Sample characterization: quality control and sample handling prior to data collection

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EMBO 16-22 Sep2024

Sample characterization prior to data collection: why?

"The correct interpretation of many biophysical/structural characterization experiments relies on the assumption that:

- the protein samples are **pure and homogeneous**
- their **concentration is assessed precisely**
- all of the protein is solubilized and in a natively **active state**"

" Those who assess and **optimize carefully the quality of their protein** preparations **significantly increase their chances of success in subsequent experiments**"

- ➢ Optimize the homogeneity
- ➢ Time-stability and storage conditions of purified samples
- ➢ Evaluate reproducibility and lot-to-lot consistency


Raynal *et al. Microbial Cell Factories* (2014) 13:180
DOI 10.1186/s12934-014-0180-6

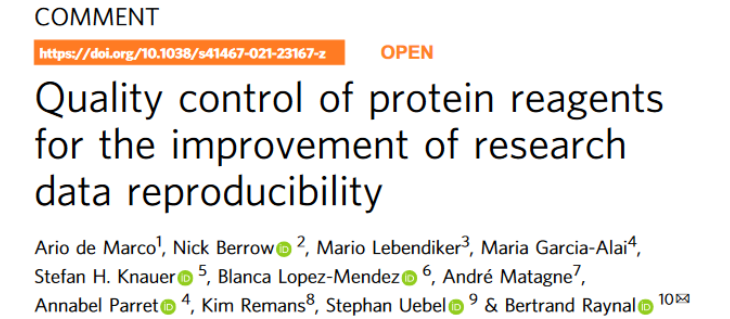
MICROBIAL CELL FACTORIES

REVIEW Open Access

Quality assessment and optimization of purified protein samples: why and how?

Bertrand Raynal[1,2*], Pascal Lenormand[1,2], Bruno Baron[1,2], Sylviane Hoos[1,2] and Patrick England[1,2*]

nature COMMUNICATIONS


COMMENT

https://doi.org/10.1038/s41467-021-23167-z OPEN

Quality control of protein reagents for the improvement of research data reproducibility

Ario de Marco[1], Nick Berrow[2], Mario Lebendiker[3], Maria Garcia-Alai[4], Stefan H. Knauer[5], Blanca Lopez-Mendez[6], André Matagne[7], Annabel Parret[4], Kim Remans[8], Stephan Uebel[9] & Bertrand Raynal[10]✉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HOME › CUSTOM PUBLISHING › WEBINARS › REPRODUCIBILITY IN CRISIS: SAMPLE QUALITY AND THE IMPORTANCE OF EARLY AND ONGOING ANALYSIS

WEBINAR | TECHNOLOGY | SPONSORED BY NANOTEMPER TECHNOLOGIES

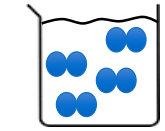
Reproducibility in crisis: Sample quality and the importance of early and ongoing analysis

14 MAR 2018 · 9:00 AM ET · SPEAKERS: JOHN P.A. IOANNIDIS, M.D., D.SC., GREGOR WITTE, PH.D. · MODERATOR: SEAN SANDERS, PH.D.

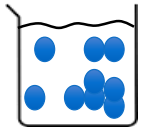
The use of Molecular Biophysics methods to characterize macromolecules and interactions

Intrinsic Properties

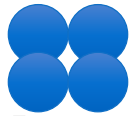
- Homogeneity
- Aggregation
- Size distribution
- Oligomeric states
- Stoichiometry of assemblies
- Secondary/tertiary Structures
- Quality control



Monodisperse



Aggregates
Polydisperse



Tetramer

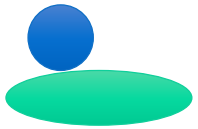
Dimer

Monomer

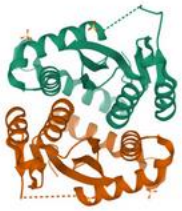
Interactions

- Kd
- k_{on} / k_{off}
- Thermodynamics ΔG, ΔH, $-\Delta DS$
- Stoichiometry of interaction

Macromolecular complex



Macromolecular interactions



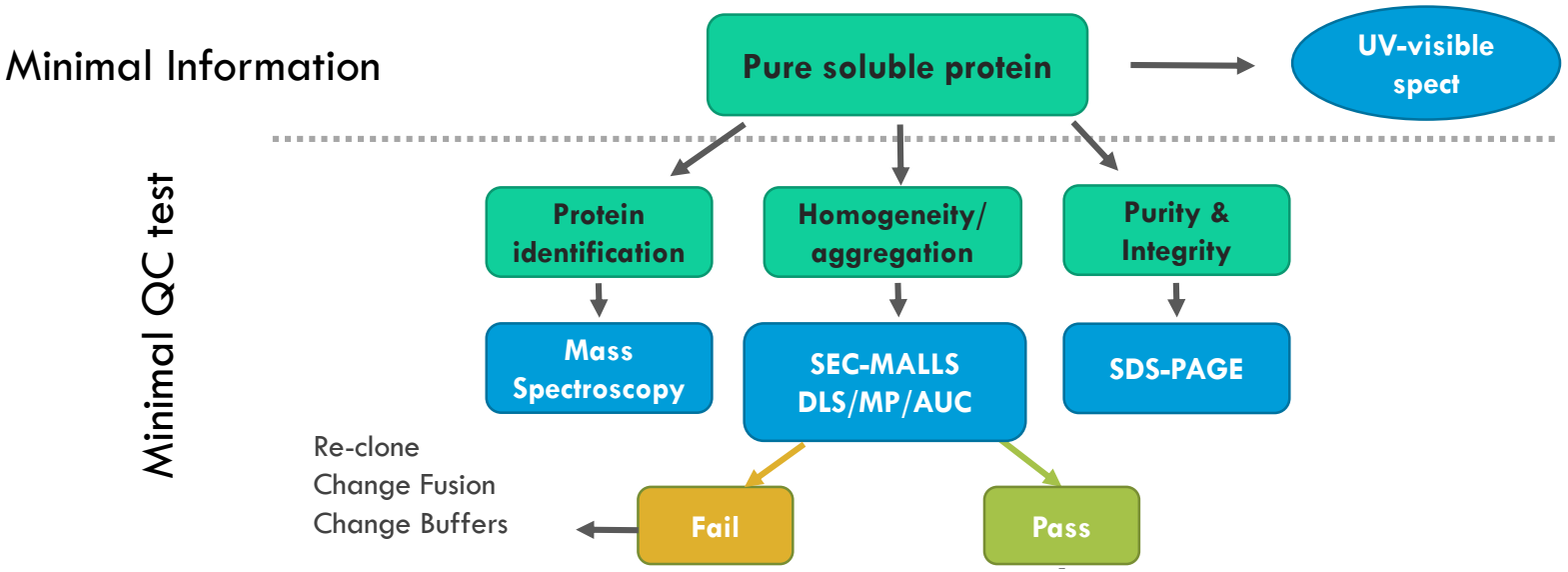
Secondary &
Tertiary Structure

How? Quality control - QC- workflow

Minimal Information

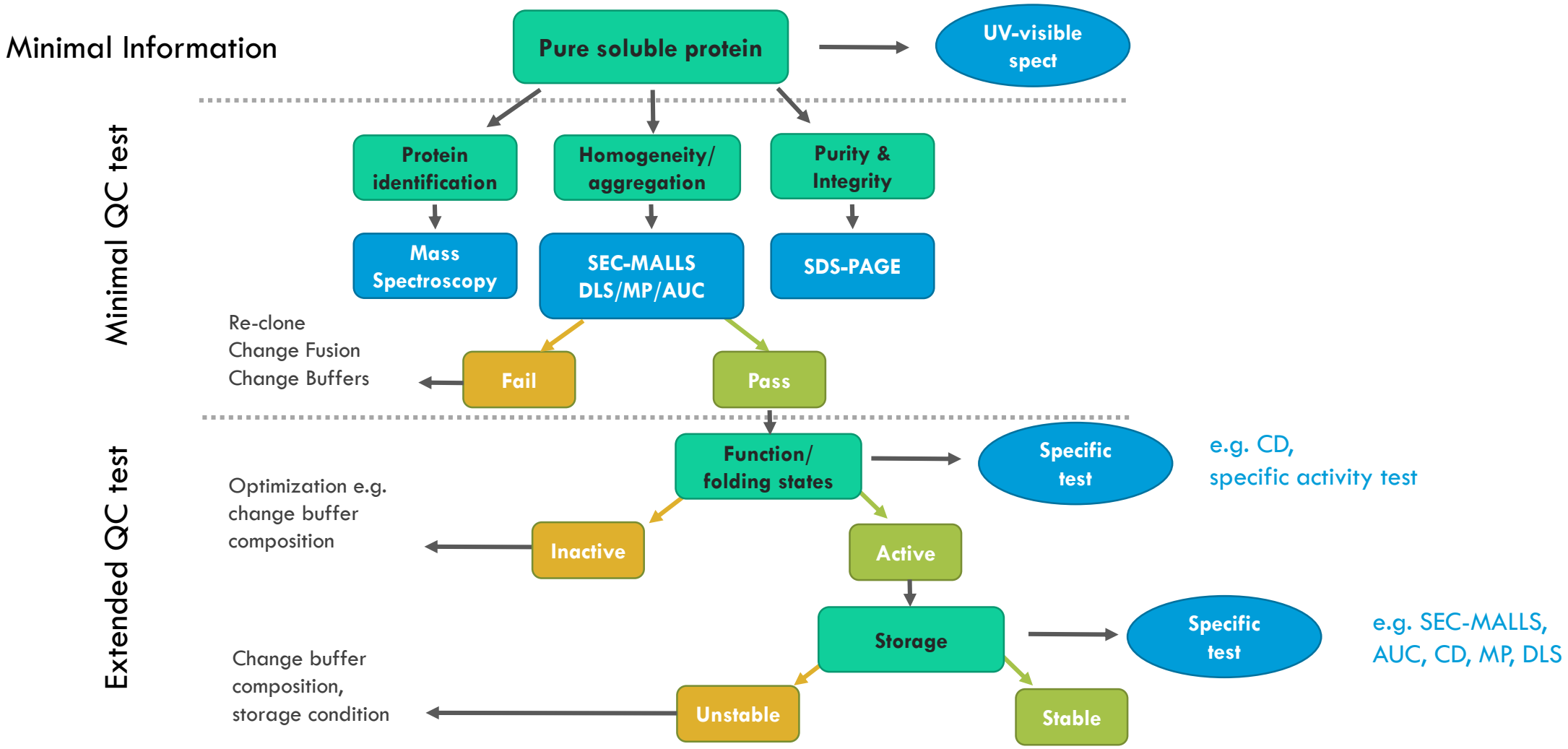
Adapted from De Marco et al., Nat Com 2021

How? Quality control - QC- workflow



Adapted from De Marco et al., Nat Com 2021

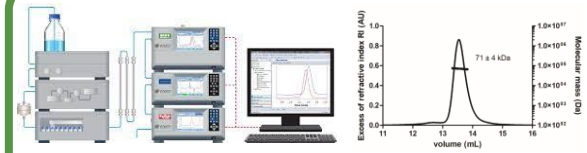
How? Quality control - QC- workflow



Adapted from De Marco et al., Nat Com 2021

Intrinsic Properties of Macromolecules and their Assemblies

- Homogeneity
- Aggregation
- Size distribution
- Oligomeric states
- Stoichiometry of assemblies
- Secondary Structures



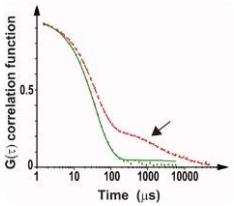
Dawn Heleos II / Optilab T-rex - WYATT

Static Light Scattering
SEC-MALS

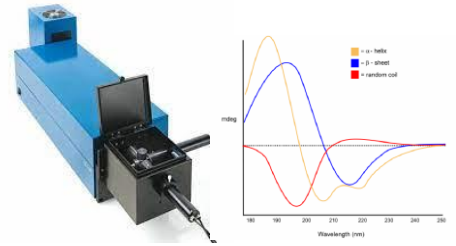
Dynamic Light Scattering

Circular Dichroism

Characterization

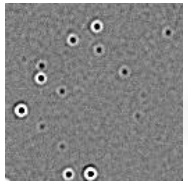


Zetasizer - MALVERN



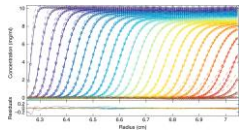
CD spectrometer MOS500 - BIOLOGIC

Mass Photometry



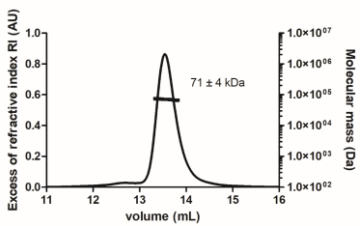
OneMP - REFEYN

Analytical Ultra centrifugation



AUC XLA / XLI BECKMAN

Size Exclusion Chromatography (SEC) coupled with Multi Angle Laser Light Scattering (MALLS)

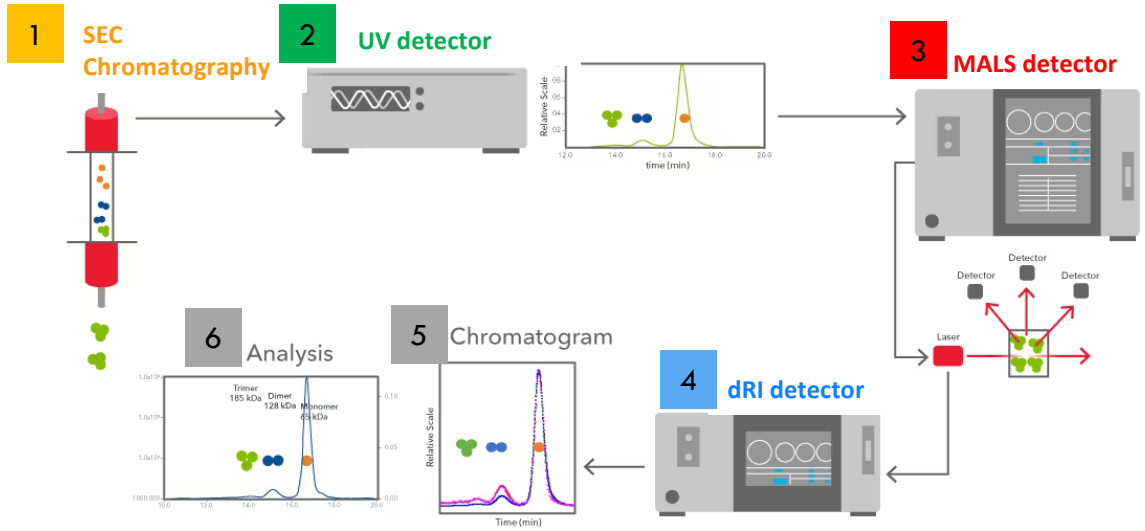


SEC-MALLS Principle

Multi-Angle Laser Light Scattering (MALLS), UV Absorbance and Refractive Index (RI) coupled to a size-exclusion chromatography (SEC) system allows the **simultaneous determination of the molecular weight of each component of a sample.**

MALLS measurements work by calculating the amount of scattered light (LS) by a sample at various angles. The intensity of the light scattered of a solution is directly proportional to :

- the concentration of its components (RI or UV)
- the average molecular weight (LS)



SEC-MALLS Principle

Macromolecules separation R_h

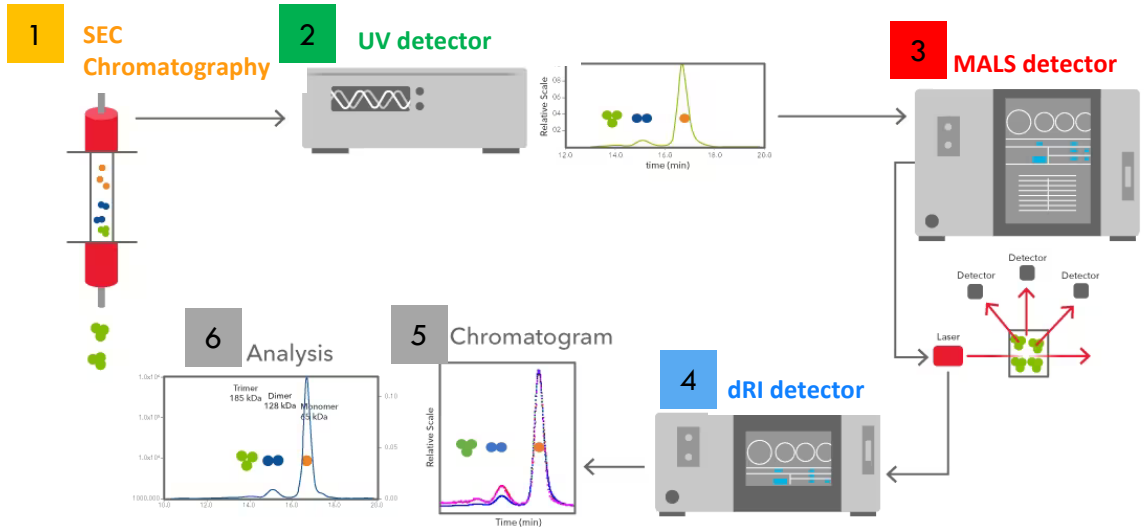
1 SEC - Size exclusion chromatography, separation according to the R_h

Macromolecules characterization with 3 detectors

2 UV $_{280nm}$

3 MALLS - Multi angle laser light scattering $I_s(\theta)$ ▶ Mw and C

4 Refractometer ΔRI ▶ C concentration



$$I_s(\theta) \propto C \times Mw \times \left(\frac{dn}{dc}\right)^2$$

The intensity of light scattering of is directly proportional to the average molecular weight and to the concentration of its components

dn/dc is a constant

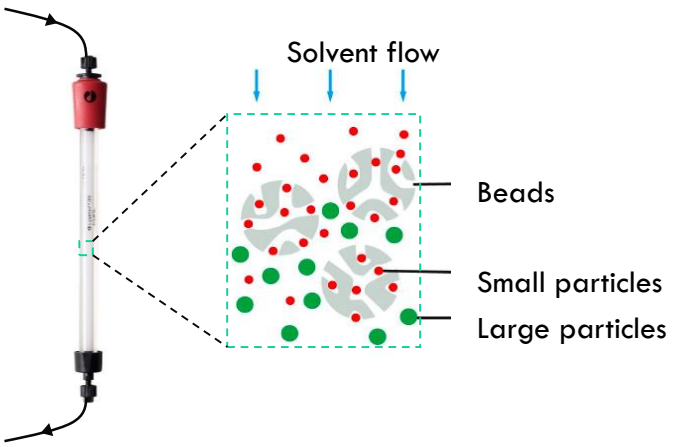
$$C = \frac{\Delta RI}{\left(\frac{dn}{dc}\right)}$$

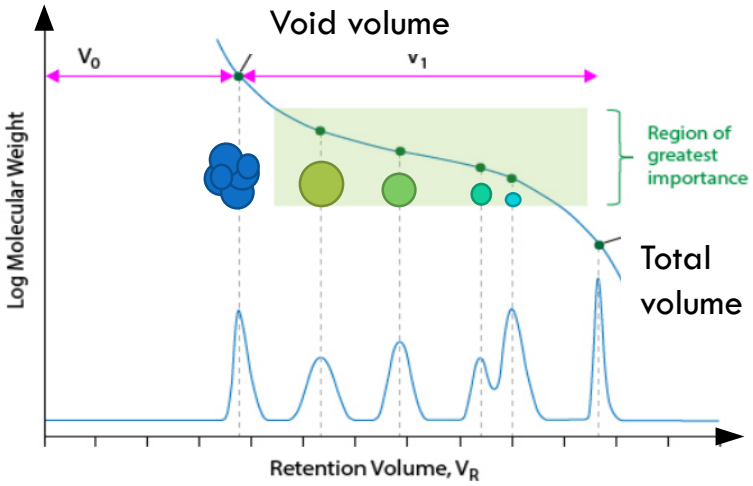
Concentration of the components is calculated with the differential refractive index

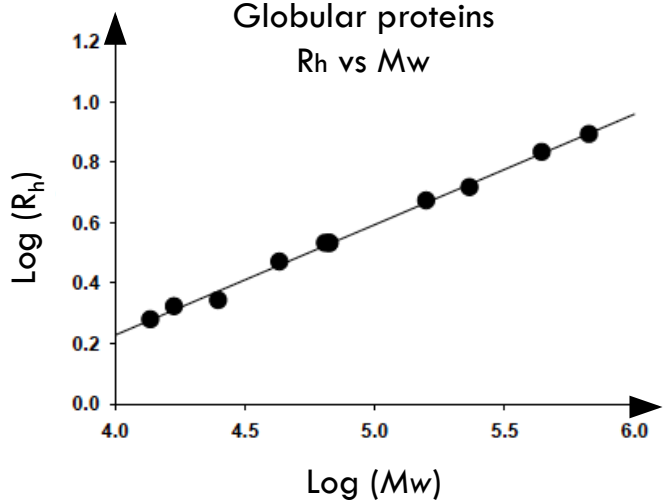
➢ Mw determination independent of the elution volume and therefore of the column calibration

https://www.bio-techne.com/reagents/proteins/sec-mals

Size exclusion chromatography - SEC



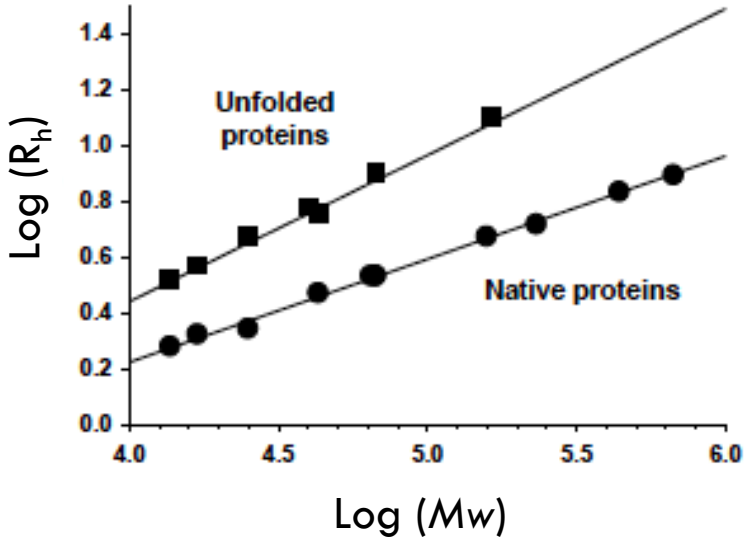


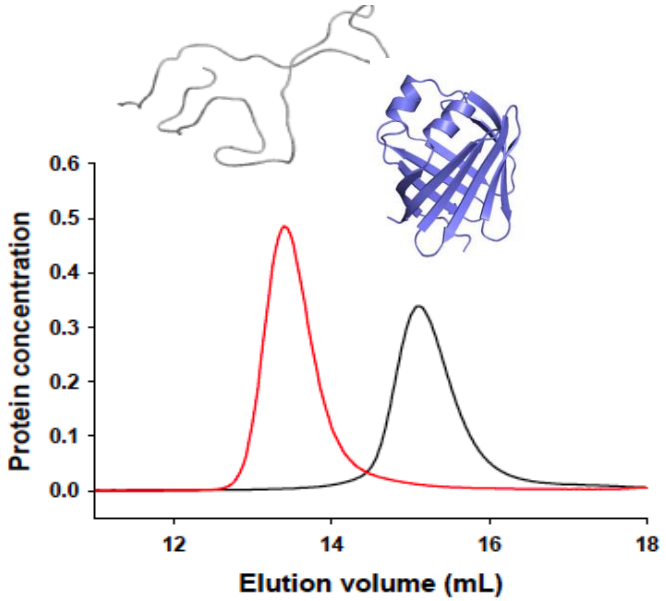


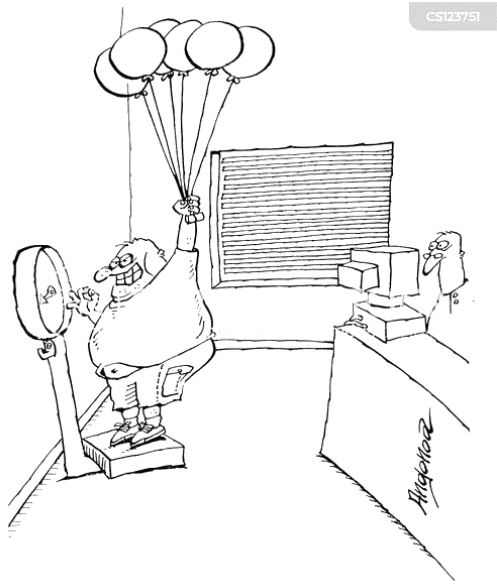
Size Exclusion Chromatography (SEC) is a chromatographic method in which molecules are separated based on their size:

- elution volume is related to their **hydrodynamic radius (Rh) and not to their molecular weight**
- To **connect Rh to the molecular weight,** it is necessary to make a **calibration with known globular molecular weight standards**
- Traditional SEC assumes that the sample of interest:
  - has the **same molecular conformation as the calibration standards**
  - **does not interact with the stationary phase** of the column

What about non-globular proteins?

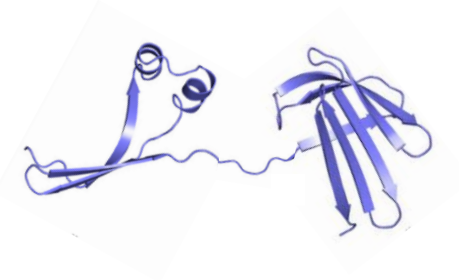




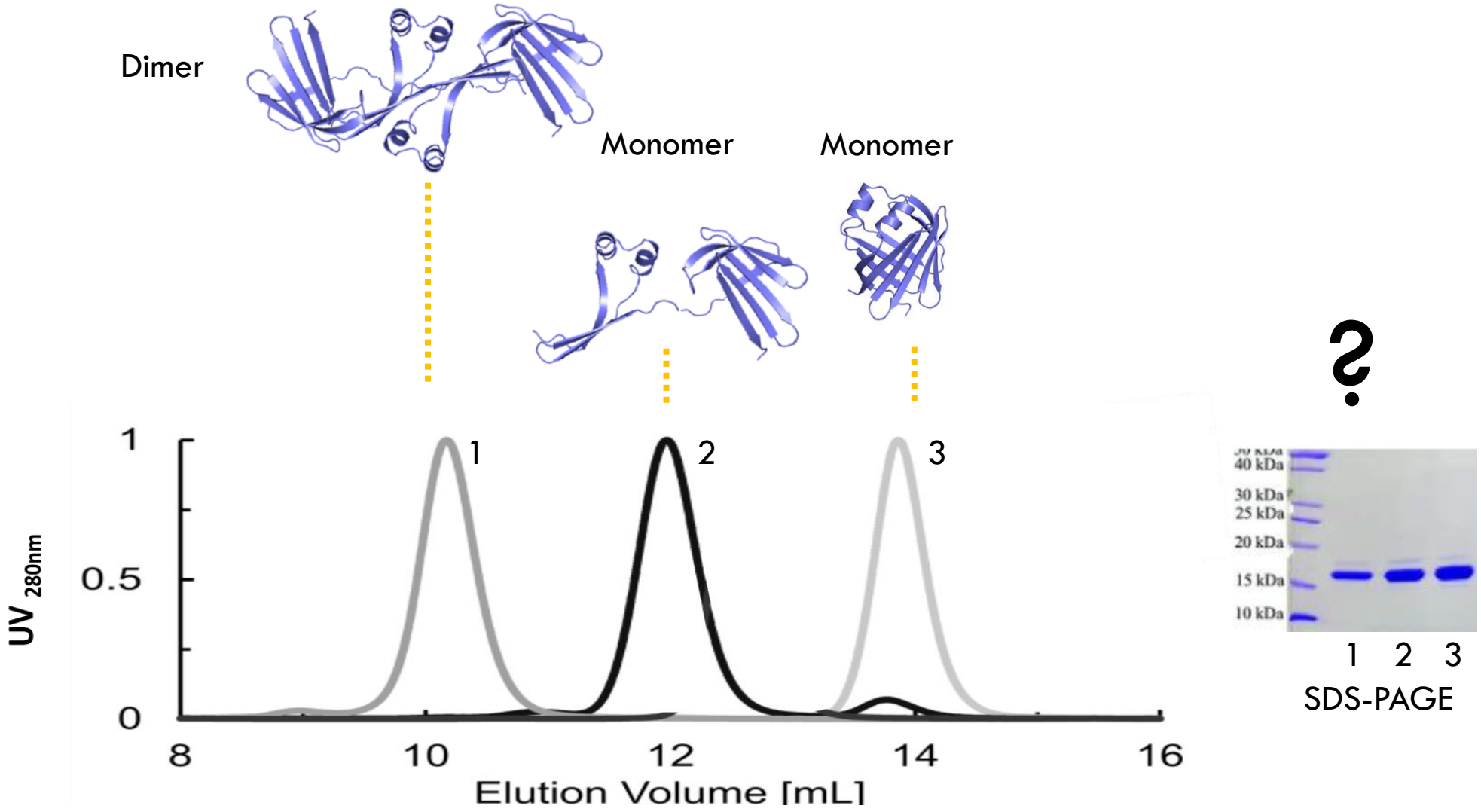


The hydrodynamic radius depends on the shape of the particle

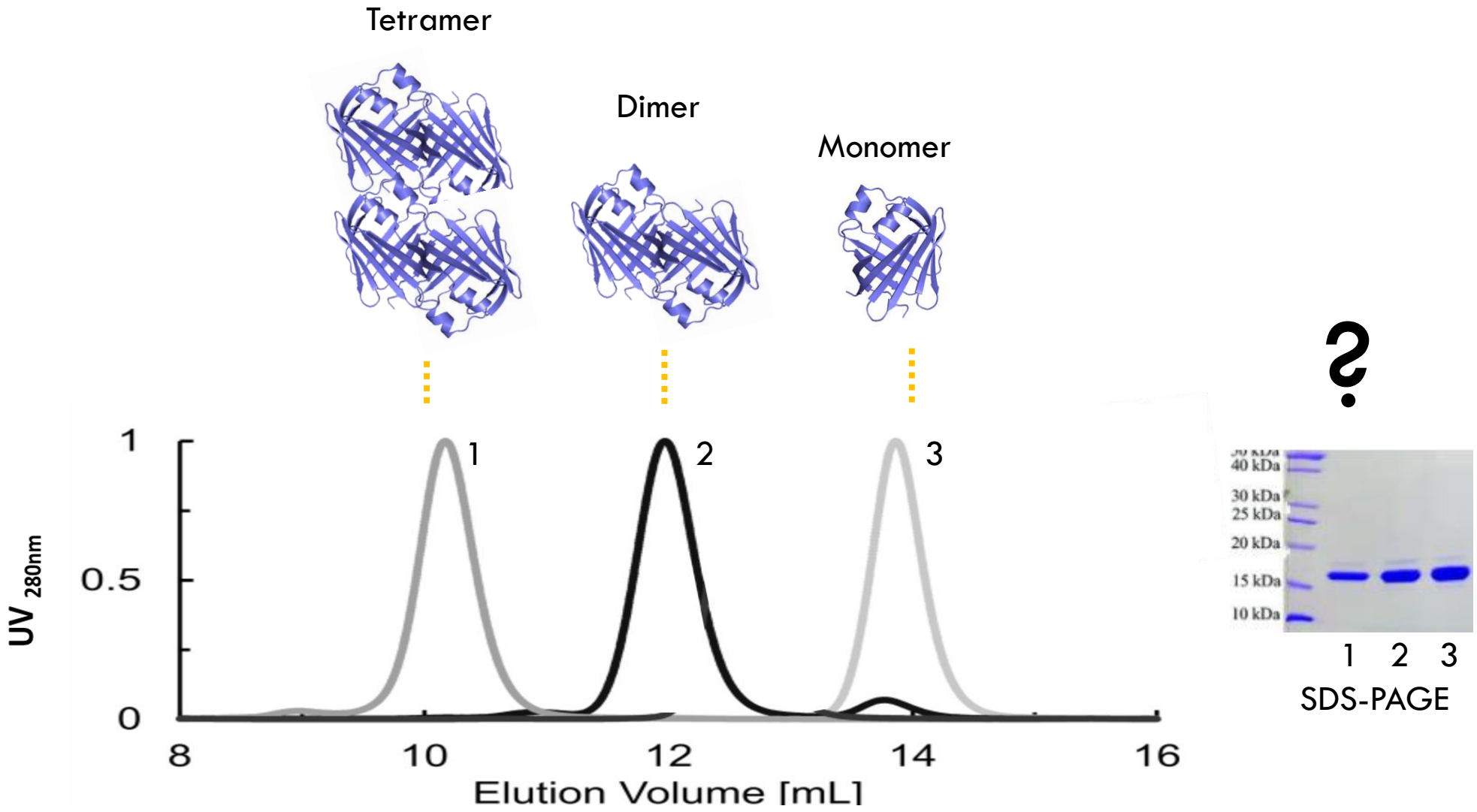
Most proteins are not globular…



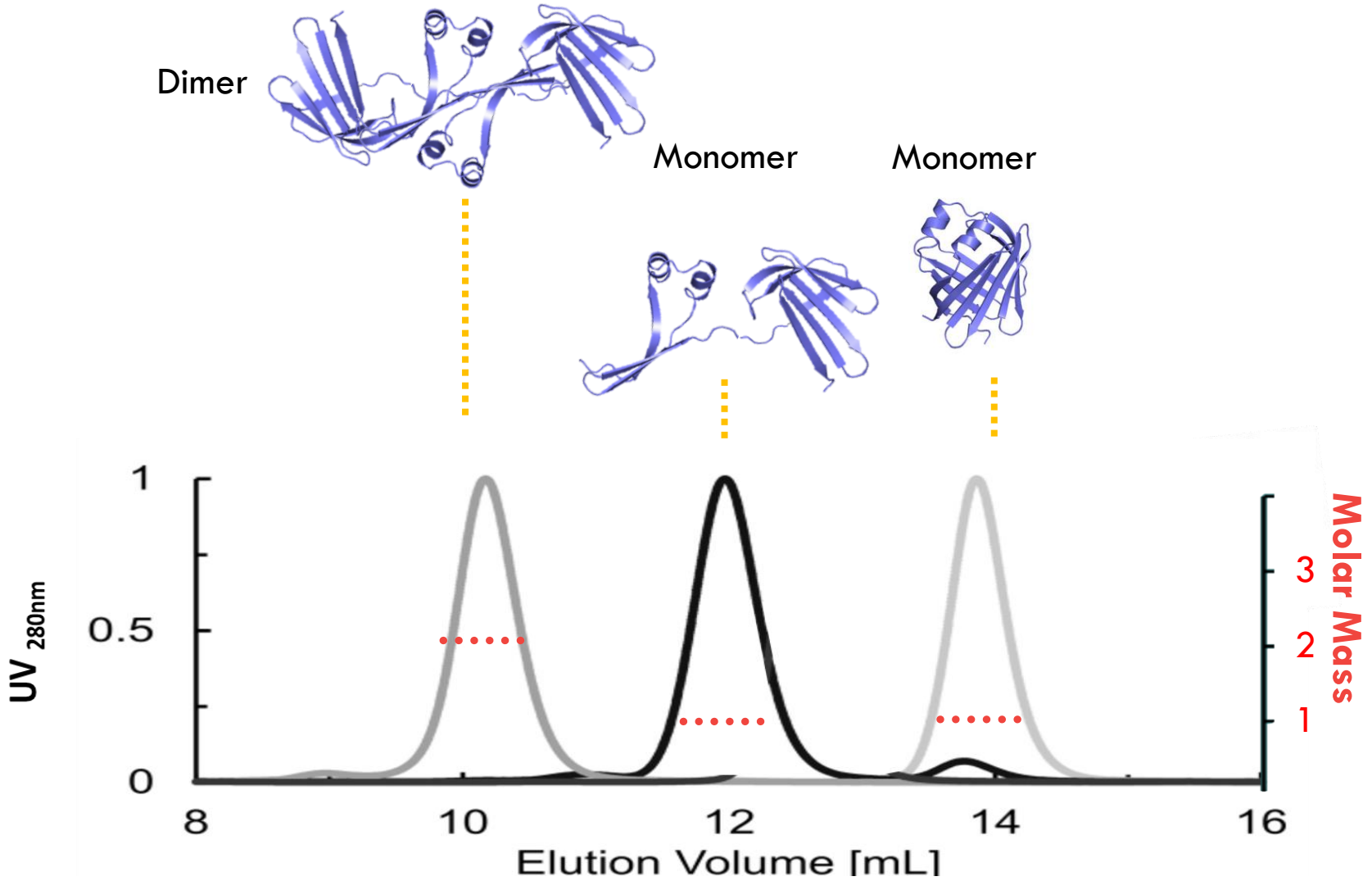
Interpretation of SEC data



Interpretation of SEC data

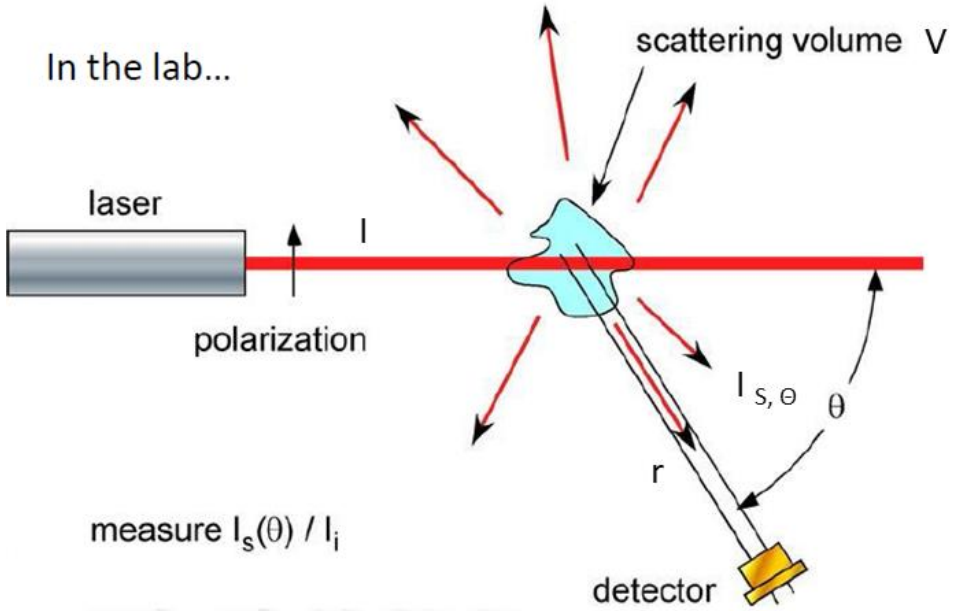


Interpretation of SEC data
Molar Mass information



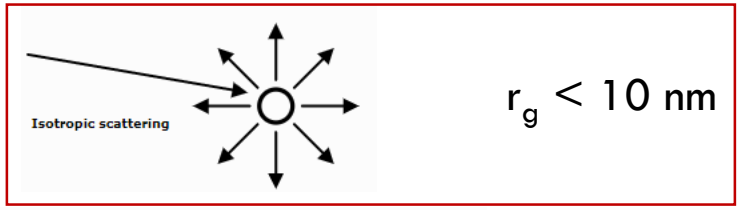
Multi Angle Laser Light Scattering

Static Light Scattering – SLS
MALLS measures the time-average intensity of scattered light



Rayleigh scattering

$$R(\theta) = \frac{I_{s,\theta}}{I_0} \frac{r^2}{V \sin^2\theta}$$



Wyatt Technology

Simple analytical description of Rayleigh scattering
The Rayleigh-Gans-Debye Equation

$$R(\theta) = \frac{4\pi^2 n_0^2}{N_A \lambda_0^4}\left(\frac{dn}{dc}\right)^2 McP(\theta)[1 - 2A_2 McP(\theta)]$$

Excess Rayleigh scatter (above solvent) at angle θ

K : optical constant

M: molar mass
C: concentration

$P(\theta)$: Form factor
Angular term reflecting Rg
> Negligible (isotropic scattering)

Term accounting for the intermolecular interference terms in the second virial coefficient A_2
> Negligible

Multi Angle Laser Light Scattering

The intensity of light scattering of a solution is directly proportional to the average molecular weight and to the concentration of its components

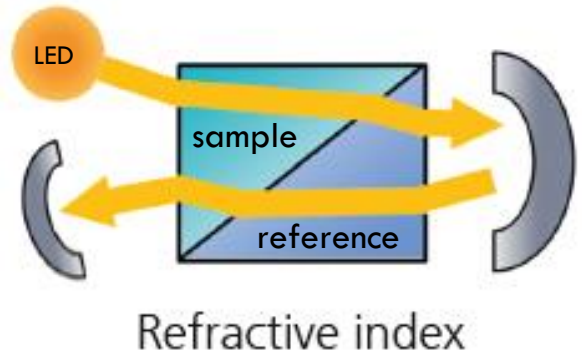
$$I_s(\theta) \propto c \times M \times \left(\frac{dn}{dn}\right)^2$$

- M is the average molar mass of the scattering macromolecules, which is to be determined
- c is the concentration of the macromolecule(in mg/ml)
- dn/dc is a sample specific value, which relates changes of refractive index of the solution in relation to the change of concentration. Averaged value for proteins: 0.185 ml/g

Refractive index

The Refractometer detector measures the difference of refractive index between sample and reference
Detection of all types of compounds even if they do not absorb.
> RI measurement is used to measure sample's concentration.

$$\Delta RI = n_s - n_r = c \times \frac{dn}{dc} \qquad c = \frac{\Delta RI}{\left(\frac{dn}{dc}\right)}$$



Refractive index

For **soluble proteins:** RI is used to measure the quantity of protein
For **membrane proteins:** RI and A_{280} are used for determination of detergent bound

$n=c/v$
c is the speed of light in vacuum
v is the speed of light in the in the medium
dn/dc is the specific refractive index increment = 0.185 ml/g for proteins

UV Absorbance

For **soluble proteins**
Absorbance is not used for the determination of the molar mass (RI is used)

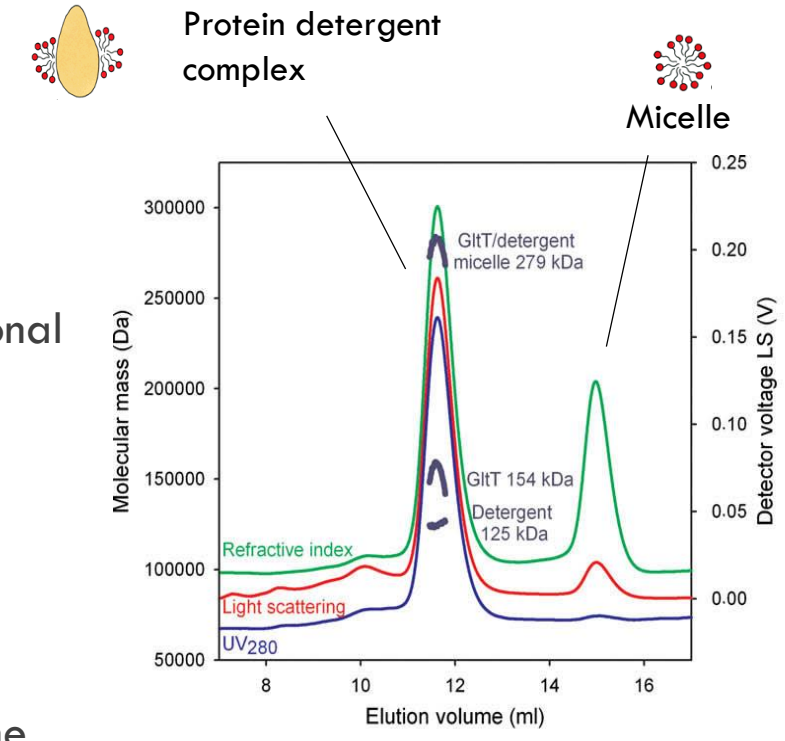
For **membrane proteins or Glycosylated proteins**
UV and RI detectors are used for concentration measurements in two orthogonal ways: Allows for deconvolution of mass contribution of two components (protein/detergent or protein/glycosylation)

Absorbance 280 nm

- concentration of protein - ε_{prot}

Deconvolution of signal RI

- used to calculate the amount and mass of detergent and calculate the mass of the protein

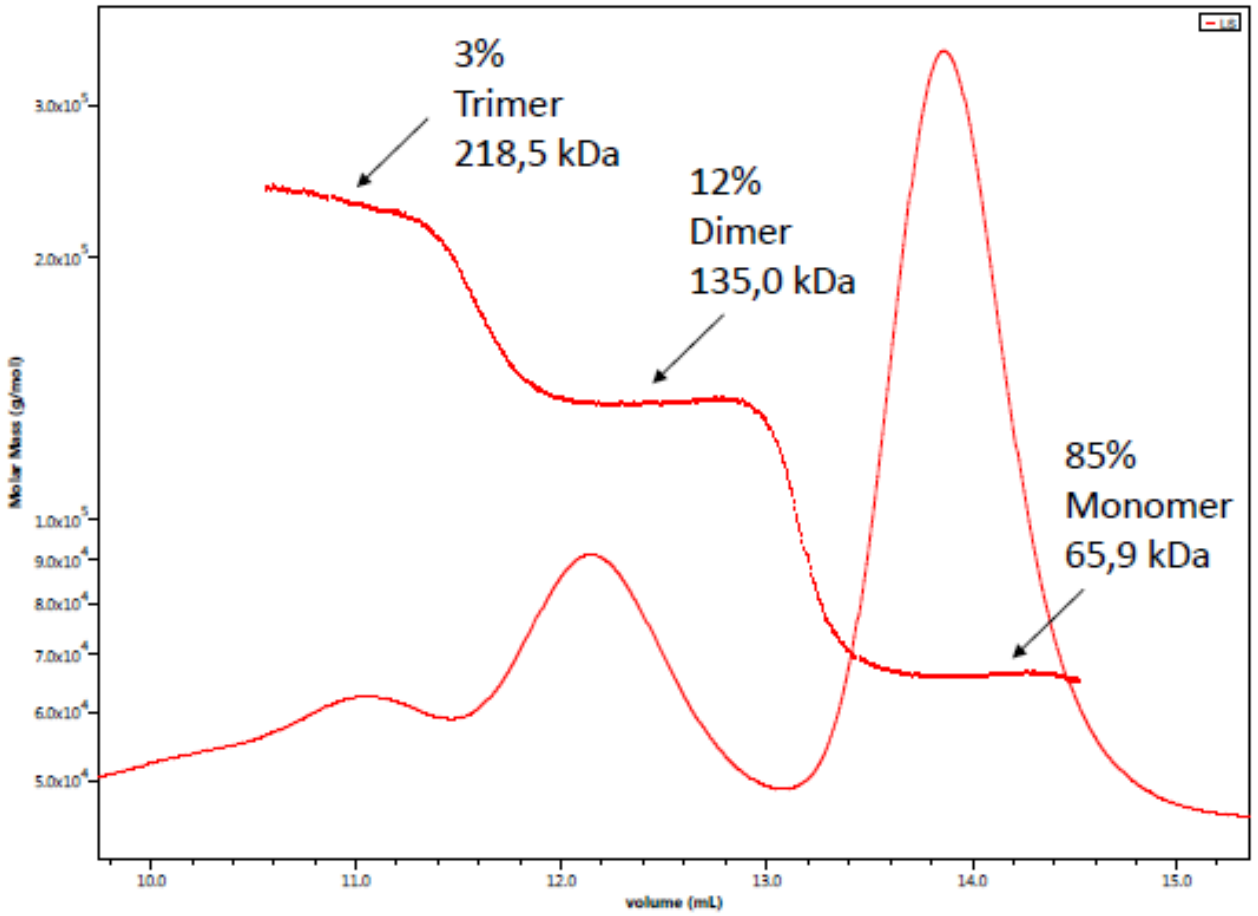


SEC-MALLS
Applications

- Simple analysis of BSA
- Detection of aggregates, Sample Quality
- Protein/protein interaction
- Membrane proteins/Glycosylated protein

Analysis of Bovine serum albumin - BSA

- Example of the BSA (50uL at 2mg/mL injected on a KW 804 Shodex column)

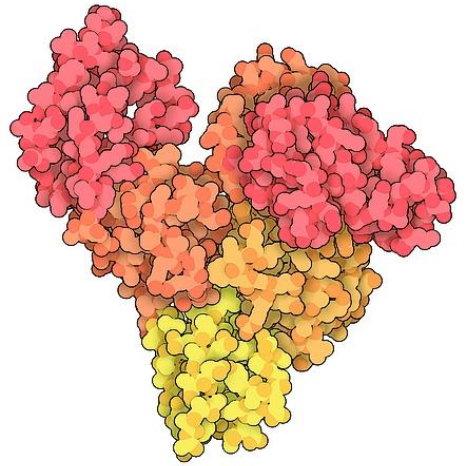


RI + LS => c + *M*

➢ RI gives the *amount (µg) under each peak*

Input : $\partial n/\partial c$

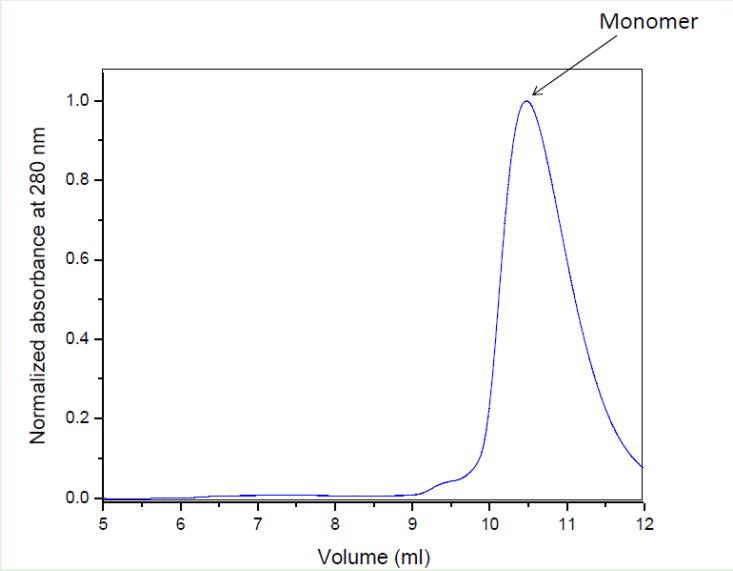
UV *not used*



BSA molecular artwork, courtesy of Dr. David Goodsell.

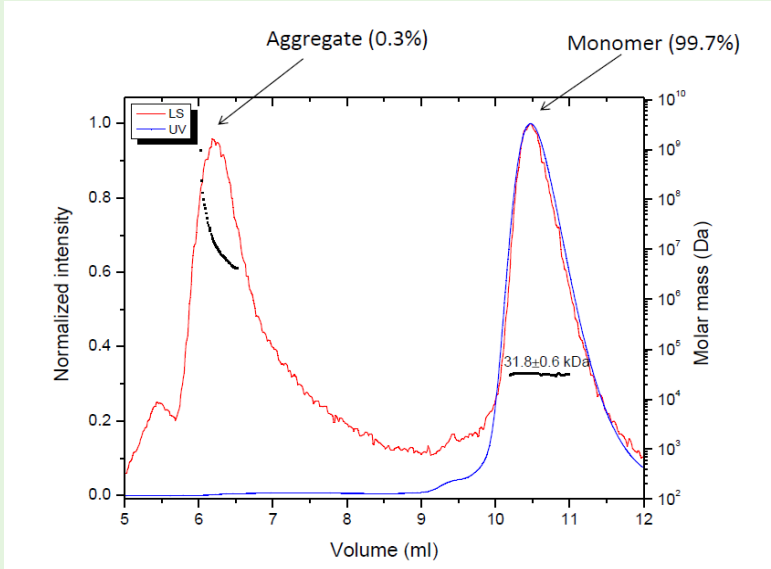
Detection of aggregates

SEC



- Separation by size
- Calculating *Mw* based on calibration curves of globular proteins
- Heterogeneity of a sample is undetectable

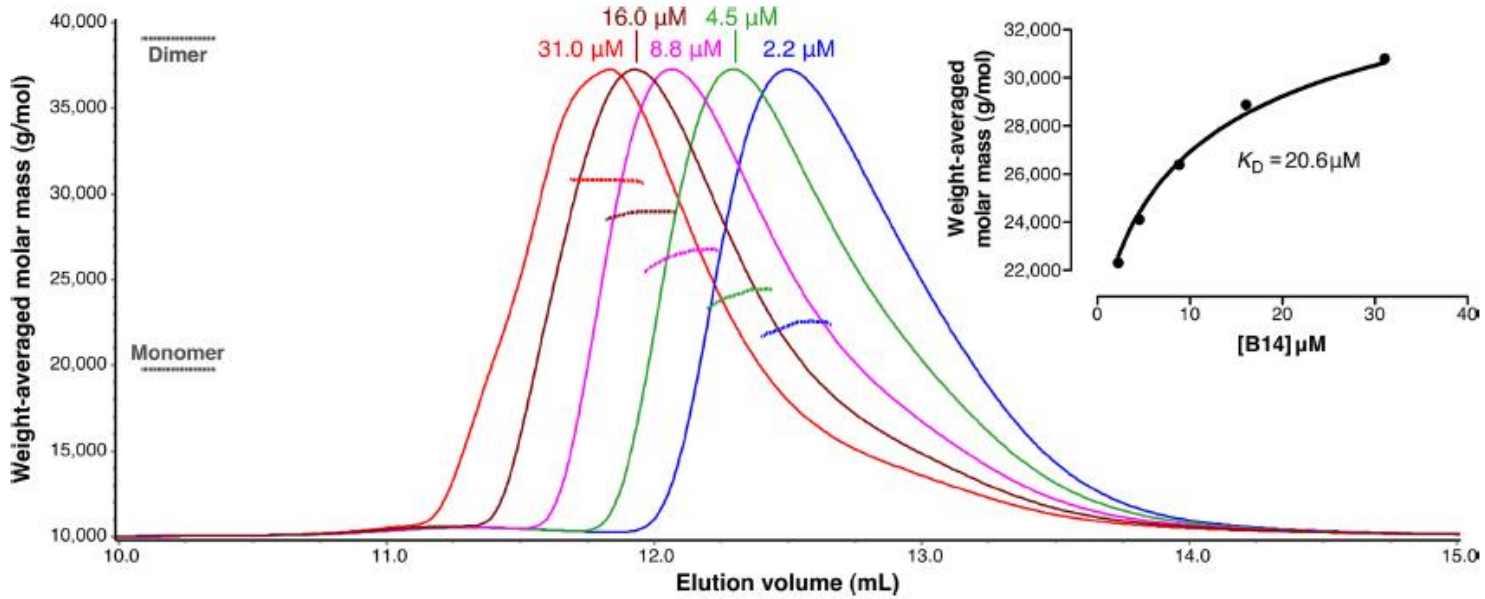
SEC- MALLS



- Separation by size
- Calculating *Mw* from the light scattering equations
- Calculate the *Mw* during the elution peaks, indicate homogeneity of a sample
- Detect low amount of aggregation : large molecules amplify the intensity of LS

- Light scattering
- Absorbance 280 nm

Monomer-dimer Fast exchange equilibrium



Weight average molar mass across the elution profile at five different concentrations.
The apparent molar mass under a range of different concentrations show that:

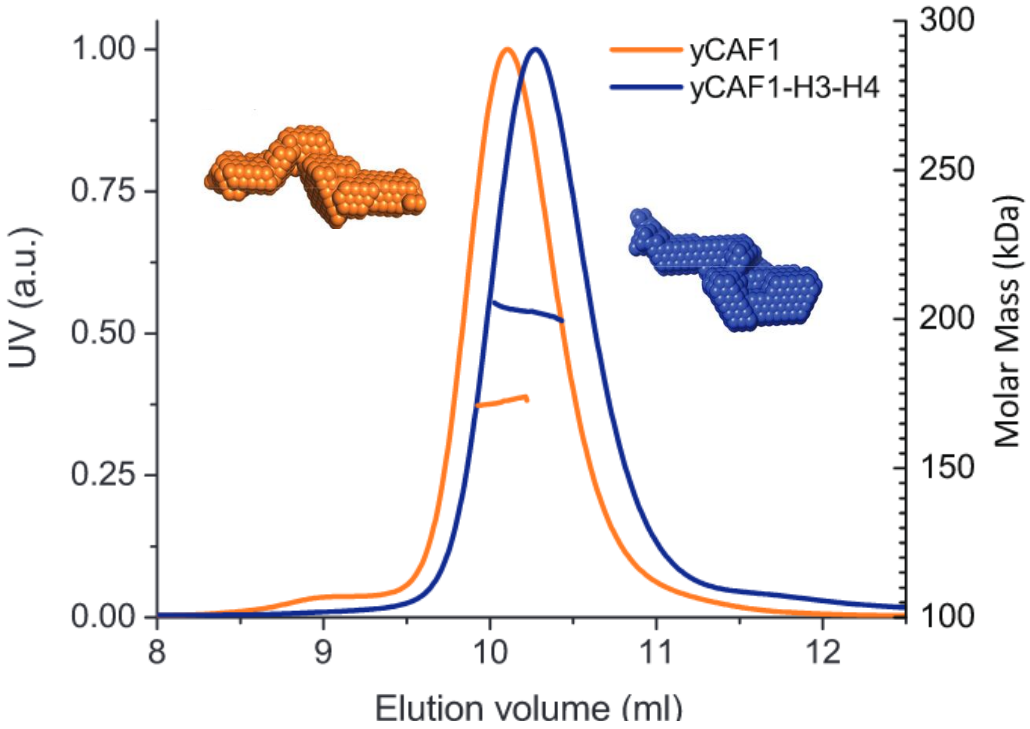
- Elution volume of the peak fraction decreased
- Average molar mass increased with increasing concentrations of protein

In solution, the protein is in monomer-dimer equilibrium, self-associating with modest affinity

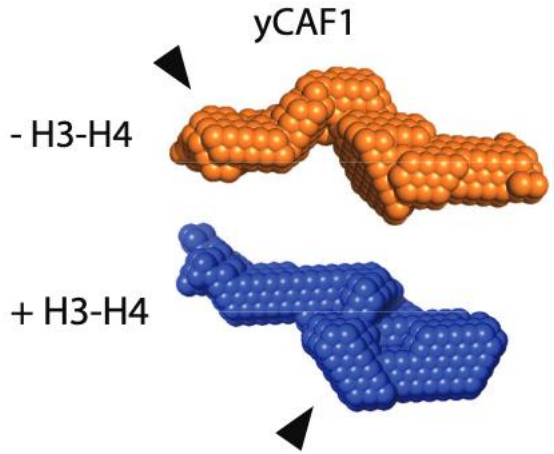
Benfield et al, JBC 2011

Protein/protein interaction

Budding yeast **CAF1 (yCAF1)** is a heterotrimeric complex containing the Cac1, Cac2 and Cac3 subunits and its interaction with **histone H3-H4**



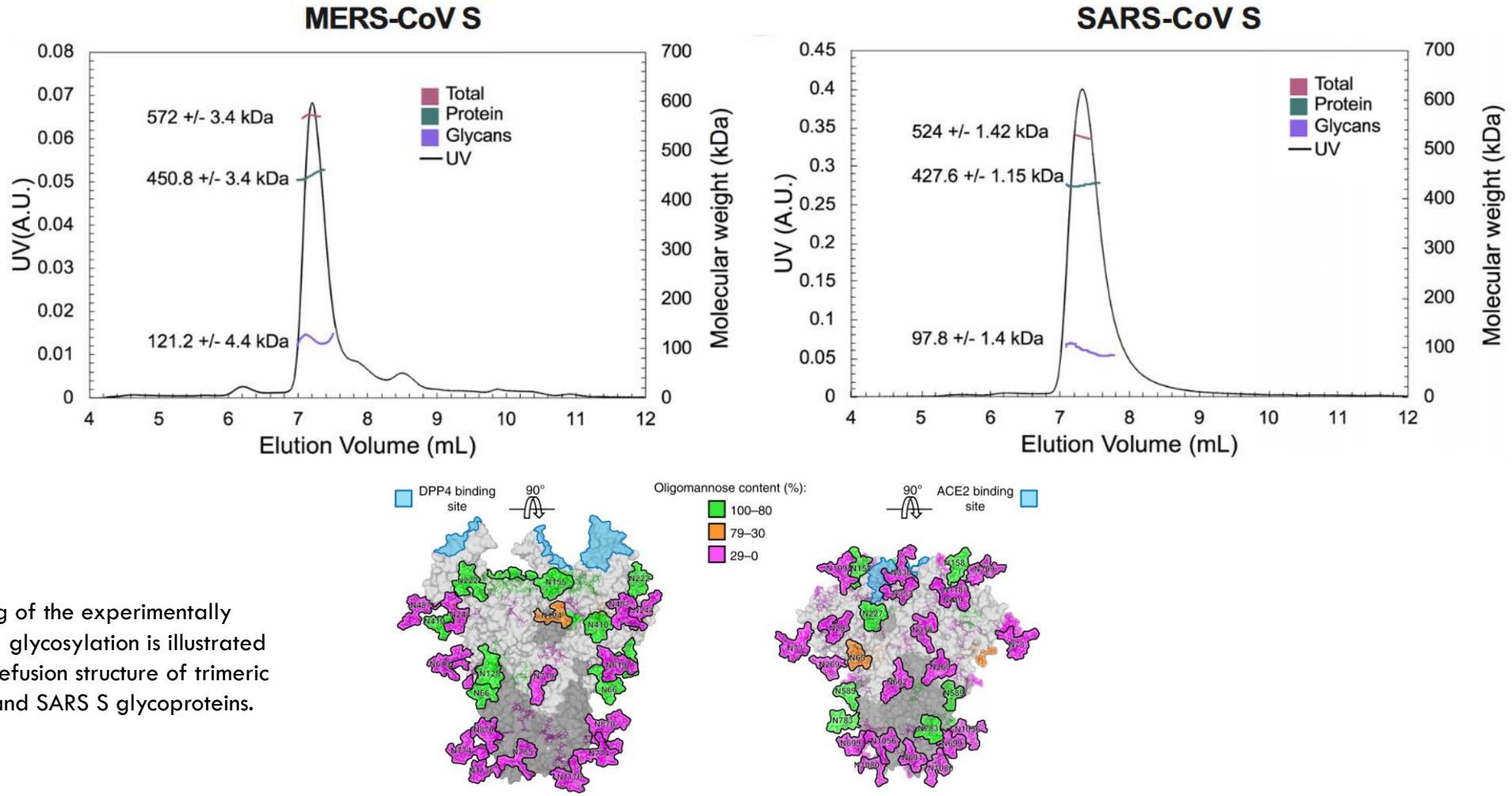
Determination of the apparent molecular mass of yCAF1 ± H3-H4 using SEC-MALLS



SAXS envelop of yCAF1 ± H3-H4

Sauer et al. (2017) ELife

Glycosylated protein



Modelling of the experimentally observed glycosylation is illustrated on the prefusion structure of trimeric MERS S and SARS S glycoproteins.

Walls et al., Cell 2019
Watanabe et al., Nat Comm 2020

Conclusions - Advantages / Limitations

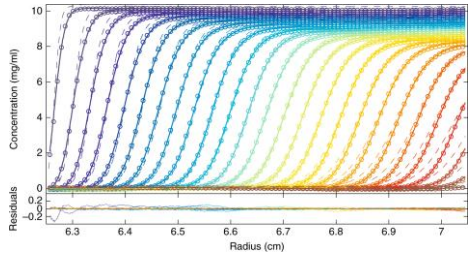
Advantages

- Simple and rapid (50 min for one injection)
- Absolute value of molecular mass
- Estimation of the polydispersity in a single chromatographic peak
- The column act as a filter and remove large aggregates

Limitations

- Sample dilution upon elution
- Not adapted to weak interactions with fast dissociation
- Require the separation of the various species upon elution

Analytical Ultrcentrifugation



Analytical ultracentrifugation

Spinning and watching molecule transportation

Measures the rate of sedimentation of your molecule

Measures the concentration as a function of the radial position at various times of centrifugation

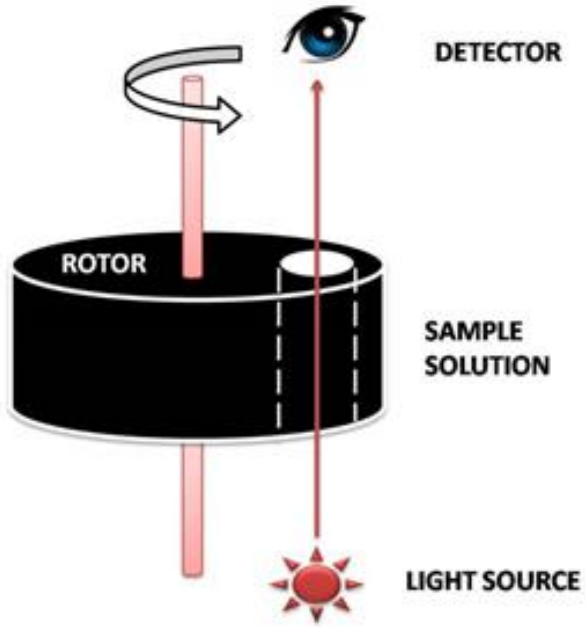
Centrifugal force: $F_c = m\omega^2 r$

m : *mass of the particule*

w : *60000 rpm*

r : *6-7cm*

➢ 300 000 g

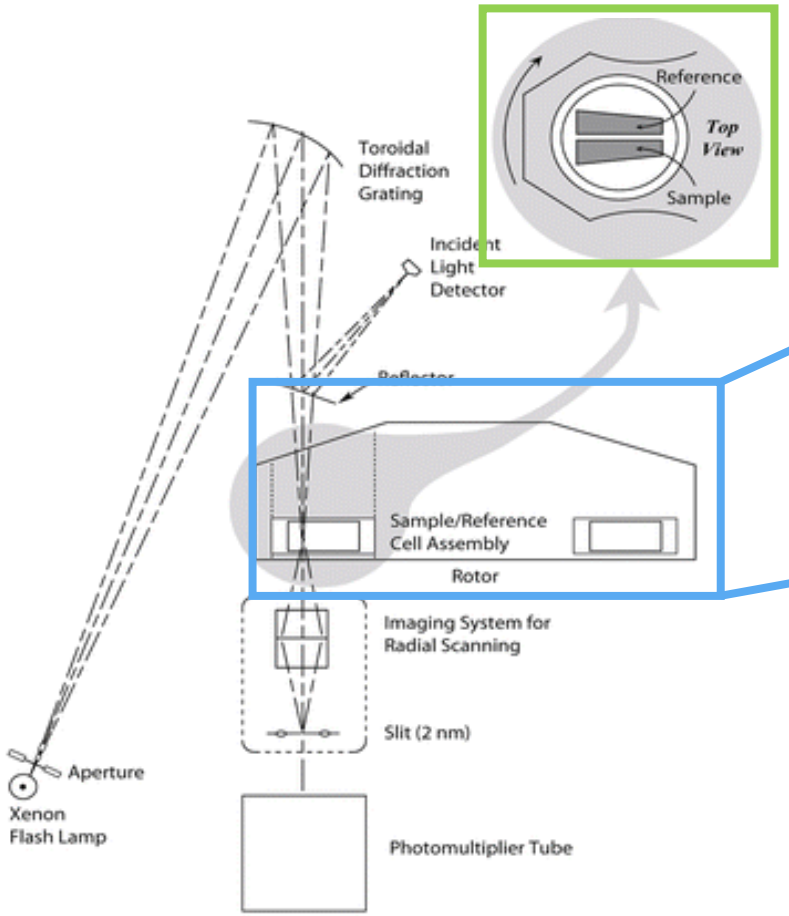


Applications

- Particle size distribution
- Particle composition
- Molecular weight distribution
- Shape factor
- Purity or heterogeneity
- Analysis of associating systems

Analytical ultracentrifugation

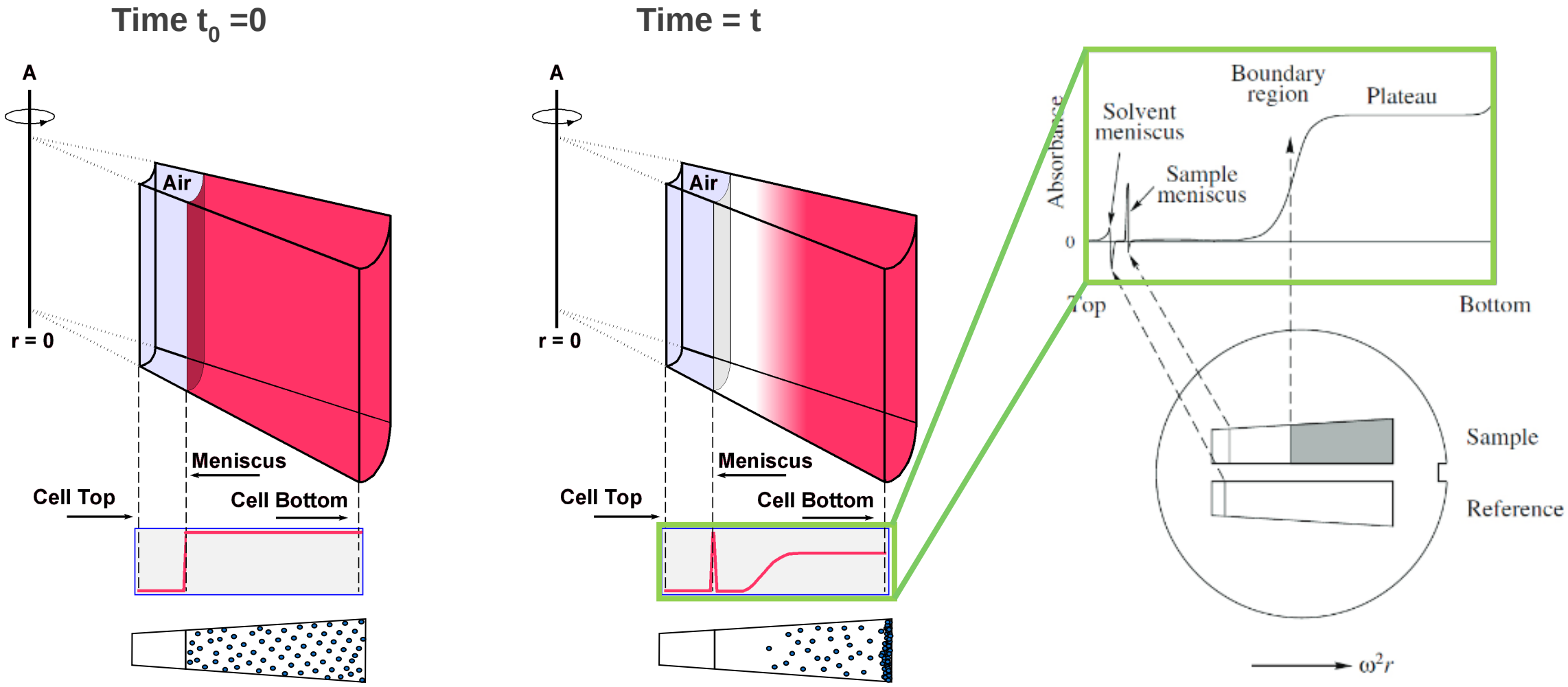
Spinning and watching molecule transportation



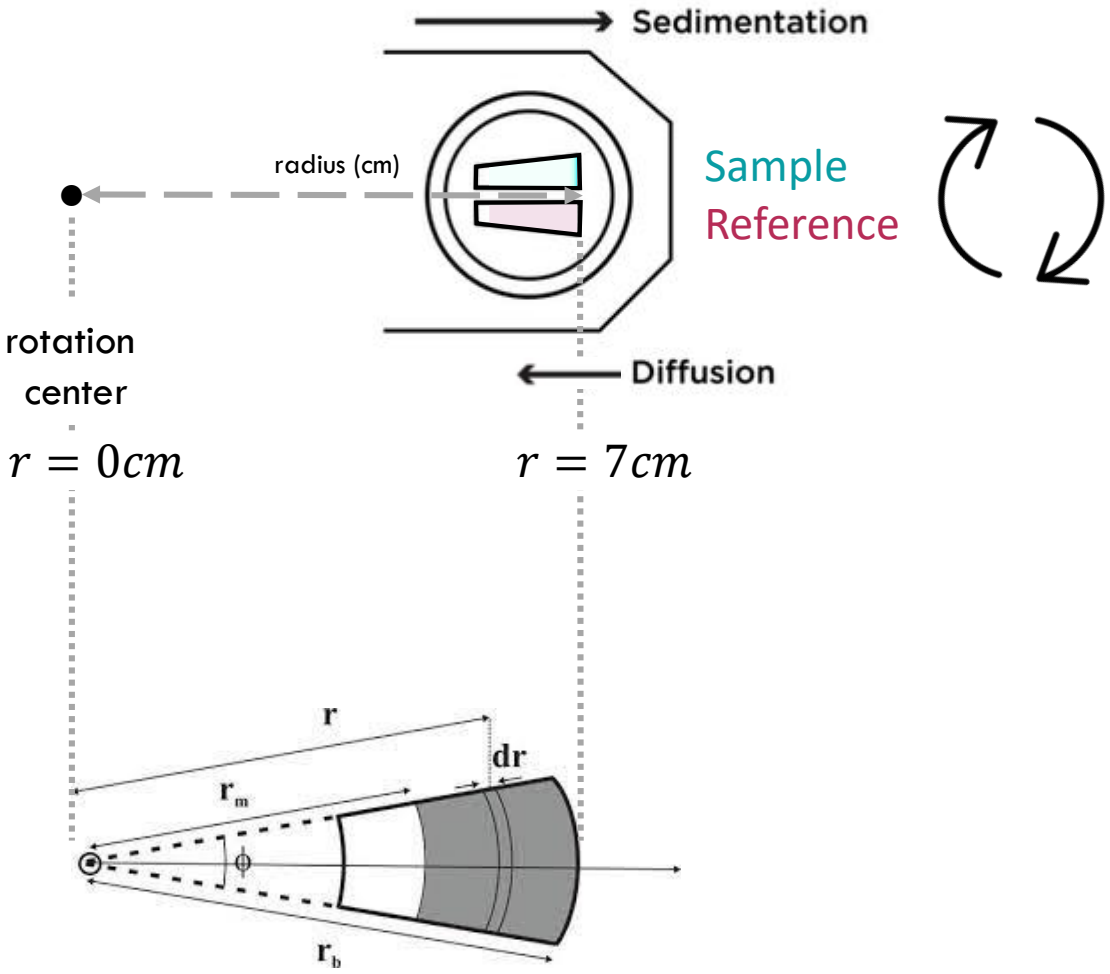
Path length (cm)	Volume (µL)	Required (µL)
1.2	400-420	450
0.3	100-110	150
0.15	50-55	75

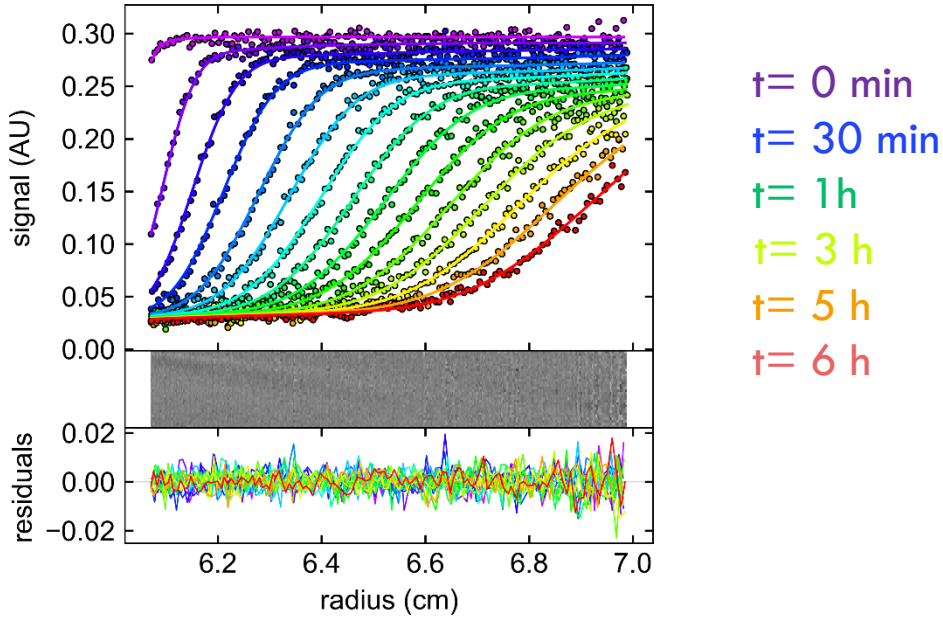
Analytical ultracentrifugation

Spinning and watching molecule transportation



Sedimentation velocity

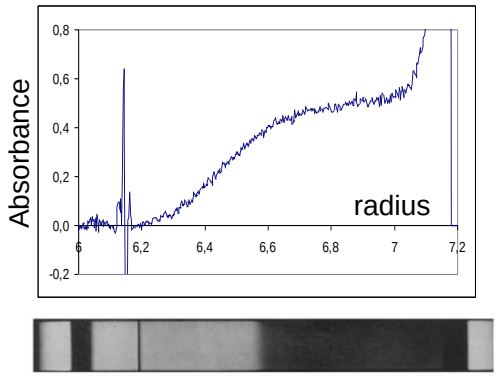




t= 0 min
t= 30 min
t= 1h
t= 3 h
t= 5 h
t= 6 h

Optical system

Absorbance



$A = E_{0.1\%} l c$

Selectivity depending on presence of chromophore

220nm < α < 600nm

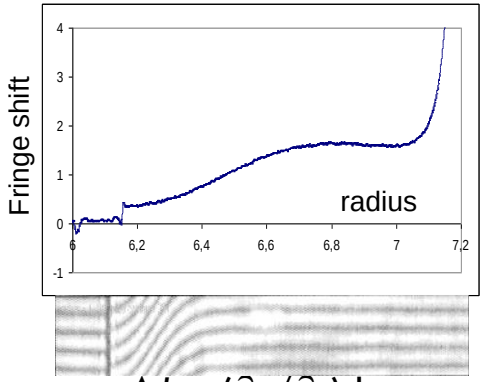
Scan of 3 α possible

up to 20 λ on the recently commercialized AUC

0.1-2 mg/mL typically

(60-500 µL)

Interference



$\Delta J \alpha (\partial n/\partial c) l c$

Not selective

Measures everything

(detergent, glycerol…)

Reference chanel should be solvent with same composition as the sample

0.1- >10 mg/mL

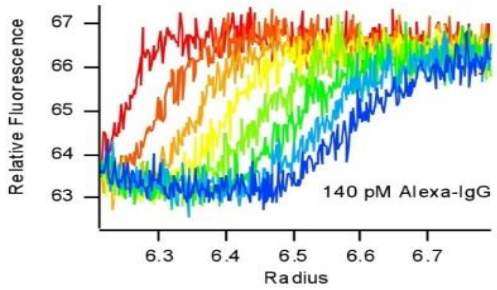
(60-500 µL)

Can be used in the same run | up to 3 or 7 samples

> duplicate analysis

> estimate of composite particle composition

Fluorescence



Signal in arbitrary units

Highly selective

Requires GFP fusion

or FITC labeling

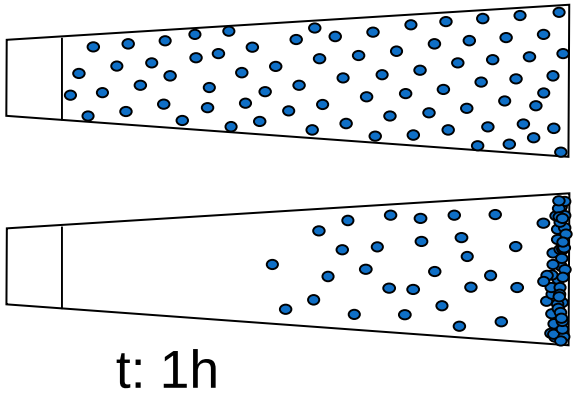
I_{exit}=488nm

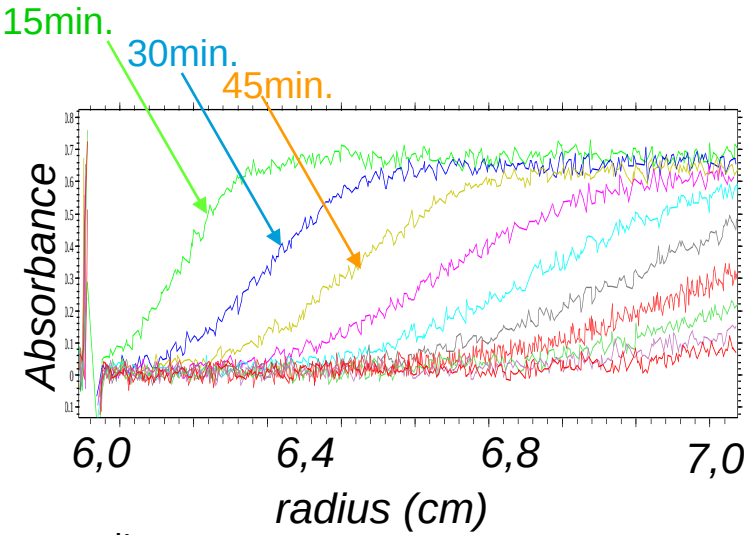
pM-µM

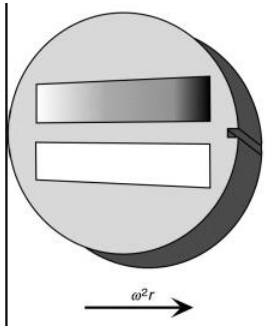
(500 µL)

up to 6 or 14 samples

Sedimentation velocity

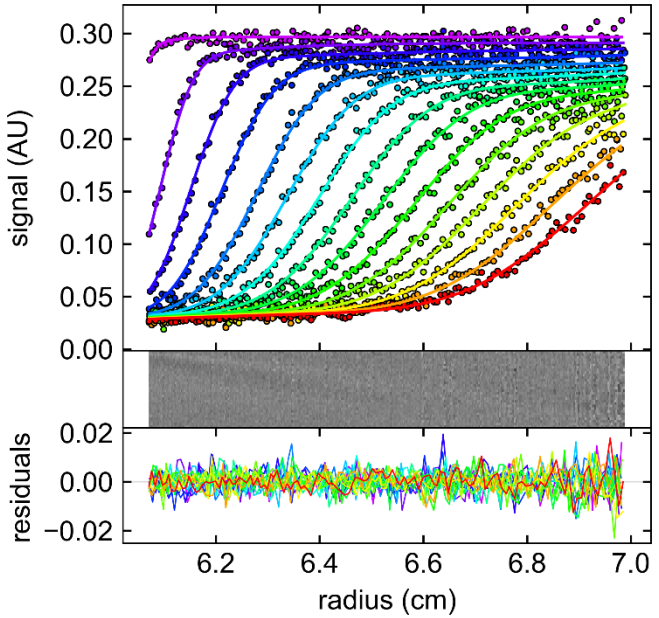






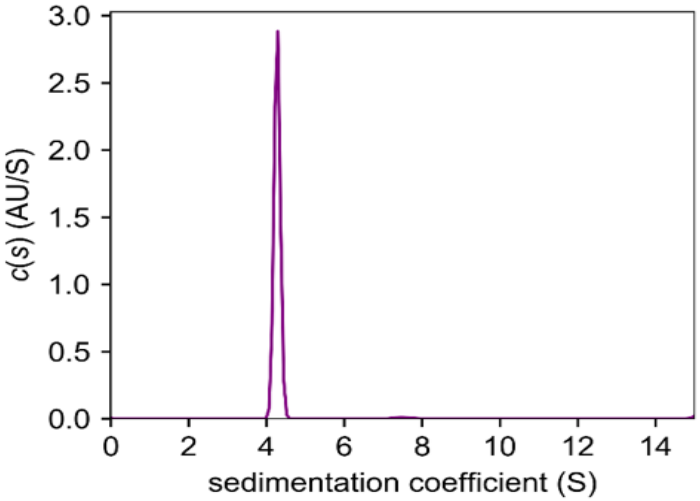
Angular velocity:	Large compared to the ability of the particle to sediment (typically 42000 revs. per min)
Duration:	Some hours
Analysis:	Measures rate of sedimentation as a function of time Formation of a boundary
Sample:	420, 110 or 55 µl (l =12, 3 or 1.5 mm)
Information:	Sedimentation coefficient (s), Frictional ratio f/fmin (shape), estimate Mw

Sedimentation velocity



Sedimentation profile

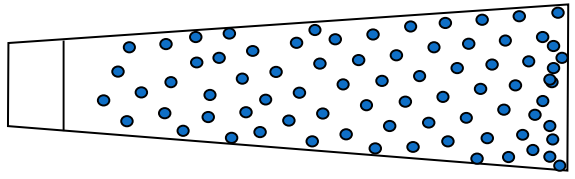
Data analysis

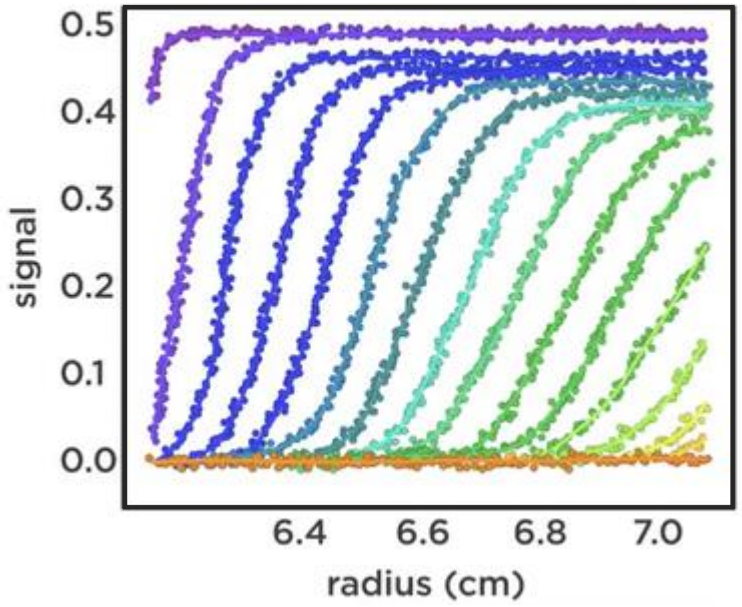


c(s) distribution

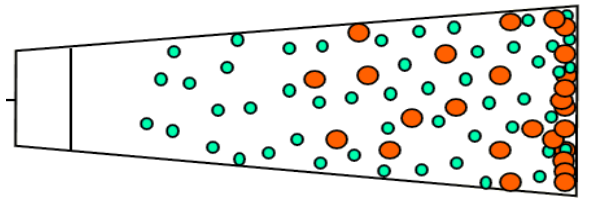
Sedimentation velocity

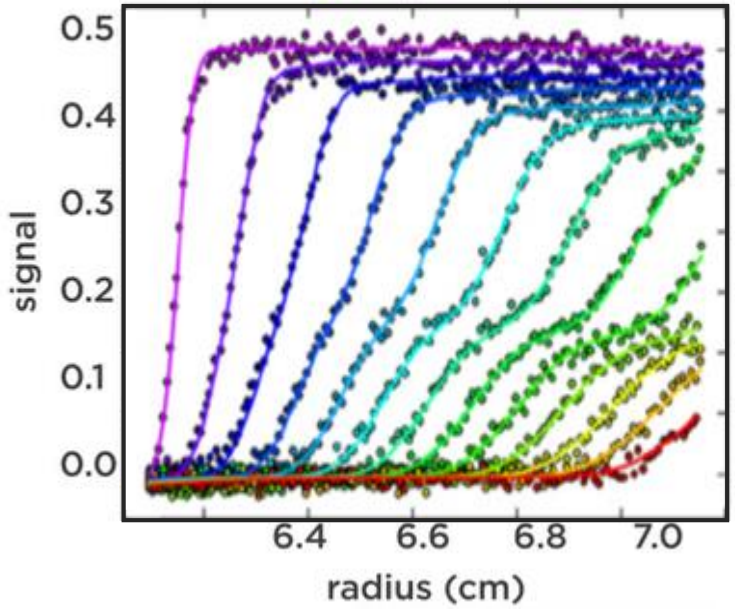
Single boundary





Multiple boundaries





AUC theoretical background

For a dilute homogeneous sample

Fc : centrifugal force

$$F_c = m\omega^2 r = \frac{M}{N_A}\omega^2 r$$

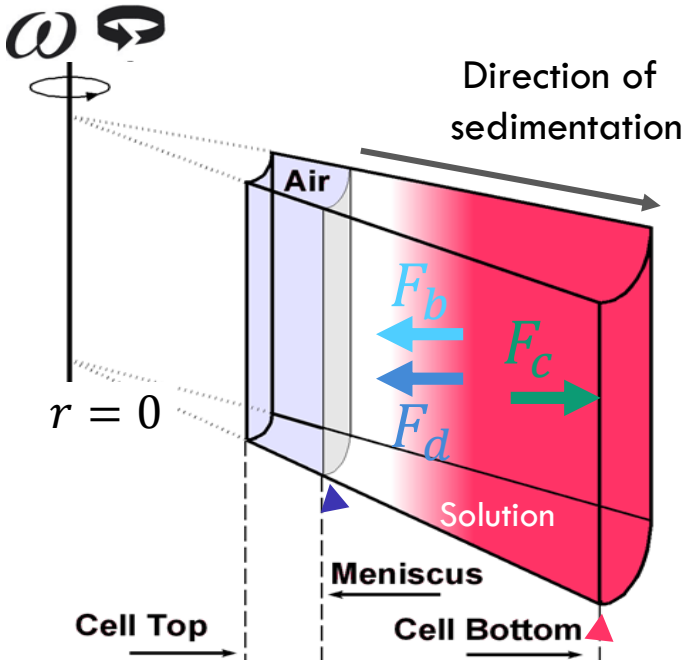
Fd : Viscous drag

$$F_d = -fv$$

Fb : buoyant force

from Archimedes' principle, is equal to the weight of fluid displaced

$$F_b = -m_0\omega^2 r = -(m\bar{v}\rho)\omega^2 r = -\left(\frac{M}{N_A}\bar{v}\rho\right)\omega^2 r$$



ω	angular velocity
r	distance to the axe of rotation
m	mass of the particle
M	molar mass
f	frictional coefficient, which depends on the shape and size of the particle
v	velocity

m_0 mass of fluid displaced by the particle

$$m_0 = m\bar{v}\rho = \frac{M}{N_A}\bar{v}\rho$$

ρ	density of the solvent (g/mL)
$\bar{v}$	partial specific volume, is the volume that each gram of the solute occupies in solution (the inverse of its density)

AUC theoretical background

$$F_c + F_b + F_d = 0$$

$$\frac{M}{N_A}(1 - \bar{v}\rho)\omega^2 r - fv = 0$$

$$\downarrow$$

$$\frac{M(1 - \bar{v}\rho)}{N_A f} = \frac{v}{\omega^2 r} = s$$

Within a very short time
the 3 forces come into balance

Sedimentation coefficient s :
velocity of the particule per unit of gravitational acceleration

- measurement

AUC theoretical background

mass relative density

Sedimentation coefficient - velocity of the particles

$$s = \frac{M(1-\overline{v}\rho)}{N_A f} = \frac{M(1-\overline{v}\rho)}{N_A 6\pi\eta R_h}$$

M_b buoyant mass

Spreading function: viscosity and shape

sedimentation coefficient s in Svedberg (S)
1 S = 10^{-13} s

with $f = 6\pi\eta R_h$

The Svedberg equation

Theodor Svedberg (1884-1971) Swedish chemist, Nobel Prize for Chemistry in 1926 for his invention of the analytical ultracentrifuge

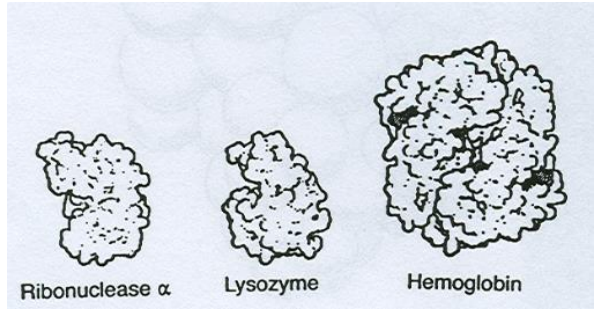
R_h hydrodynamic radius
η solvent viscosity
f frictional coefficient of a molecule
depends on the size of the particule, it is proportional to the hydrodynamic radius R_h

Approximate Values of Partial Specific Volumes $\overline{v}$ and frictional ratios f/f_{min}

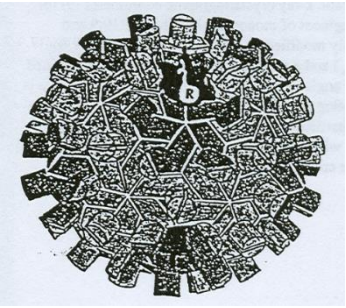
$\overline{v}$ (ml/g)

Protein: ≈ 0.74
Sugar: ≈ 0.62
DNA, Na^+: ≈ 0.54
DDM: 0.82
LAPAO: 1.067
lipid: ≈1
H_20: 1

f/f_{min}

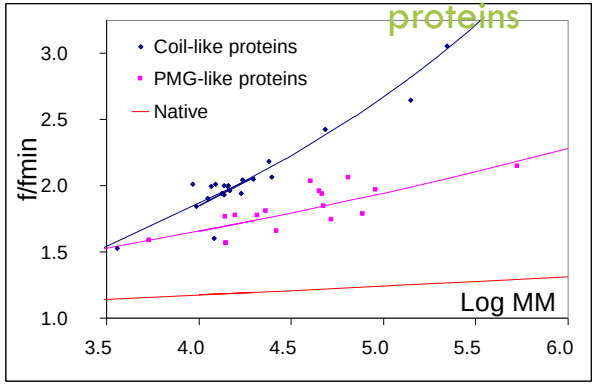


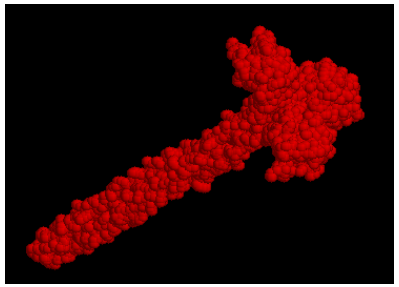
f/f_{min}: 1.29 1.22 1.28



1.27

Unfolded proteins

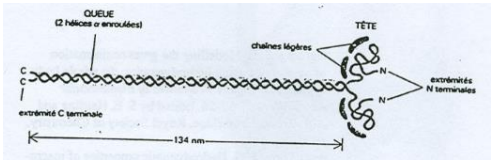




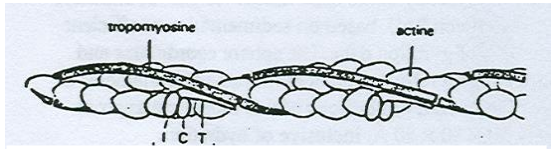
Langerin ECD f/f_{min}=1.8

Globular compact macromolecule
f/f_{min}≈1.25

Glycosylated protein:
typical f/fmin = 1.5-1.8

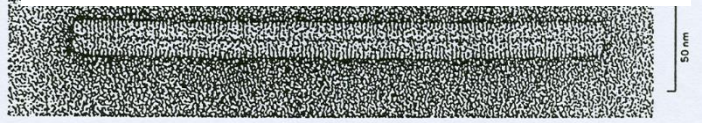


Myosin tail: f/f_{min}=3.63



tropomyosin: f/f_{min}=2.65

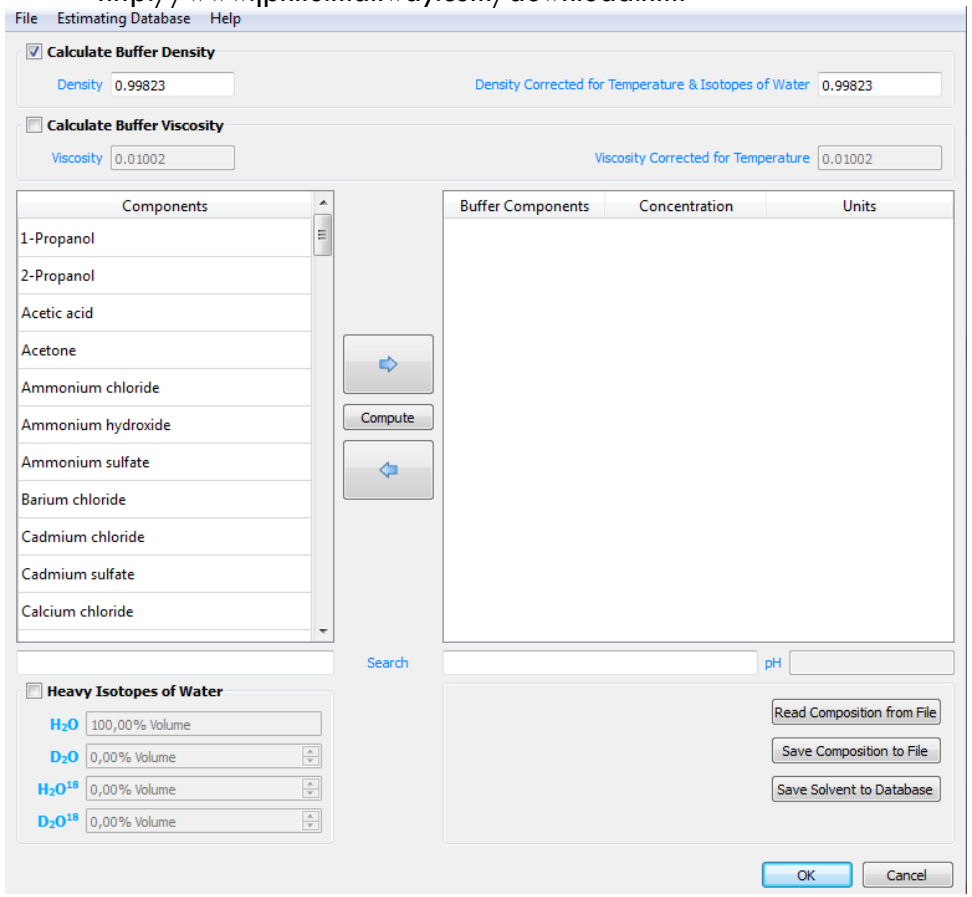
tobacco mosaic virus : f/f_{min}= 2.65



ρ, η : Density and viscosity of the solvents

calculated by SEDTERP / UltraScan

http://www.jphilo.mailway.com/download.htm



Or measured..

The Lamm equation

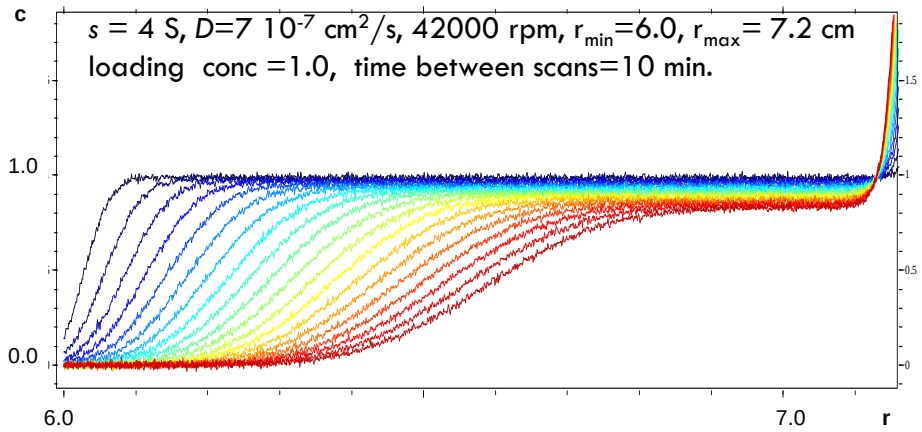
- Equation for the change in concentration over change in time
- Used to predict what the boundary shapes will look like

$$\frac{\delta C}{\delta t} = -\frac{1}{r}\left\{\frac{\delta}{\delta r}\left[\omega^2 r^2 sC - Dr\frac{\delta C}{\delta r}\right]\right\}$$

Sedimentation flux Diffusion flux

The Lamm equation allows to **calculate the sedimentation concentration profile c(*r*,*t*)** for a **single component** with a sedimentation coefficient ***s*** and a diffusion coefficient ***D*** at a given angular velocity ω

s, *D* ➡ c (*r*,*t*)



The Lamm equation

The Lamm equation can be solved **numerically**.
Computer programs like **SEDFIT** developed by P. Schuck fit the experimental data, by considering a finite number of solutions (50-250) and by applying a non linear least square analysis (or regularization process).

$$c(r,t) = \int c(s)\, f(s, D, r, t)\, ds \approx \sum c_n(s) f(s_n, D_n, r, t)$$

- $c(r,t)$: Experimental data for multiple components
- $c(s)$: Concentration of each specie
- $f(s, D, r, t)$: Lamm equation for one specie
- $c_n(s) f(s_n, D_n, r, t)$: Calculated data with *n* species defined by c, s and *D*

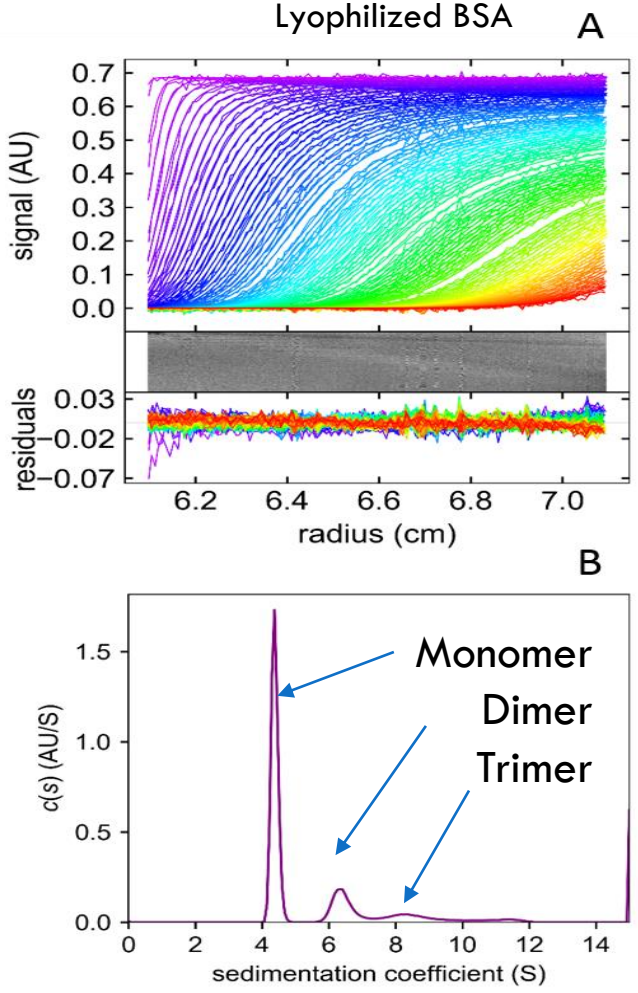
Different models are available, including:

- c(s) model: **diffusion + sedimentation** taken into account (proteins, small molecules)
- ls-g*(s): **Only sedimentation taken into account** (nanoparticles > 20 nm)

BSA SV-AUC Sample homogeneity

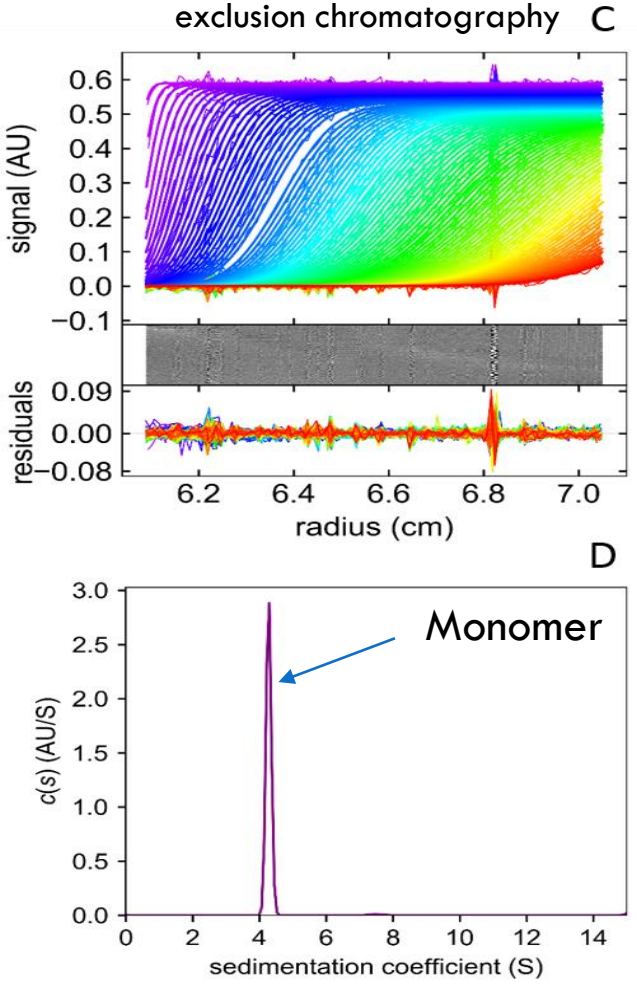
Non-interacting species analysis
Fitting *s* and *D*

Lyophilized BSA



➢ **erroneous M=27.4 kDa**
model of 1 species is inappropriate

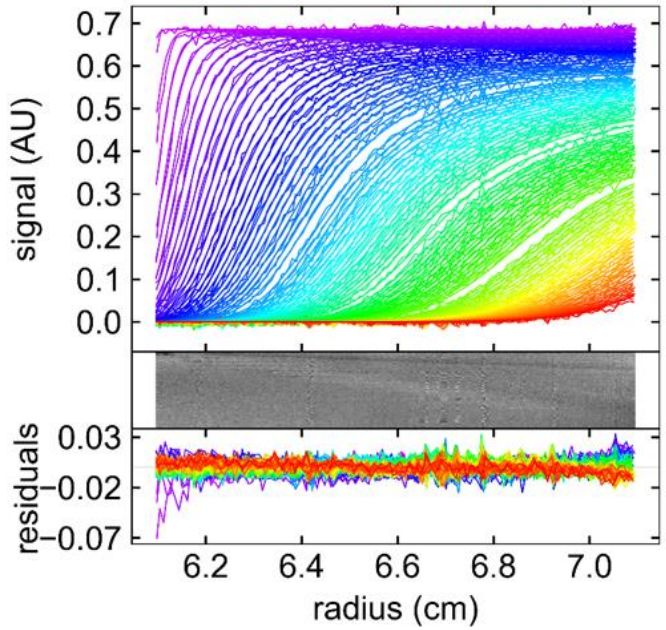
After purification of the monomer with size exclusion chromatography

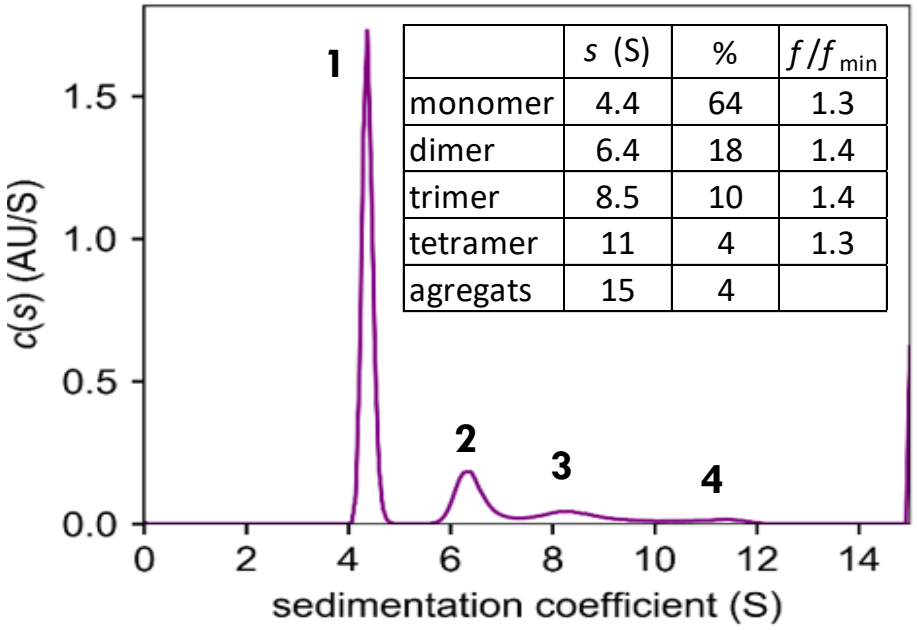


➢ **M=65.9 kDa**
M_{theo}=66kDa
s = 4.3 S
Rmsd = 0.009

Aline Le Roy & Christine Ebel

Sample homogeneity, composition from c(s)





	s (S)	%	f/f_{min}
monomer	4.4	64	1.3
dimer	6.4	18	1.4
trimer	8.5	10	1.4
tetramer	11	4	1.3
agregats	15	4	

- Integration of each peak allows to determine *s*, and concentration from signal.
- Association states are here confirmed by f/f_{min} indicating a globular compact shape
- Measurement of traces of aggregates in samples of therapeutic proteins in the biopharmaceutical industry remains tricky & requires rigorous analysis

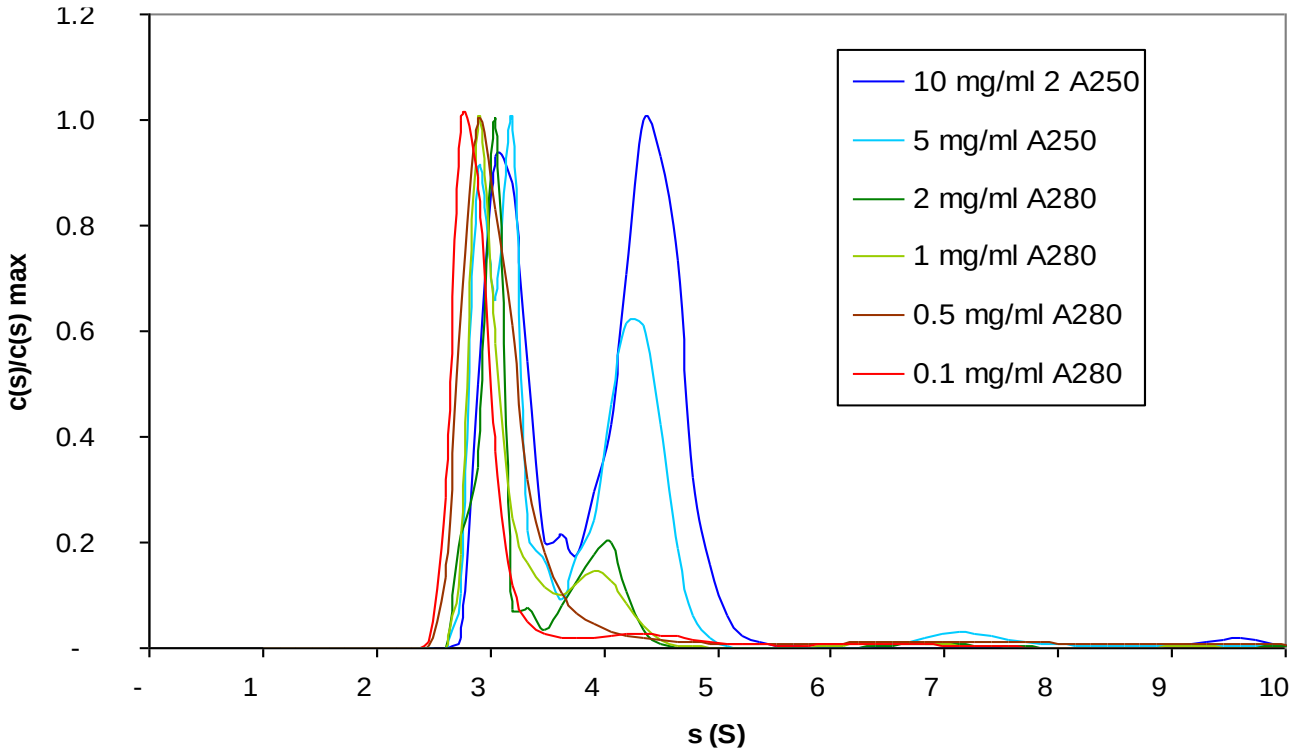
EMBO 16-22 Sep2024

Ebel & Birck Meth Mol Biol 2021

Arthur et al Methods Enzymol 2015

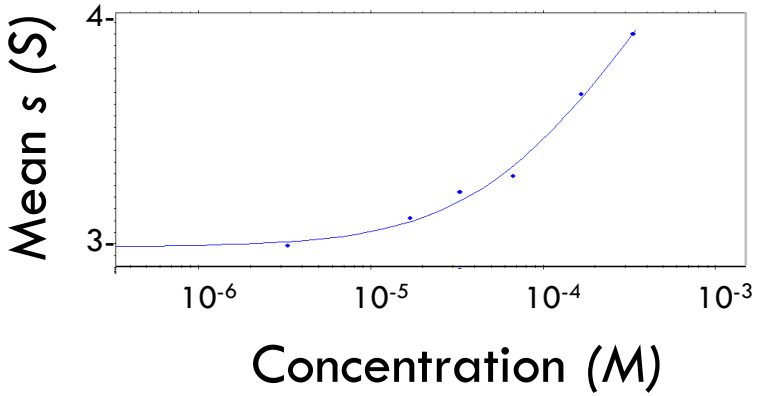
Bou-Assaf et al J Pharm Sci 2022

Equilibrium monomer-dimer



$$s = \frac{\sum c_i S_i}{\sum c_i}$$

Fitting $s = f(c)$



$$A + A \leftrightarrow A2$$

s_{20w} mono=3.13 S

s_{20w} dimer =5.69 S

$$K_d = 0{,}7\ mM\ (0.4 - 1.5\ mM)$$

Echallier et al PNAS 2013

Conclusions
AUC sedimentation velocity is a versatile technique

- **No sample dilution**
- It allows the characterization of complex samples
- It addresses a **very large range of molar mass/size/density** (evaluated at different rotor speeds/solvent densities)
- Investigation of a **rather large concentration range** depending on the choice of the optical system, cells with different optical paths
- The sample is analyzed in a robust way, in terms of a **distribution of sedimentation coefficients** which is then interpreted in terms of a distribution of molar masses
- Information on **particle composition may be obtained using different optics or different buffer densities**
- More sophisticated analysis are available depending on the specificity of the samples

MASS PHOTOMETRY

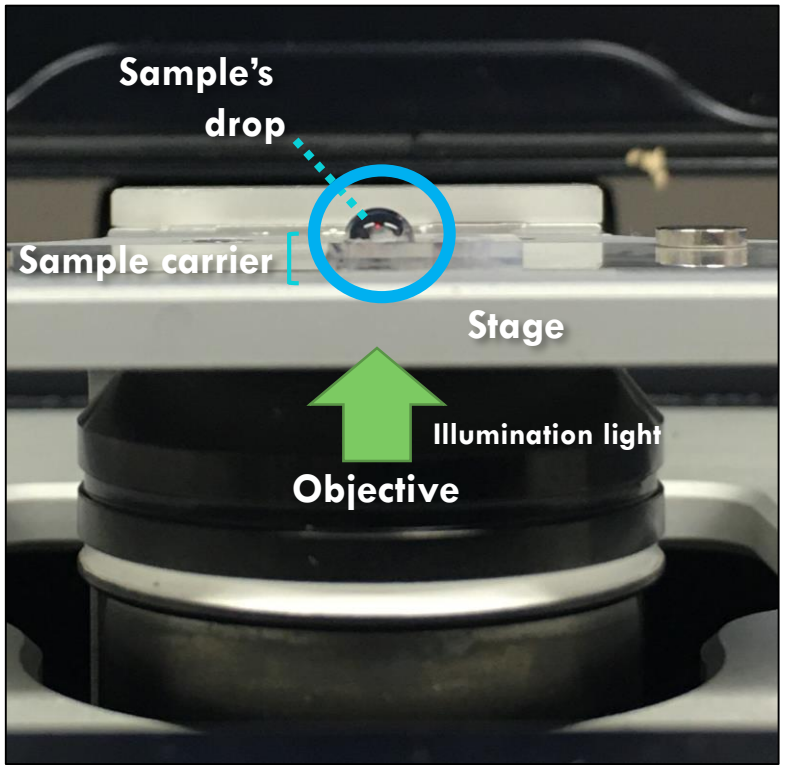
New technology to characterize mass distribution at low concentration

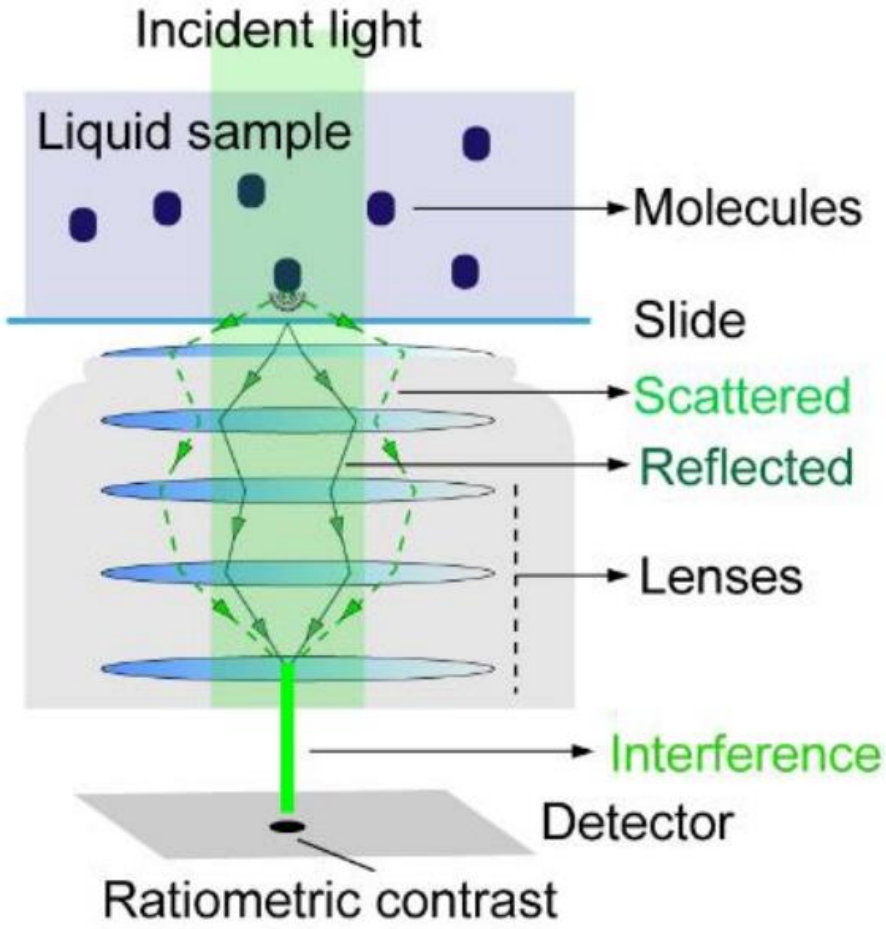
Mass Photometry - Principle

Mass Photometry is **a label free single-molecule** technique based on optical detection of the **scattering signal generated by a single particule at glass-water interface**

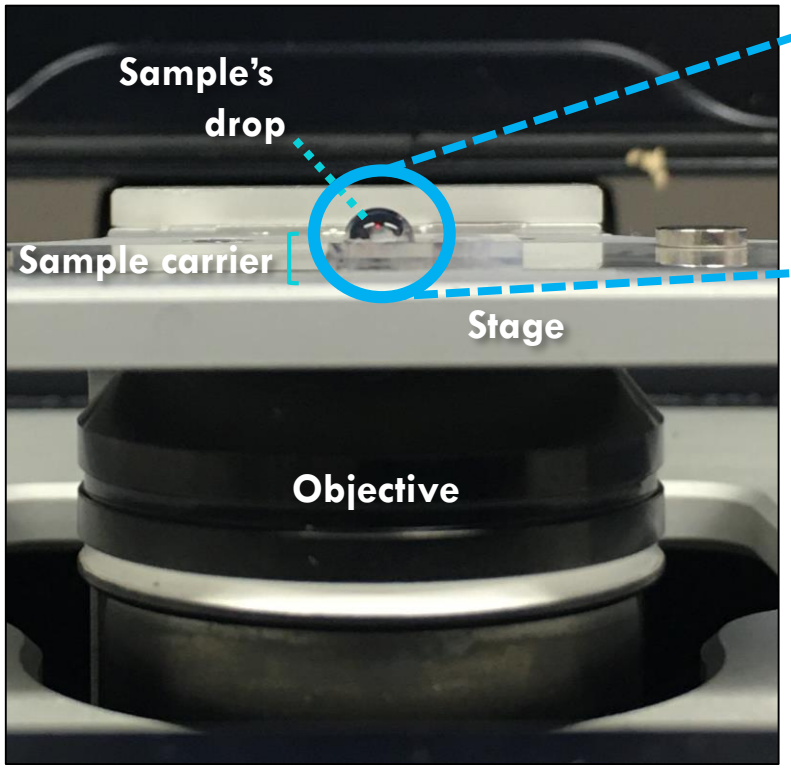
Measures the **mass of individual molecules** and thereby determines **mass distributions of biomolecule samples in solution**

Mass Photometry – Principle
Interferometric scattering iSCAT





Mass Photometry – Principle
Interferometric scattering iSCAT



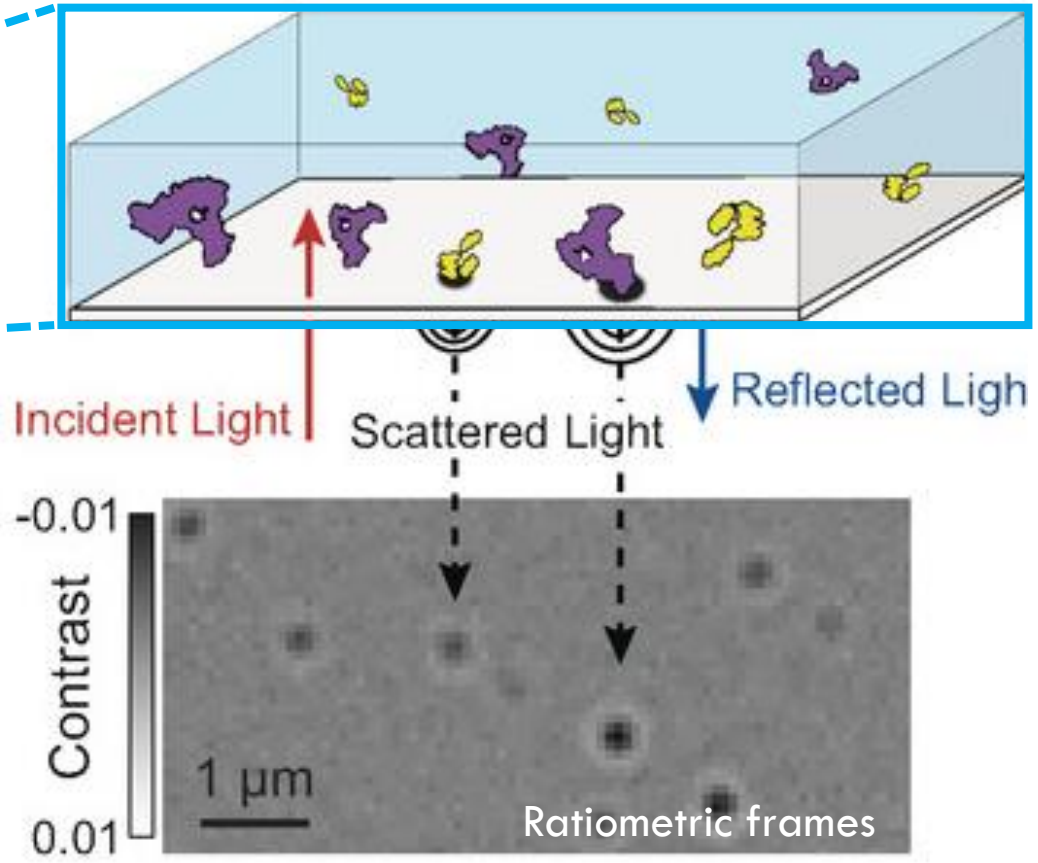
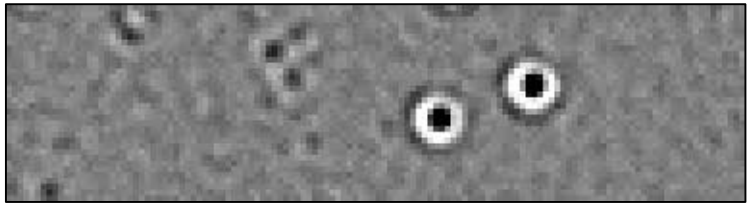


Image the coverslip to record a movie of the landings of macromolecules

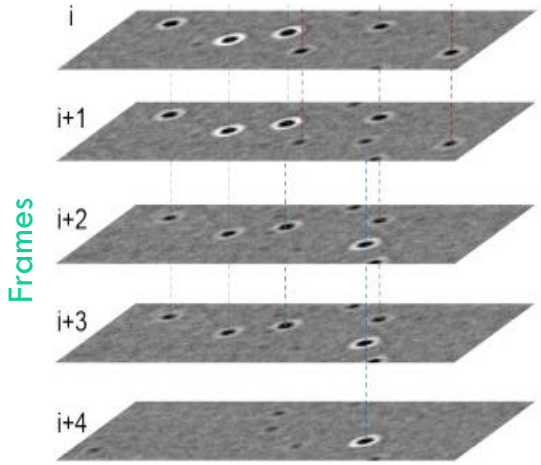
Angew. Chem. Int. Ed., Volume: 59, Issue: 27, Pages: 10774-10779 2020

Mass Photometry - Principle

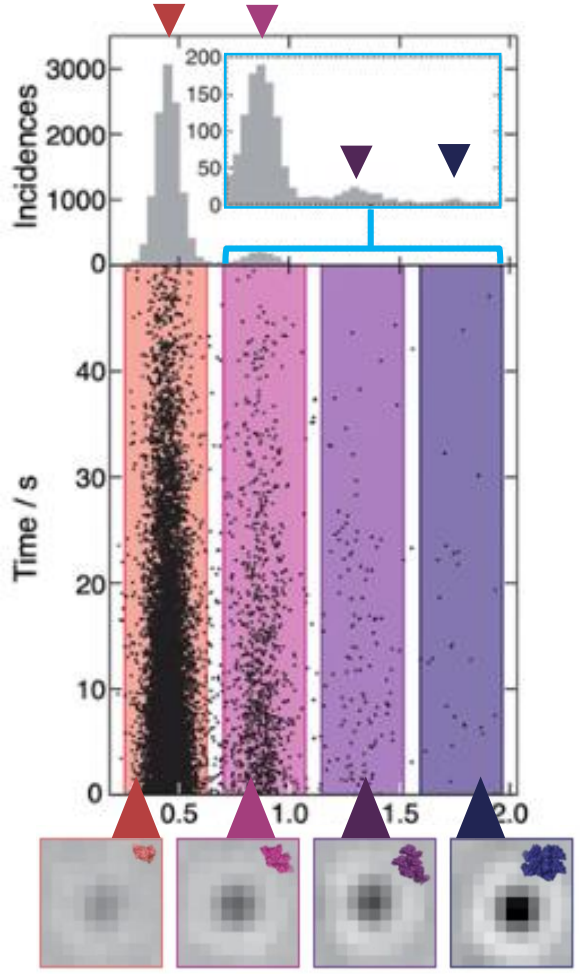
1 - Movie recording



Movie of particles landing on the coverslip



2 - Contrast / Mass



Contrast of various oligomeric states

3 - Sample's requirement

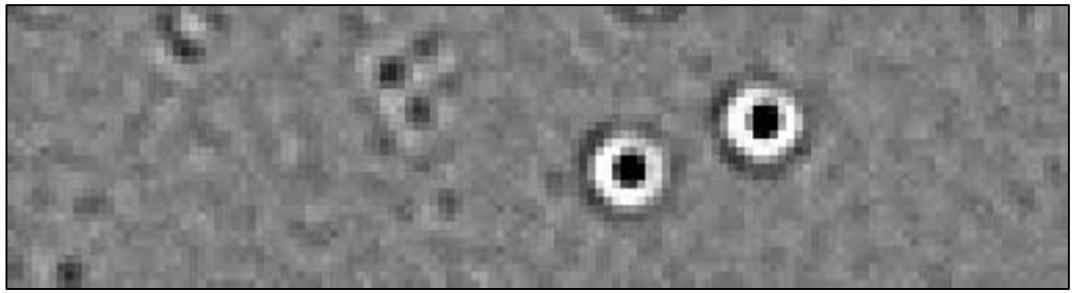
- Few µL at ~100-10 nM
- 40 kDa - 5 MDa

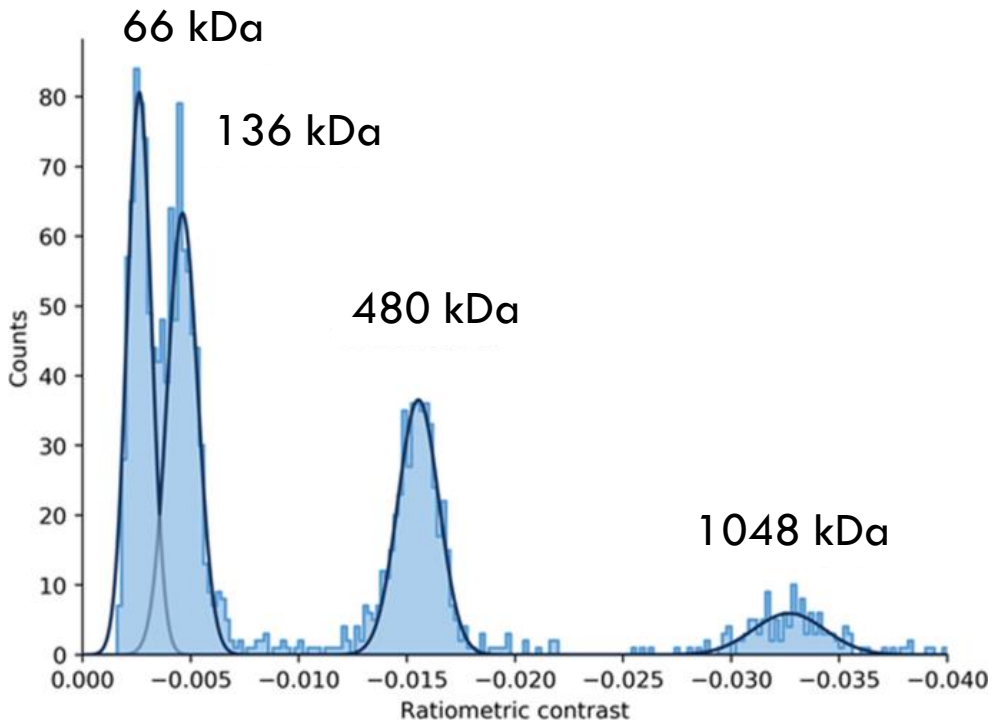
4 - Applications

- Protein
- Unfolded protein
- RNA / DNA
- Membrane proteins
- Adeno-associated virus
- Interactions

Nikolas Hundt, 2020

Mass Photometry Movie and Histogram : Example of calibration



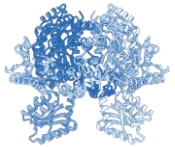


- Linear relationship contrast *vs* molecular mass

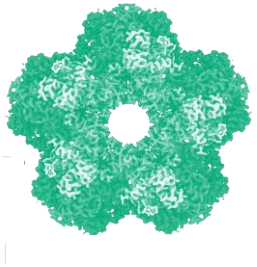
Oligomeric state of an arginine decarboxylase at various pHs

Monomer

Dimer



Decamer



communications biology

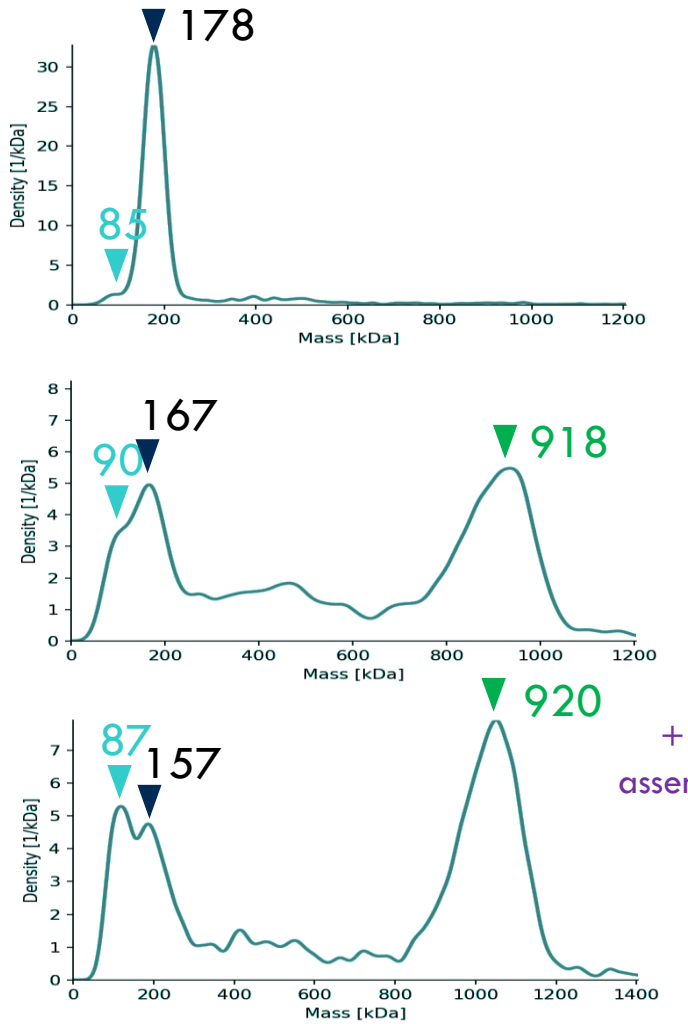
ARTICLE

https://doi.org/10.1038/s42003-022-03276-1 OPEN

Structural and biochemical characterisation of the *Providencia stuartii* arginine decarboxylase shows distinct polymerisation and regulation

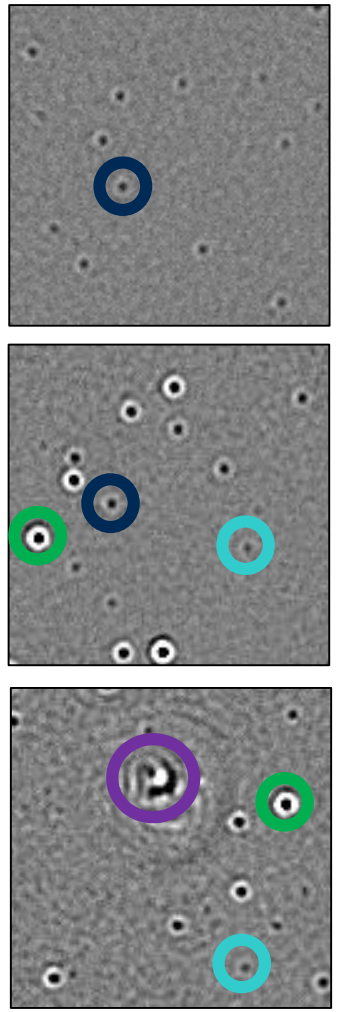
Matthew Jessop[1,2], Karine Huard[1], Ambroise Desfosses[1], Guillaume Tetreau[1], Diego Carriel[1], Maria Bacia-Verloop[1], Caroline Mas[1], Philippe Mas[1], Angélique Fraudeau[1], Jacques-Philippe Colletier[1] & Irina Gutsche[1]✉

Mass distribution



+ large assemblies

Ratiometric Frame



pH8

pH6.5

pH5

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Conclusions - Advantages / Limitations

Advantages

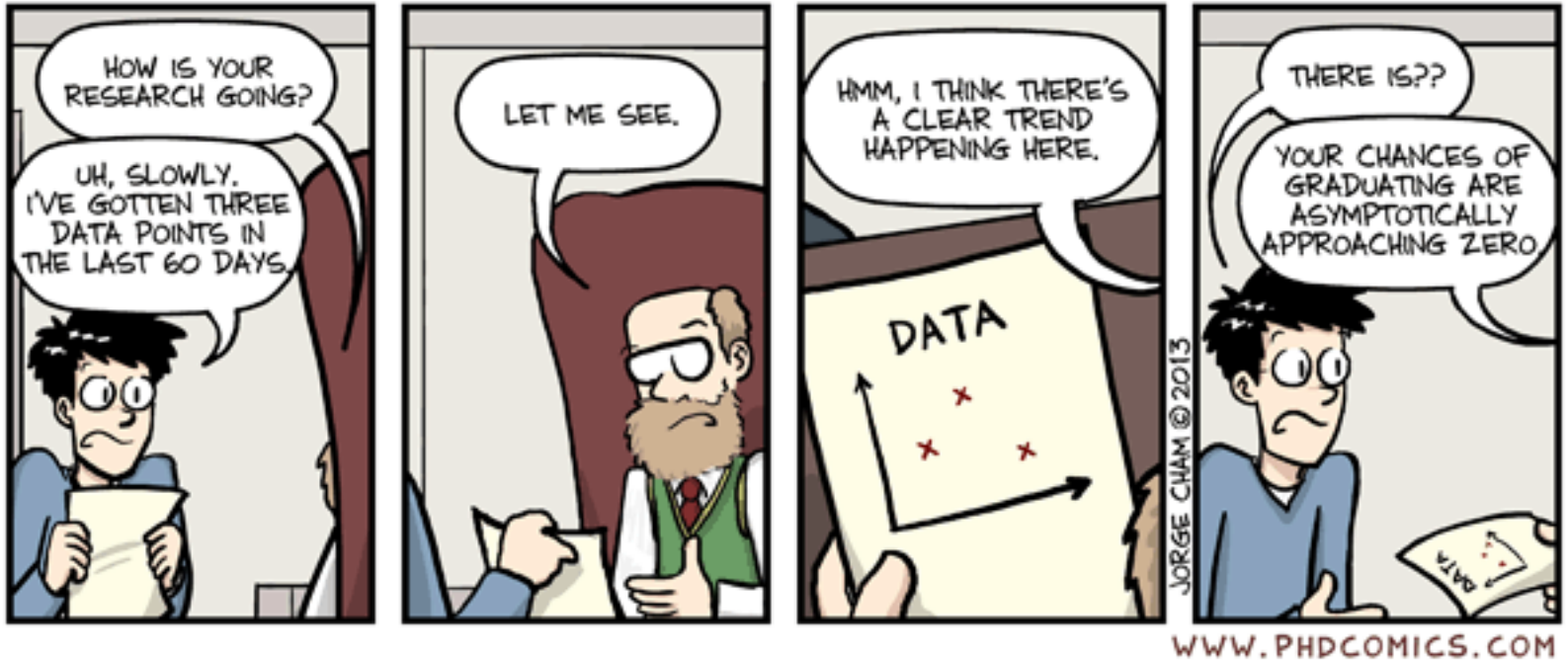
- Simple and rapid: 1 min/movie
- Low amount of sample required: few µM at concentration of nM

Limitations

- Need a calibration
- Sample dilution
- Size limitation: 40kDa-5MDa
- Not adapted to weak interactions with fast dissociation
- Resolution of various species

Sample characterization and quality control: why?

" Those who assess and **optimize carefully the quality of their protein** preparations **significantly increase their chances of success in subsequent experiments**"




Raynal et al. Microbial Cell Factories (2014) 13:180
DOI: 10.1186/s12934-014-0180-6

MICROBIAL CELL FACTORIES

REVIEW Open Access

Quality assessment and optimization of purified protein samples: why and how?

Bertrand Raynal[1,2*], Pascal Lenormand[1,2], Bruno Baron[1,2], Sylviane Hoos[1,2] and Patrick England[1,2*]

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Thanks for your attention

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