Significance of particles in the pharmaceutical technology

Particle size determinating methods

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What is particle?

Definition

In a **continuous phase** the **particle** is an (mostly in gaseous or liquid material) existing, **dispersed, interface separated** (mostly liquid or solid material) smallest, yet homogeneously structured, and consisted part.

A single unit of solid particle-set (aggregation) **is defined as a particle.**

Particle characterisation

- Size/distribution
- Shape
- Surface
- Mechanical properties
- Charge
- Microstructure

Significance of particles in pharmaceutical technology

Solution - dissolution rate (speed) depends on particle size and porosity

Suspension - settling speed

Ointment - particle size dispersion and its homogeneity in case of suspensional and emulsional ointment

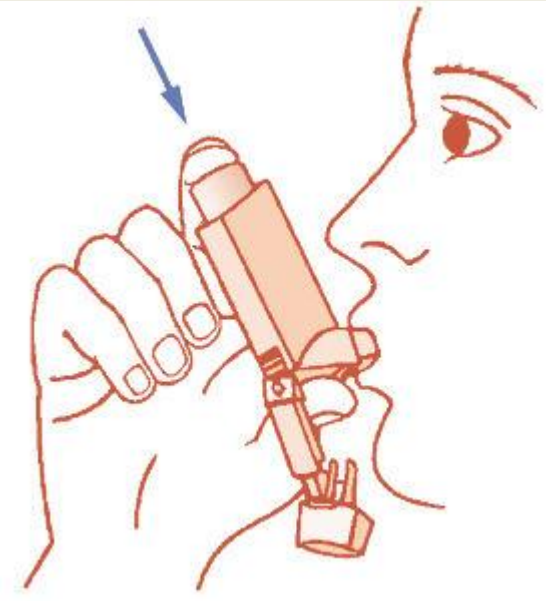
Suppository - settling, dispersion

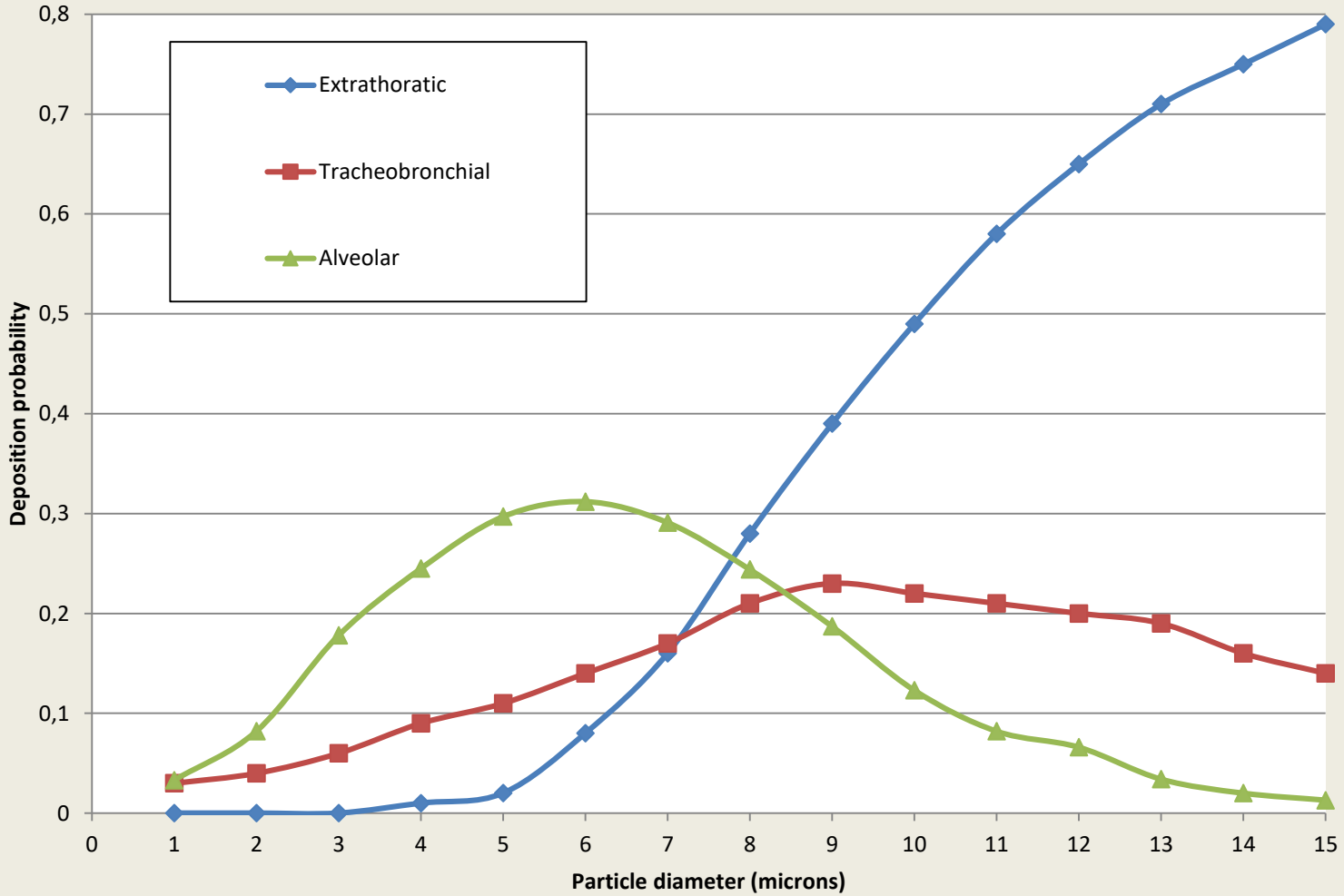
Microcapsule - spherical shape, drug delivery

Tablet - granulation, tablet disintegration to particles, dissolution

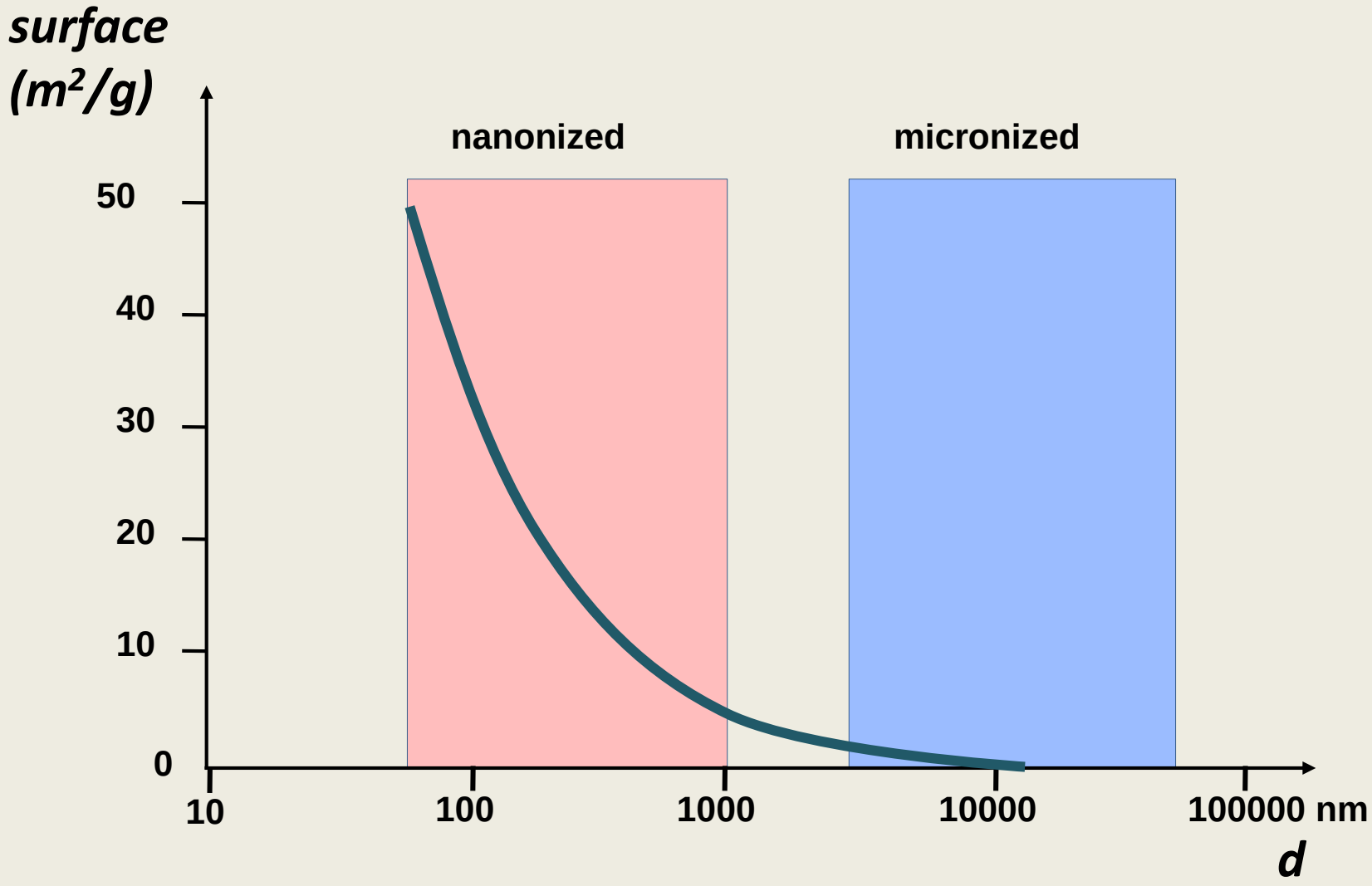
Aerosol - location of particle sedimentation

Particle deposition in airway system

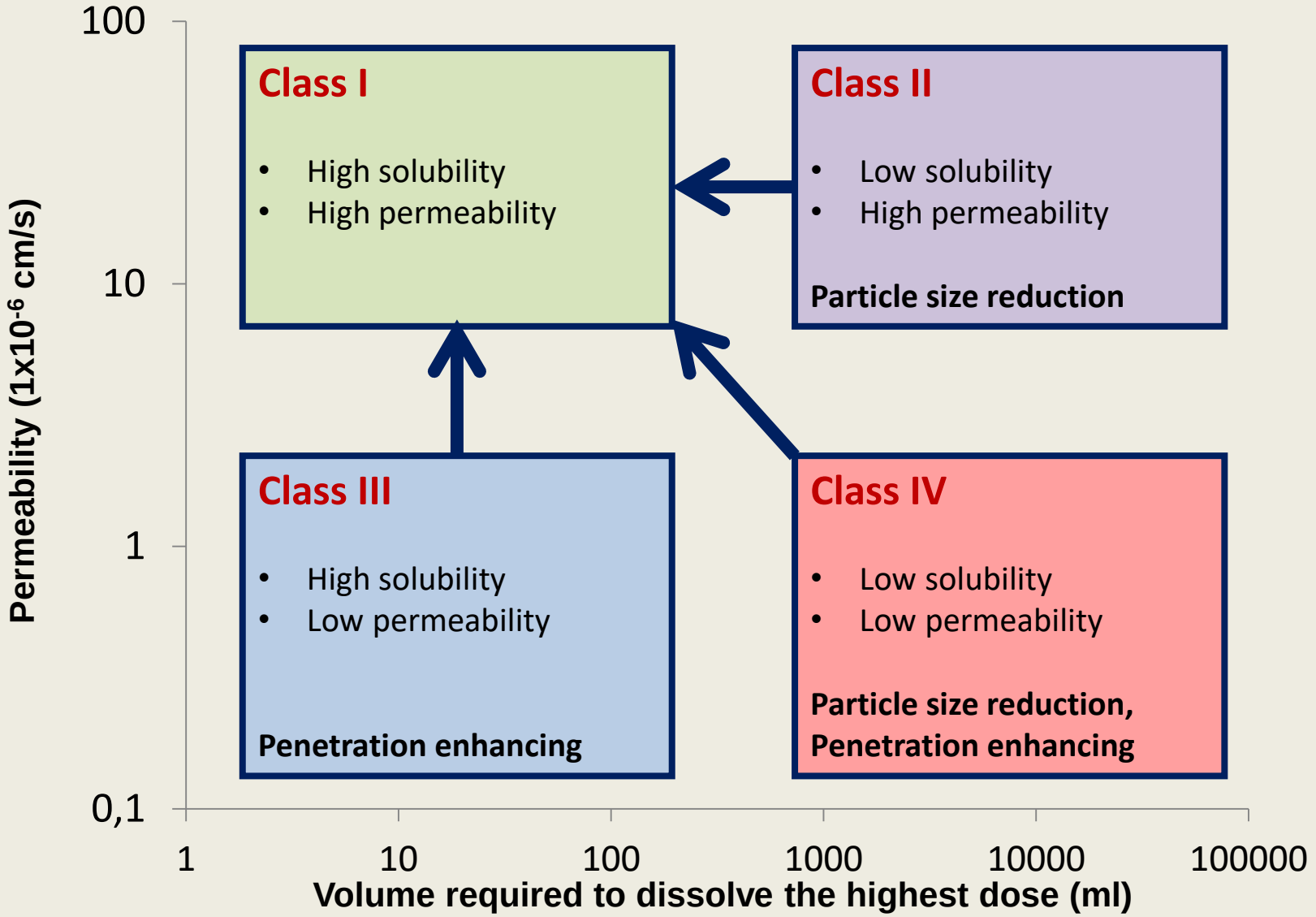




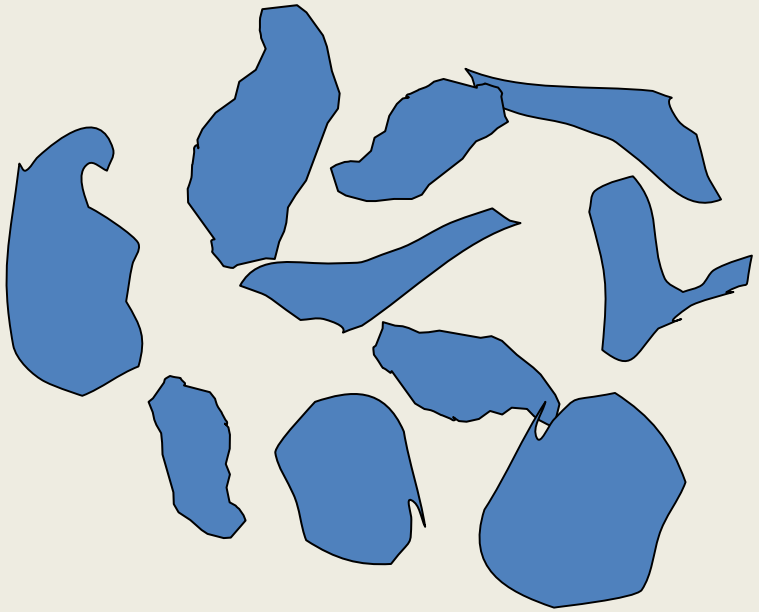
Effect of particle size/surface



Biopharmaceutical Classification System



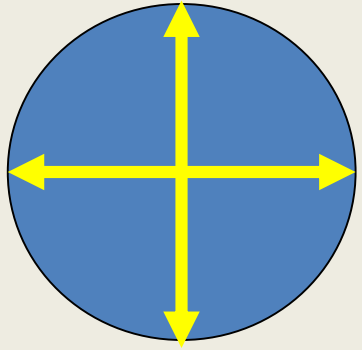
Particle's shape



Particle shape

Shape factor (α)

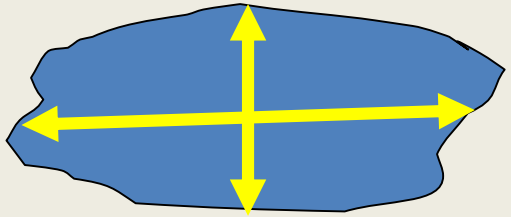
$$\alpha = \frac{D_{min}}{D_{max}}$$



Sphere, drop

α=1

$D_{min} = D_{max}$



Granules

α ≤1

$D_{min} < D_{max}$

Crystal

α <<1

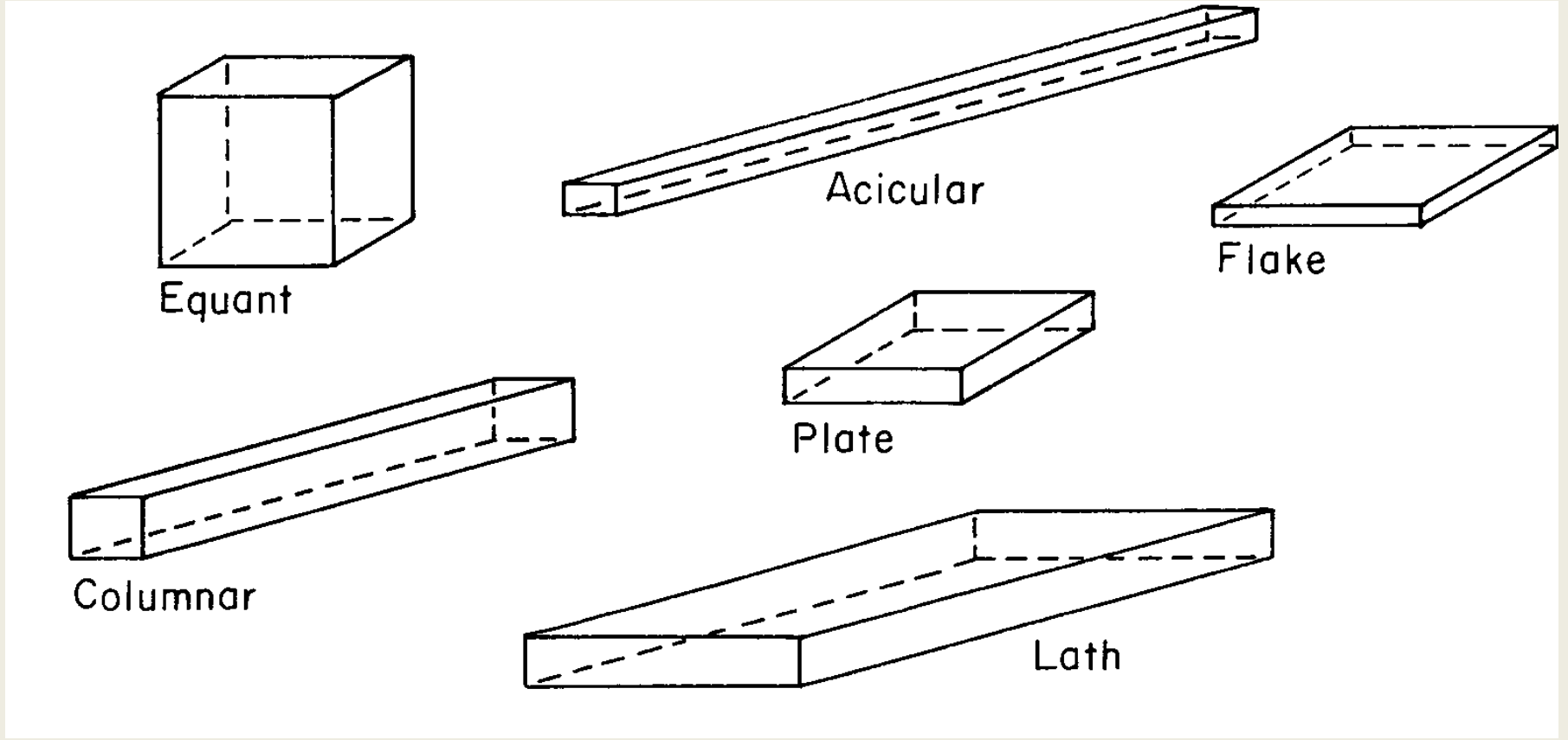
Isometric particle

α ≈ 1

Particle shape

- ***Acicular**: similar width and thickness, thin, needle like particles,*
- ***Columnar:** wider and thicker than the needle-shaped, long, thin particles,*
- ***Flake:*** thin, flat particles, which have similar length and width,
- ***Plate:** thicker than flake particles, flat particles, whose length and width, similar / same*
- ***Lath:** long, thin, blade-like particle,*
- ***Equant:** the same length, width and thickness of particles, can be cube-shaped or spherical as well.*

Particle shape



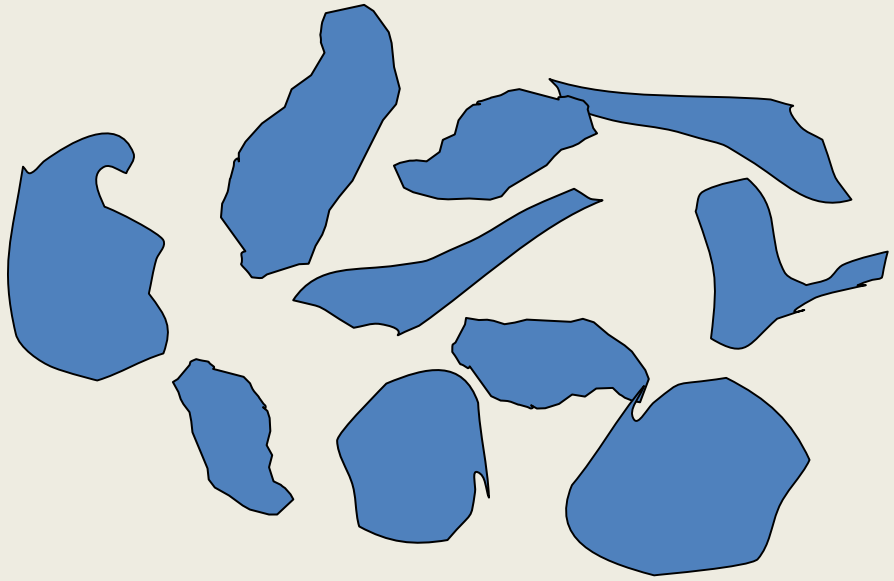
Classification of particles

- ***Lamellar (plate-like):*** stacked plates,
- ***Aggregates (group):*** stacked particles,
- ***Agglomerate:*** merged or cemented particles,
- ***Conglomerate:*** the mix of two or more types of particles,
- ***Spherolite:*** radial string,
- ***Druse:*** small particles coated (bigger) particle.

Surface of particles

- ***Fragmented:*** partially split, broken or cracked,
- ***Smooth:*** free from irregularities, roughness, protruding,
- ***Porous:*** contained openings, passageways (wells),
- ***Coarse:*** bumpy, uneven, not smooth,
- **Hollow/pitted:** small bashes covered.

Particle size



Particle size

Particle size is usually defined as **separated particles diameter**.

The particles usually create **heterodisperse** systems, therefore beside the average size the **particle size** distribution is also an important the **shape** of particles.

Particle size

Average particle size ($\bar{x}$):

$$\bar{x} = \frac{x_1 + x_2 + x_3 \ldots + x_n}{n} = \frac{\sum_{i=1}^{n} x_i}{n}$$

$\bar{x}$	= average size
x_1, x_2, x_n,	= particle size (individual)
n	= number (amount) of particles

Particle size

Standard deviation of particle size:

$$\sigma = \sqrt[2]{\frac{\sum_{i=1}^{n}(x_i - \overline{x})^2}{n-1}}$$

x_i = particle size

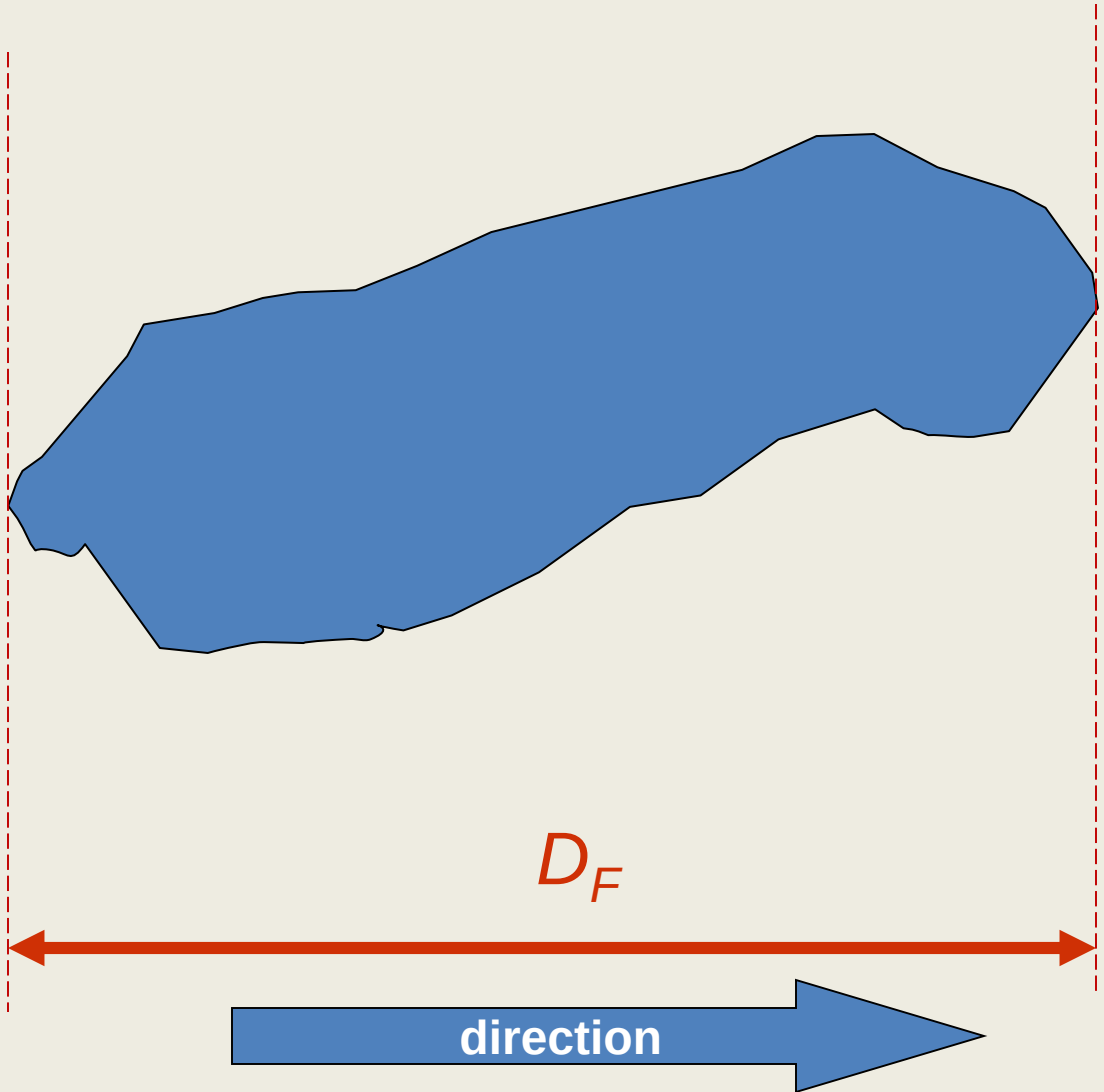
n = number of measured particles

Particle size

- Circumferential diameter
- Projectional circle diameter
- Feret diameter
- Martin diameter
- Equivalent spherical diameter
- Stokes diameter

Particle size

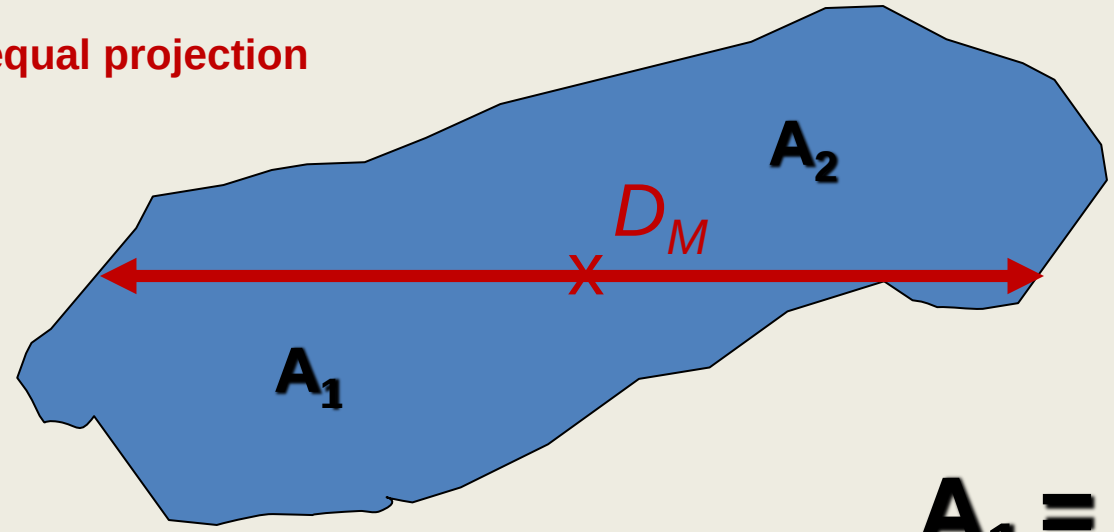
Feret diameter (D_F)



Particle size

Martin diameter (D_M),

equal projection

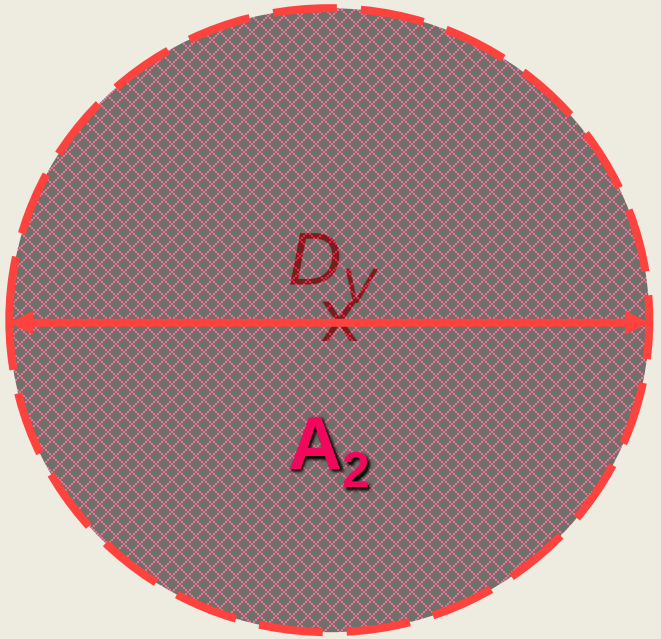


$A_1 = A_2$

direction

Particle size

Projectional circle diameter (D_V)

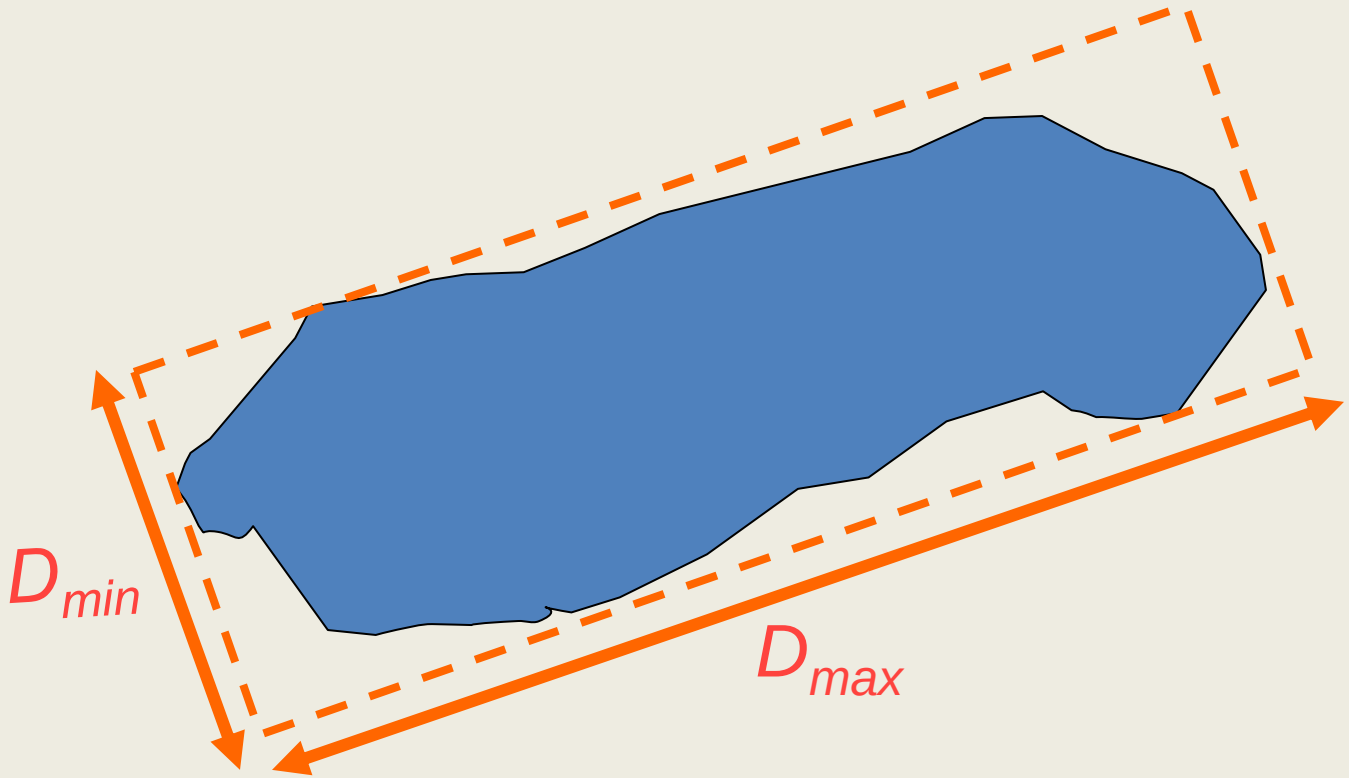


$A_1 = A_2$

direction

Particle size

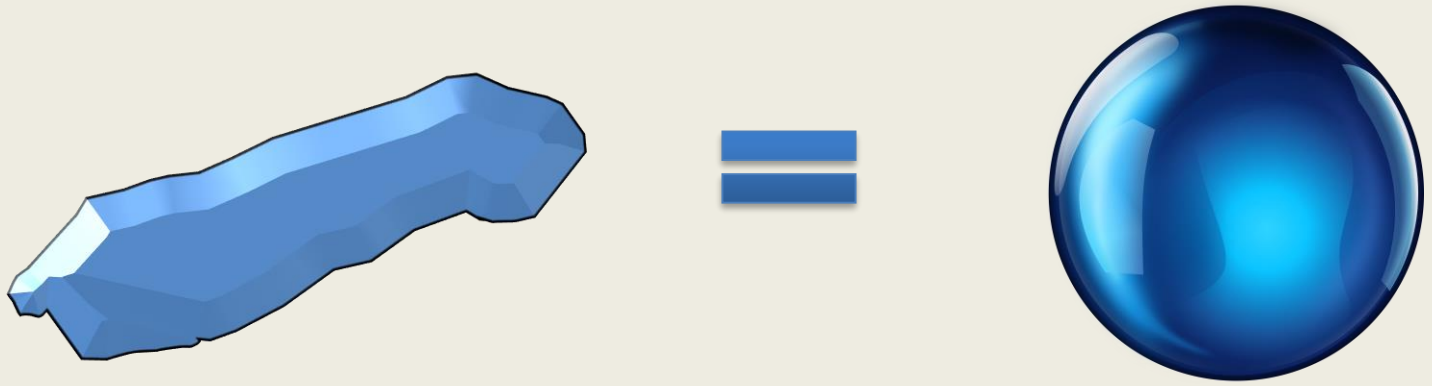
Minimal (D_{min}) and maximal (D_{max}) diameter



Particle size

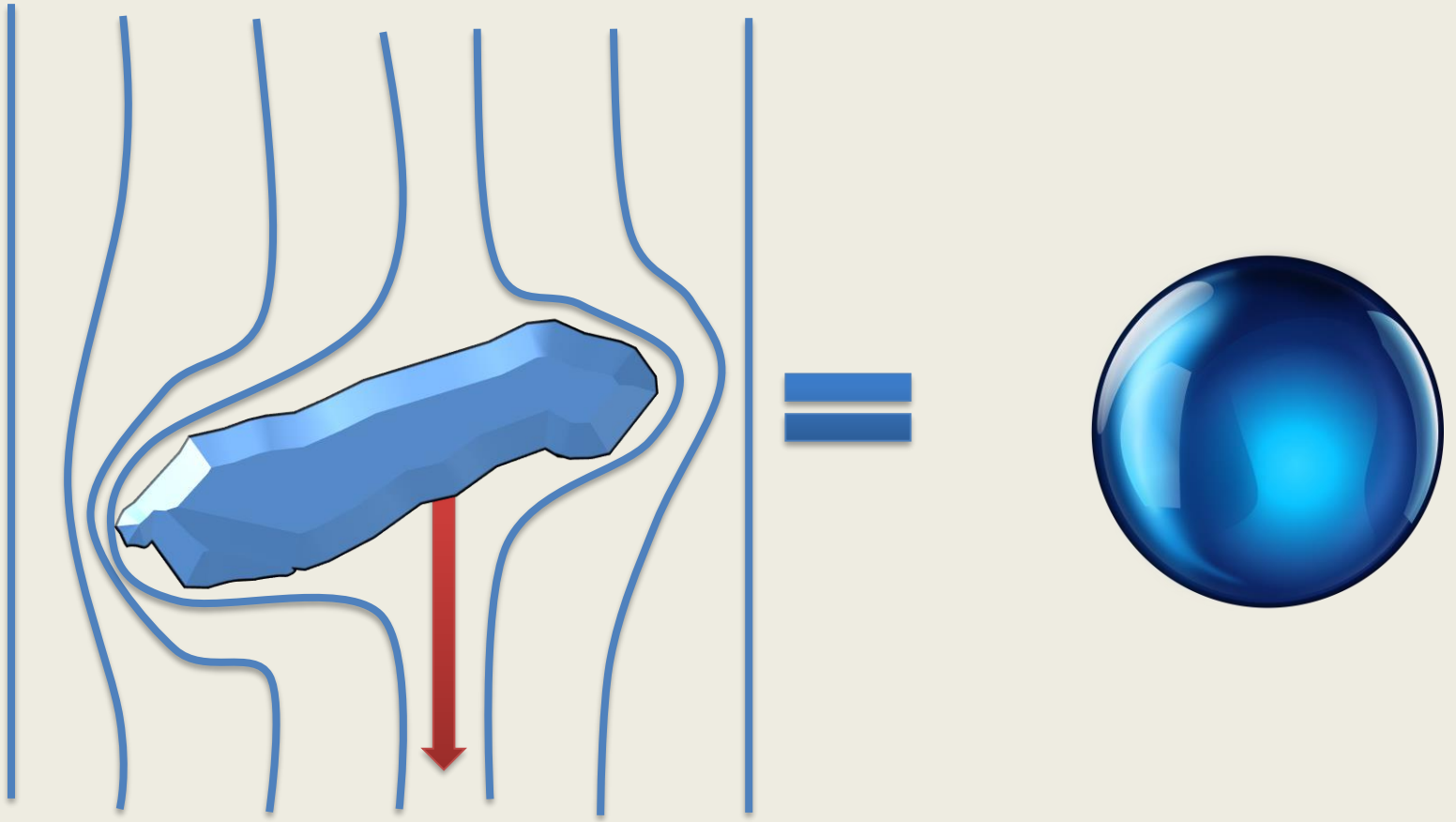
Equivalent spherical diameter

- **volume**
- **surface**



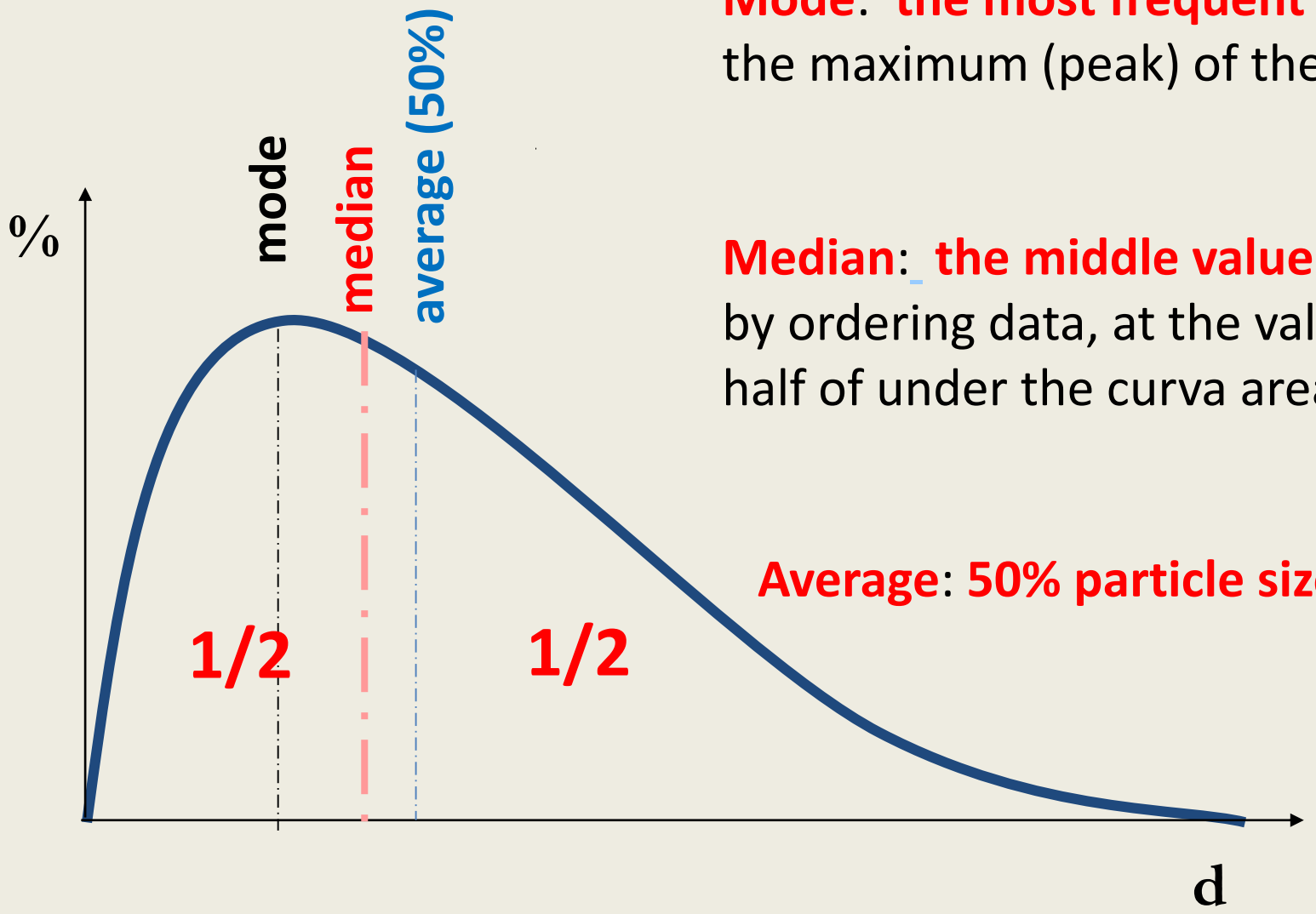
Particle size

Stokes diameter



Particle size distribution

Details of distribution

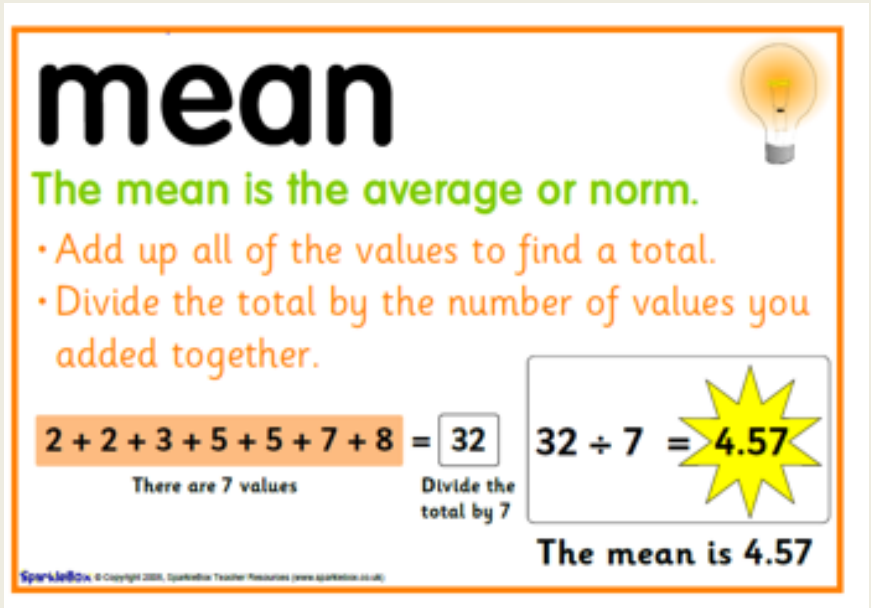


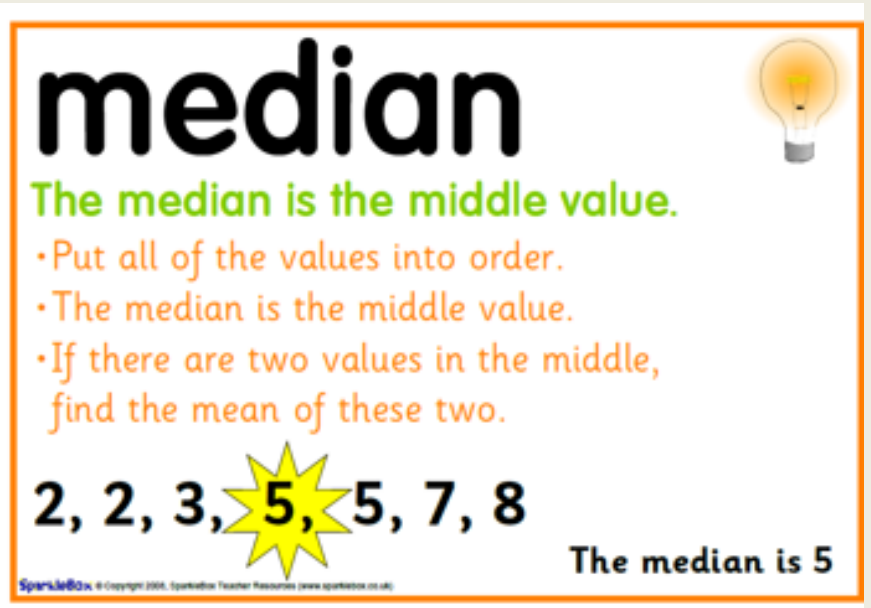
Mode: **the most frequent value**, most likely the maximum (peak) of the curve

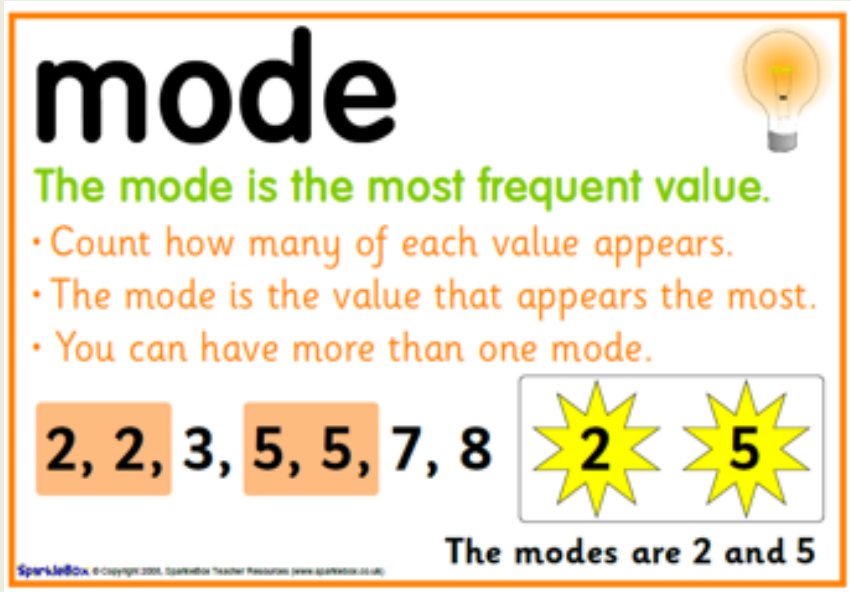
Median: **the middle value** can be determinde by ordering data, at the value which take the half of under the curva area.

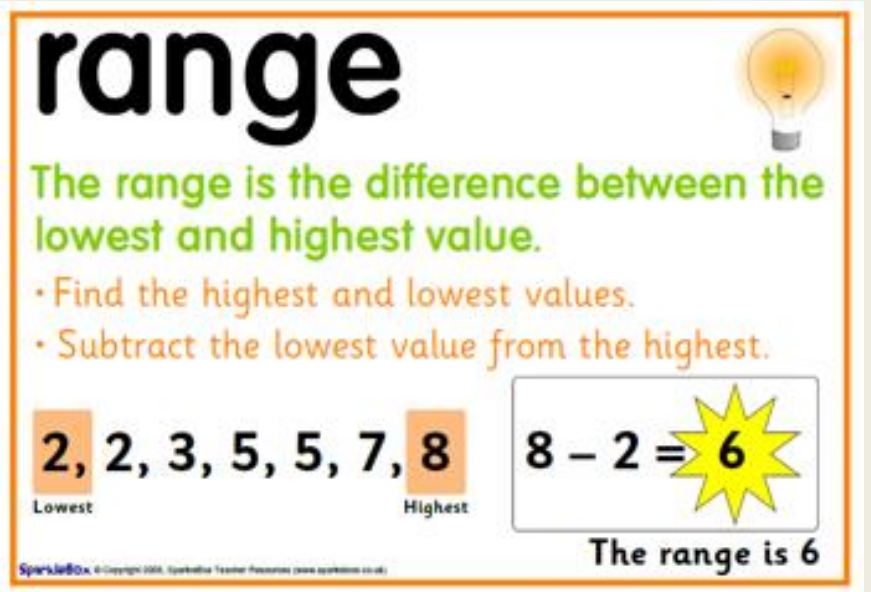
Average: **50% particle size** value

Particle size distribution

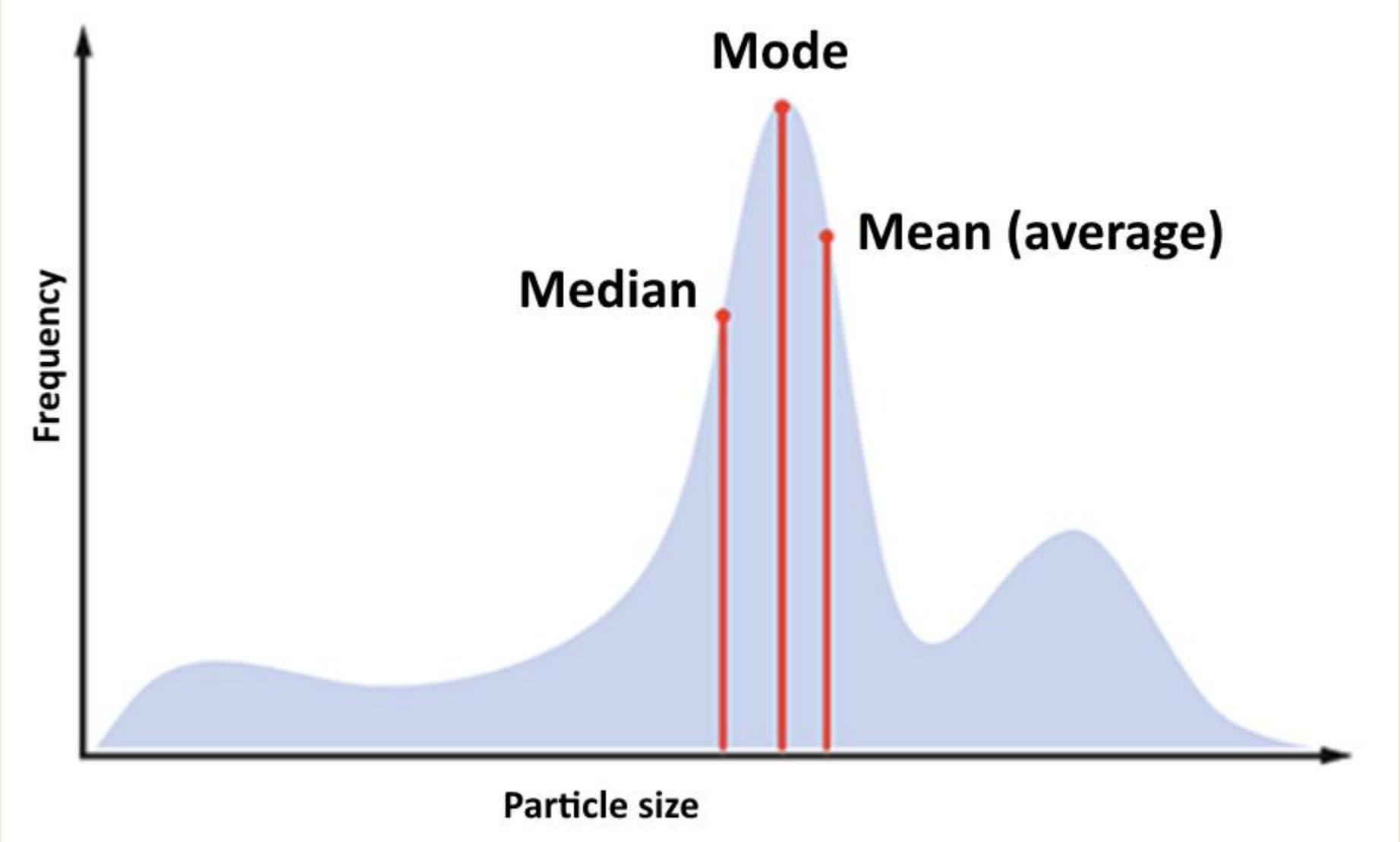






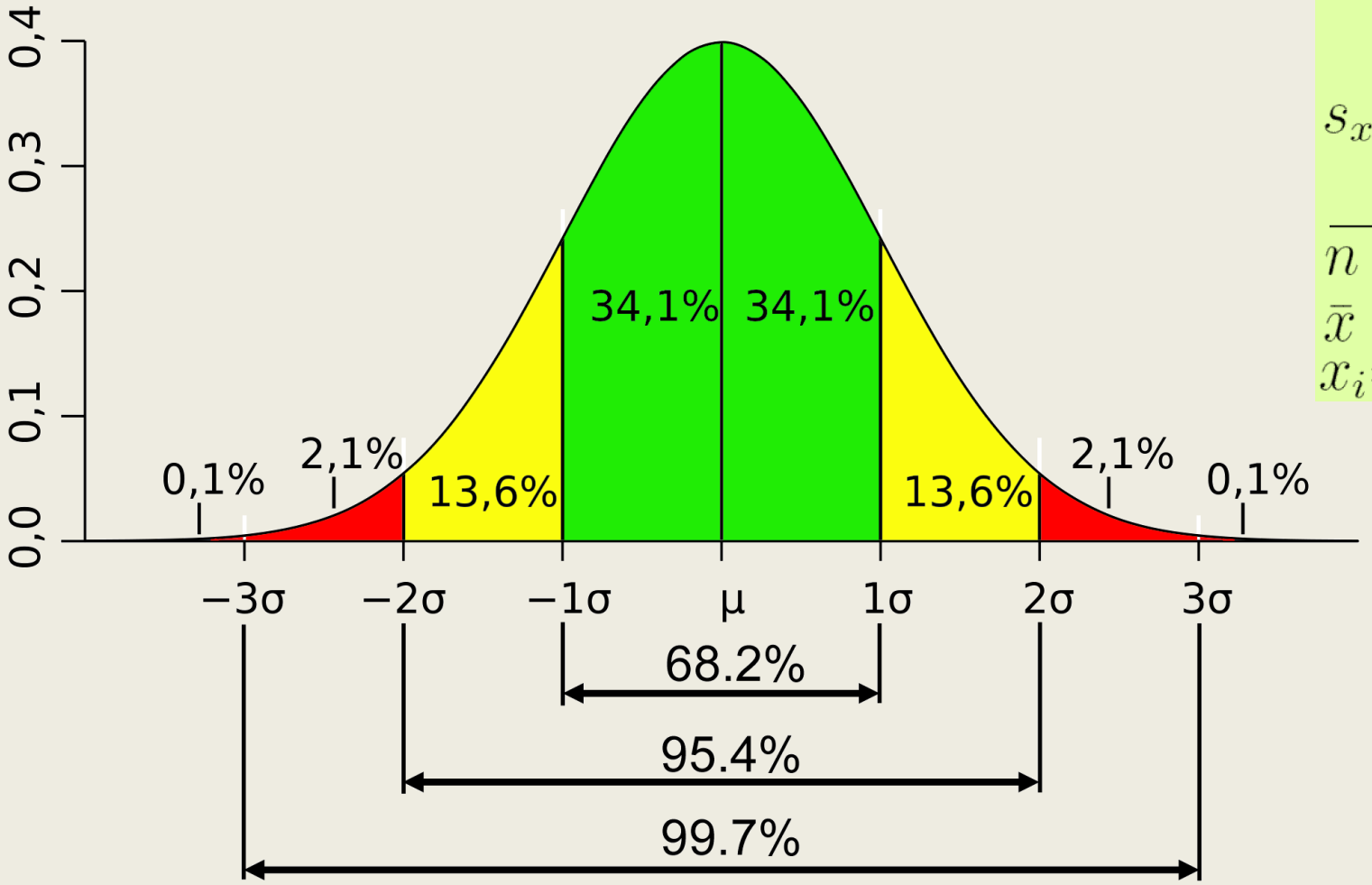


Particle distribution



Normal distribution

Details of normal distribution function



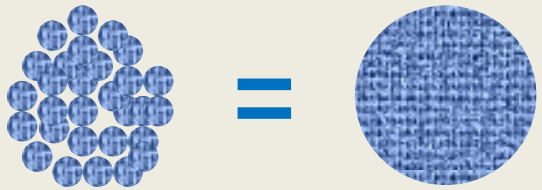
$$s_x = \sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n-1}}$$

n = The number of data points

$\bar{x}$ = The mean of the x_i

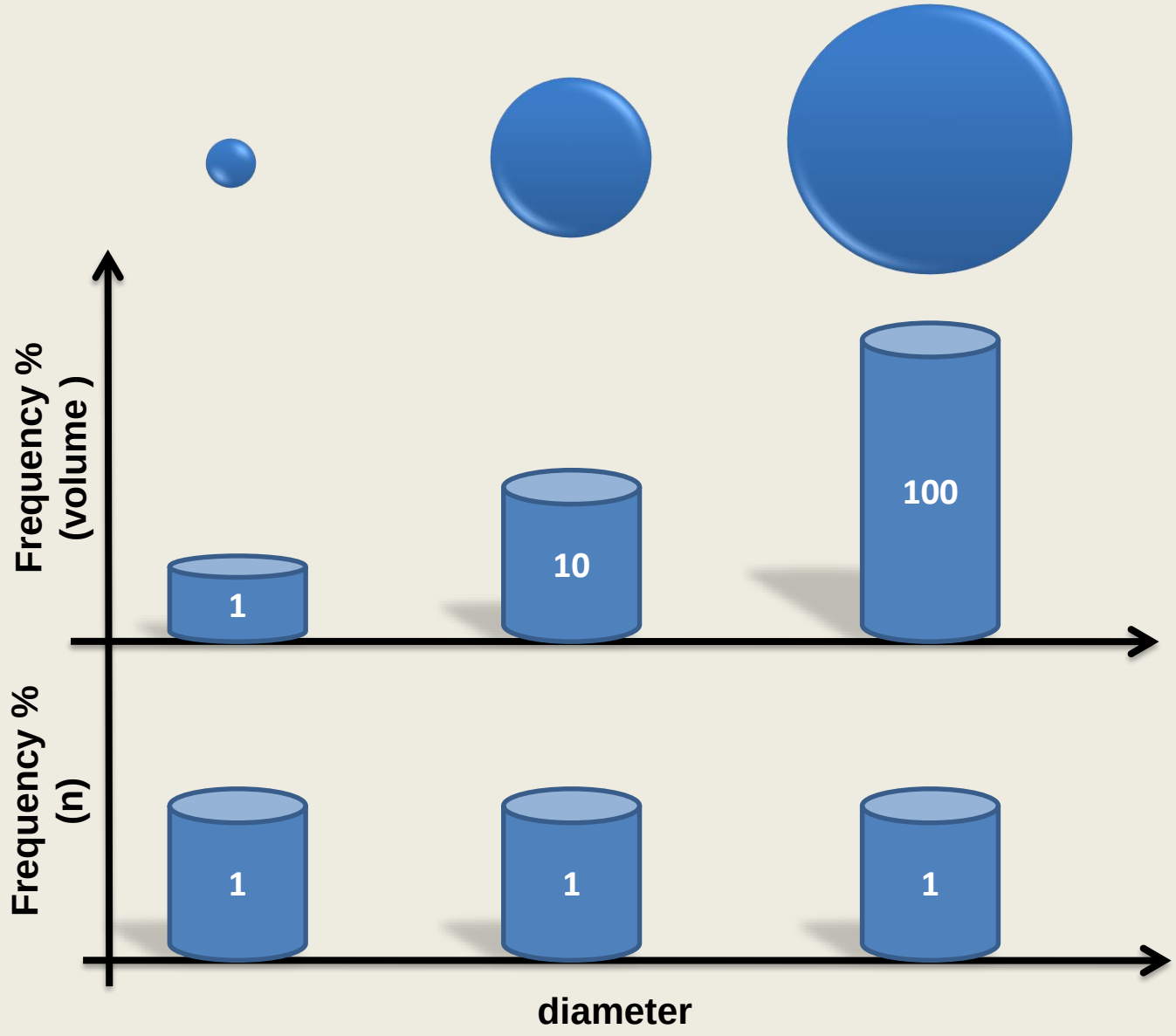
x_i = Each of the values of the data

Particle size distribution

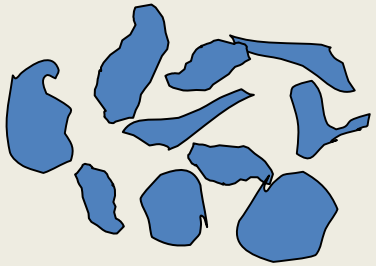


Volume	1	:	1
Number of particles	100	:	1

Particle size distribution



Deteremination of particle size



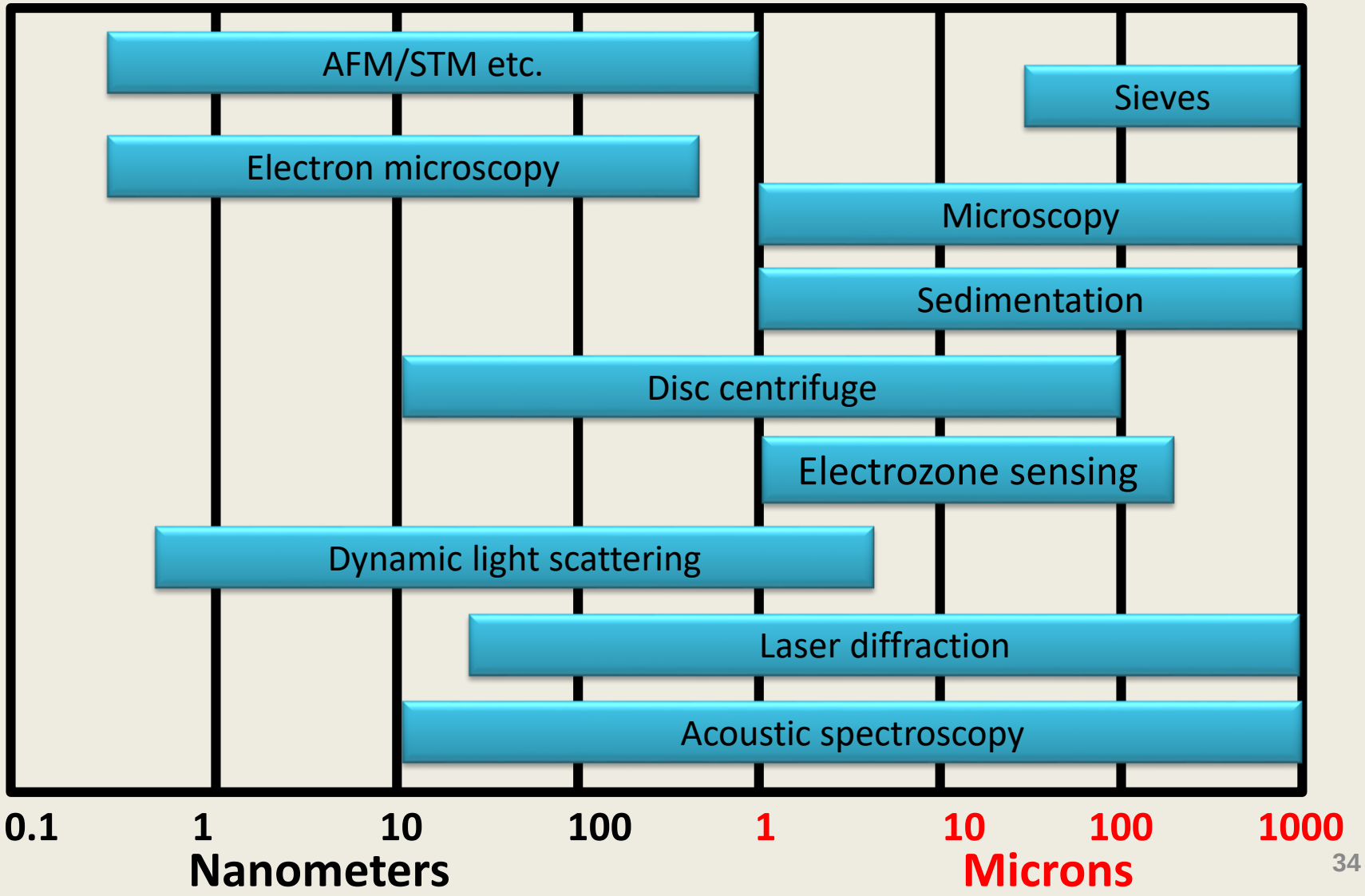
Methods of particle size determination

- Sieve analysis
- Methods based on sedimentation
- Optical methods
- Conductivity-based methods
- Laser light based methods
- Acoustic spectroscopy

Methods of particle size determination

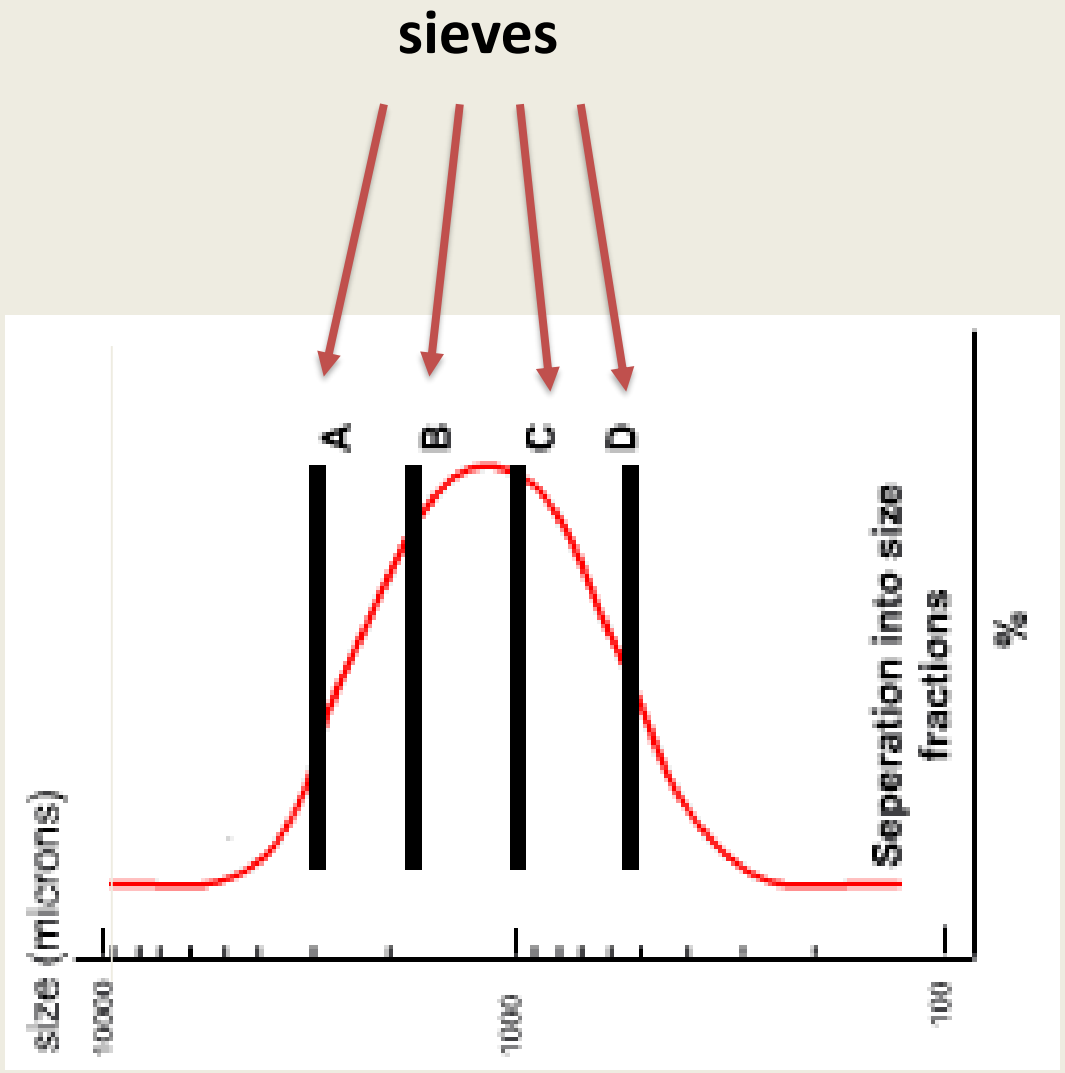
Methods	**d** (µm)
Sieving	20 – 20 000
Light microscope	> 1
Centrifugation analysis	0.01-40
Coulter counter mehtod	0.1-1000
Photon-correlational spectroscy (PCS)	0.001-1
Sedimetation X-ray analysis	0.1-300
Laser light diffraction	0.05 – 1000

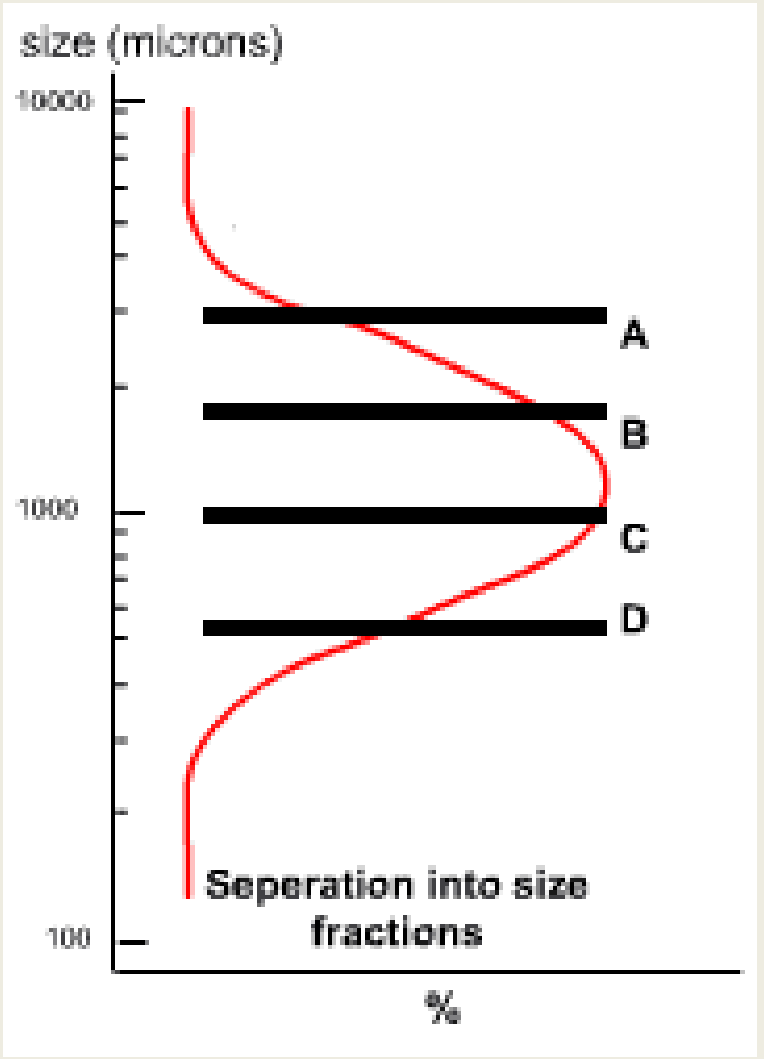
Methods of particle size determination



Sieve analysis

Particle size analysis

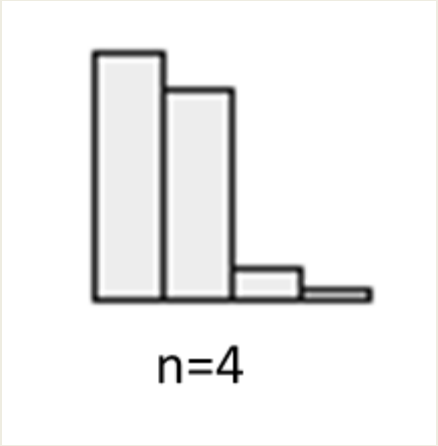


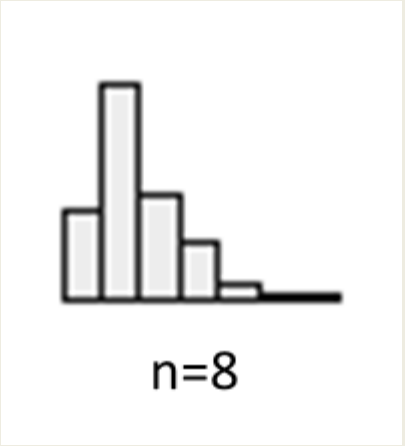


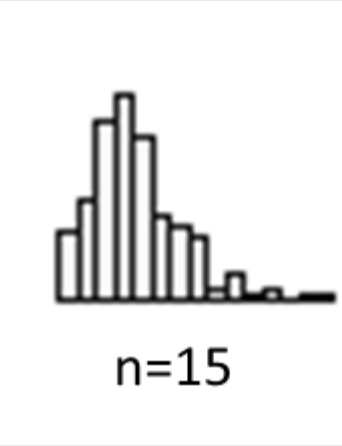
Particle size distribution

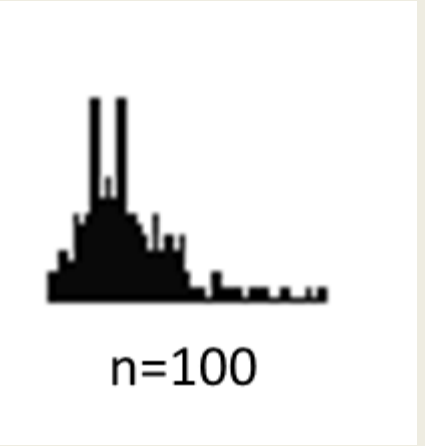
Illustration of distribution

The effect of fraction number of particles

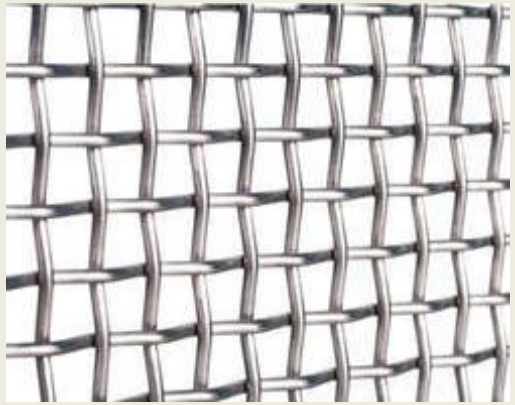






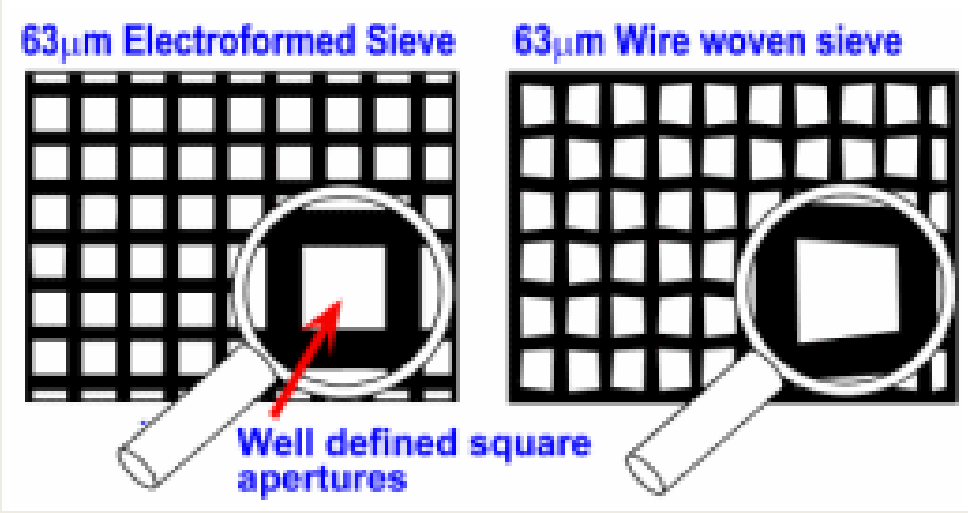


Sieve analysis for examinatation of particle size distribution

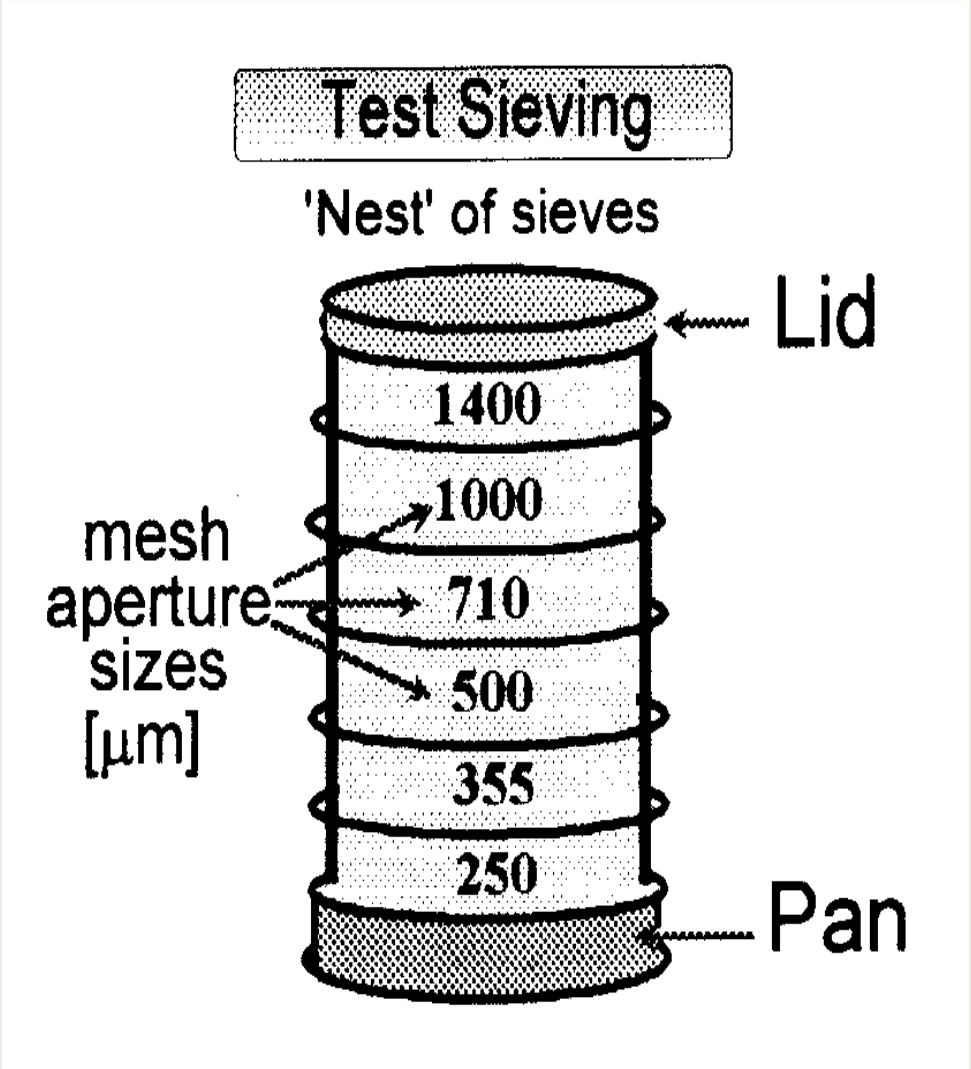
a. 

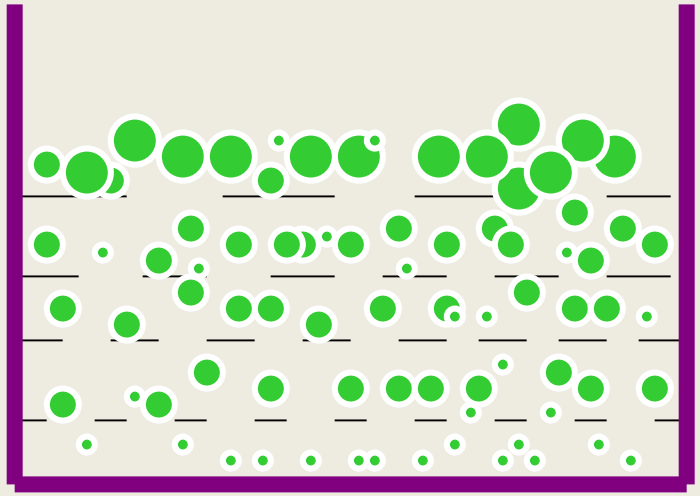
b. 

Photomicrographs of (a) Woven-wire screen and (b) micromesh screen



Sieve analysis





Sieve analysis for examinatation of particle size distribution

Sieve analysis

Advantages

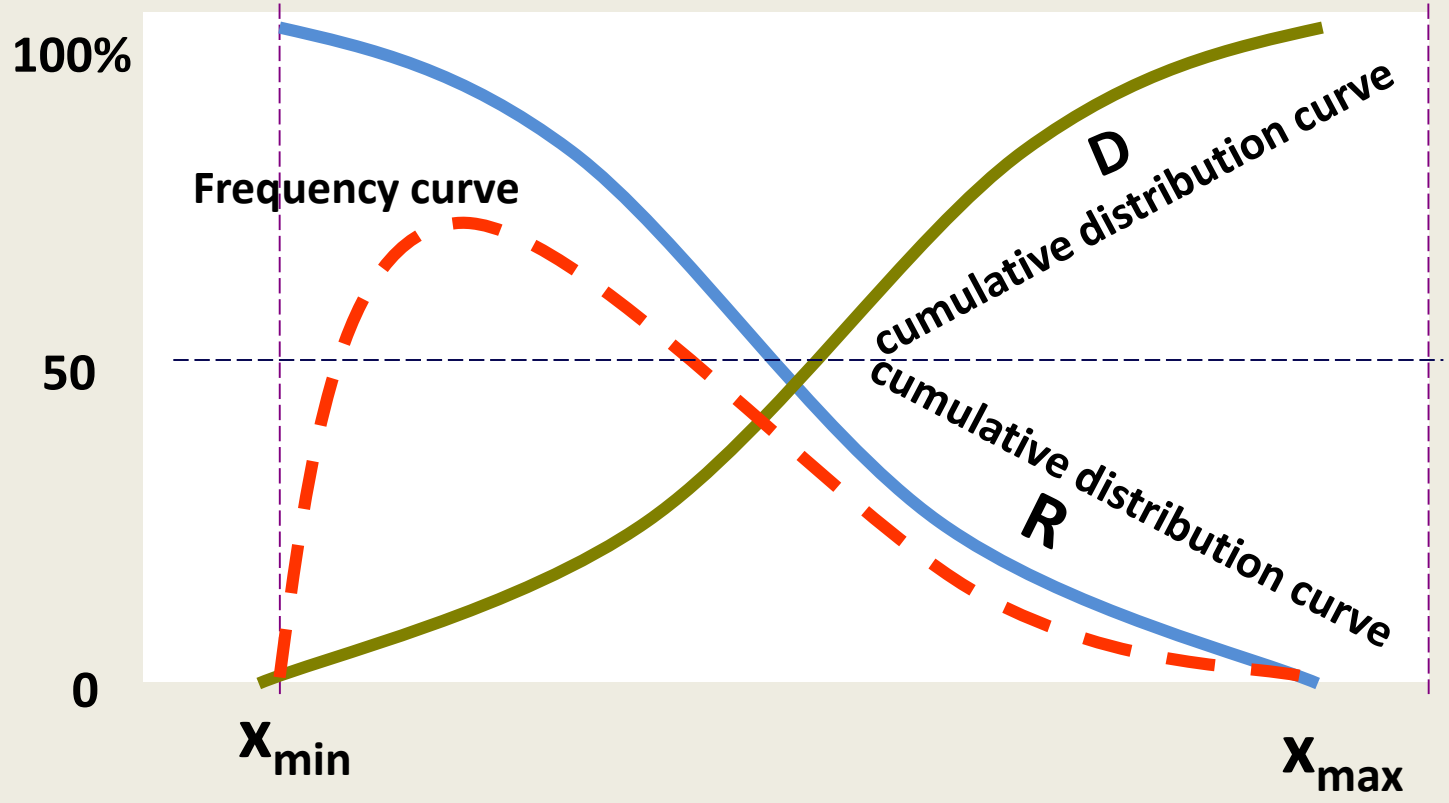
- Possibility to examine wide particle size distribution
- Simple examination
- Sieves can be calibrated
- Particle fractions can be separated

Disadvantages

- Large amount of material
- Lowest particle size limit $d > 20\ \mu m$
- Not too fast

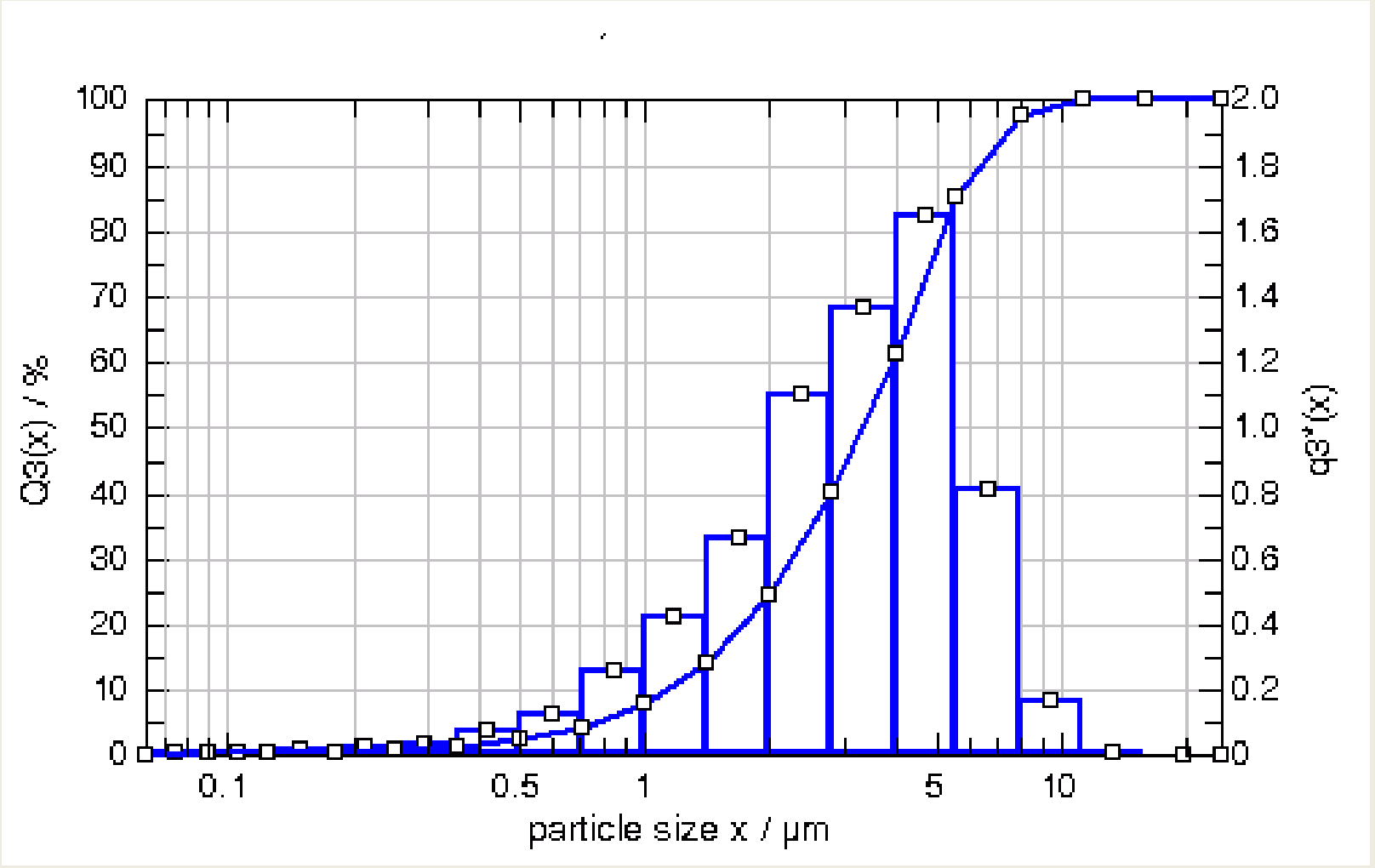
Particle size

Distribution and frequency curves



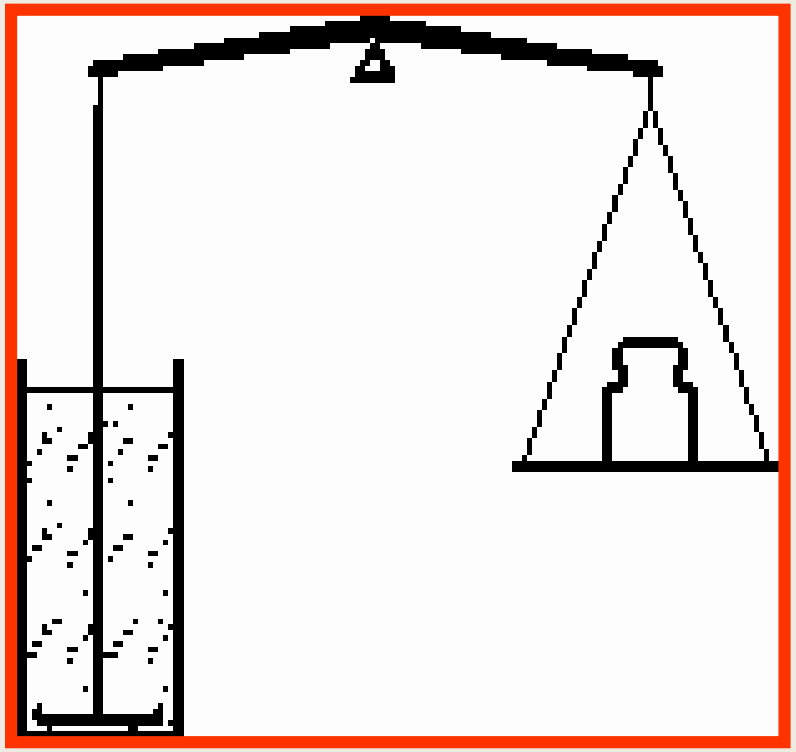
amount came through the sieves (D)
amount remained on sieves (R).

Frequency and cumulative curve



Sedimentation methods

Particle size examination
Sedimentation analysis

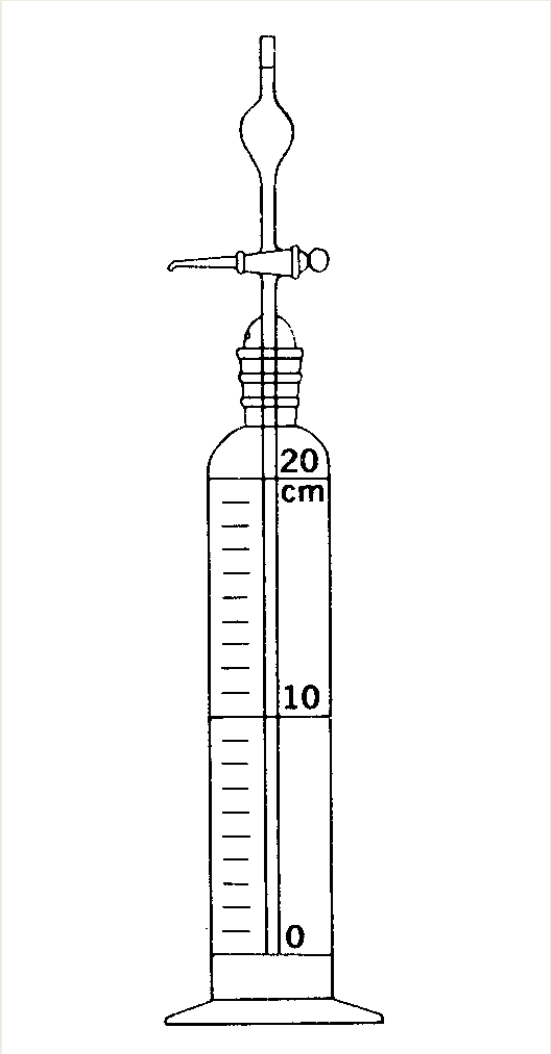


According to the measurement of mass accumulated in the plate

Sedimentation scale

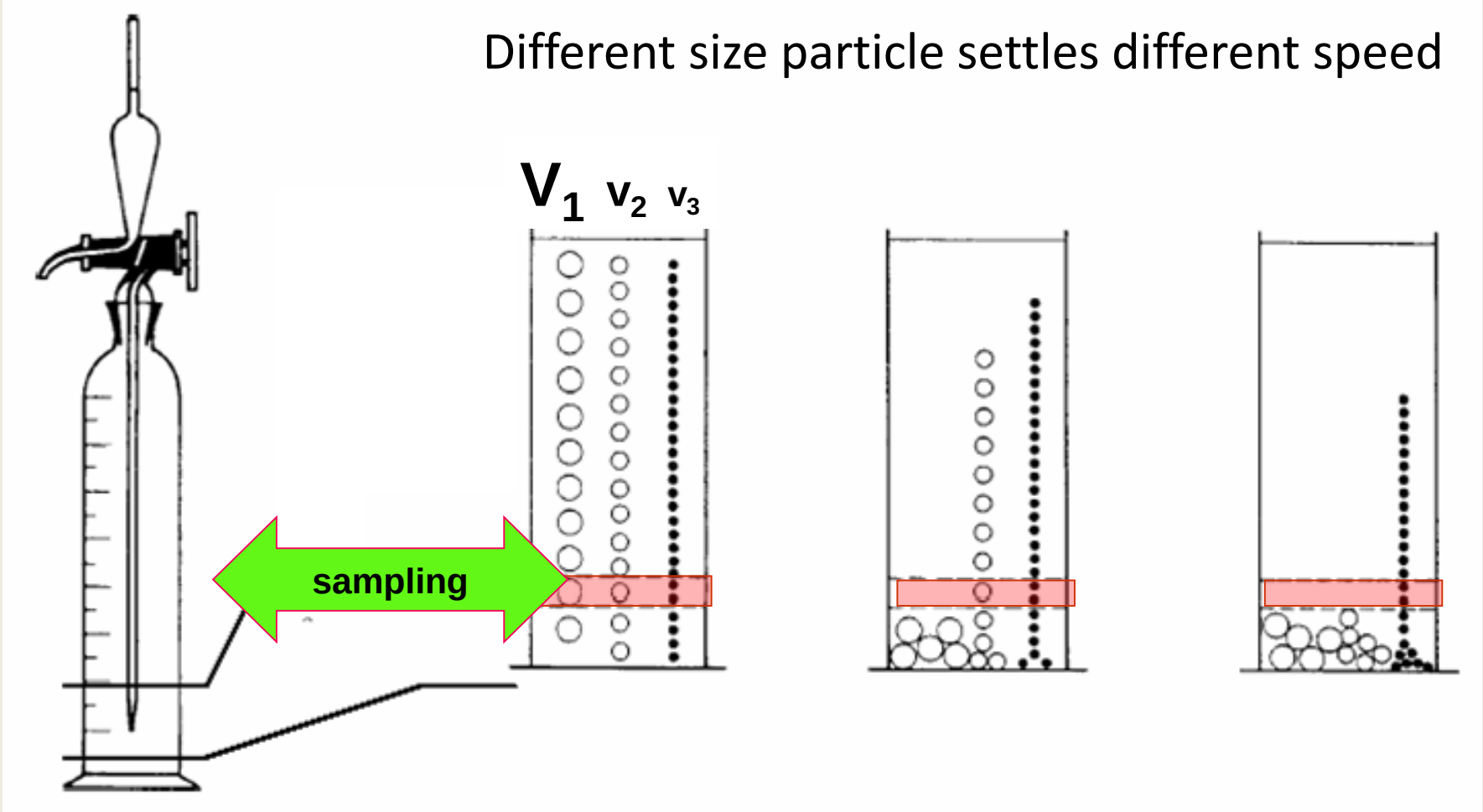
Particle size examination
Sedimentation analysis

Depending particle density 2 - 100 µm large particles can be measured with this method.

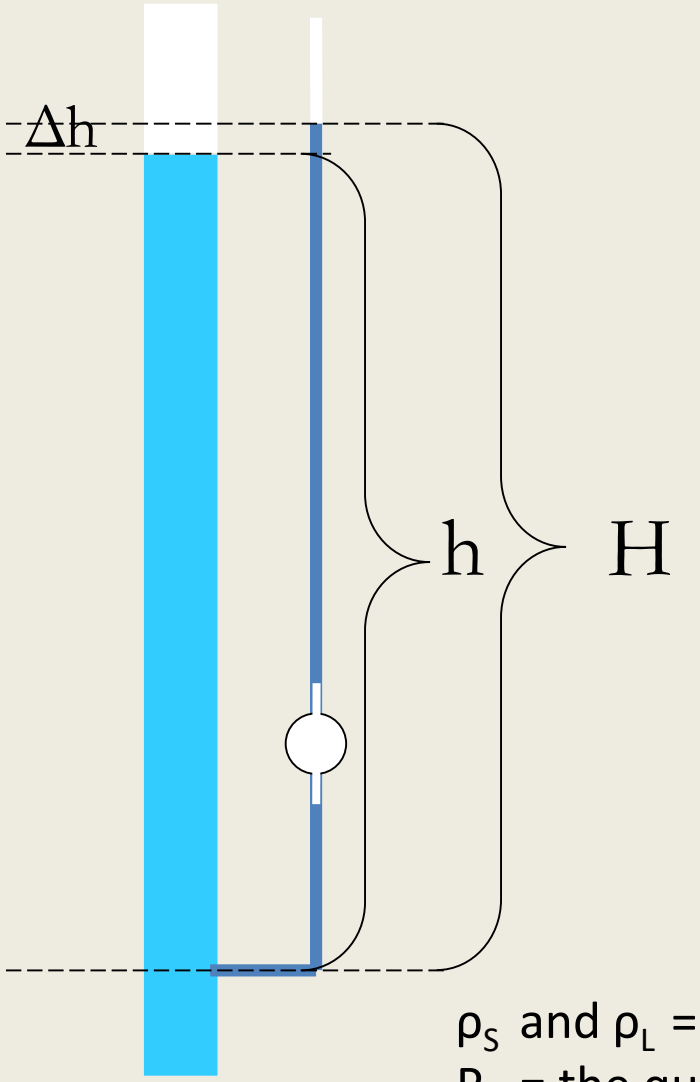


Andreasen apparatus for determining particle size by the gravity sedimentation method

Andreasen apparatus



Wigner tube



$$\frac{H}{h} = \frac{\rho_S}{\rho_L}$$

$$\Delta h = \frac{h}{\rho_L}(\rho_S - \rho_L)$$

$$P = \frac{A}{\frac{1}{\rho_L} - \frac{1}{\rho_S}} \Delta h$$

ρ_S and ρ_L = the density related to the liquid and solid material

P = the quantity of suspended material at height h

A = diameter of the settling tube

Sedimentation analysis

Sedimentograph

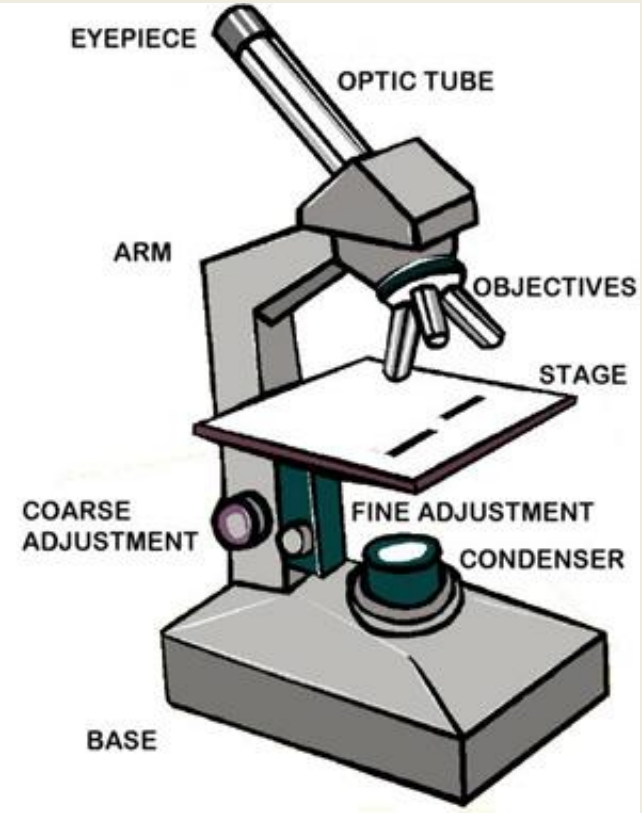
According to the Stokes rule, the device measures the sedimentation and determine the particle size dispersion. The conventional method lasts long, needs usually some hours.

Measurement interval: 0.5µm - 500µm
Maximal volume quantity: 0.5 - 3 ml
Time of analysis: 3 – 10 minutes

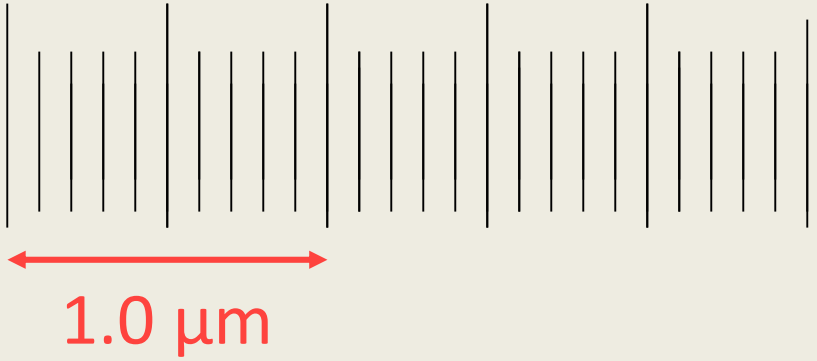
Optical methods

Determination of particle size of disperse system with conventional light microscope

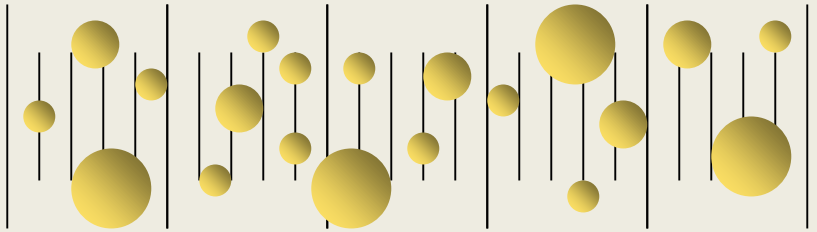
ocular micrometer



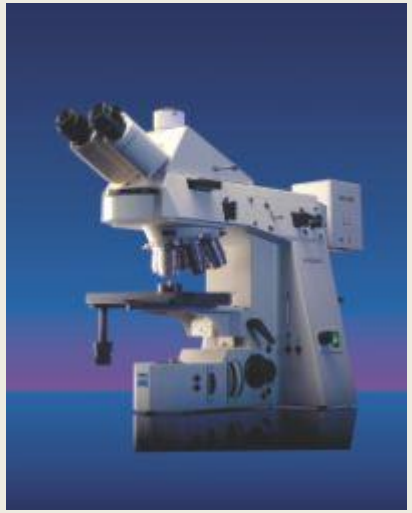
1. calibration

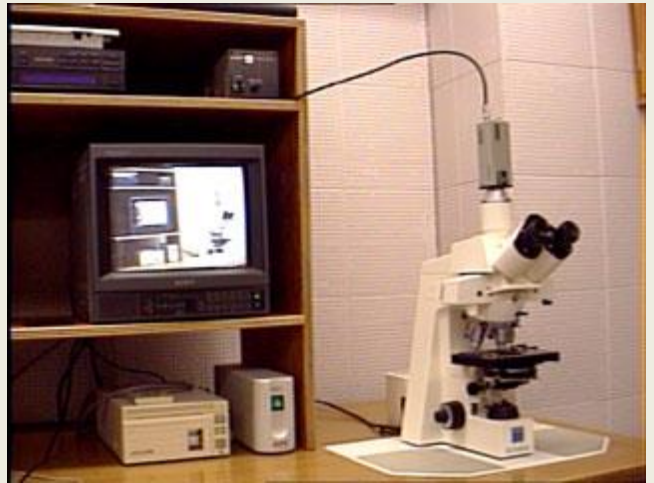


2. measurement



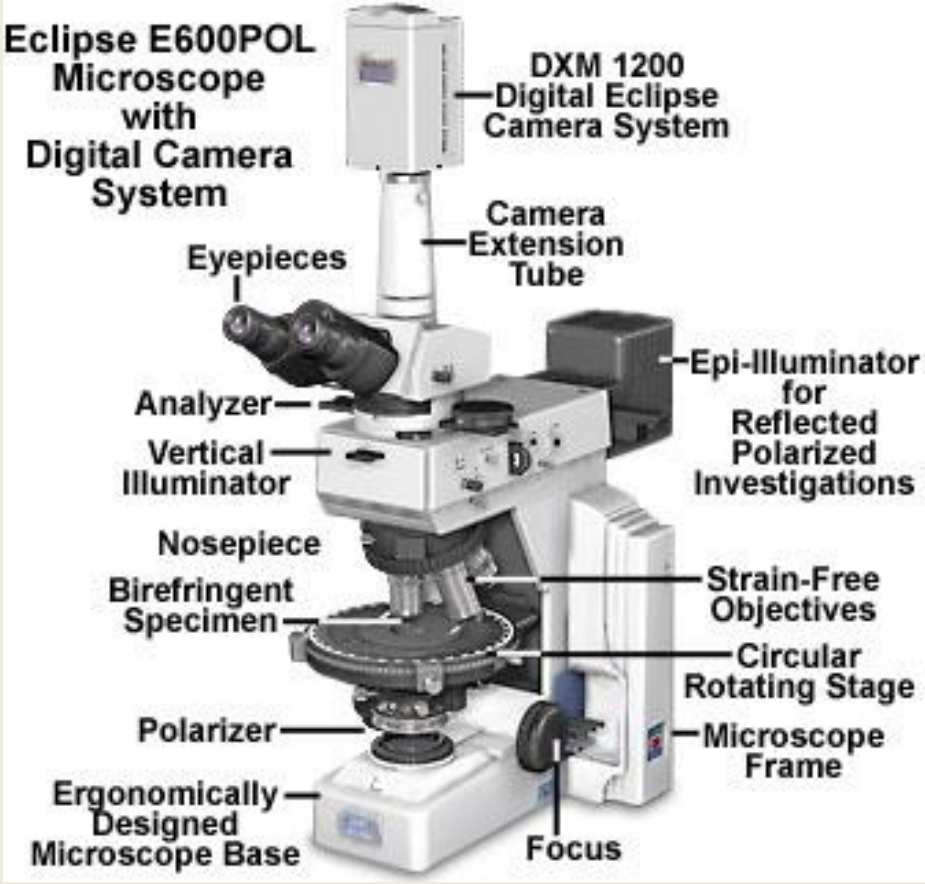
Determination of particle size of disperse system with conventional light microscope





Determination of particle size of disperse system with conventional light microscope

Digital imaging



Determination of particle size of disperse system with conventional light microscope

ImageJ

$$Circularity = 4\pi * \frac{Area}{Perimeter^2}$$

$$Aspect\ ratio = \frac{Major\ axis}{Minor\ axis}$$

$$Roundness = 4 * \frac{Area}{\pi * Major\ axis^2}$$

$$Solidity = \frac{Area}{Convex\ area}$$

Microscopy

Advantages

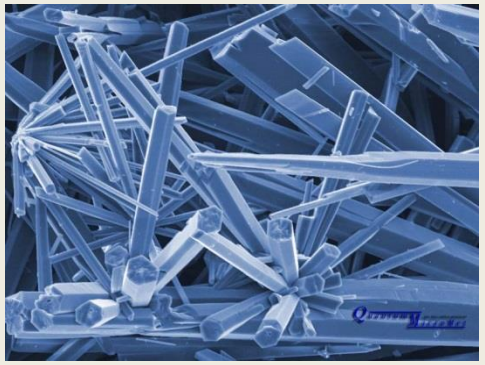
- Direct examination
- 2D shape of particles can be examined
- Image analysing system can be applied
- Can be calibrated

Disadvantages

- Hard to apply statistical evaluation
- In case of wide disperse or submicroscopic particle hard to apply or cannot be applied
- Slow
- Previous preparation of samples is needed
- Two-dimensional analysis

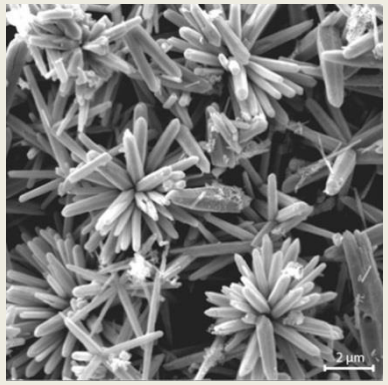
Determination of particle size of disperse system with scanning or transmission electron microscope

SCANNING ELECTRON MICROSCOPY
TRANSMISSION ELECTRON MICROSCOPY

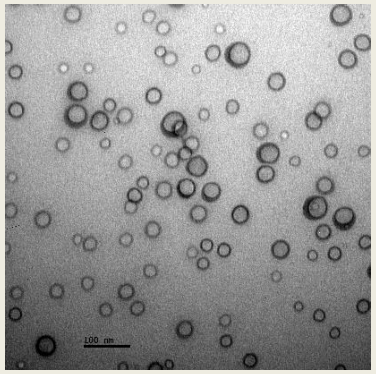


Potassium carbonate crystals (SEM)

NaCl crystals (SEM)

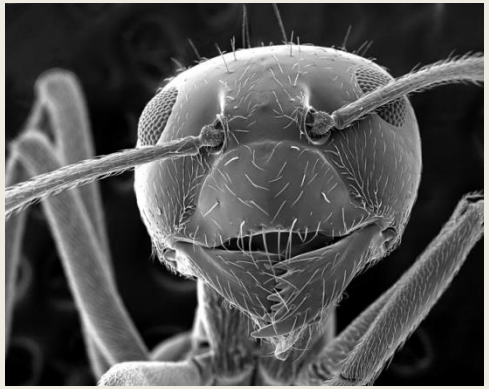


Zinc-oxide crystals (SEM)

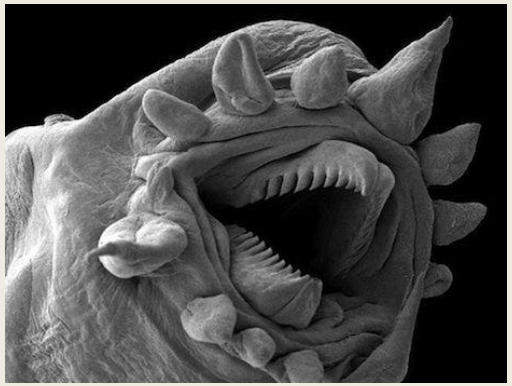


PEG-G2-DCA-cisplatin (TEM)

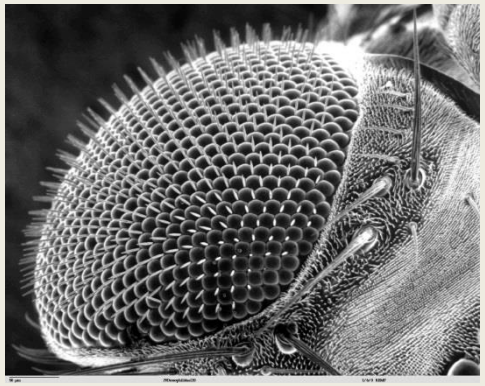
SEM/TEM



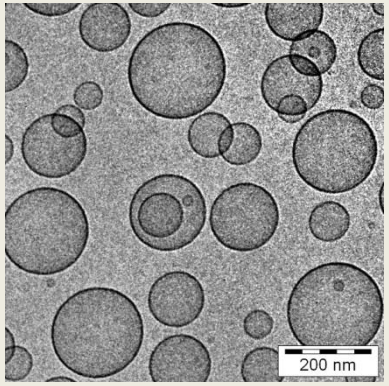
Ant head



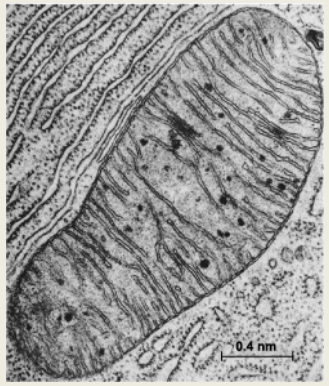
Hydrothermal worm



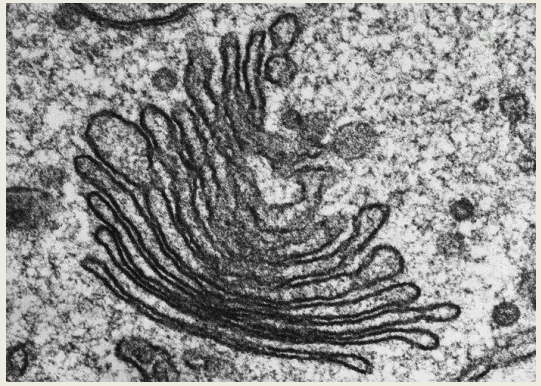
Drosophilia eye



Liposomes

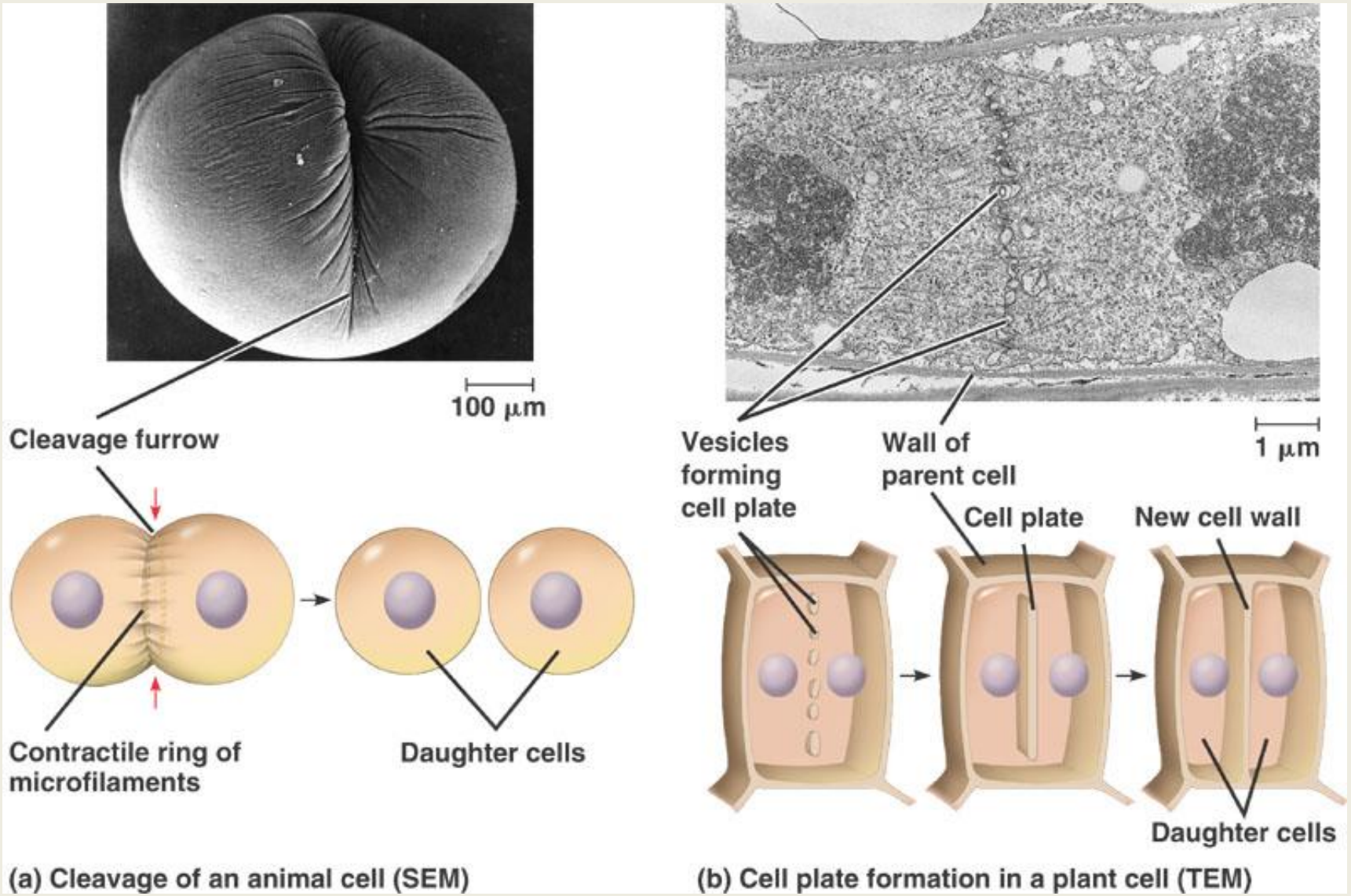


Mitochondrium

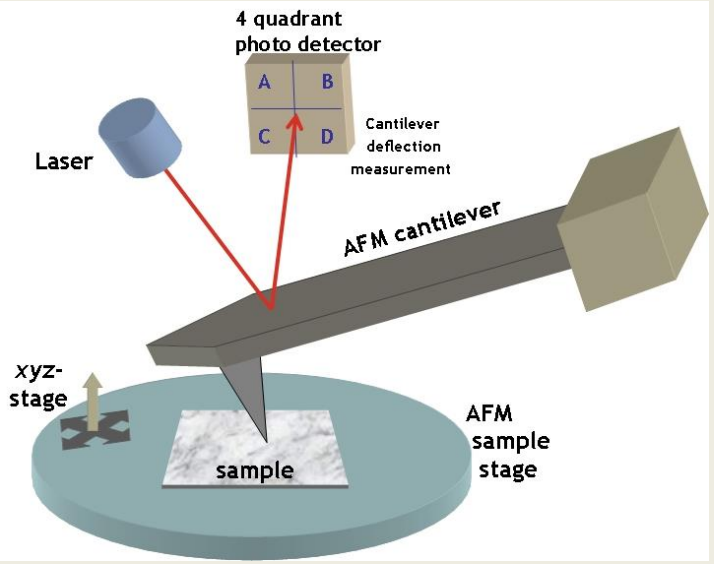


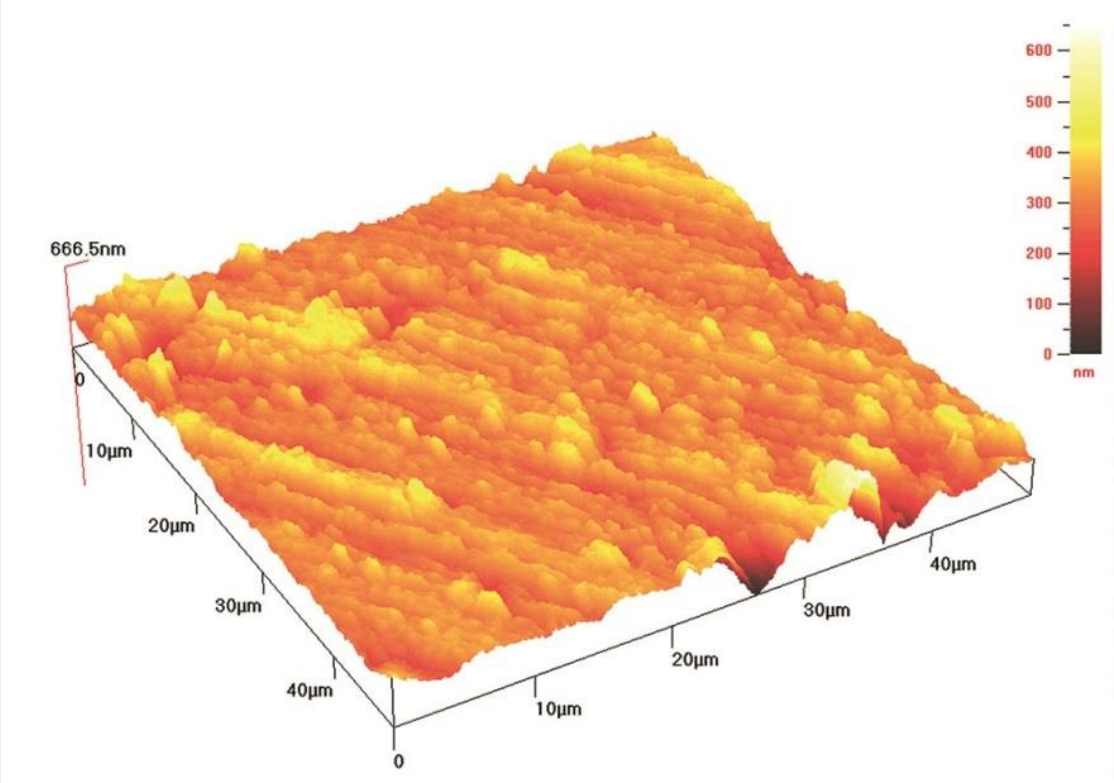
Golgi apparatus

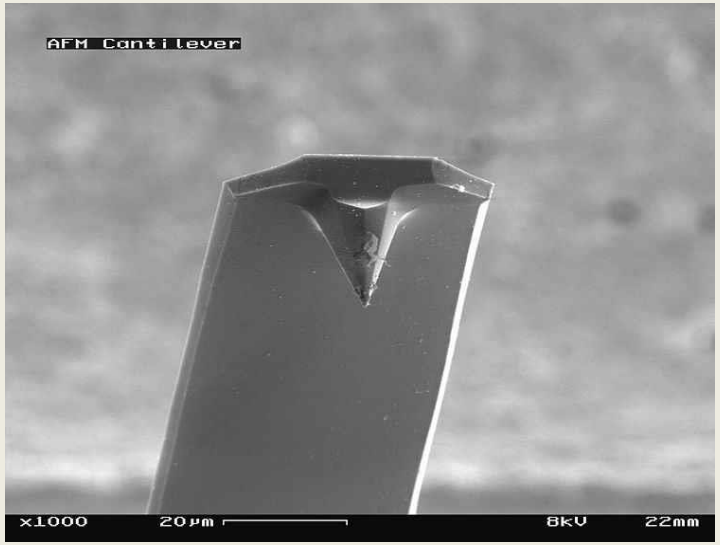
SEM/TEM


100 µm
Cleavage furrow
Contractile ring of microfilaments
Daughter cells
(a) Cleavage of an animal cell (SEM)
1 µm
Vesicles forming cell plate
Wall of parent cell
Cell plate
New cell wall
Daughter cells
(b) Cell plate formation in a plant cell (TEM)

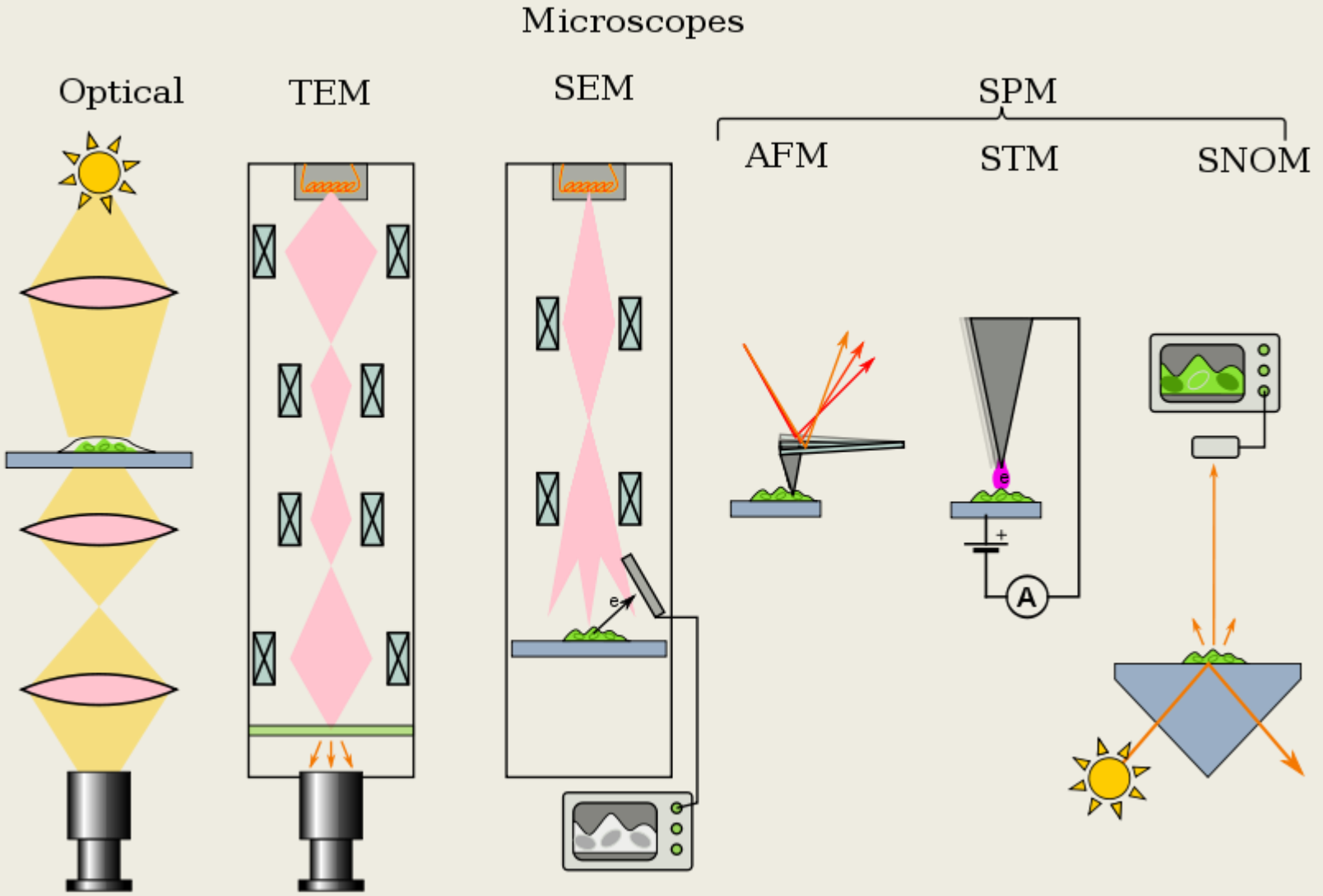
AFM – Atomic Force Microscopy



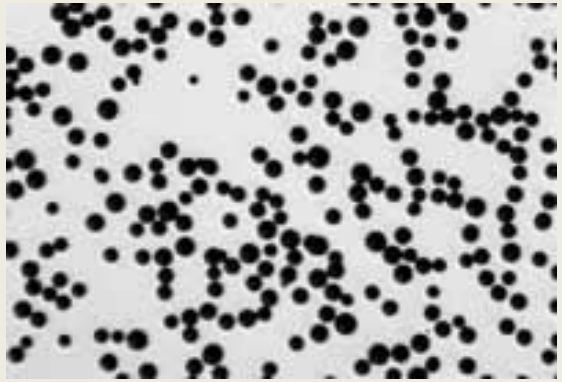




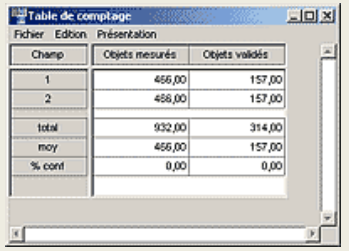
Optical particle size determination (*summary*)

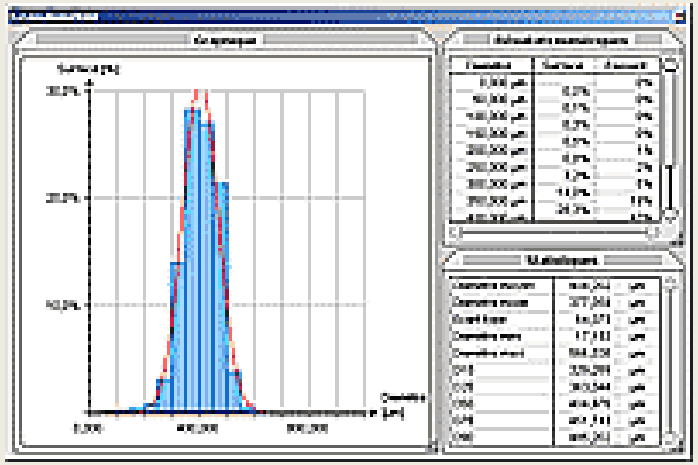


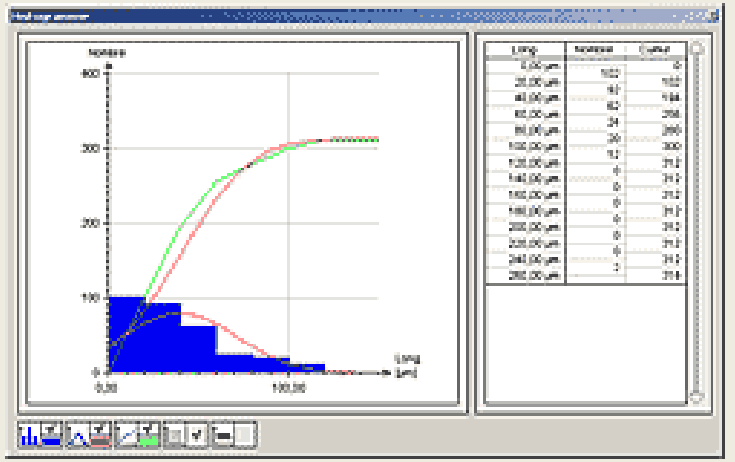
Examined parameters



Particle numbers
Particle size
Average particle size
Particle size distribution



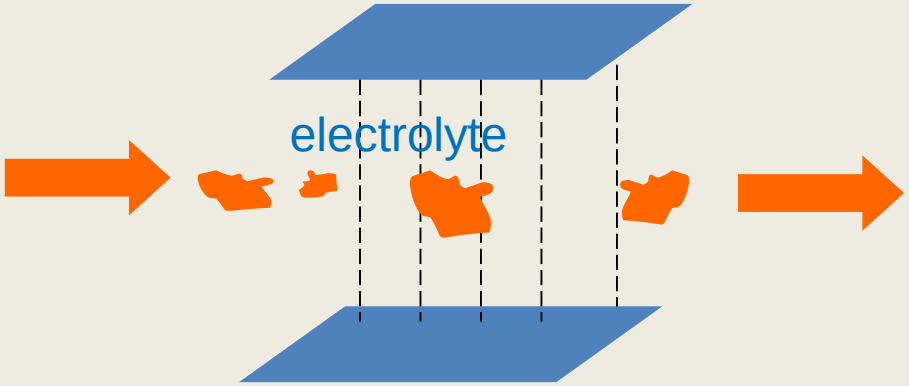


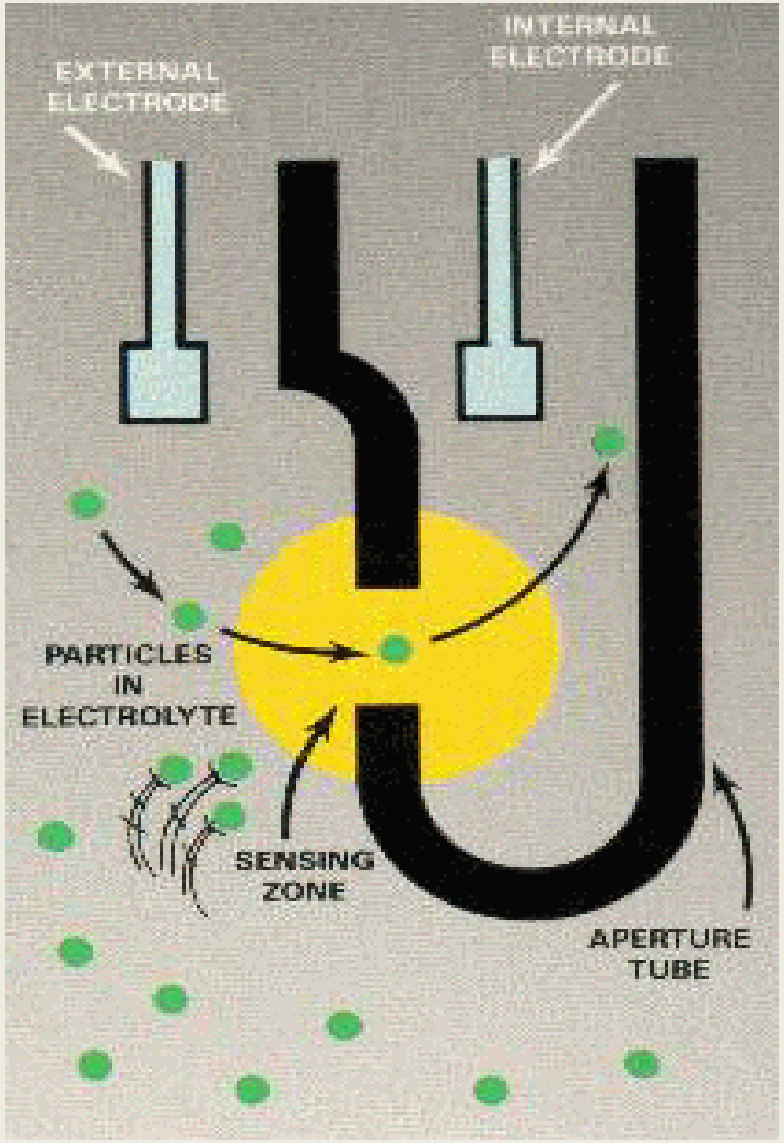


Other methods

Conductivity-based methods

Coulter Counter





Particle size determination of disperse system with laser light scattering method

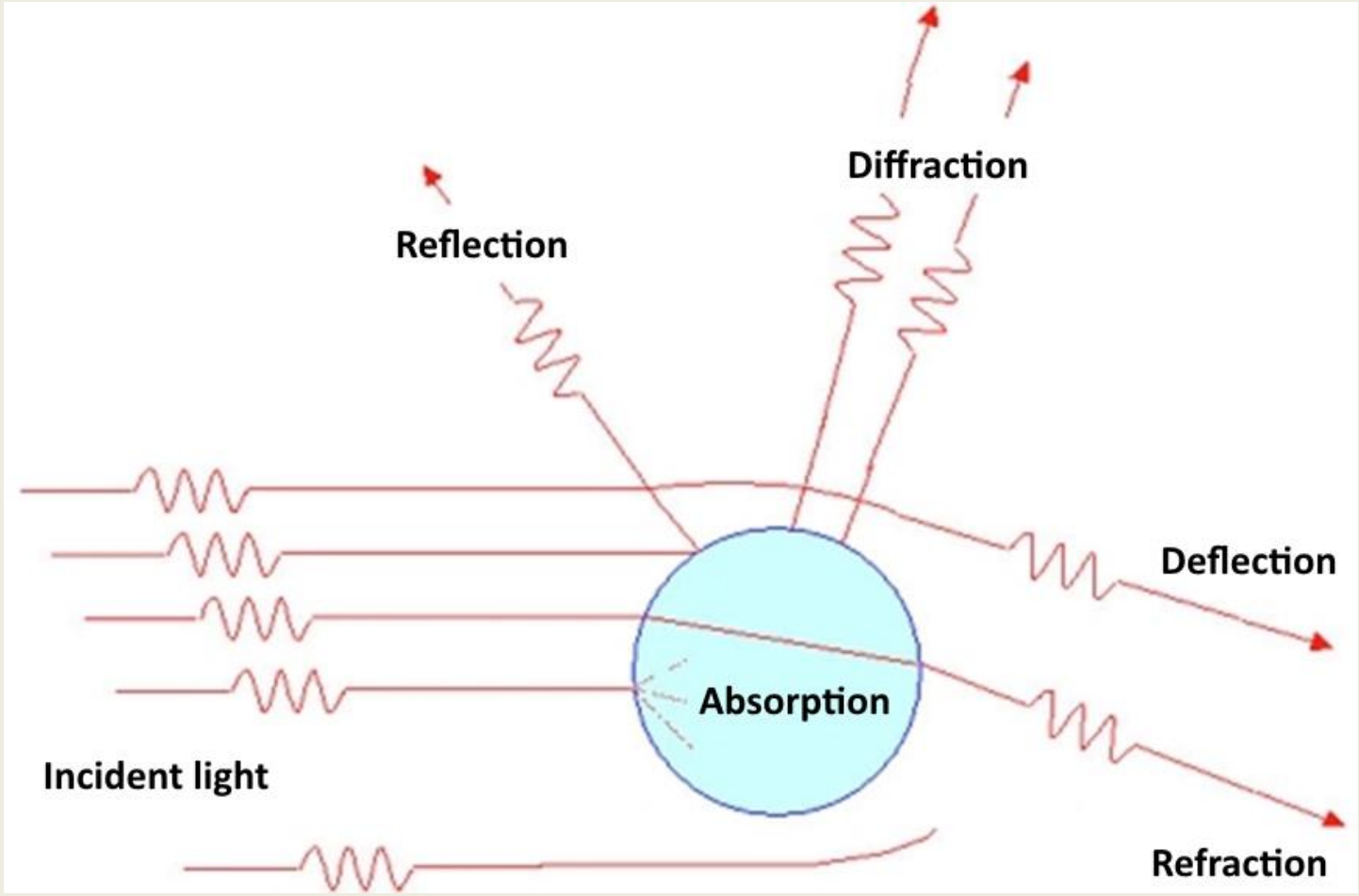
This method is based on **light scattering** and scattered light on particles of disperse system, which is detected.

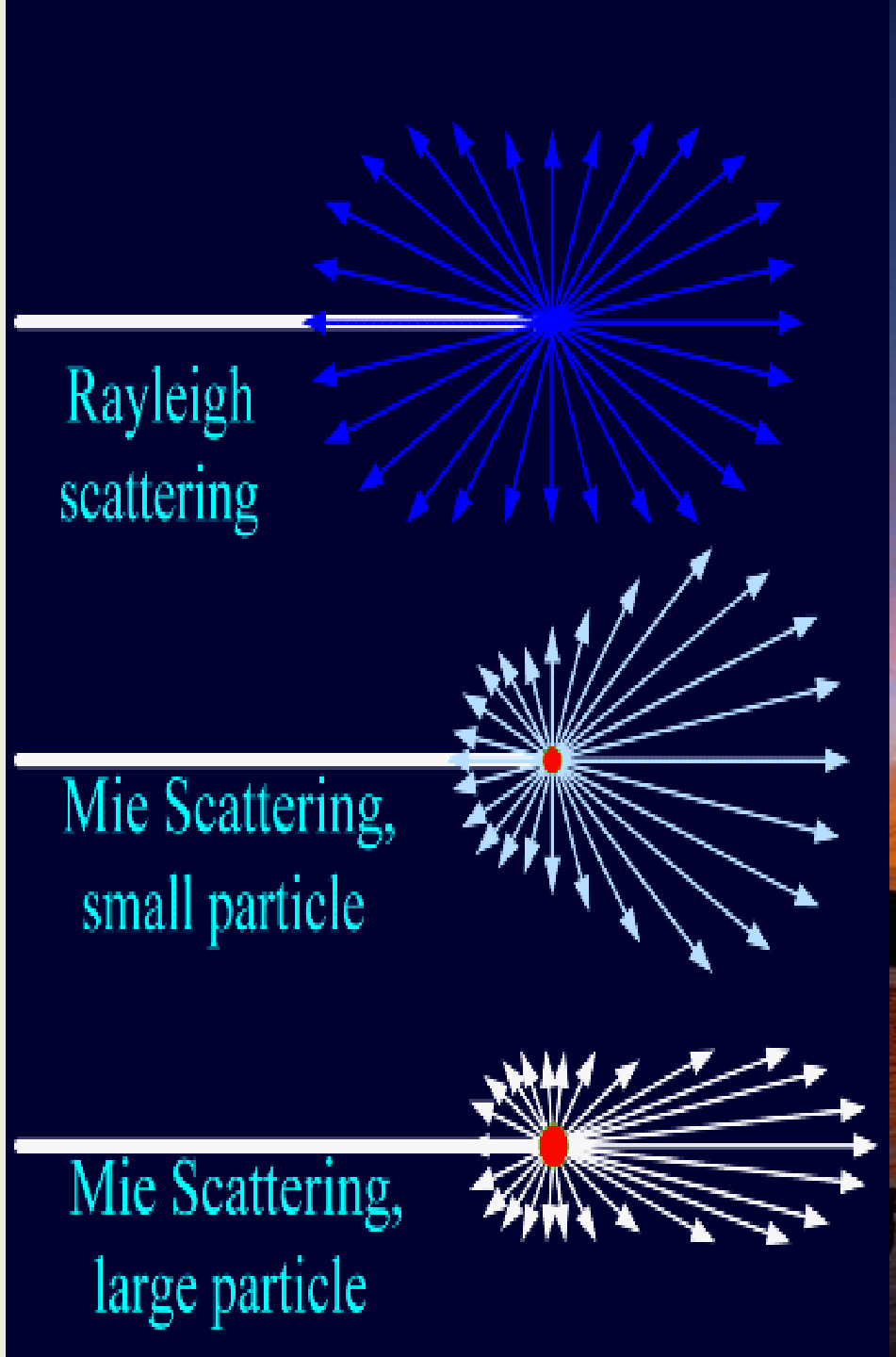
It is according to Mie theory, who has identified , that known size spherical particle with particular reflection index scatter the light to particular direction.

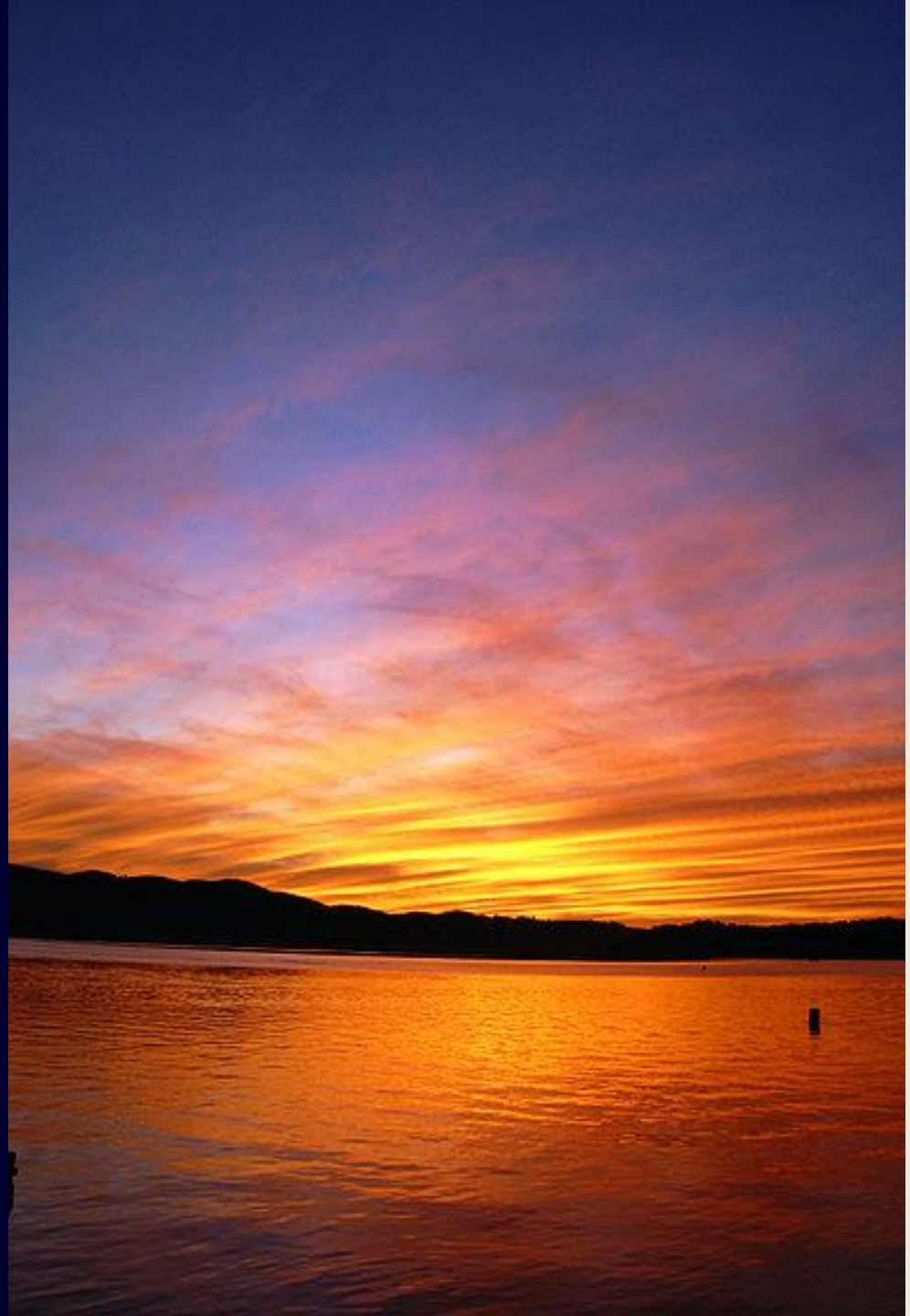
$$\alpha = \frac{2\pi r}{\lambda}$$

α	Mie parameter
r	radius of particle
λ	wavelength of scattered light

Particle size determination of disperse system with laser light scattering method



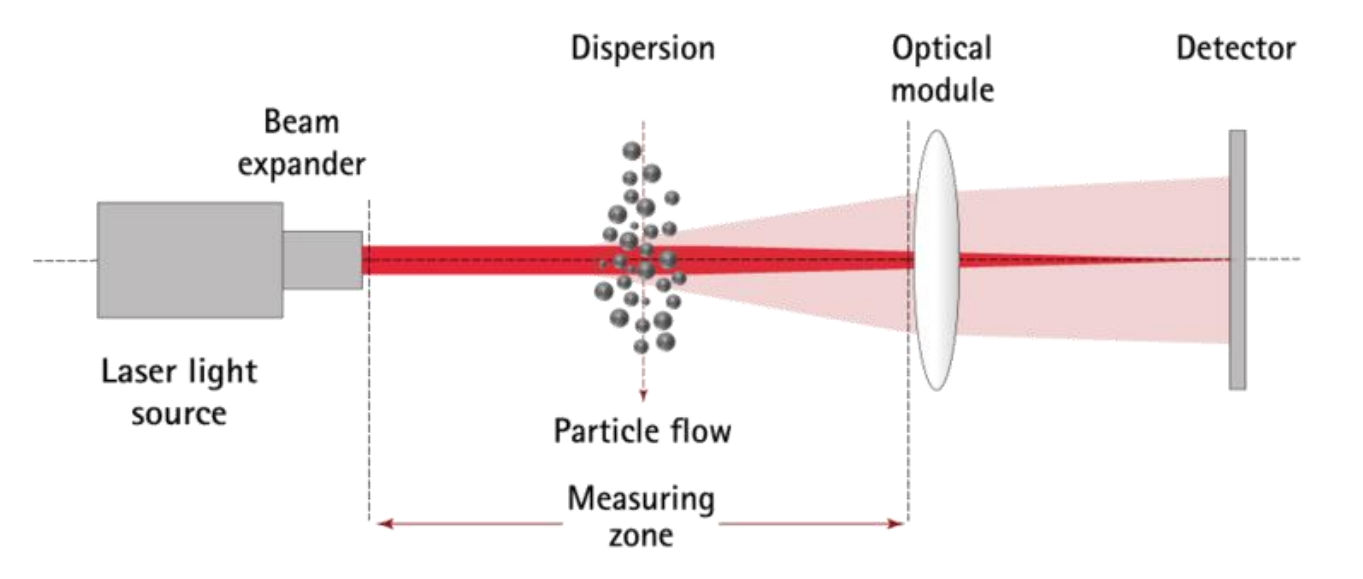

Rayleigh
scattering
Mie Scattering,
small particle
Mie Scattering,
large particle

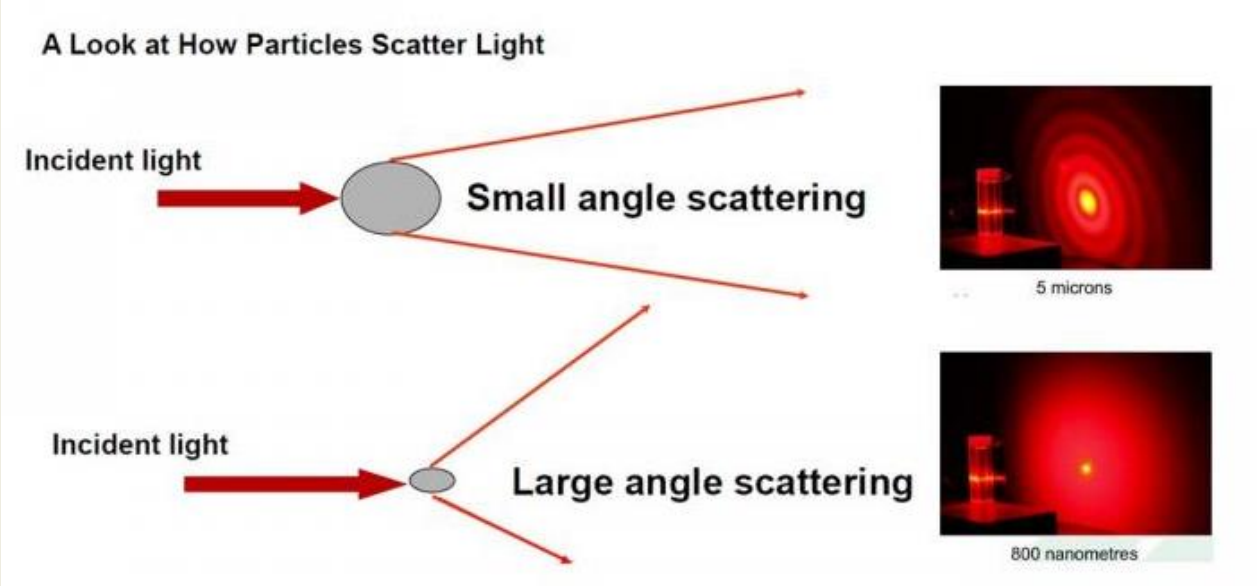


Particle size determination of disperse system with laser light scattering method

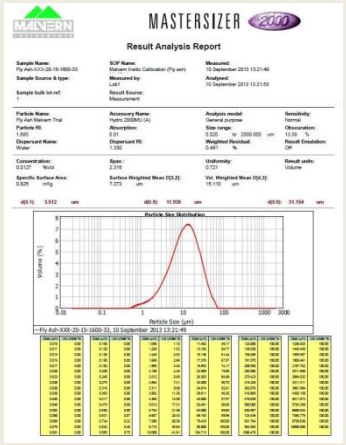
Malvern Mastersizer

Laser diffraction





Malvern Mastersizer report



MASTERSIZER 2000

Result Analysis Report

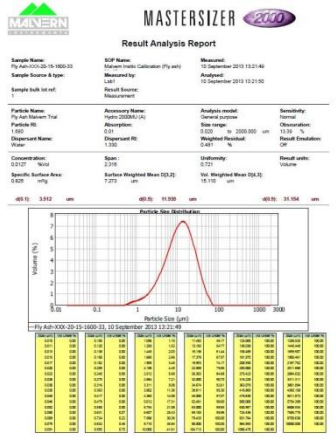
MALVERN INSTRUMENTS

MASTERSIZER 2000

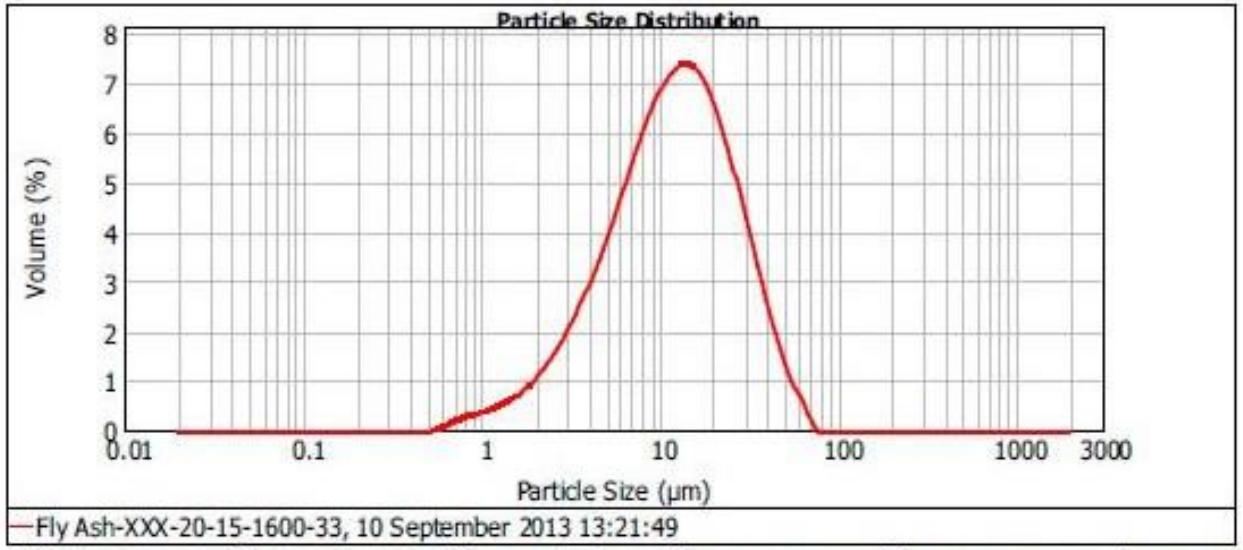
Result Analysis Report

Sample Name: Fly Ash-XXX-20-15-1600-33	**SOP Name:** Malvern Insitic Calibration (Fly ash)	**Measured:** 10 September 2013 13:21:49	
Sample Source & type:	**Measured by:** Lab1	**Analysed:** 10 September 2013 13:21:50	
Sample bulk lot ref: 1	**Result Source:** Measurement		
Particle Name: Fly Ash Malvern Trial	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 1.680	**Absorption:** 0.01	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 13.39 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.481 %	**Result Emulation:** Off
Concentration: 0.0127 %Vol	**Span :** 2.316	**Uniformity:** 0.721	**Result units:** Volume
Specific Surface Area: 0.825 m²/g	**Surface Weighted Mean D[3,2]:** 7.273 um	**Vol. Weighted Mean D[4,3]:** 15.110 um	

Malvern Mastersizer report



d(0.1): 3.512 um d(0.5): 11.935 um d(0.9): 31.154 um

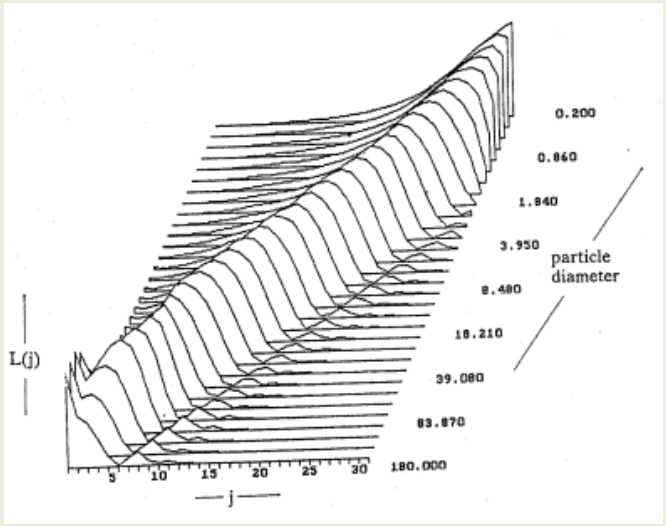


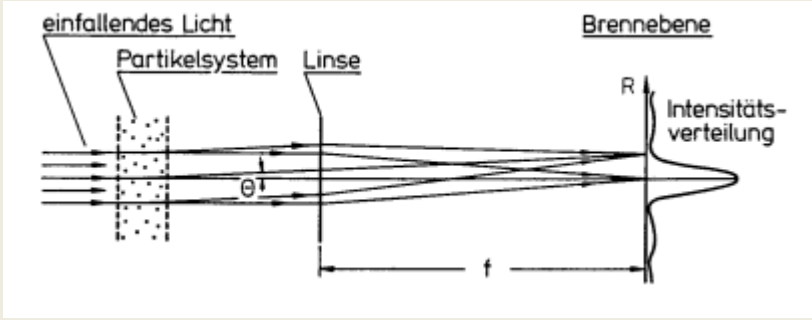
Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %
0.010	0.00	0.105	0.00	1.096	1.10	11.482	48.17	125.000	100.00	1258.925	100.00
0.011	0.00	0.120	0.00	1.259	1.52	13.183	54.77	138.038	100.00	1445.440	100.00
0.013	0.00	0.138	0.00	1.445	2.03	15.136	61.44	158.489	100.00	1659.587	100.00
0.015	0.00	0.158	0.00	1.660	2.66	17.378	67.97	181.970	100.00	1905.461	100.00
0.017	0.00	0.182	0.00	1.905	3.46	19.953	74.17	208.930	100.00	2187.762	100.00
0.020	0.00	0.209	0.00	2.188	4.45	22.909	79.86	250.000	100.00	2511.886	100.00
0.023	0.00	0.240	0.00	2.512	5.68	26.303	84.88	275.423	100.00	2884.032	100.00
0.026	0.00	0.275	0.00	2.884	7.21	32.000	90.70	316.228	100.00	3311.311	100.00
0.030	0.00	0.316	0.00	3.311	9.08	34.674	92.61	363.078	100.00	3801.894	100.00
0.035	0.00	0.363	0.00	3.802	11.36	39.811	95.30	416.869	100.00	4365.158	100.00
0.040	0.00	0.417	0.00	4.365	14.08	45.000	97.07	478.630	100.00	5011.872	100.00
0.046	0.00	0.479	0.00	5.012	17.31	52.481	98.60	500.000	100.00	5754.399	100.00
0.052	0.00	0.550	0.00	5.754	21.08	63.000	99.65	630.957	100.00	6606.934	100.00
0.060	0.00	0.631	0.07	6.607	25.43	69.183	99.96	724.436	100.00	7585.776	100.00
0.069	0.00	0.724	0.22	7.586	30.36	79.433	100.00	831.764	100.00	8709.636	100.00
0.079	0.00	0.832	0.46	8.710	35.84	90.000	100.00	954.993	100.00	10000.000	100.00
0.091	0.00	0.955	0.75	10.000	41.81	104.713	100.00	1096.478	100.00		

Laser diffraction

In case of monodisperse systems a from the specific diffraction result (picture) the particle size can be determined.

In case of polidisperse systems the diffraction picture has to be analyzed with a special evaluating system. From the intensity dispersion the particle size dispersion can be calculated. d= 0.2 , 1500 µm. Concentration of suspension <1%





Laser diffraction

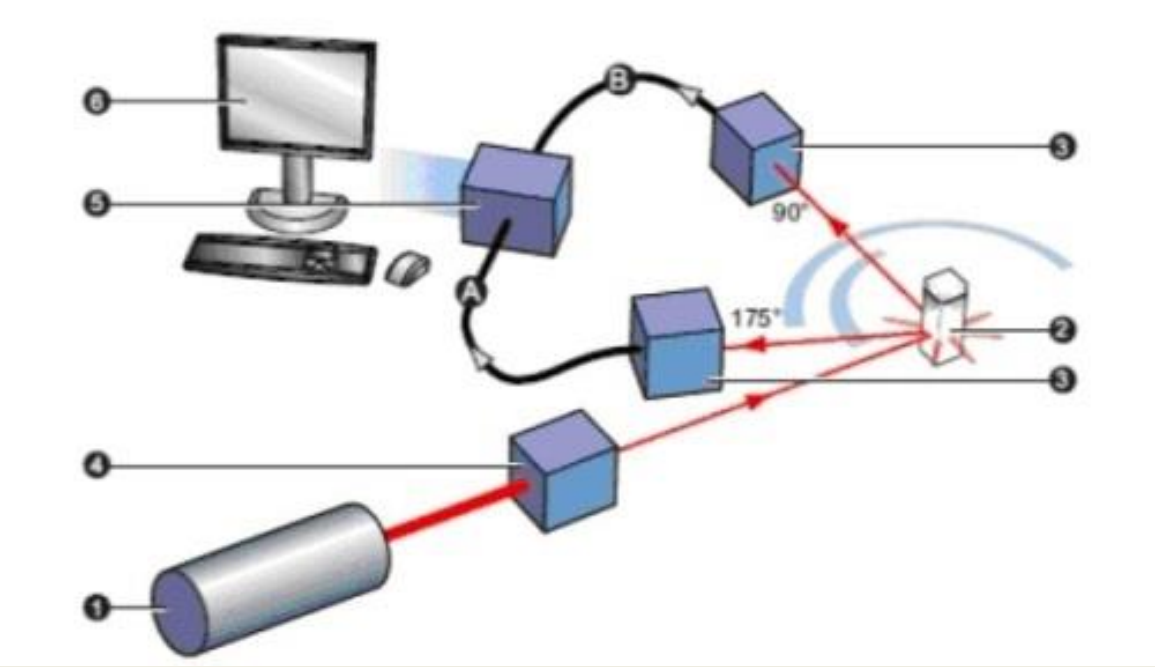
Advantages

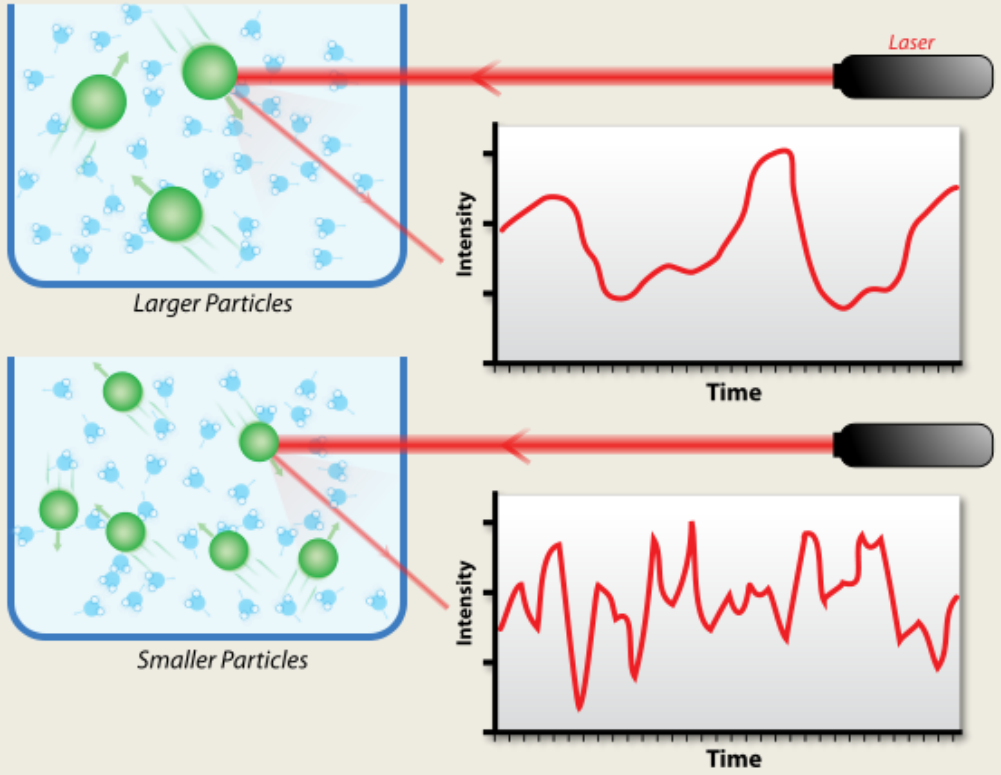
- Fast analysis
- Accurate measurement
- Well automated system
- Small amount of sample needed
- The result, the dispersion represents well the system
- Can be evaluated statistically
- Accepted

Disadvantages

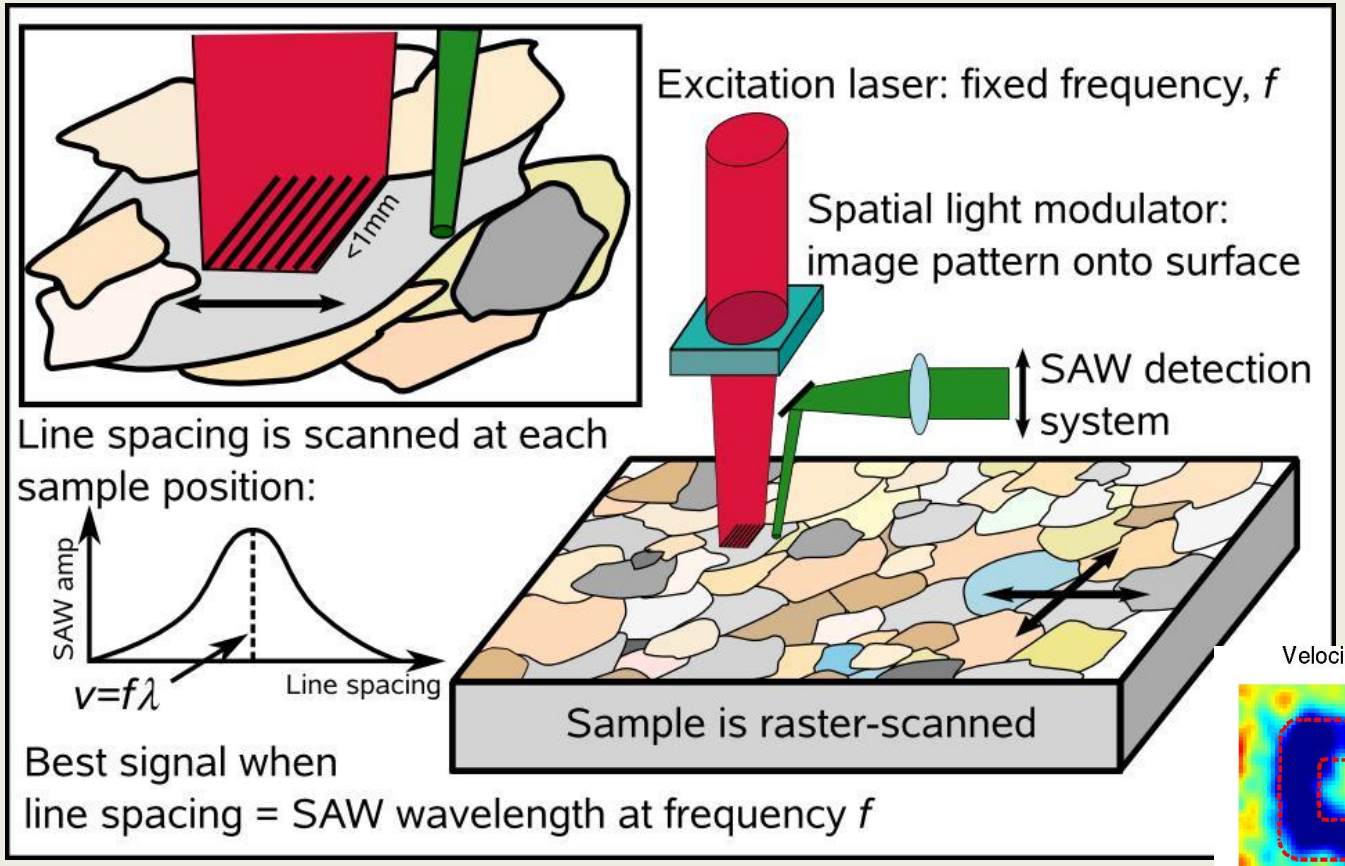
- Cannot distinguish the aggregated particles
- Indirect method
- Measures in liquid phase
- The method of counting affects the final result

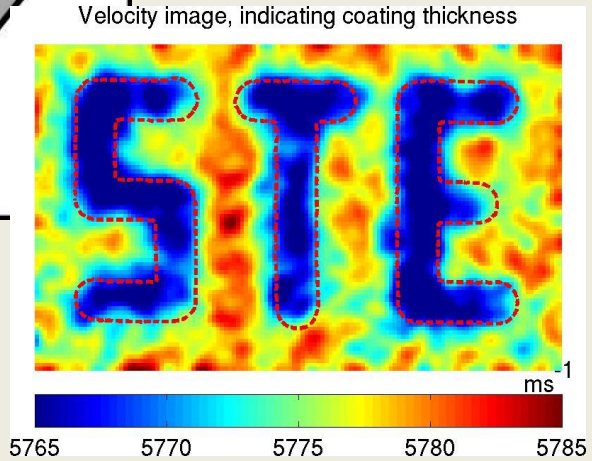
Dynamic light scattering





Acoustic spectroscopy





Thank you for your attention!