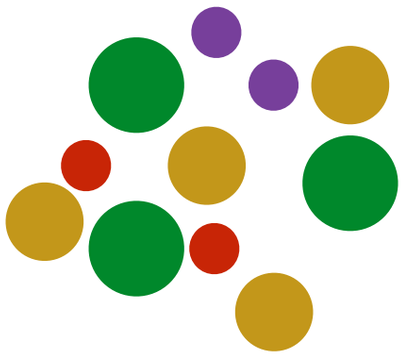
1996

Bicout&Field

ribosomes,tRNAs,proteins

spheres {r}
Langevin Dynamics

N_p~340



2008

Ellison et al.

composition as in E.coli

spheres {r}
specialised RandomDynamics

N_p~1.7 million

2010

McGuffee&Elcock

composition as in E.coli

all atoms
rigid body BD

N_p~1000

Here we are

Feig&Sugita

all atoms
+
water

Ando&Skolnick

composition as in E.coli

spheres
Stokesian Dynamics

Hydrodynamics is included

Diffusion only mildly slowed down by excluded volume, only including Hydrodynamics there is agreement with experiments

Conclusion&Perspective

Proteins in cell: a new frontier for Computational Biology

Effect of crowding on diffusion, stability and aggregation is a major challenge for both experiments and simulations

Simplified models are necessary but is key to keep solvent effects

Brownian Dynamics with Hydrodynamics is a standard way
Lattice Boltzmann coupled to MD is a valuable alternative

Friends & "Money"

M. Chiricotto (IBPC, Paris)
P. Derreumaux (IBPC, Paris)

S. Melchionna (CNR, Rome)

http://x-proteins.blogspot.fr

IDRIS::big-challenge

LBX::Dynamo
Gral

Thermos

Muphy/OPEP: Shear

Amyloid in shear flow

FS et al ChemRev (2015)

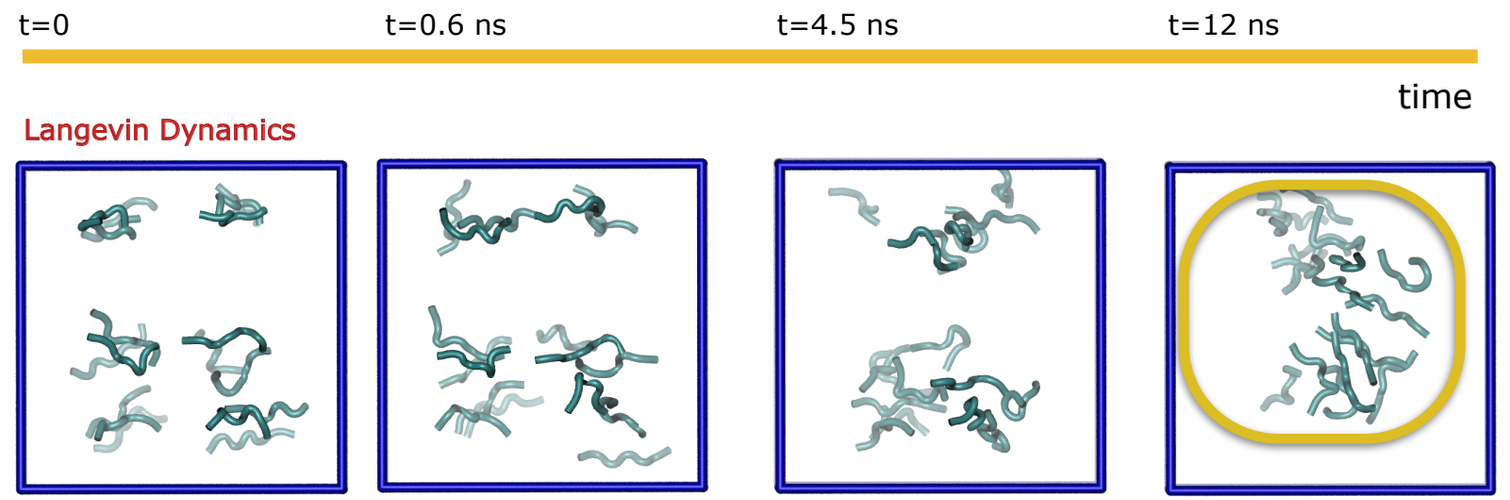
SHEAR

A model for understanding agitation processes and steps of fibril growth.

OPEN QUESTION

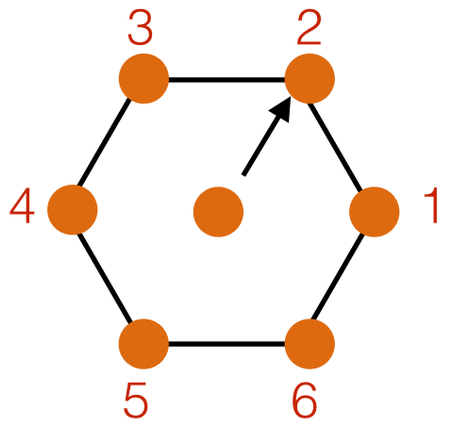
do amyloids aggregate faster under shear?

Same overall kinetics
but different
peptide organisation



Hamilton-Brown et al, JPCB (2008), Dunstan et al, ProteinEngDesSel (2009), Lee et al, JBC (2012)

Lattice Gas Cellular Automate



Rules

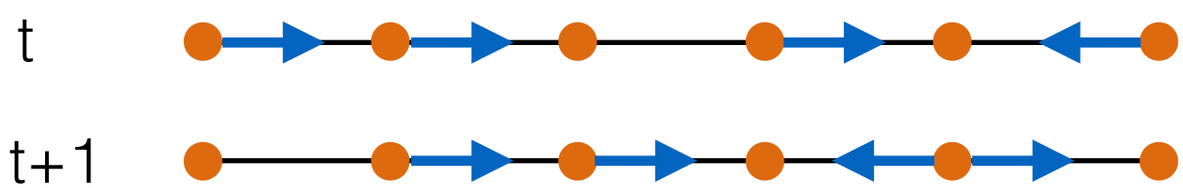
- each site hosts up to 6 particles
- particles move along 6 discrete velocities
- 2 particles sitting on same site NOT move along same directions

- occupation site $n_i(x,t)=1,0$ Lattice State for N site= 2^{6N}

for site i where particles go $|n_1n_2n_3n_4n_5n_6\rangle$ i.e. $|001010\rangle$

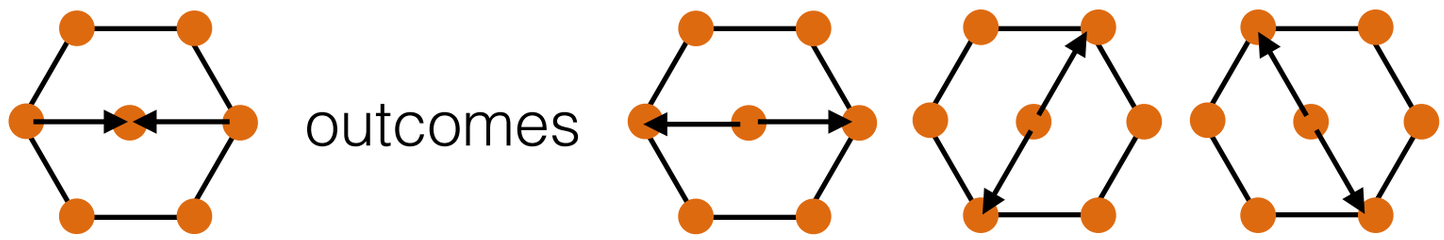
Streaming

$$n_i(\vec{x}+\vec{e}_i, t+1) = n_i(\vec{x}, t)$$



Collision

Operator altering the vector state n (+1,-1,0) $n_i' - n_i = \Omega(\vec{n})$



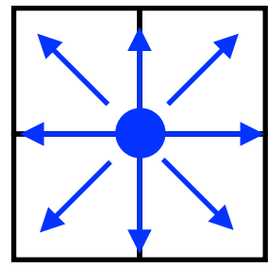
LGCA crude BUT essential :
conserve particle number, total momentum, if lattice is good invariant rotation!!!!!

Succi, The LBE for fluid Dynamics and Beyond (2001)

Lattice Boltzmann Method

Distribution function of displacement discrete states **f(x,t)**

$$f_i =< n_i >$$

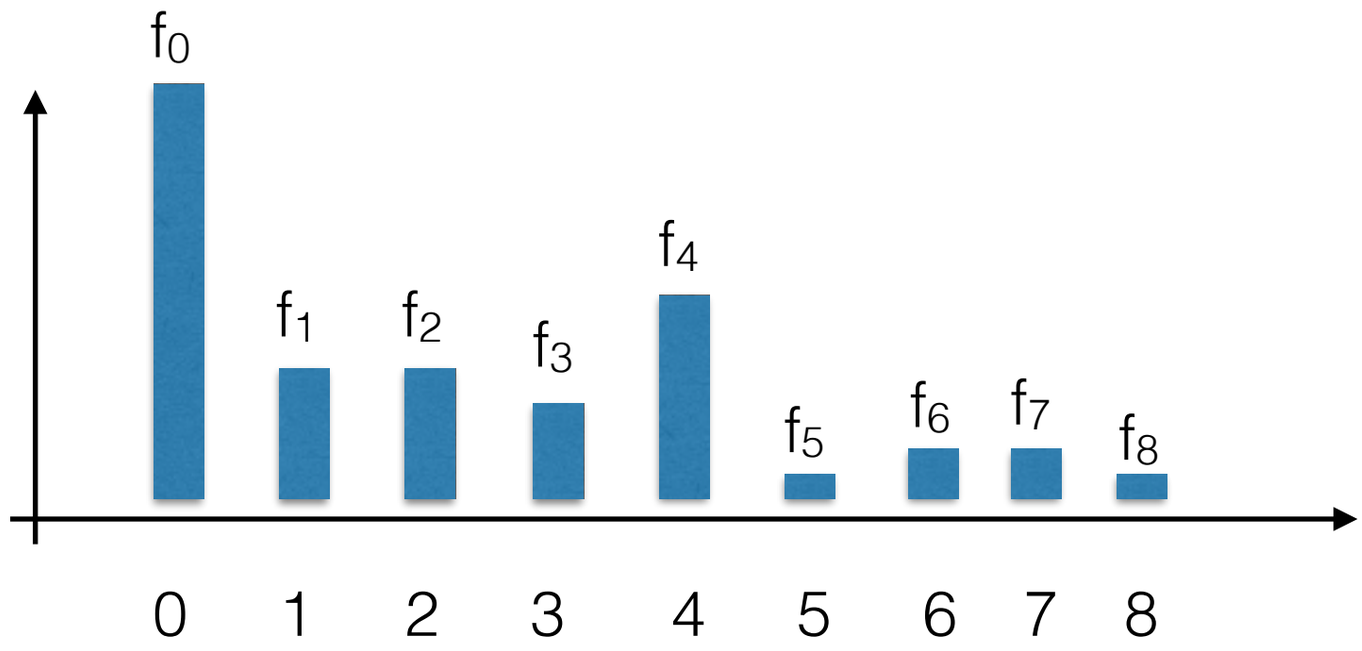


ie 2 dimensional lattice D2Q9

9 velocity directions

Fluid Density $\rho = \sum_{a=0}^{8} f_a$

Macroscopic velocity $\mathbf{u} = \frac{1}{\rho} \sum_{a=0}^{8} f_a \mathbf{e}_a$



Succi, The LBE for fluid Dynamics and Beyond (2001)

Lattice Boltzmann Method

i=0,.,.,M directions

Kinetic equation $$f_i(\mathbf{x} + \mathbf{e}_i \Delta x, t + 1) = f_i(\mathbf{x}, t) + \Omega_i(f(\mathbf{x}, t))$$

Total Mass Conservation $$\sum_i \Omega_i = 0$$

Total momentum conservation $$\sum_i \Omega_i \mathbf{e}_i = 0$$

Problems

Construct a functional form for collisions

Derive macroscopic hydrodynamic equation, Navier-Stokes

Strategy

Focus on long-wave-length and low-frequency

$$\Delta x \sim \epsilon \qquad \Delta t \sim \epsilon$$

incremental length and time are small and of the same order **ε**

Succi, The LBE for fluid Dynamics and Beyond (2001)

The collision term

Multi-scale separation $$f_i = f_i^{eq} + \epsilon f_i^{neq}$$

equilibrium fluid

$$\sum_i f_i^{eq} = \rho$$

$$\sum_i f_i^{eq} \mathbf{e_i} = \rho \mathbf{u}$$

$$f_i^{neq} = f_i^1 + \epsilon f_i^2 + O(\epsilon^2)$$

$$\sum_i f_i^k \mathbf{e_i} = 0$$

$$\sum_i f_i^k = 0$$

perturbation

Taylor expansion of collision term $$\Omega_i(f) = \Omega_i(f^{eq} + \epsilon f^{neq})$$

Equilibrium condition $$\Omega_i(f^{eq}) = 0$$

→ Linearised collision $$\Omega_i(f) = \frac{\partial \Omega_i(f^{eq})}{\partial f_j}(f_j - f_j^{eq})$$

BGK

if one single rate for relaxation to equilibrium $$\Omega_i(f) = -(f_i - f_i^{eq})/\tau$$

BGK==Bhatnagar-Gross-Krook

Succi, The LBE for fluid Dynamics and Beyond (2001)

Starting from Boltzmann Equation

Probability in phase-space dxdp at time t $f(\vec{x}, \vec{p}, t)$ Core of Kinetic Theory

Evolution of one-body distribution $D_t f = [\partial_t + \frac{\vec{p}}{m} \cdot \partial_{\vec{x}} + \vec{F} \cdot \partial_{\vec{p}}] f(\vec{x}, \vec{p}, t) = C_{12}$

Evolution of one particle distribution — Collision

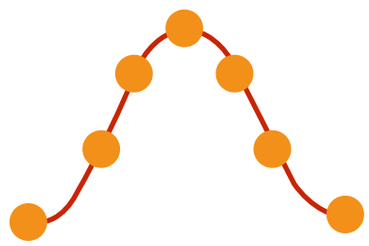
C_{12} depends hierarchically on 2,3,4… n body

BGK for C_{12} $-\frac{1}{\tau}(f - f^{eq})$

Assume Maxwell-Boltzmann Expansion of MB $f^{eq} \simeq A \exp(-3/2\chi^2)[1 + 3(\chi \cdot \mathbf{u}) + \frac{9}{2}(\chi \cdot \mathbf{u})^2 - \frac{3}{2}u^2]$

$\mathbf{u}$ fluid velocity χ particle velocity

Discrete f —> f^D
Obtain weight for lattice $f_i^D = W_i f_i$



discrete velocity $\mathbf{e}_i$

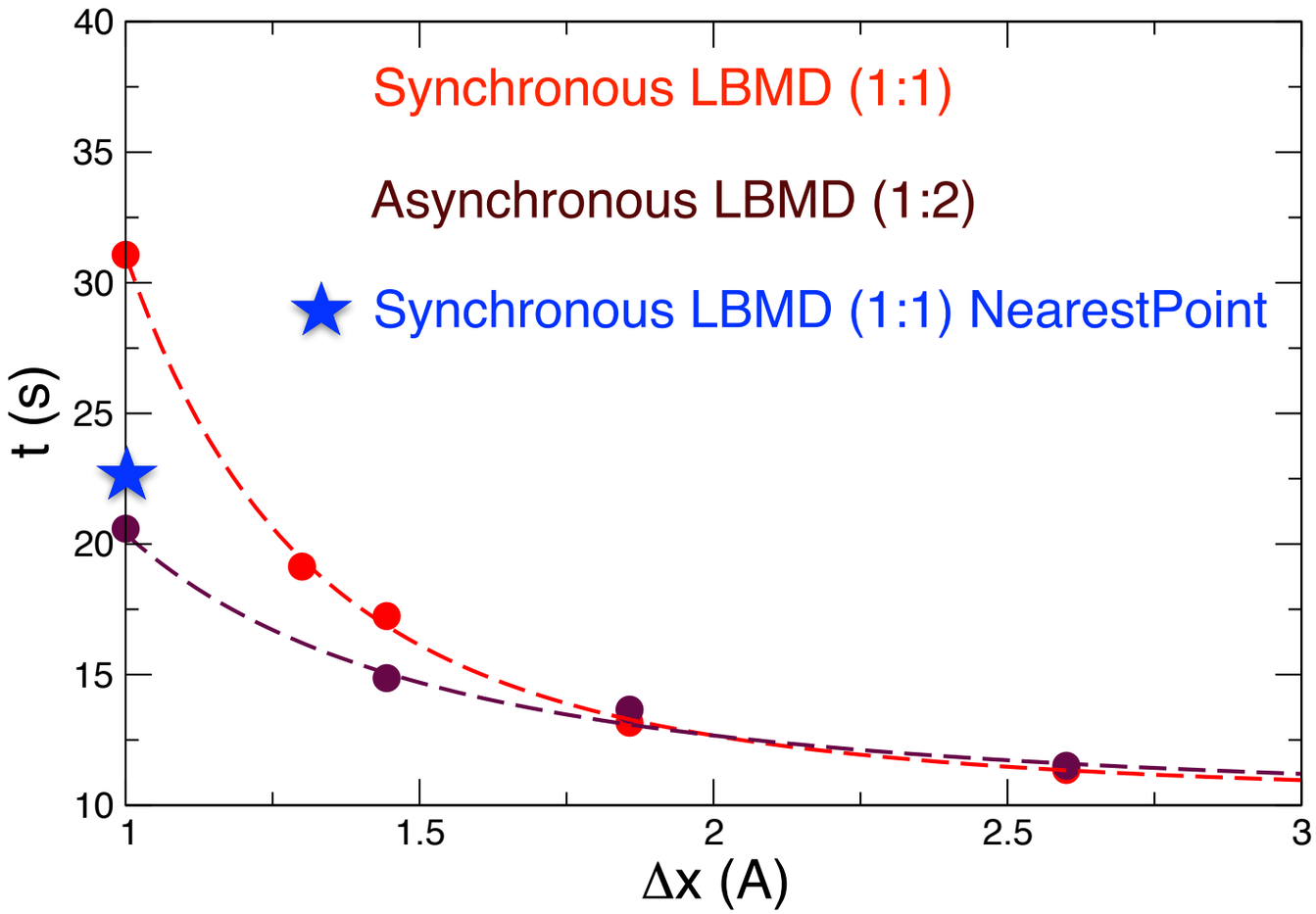
LBM

$$f_i(\mathbf{x} + \mathbf{e}_i \Delta x, t + 1) = f_i(\mathbf{x}, t) + \Omega_i(f(\mathbf{x}, t))$$

A solute in fluid

Multi-scaling

time for 1000 MD step
solute 864 particle
Lx=Ly=Lz=65 Å
Intel Xeon 5660



MD time + mapping

$$t = A * (\Delta x^{-\alpha} + t_0)$$

LBM

Synchronous α~3

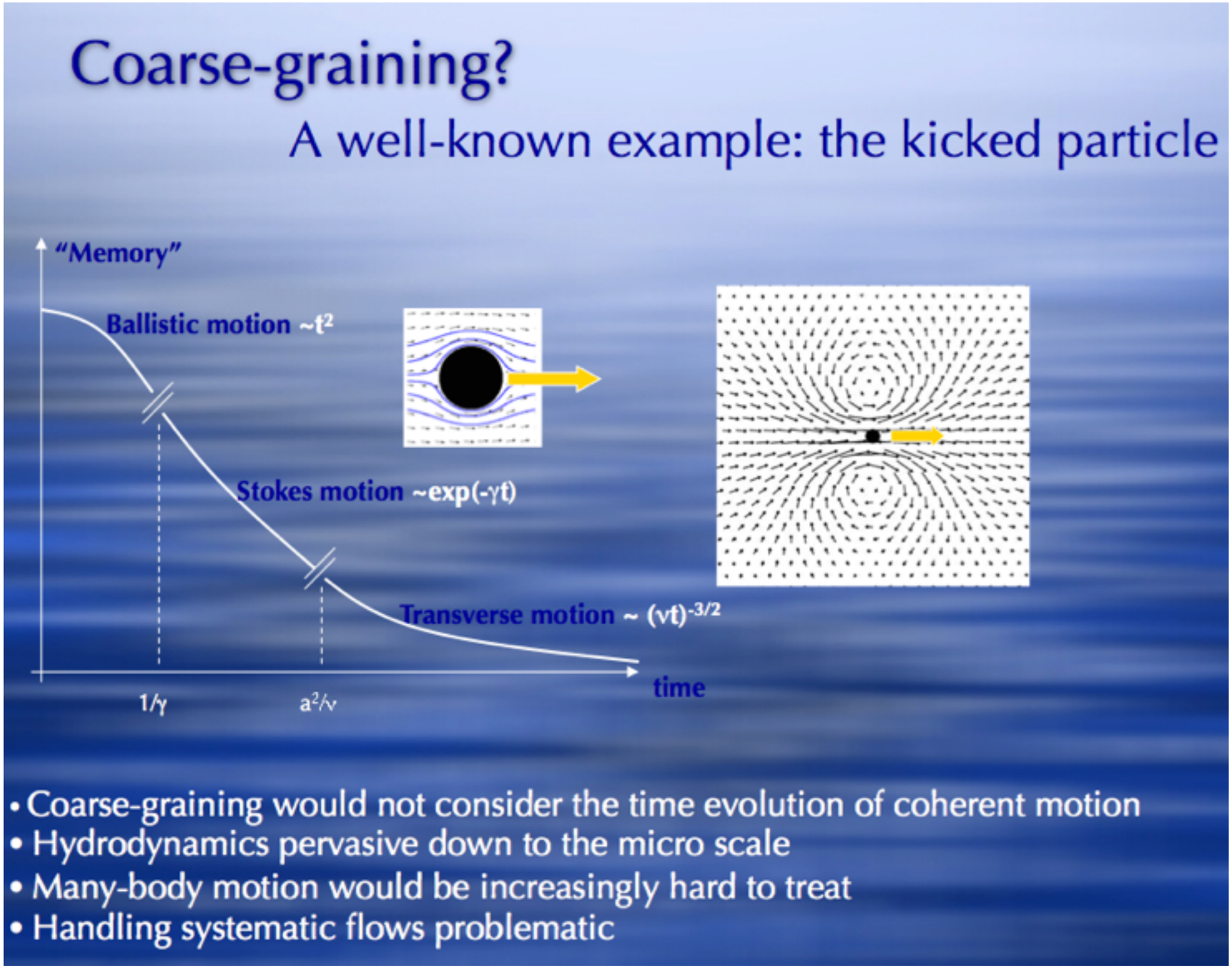
Asynchronous α~2

t_0~12 s

$time_{NearestPoint}/time_{MultipleSupport}$ ~ 0.7

A solute in fluid

Multi-scaling



Chen&Doolen Ann Rev Fluid Mech (1998)

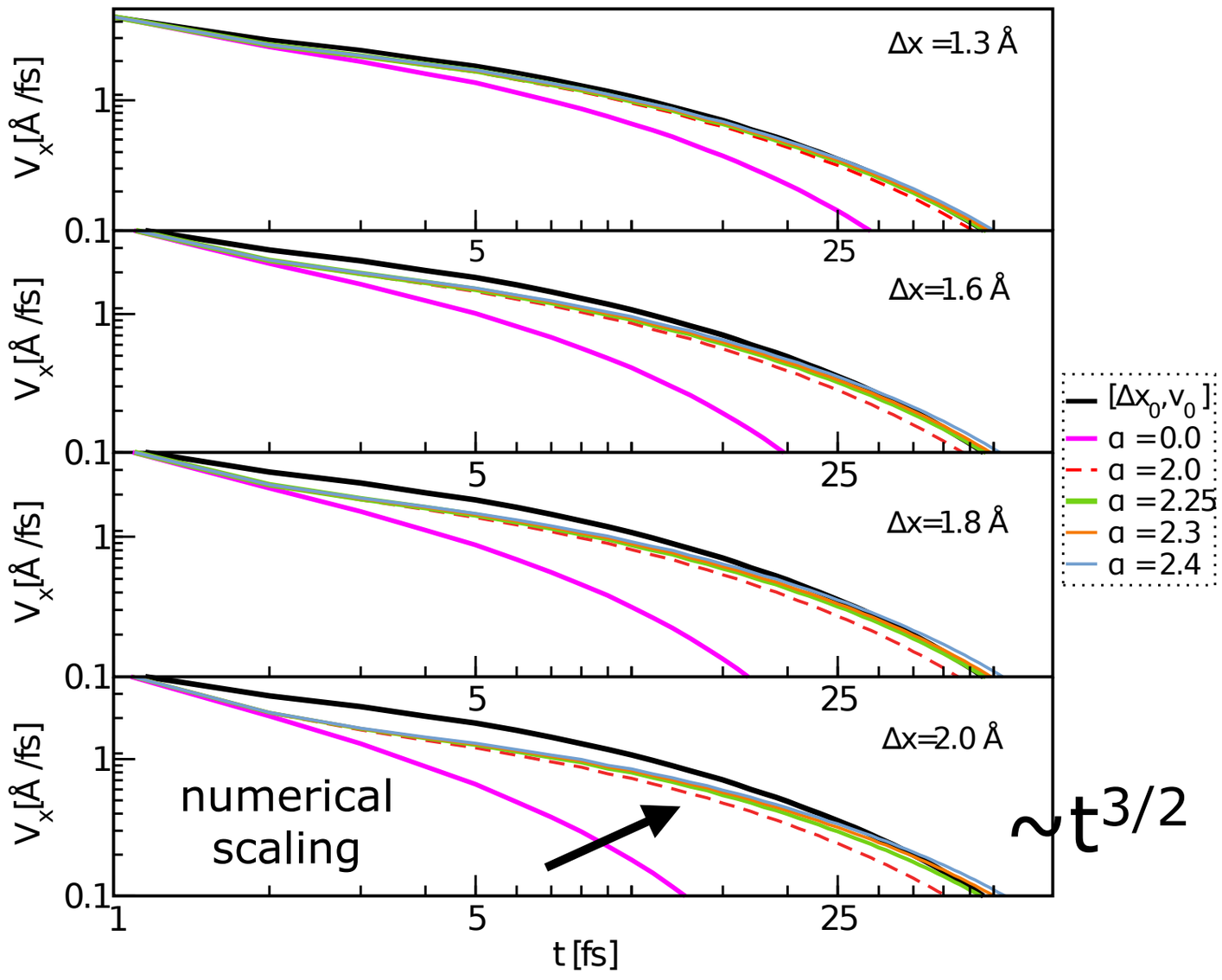
A solute in fluid

Multi-scaling

$$\nu = \nu_0 (\Delta x_0 / \Delta x)^{\alpha}$$

$[v]=[L^2]/[t]$

expected α=2



Questions:
How molecularity affects dimensional scaling?
How molecule length scale affects scaling at lower and lower resolution?

A solute in fluid

Multi-scaling

Chapman-Enskog $\nu = c_s^2(\frac{1}{\omega} - \frac{\Delta t}{2})$

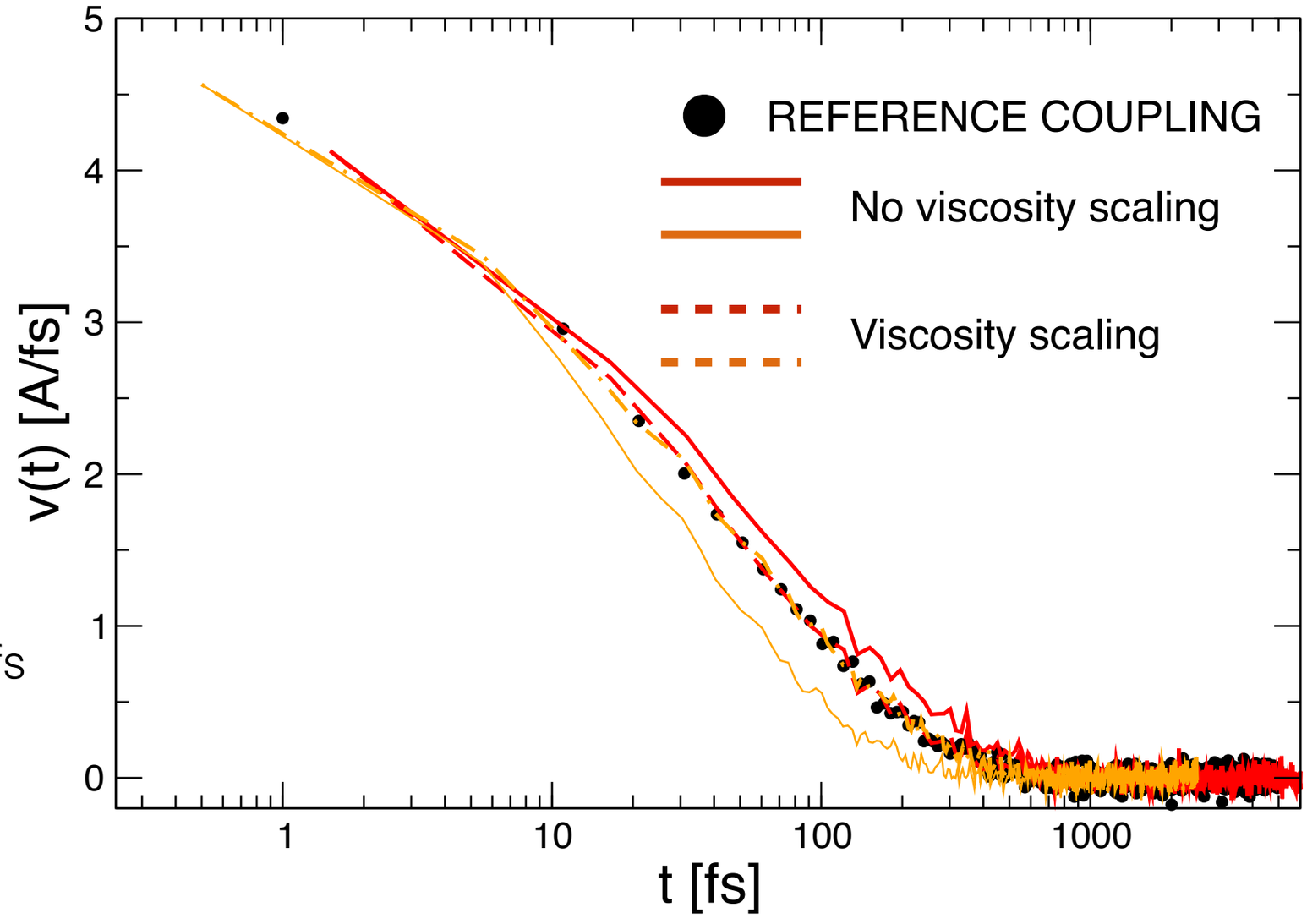
LB :: viscosity
MD :: timestep

1 monomers $A\beta_{16\text{-}22}$
T=0 K
$v(t=0)=10^{-4}$ A/fs
Δx=1 A

Rerence Relaxation
τ_0= 1 fs
v_0= 0.1666 —> 0.1666A^2/fs

Relaxation 1
τ= 1.5 fs
v= 0.1666 [$\Delta X^2/\Delta t$]

Relaxation 2
τ= 0.5 fs
v= 0.1666 [$\Delta X^2/\Delta t$]



Scaling $\nu = \nu_0(\tau/\tau_0)$

Chen&Doolen Ann Rev Fluid Mech (1998)

Brownian Dynamics

The phase-space distribution function W({r},{p},t)

The Fokker-Plank eq

$$D_t W = \sum_{i,j} \frac{\partial}{\partial p_i} \gamma_{ij} (m_j^{-1} p_j W + kT \frac{\partial W}{\partial p_j})$$

friction tensor incorporating hydrodynamic interactions (2 body)

From the Fokker-Plank eq to the Diffusion eq, W({r},t)

$$\frac{\partial W}{\partial t} = \sum_{i,j} \frac{\partial}{\partial r_i} D_{i,j} (\frac{\partial W}{\partial r_j} - \frac{1}{kT} F_j W)$$

Diffusion tensor related to friction

inter-particles + external

N Brownian Particles in Fluid

$M_i >> m_i$

main assumptions

p_i relaxes more rapidly than r_i
F_i smooth for Δr_i
v(t+Δt) and v(t) uncorrelated

time

t=0 — solution at first order of W(r,t+Δt) — extract {r} from W — .....

{r}
W(r,0)

$$< \Delta r_i(\Delta t) >= \sum_j (\frac{\partial D_{ij}}{\partial r_j} + \frac{D_{ij}}{kT} F_j) \Delta t$$

$$< \Delta r_i(\Delta t) \Delta r_j(\Delta t) >= 2 D_{ij} \Delta t$$

{r}
W(r,t)

Ermak&McCammon JCP (1978)

Brownian Dynamics

Ermak-McCammon

Time evolution of particles

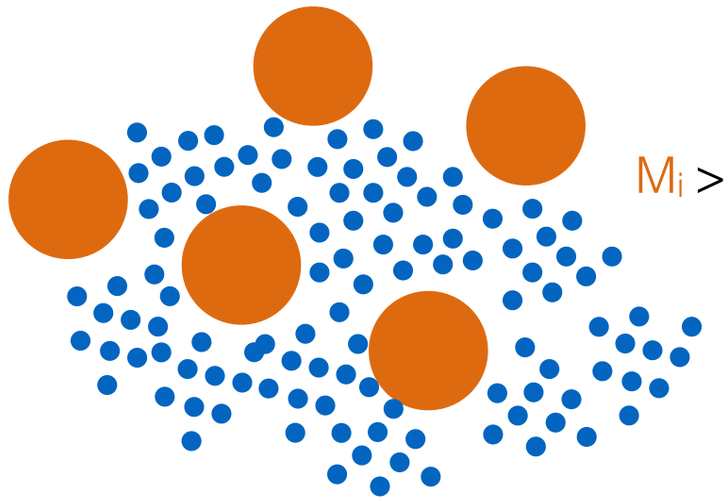
Langevin eq + Hydrodynamics

white noise

$$M_i \dot{v}_i = -\sum_j \gamma_{ij} v_j + F_i + \sum_j \alpha_{ij} f_j$$

friction tensor
for hydrodynamic interactions
(2 body)

N Brownian Particles in Fluid



Evaluated before displacement

$$r_i = r_i^0 + \sum_j \frac{\partial D_{ij}^0}{\partial r_j}\Delta t + \sum_j \frac{D_{ij}^0 F_{ij}^0}{kT}\Delta t + R_i(\Delta t)$$

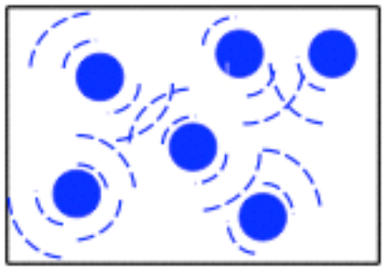
Random Displacement
(Depends on $(Dij)^{1/2}$)

Problem : Functional form for D_{ij}

Ermak&McCammon JCP (1978)

Brownian Dynamics

idea : sphere perturbs a fluid, this in turn acts on a probe sphere at distance r



expansion for r >> a (far field contribution)
NB a term for near field (r < 2a) can be added!
(Lubrication Forces)

Oseen Tensor

$$D_{ij} = \frac{kT}{6\pi\eta a}\delta_{ij}$$

$$D_{ij} = \frac{kT}{6\pi\eta r_{ij}}(I + \frac{\mathbf{r}_{ij}\mathbf{r}_{ij}}{r_{ij}^2})$$

$$\sum_j \frac{\partial D_{ij}}{\partial r_j} = 0$$

Rotne-Prager Tensor

$$D_{ij} = \frac{kT}{6\pi\eta a}\delta_{ij}$$

$$D_{ij} = \frac{kT}{8\pi\eta r_{ij}}[(I + \frac{\mathbf{r}_{ij}\mathbf{r}_{ij}}{r_{ij}^2}) + \frac{2a^2}{r_{ij}^2}(\frac{1}{3}I - \frac{\mathbf{r}_{ij}\mathbf{r}_{ij}}{r_{ij}^2})]$$

Brownian Dynamics

Random Displacement

Hydrodynamically Correlated Motion

$$< R_i(\Delta t) >= 0$$

$$< R_i(\Delta t) R_j(\Delta t) >= 2 D_{ij} \Delta t$$

Long Range Nature HI ~1/r

$$\mathbf{D} = \mathbf{B}\mathbf{B}^{\mathbf{T}}$$

$$\vec{R} = \mathbf{B}\vec{X}$$

Cost N^3

SQRT of D

X vector of 3N random numbers

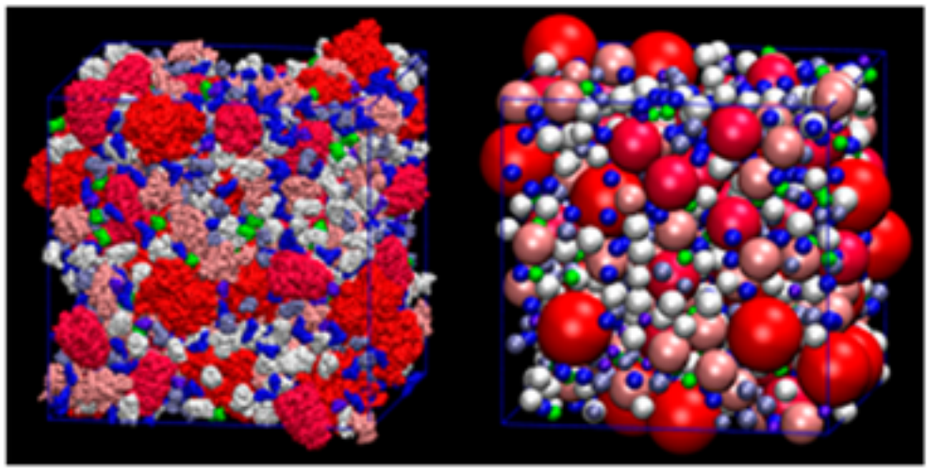
Strategies

Mean Field (from Dij —> Di)
Screening (remove long range rij)
Long range part as PME

Crowding in silico

Skolnick group

Cell Crowding



macromolecules as spheres
short range LJ interactions

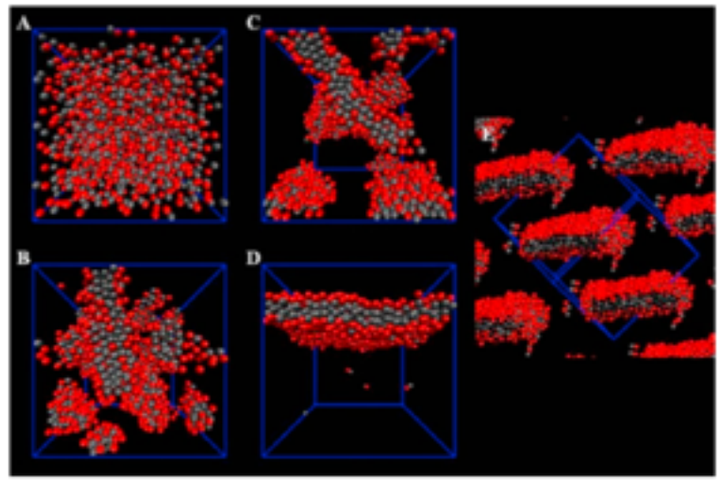
concentration 250/300/350 mg/mL
np 400 - 1200

Stokesian Dynamics
(BD + far + near + mb interactions)

D^L/D^0 ~0.1 for c=300 mg/mL

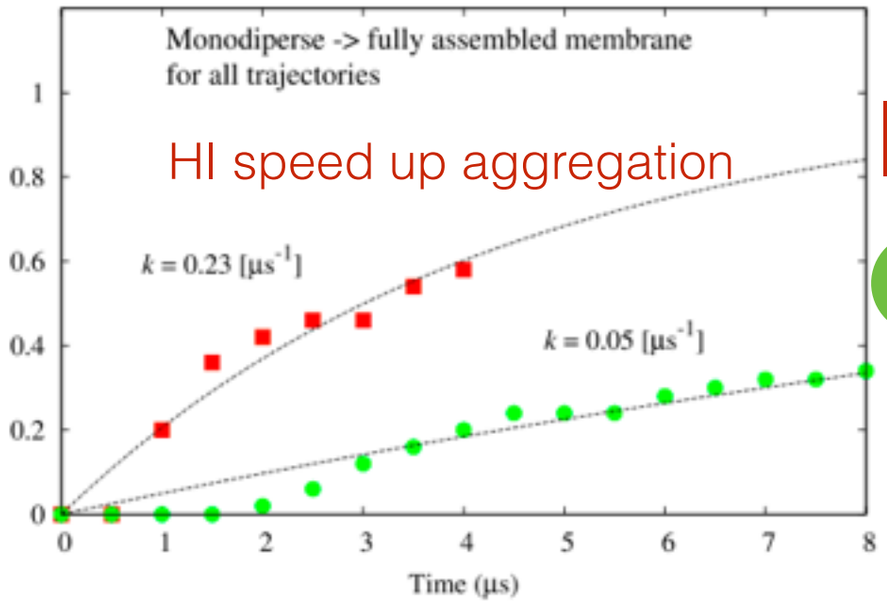
Ando&Skolnick, PNAS (2010), BJ (2013)

Lipid Aggregation



lipid as dumbbell model

BD + Rotne-Prager-Yamakawa



with HI

without HI

Muphy/OPEP: Protein Relaxation

Tuning the coupling

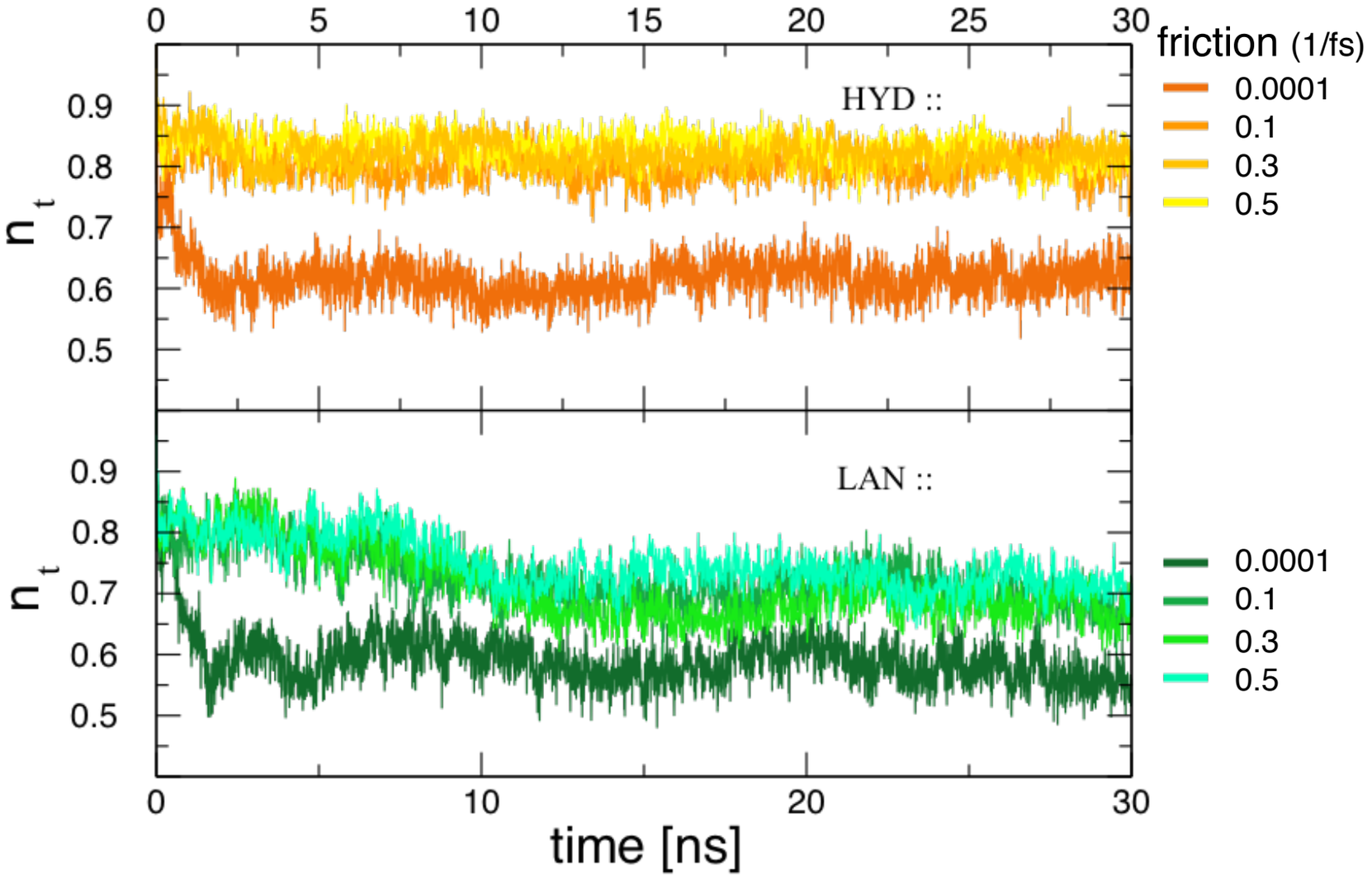
$$\mathbf{F}_{drag,i} = -m\gamma(\mathbf{v}_i - \mathbf{u}_i)$$

Hydrodynamics

Fluctuations around initial state
Drift at weak coupling

Langevin Dynamics

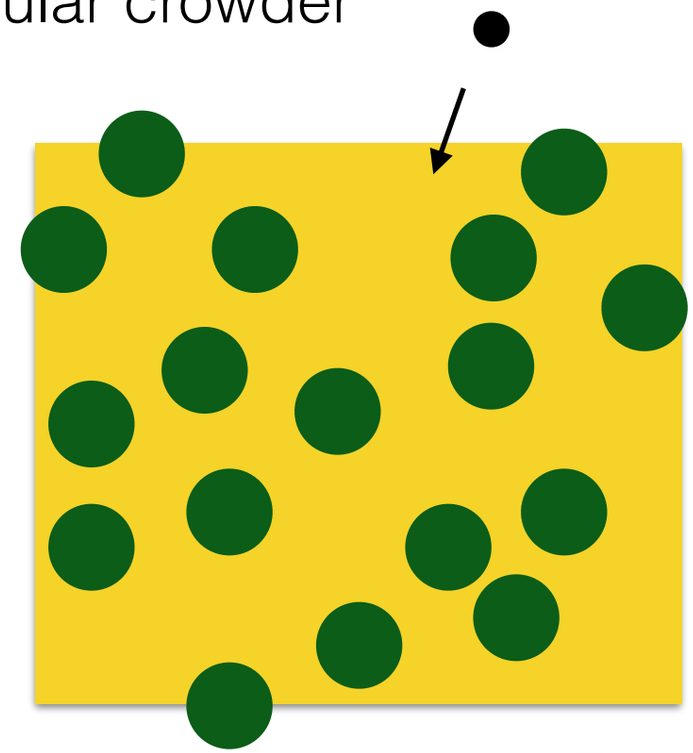
Drift for all coupling



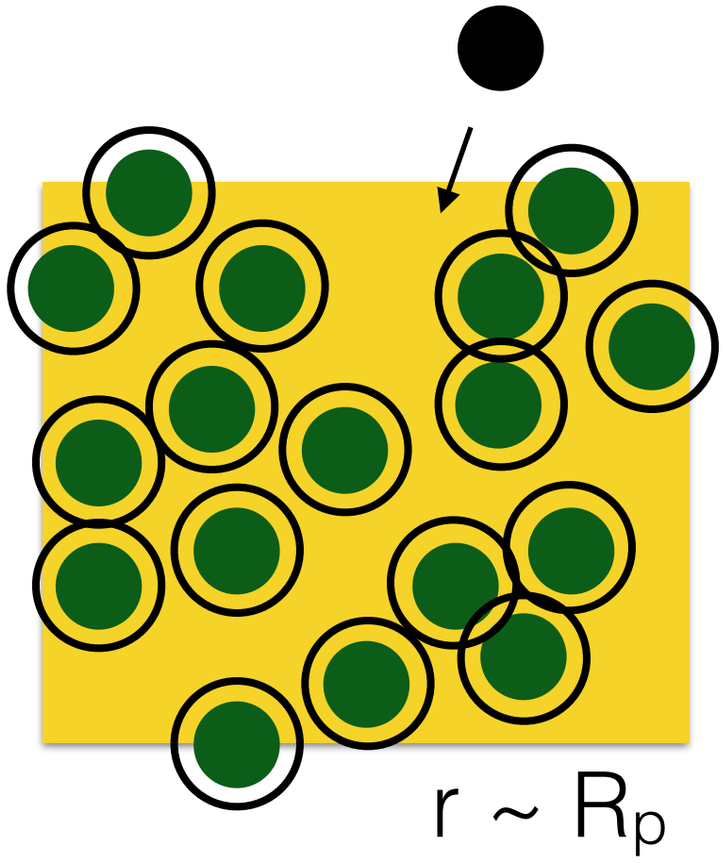
Fluid pumps/dissipates energy and controls solute relaxation

Excluded Volume

Molecular crowder



$r << R_p$



$r \sim R_p$

in Cell 20-40 % of volume is occupied by macromolecules

the effect of excluded volume is non-linear with size of “probe”

Excluded Volume

a chemical perspective

chemical potential $\mu_i = \mu_i^{ideal} + \mu_i^{nonideal}$

effect of concentration $\mu_i^{ideal} = \mu_i^0 + kT \ln c_i$

effect of intermolecular interactions $\mu_i^{nonideal} = kT \ln \gamma_i$

macromolecules get closer under crowding → free energy of interactions between species i and the other macromolecules

Crowding enhances the effect of concentrations

$kT \ln \gamma_i c_i$

thermodynamic activity

Ellis, Trends in Biochemical Sci (2001), Zhou, Febs Lett (2013)

Excluded Volume

a physics perspective

free energy of confinement $\Delta F^c = -kT \frac{Z^0}{Z^c}$

partition function $\int_\Omega dr^{3N} e^{-\beta U}$

volume accessible

Crowding affects both thermodynamics and kinetics

overall exclude volume

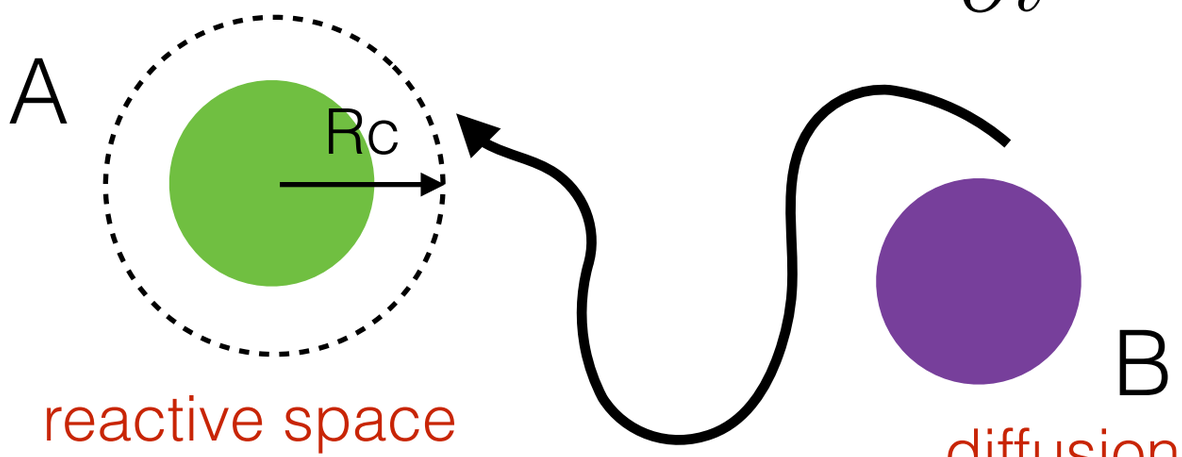
exclude volume of TS configurations

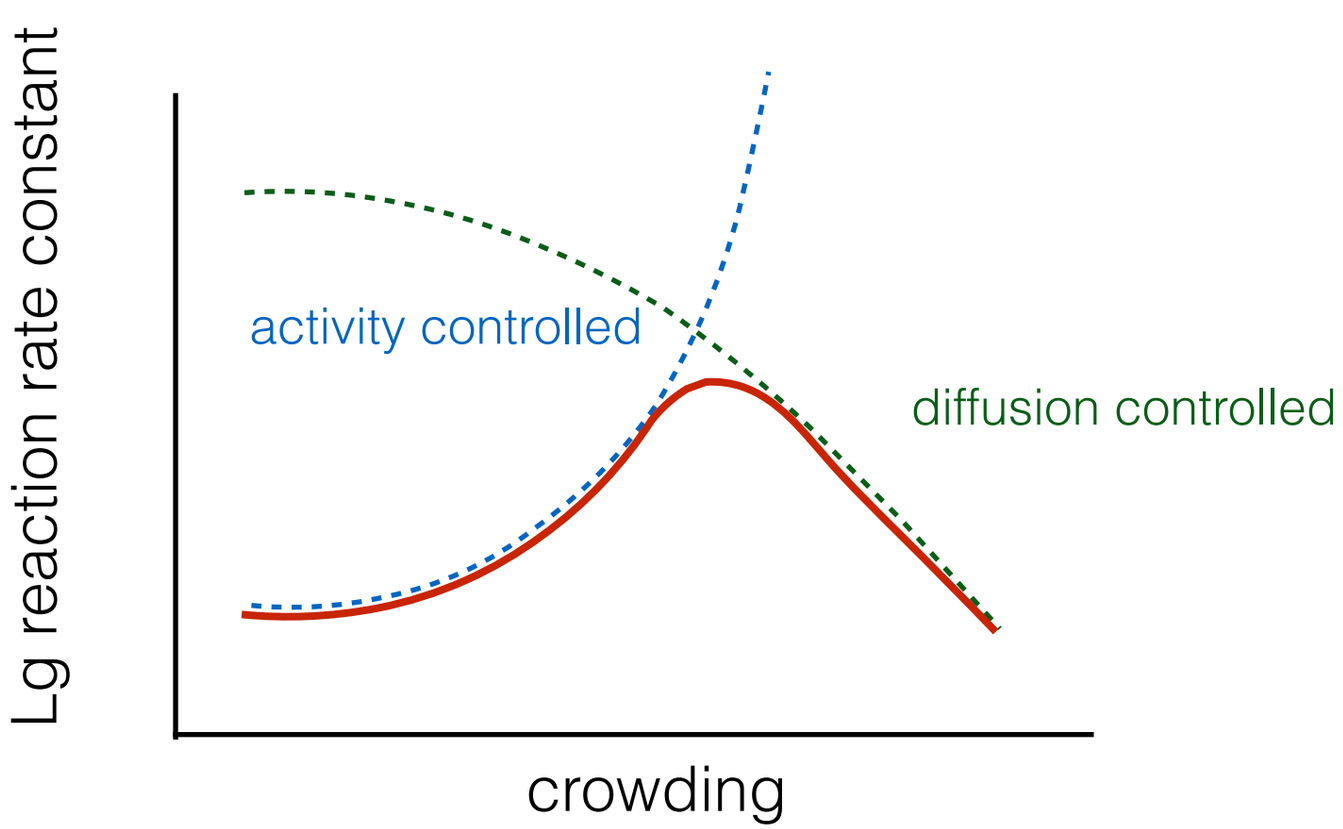
Zhou, Rivas, Minton, Ann Rev Biophys (2008)

Reaction-diffusion

species A and B react (k_s)

$$\frac{\partial C_B}{\partial t} = \underbrace{D\nabla^2 C_B}_{\text{diffusive term}} - \underbrace{ksC_BC_A}_{\text{reactive term}}$$





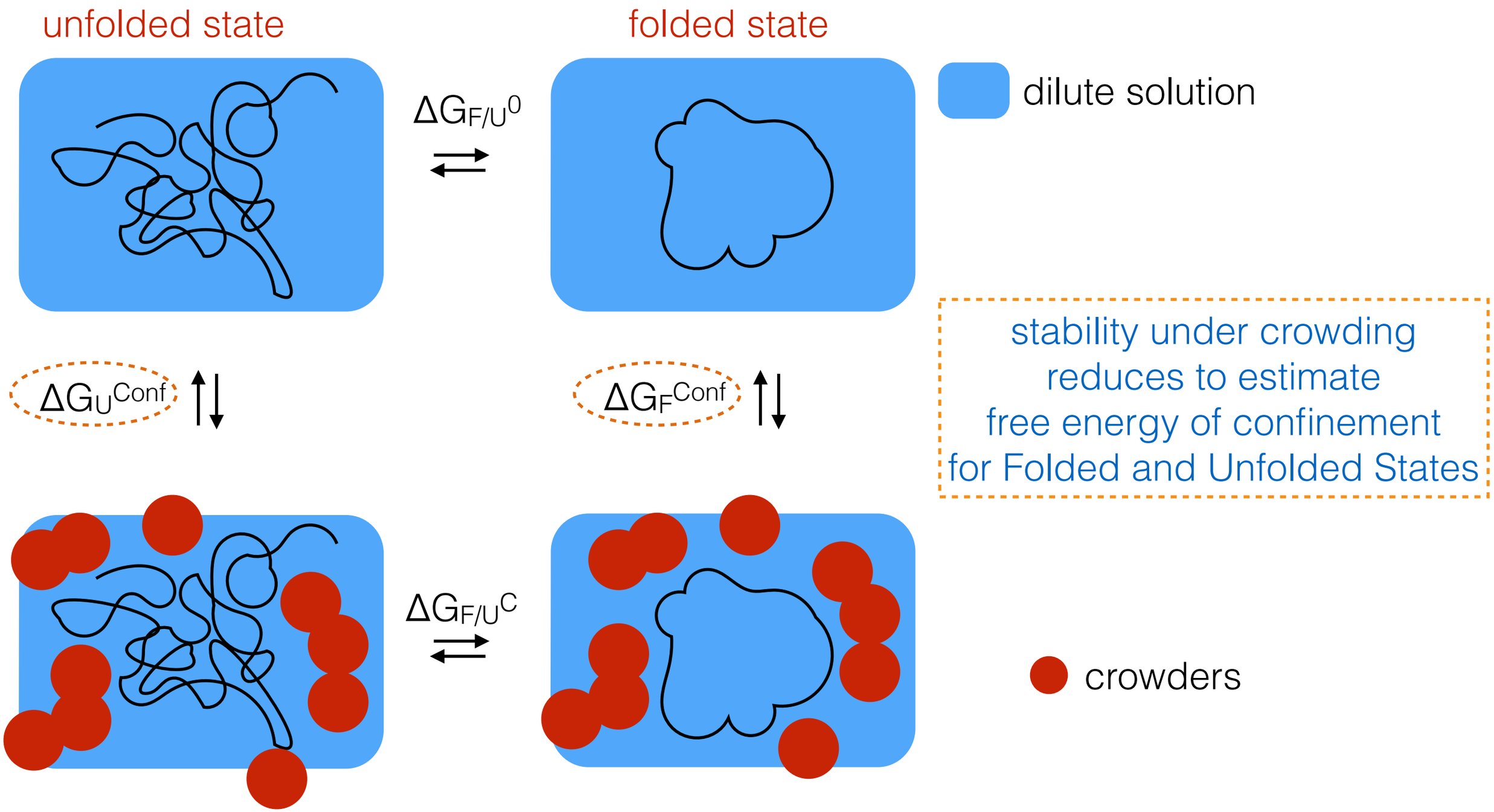
crowding enhances activity

crowding reduces diffusivity

Ellis, Trends in Biochemical Sci (2001)

Protein stability

crowding

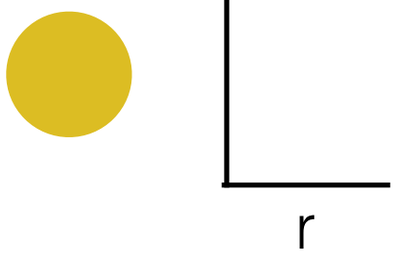


Zhou, Rivas, Minton, Ann Rev Biophys (2008), Zhou, Febs Lett (2013)

Confining the folded state

Scaled Particle Theory

hard sphere



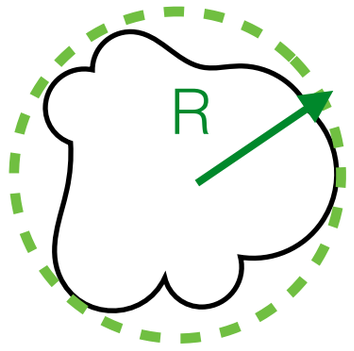
V(r)=∞ r< σ

V(r)=0 r> σ

$$\Delta G_F^{Conf} = -kT\ln(1-\phi) + \sum_{i=1}^{3} A_i Q^i$$

$Q=\phi/(1-\phi)$

$A_i=f(R)$



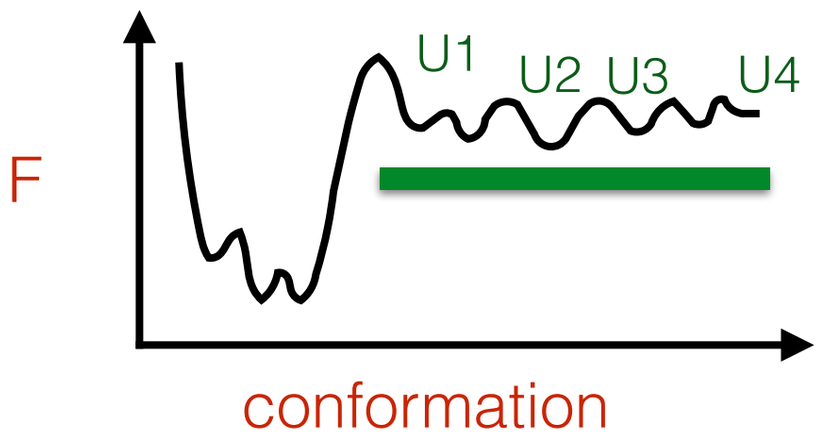
folded state == globular state

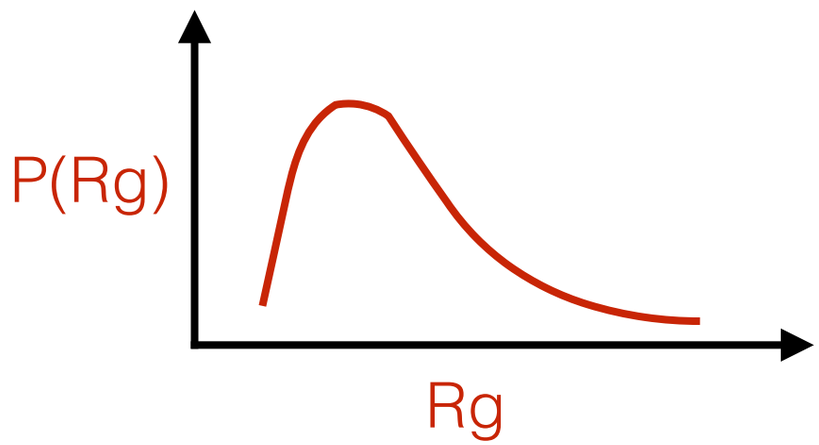
Free energy to transfer an ideal spherical particle of radius R in environment with occupied volume ϕ

Zhou, Rivas, Minton, Ann Rev Biophys (2008), Zhou, Febs Lett (2013)

Confining the unfolded state

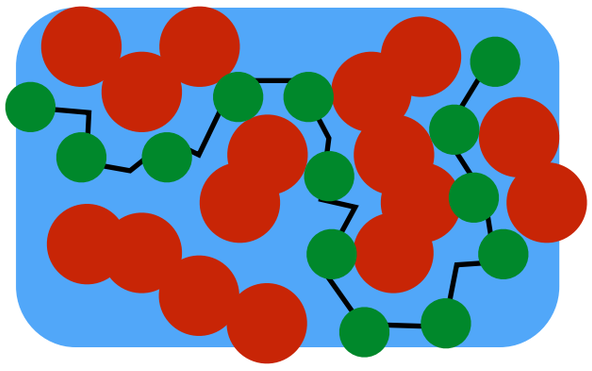
PROBLEM : unfolded state NOT globular





STRATEGIES

— Random Walk
in crowded space



low ϕ Folded is stabilised

high ϕ Unfolded is stabilised

— Generate representative Unfolded states from P(Rg)
and try to insert in the crowded space or compute Excluded Volume

Zhou, Rivas, Minton, Ann Rev Biophys (2008), Zhou, Febs Lett (2013)