PURDUE UNIVERSITY

Weldon School of Biomedical Engineering

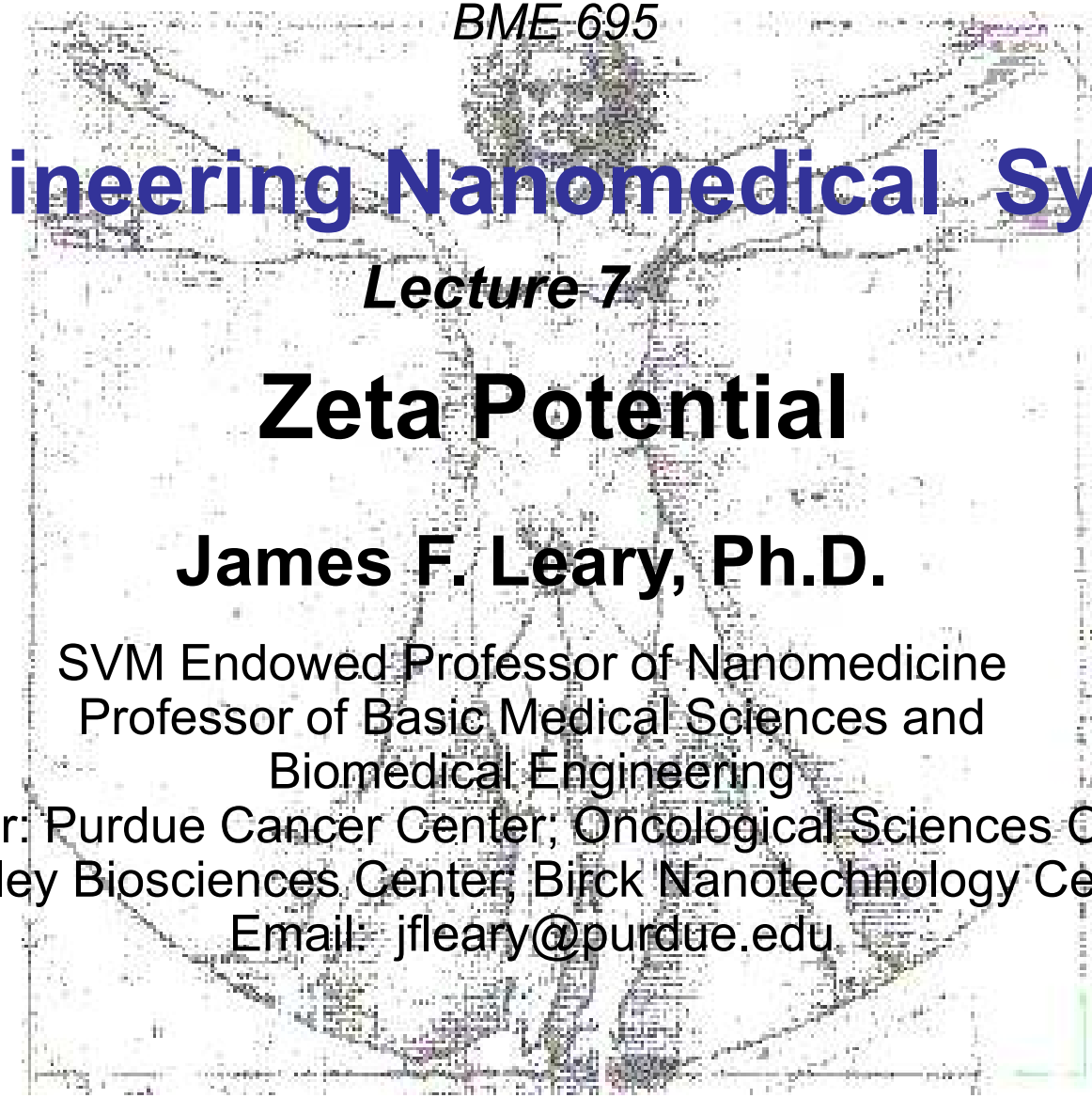
The Convergence of Differences, The Future of Excellence

*BME 695*

# Engineering Nanomedical Systems

***Lecture 7***

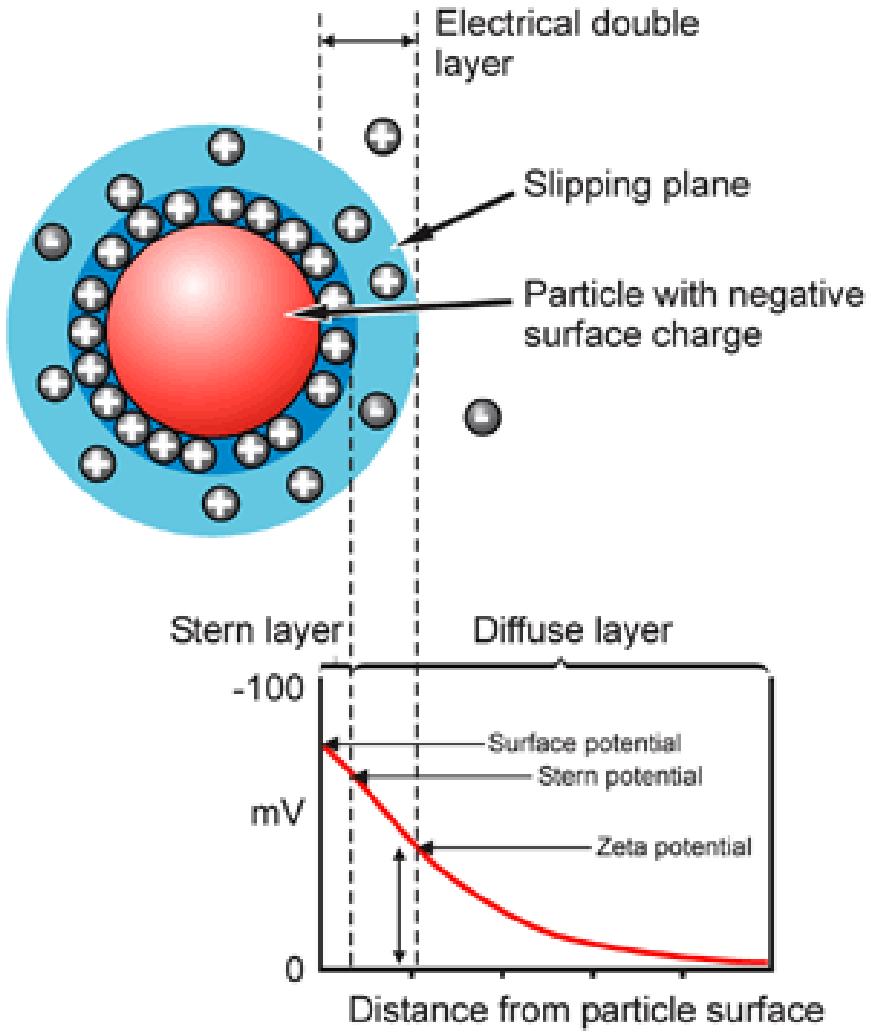
# Zeta Potential




**James F. Leary, Ph.D.**

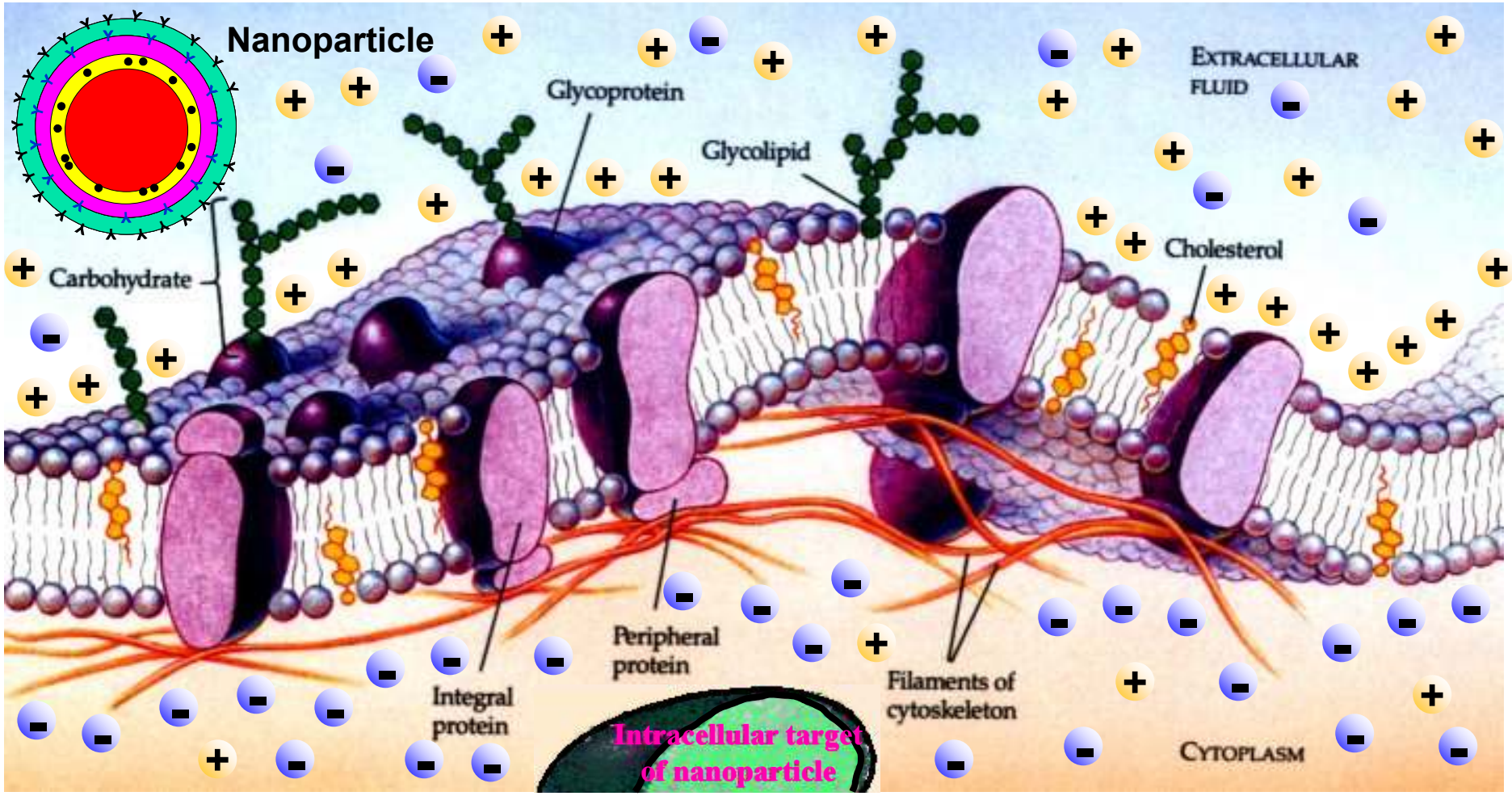
SVM Endowed Professor of Nanomedicine
Professor of Basic Medical Sciences and
Biomedical Engineering
Member: Purdue Cancer Center; Oncological Sciences Center;
Bindley Biosciences Center; Birck Nanotechnology Center
Email: jfleary@purdue.edu

# Zeta Potential – Electrostatics in Fluids




Zeta potential describes the electrostatic interactions of cells and particles in a fluid environment. The liquid layer surrounding the particle exists as two parts; an inner region (Stern layer) where the ions are strongly bound and an outer (diffuse) region where they are less firmly associated. Within the diffuse layer there is a notional boundary inside which the ions and particles form a stable entity. When a particle moves (e.g. due to gravity), ions within the boundary move it. Those ions beyond the boundary stay with the bulk dispersant. The potential at this boundary (surface of hydrodynamic shear) is the zeta potential.

# Interaction of Nanoparticles with the Cell Surface Based on Zeta Potential and Size




Adapted from Campbell, Neil A., and Jane B. Reece. Biology. 6th ed. San Francisco: Benjamin Cummings, 2002.

# Introduction – the importance of the zeta potential

A. nanoparticle-nanoparticle interactions

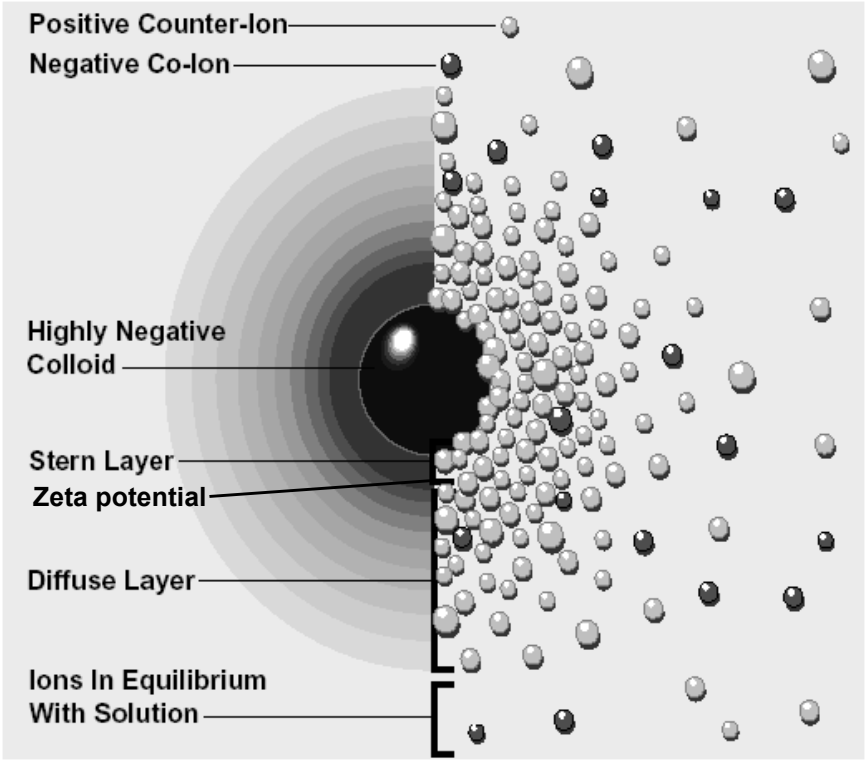
B. nanoparticle-cell interactions

C. part of the initial nanomedical system-cell targeting process

D. low zeta potential leads to low serum protein binding and potentially longer circulation

# Zeta Potential Properties of Nanoparticles

- The zeta potential is the electric potential at the shear plane, which is the boundary between the stern layer and the diffuse layer.
- This electrical property determines if a colloidal solution will agglomerate or remain a stable suspension.
- Zeta potential must be determined and controlled at each step in the construction of nanoparticles.
- Zeta potential of complete nanoparticle is important for controlling *in vivo* interactions.




Charge density and ion concentration surrounding a highly negatively charged nanoparticle.

Figure adapted from Zeta-Meter, Inc. Zeta-Potential: A Complete Course in 5 Minutes. Staunton: Zeta-Meter, Inc., 1997.

# Characteristics of the zeta potential

- Zeta potential is the electrical potential at the hydrodynamic plane of shear.
- Zeta potential depends not only on the particle's surface properties but also the nature of the solution (e.g. Ionic strength, pH, etc.).
- Zeta potential may be quite different from the particle's surface potential.
- Small changes in ionic strength and pH can lead to large effects in zeta potential.
- Zeta potential can be used to predict the monodispersity (or agglomeration) of particles.
- High zeta potential (either positive or negative) ( > 30 mV) lead to monodispersity. Low zeta potential (<5 mV) can lead to agglomeration.

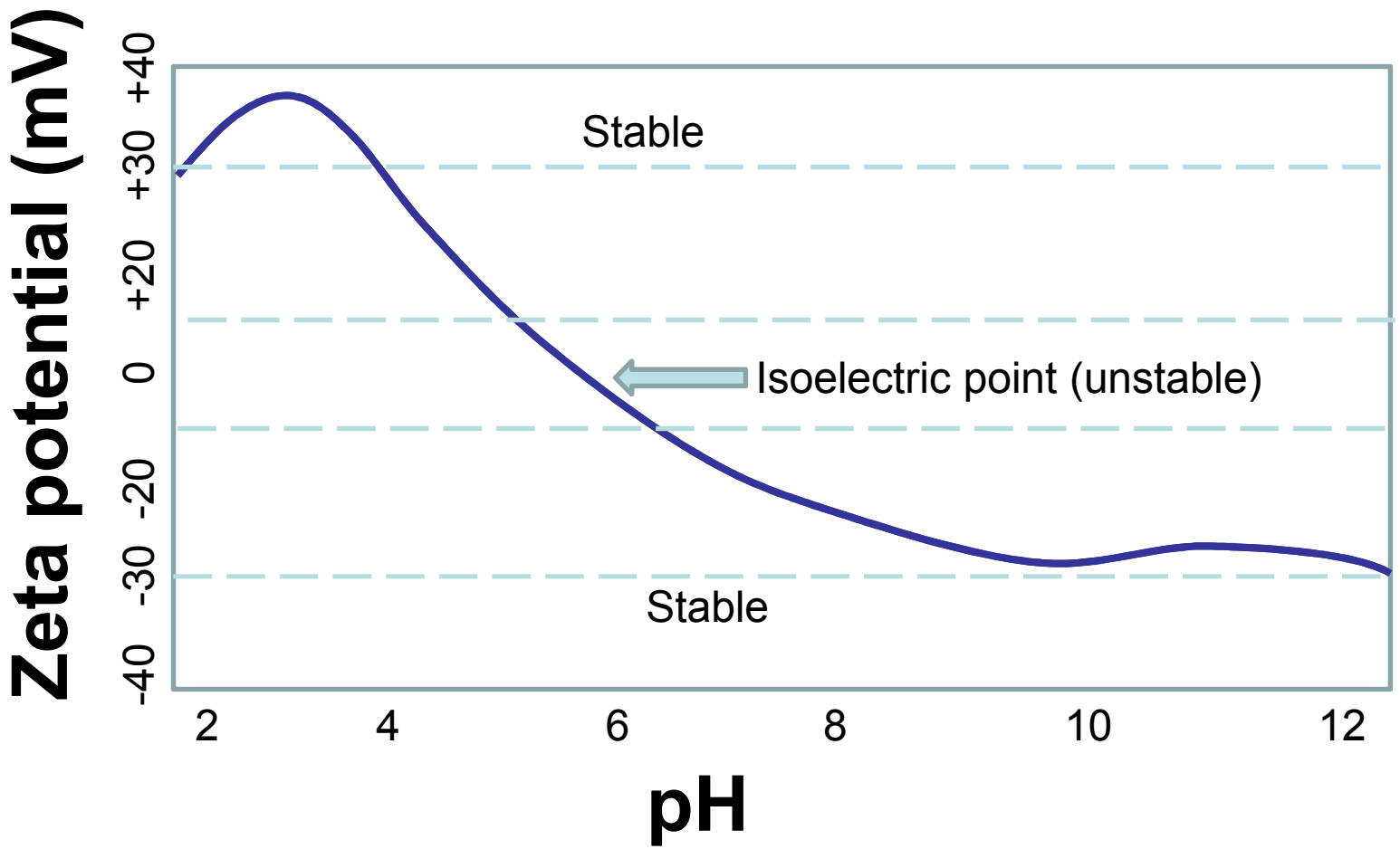
**Most importantly, nanoparticles and cells interact according to the magnitude of each of their zeta potentials, not their surface charges!**

# Some factors affecting the zeta potential that are important in nanomedicine

A. pH
B. ionic strength

The local pH and ionic strength can vary greatly in the different parts of the human body. These factors also change within different regions INSIDE human cells. So it is a challenge to design nanoparticles that have the optimal zeta potentials by the time they reach their final destinations.

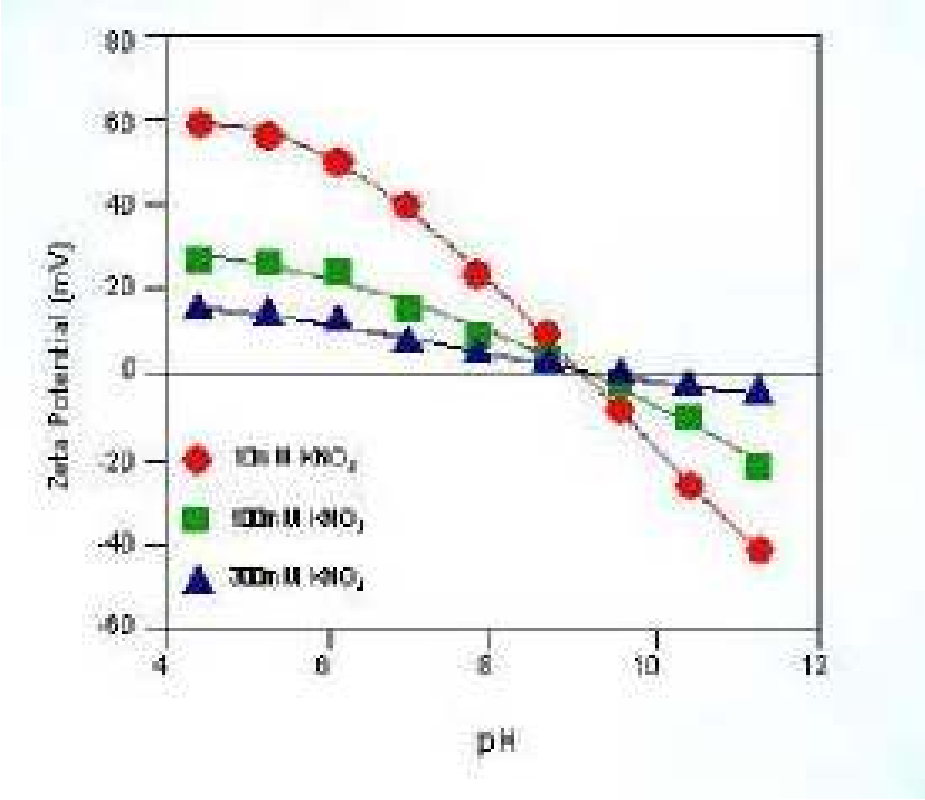
# Zeta Potential and pH




Typical plot of zeta potential versus pH showing the position of the isoelectric point and the pH values where the dispersion would be expected to be stable

# Effect of solution ionic strength or conductivity on zeta potential

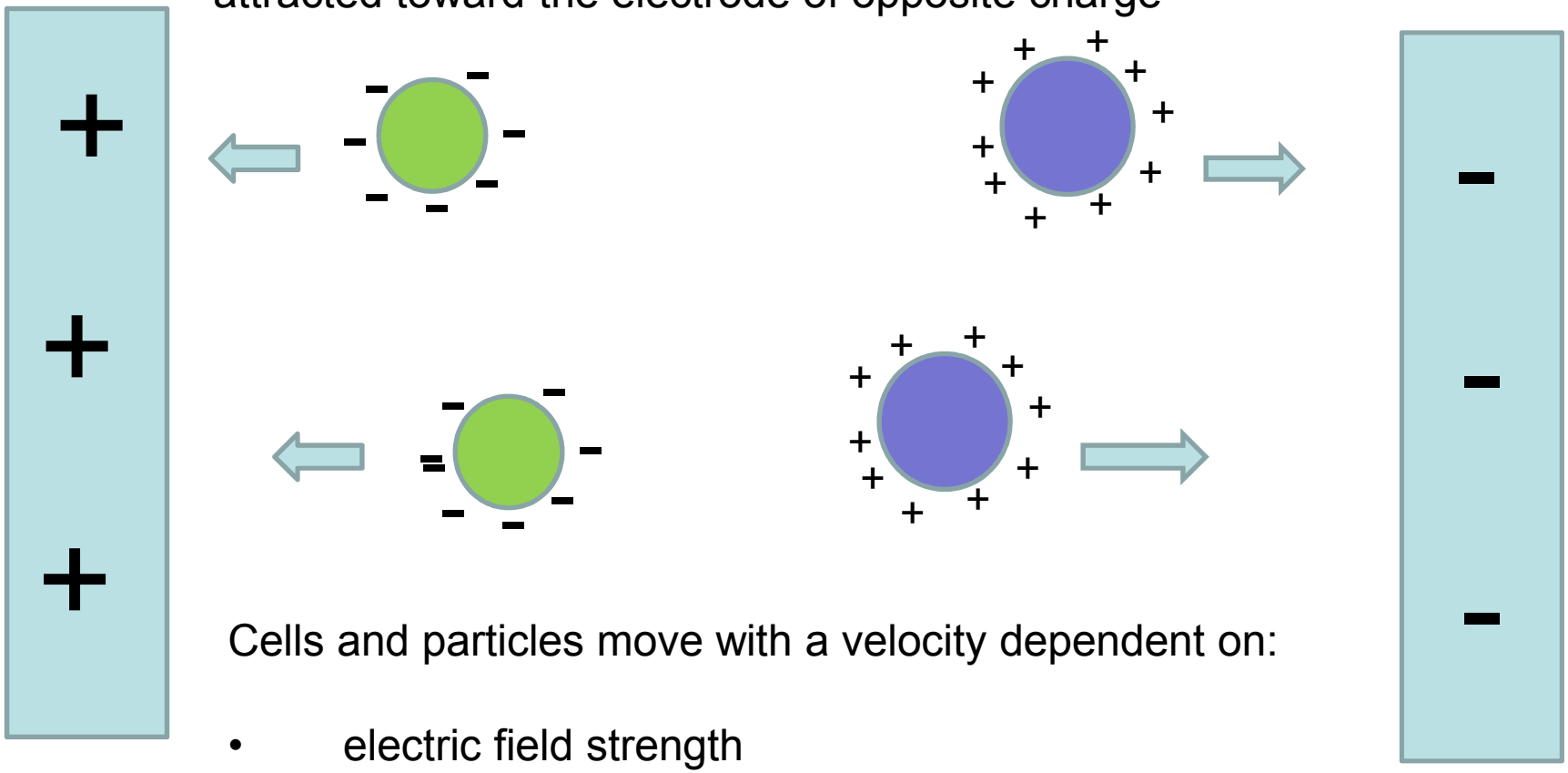
- Non-specific ion adsorption may, or may not, have an effect on the isoelectric point.
- Specific ion adsorption usually leads to a change in the isoelectric point




Source: http://www.malvern.com

# Measuring zeta potential by electrophoresis

If an electric field is applied across a sample containing charged cells and/or particles, those cells and particles are attracted toward the electrode of opposite charge



Cells and particles move with a velocity dependent on:

- electric field strength
- dielectric constant of the medium
- viscosity of the medium
- zeta potential

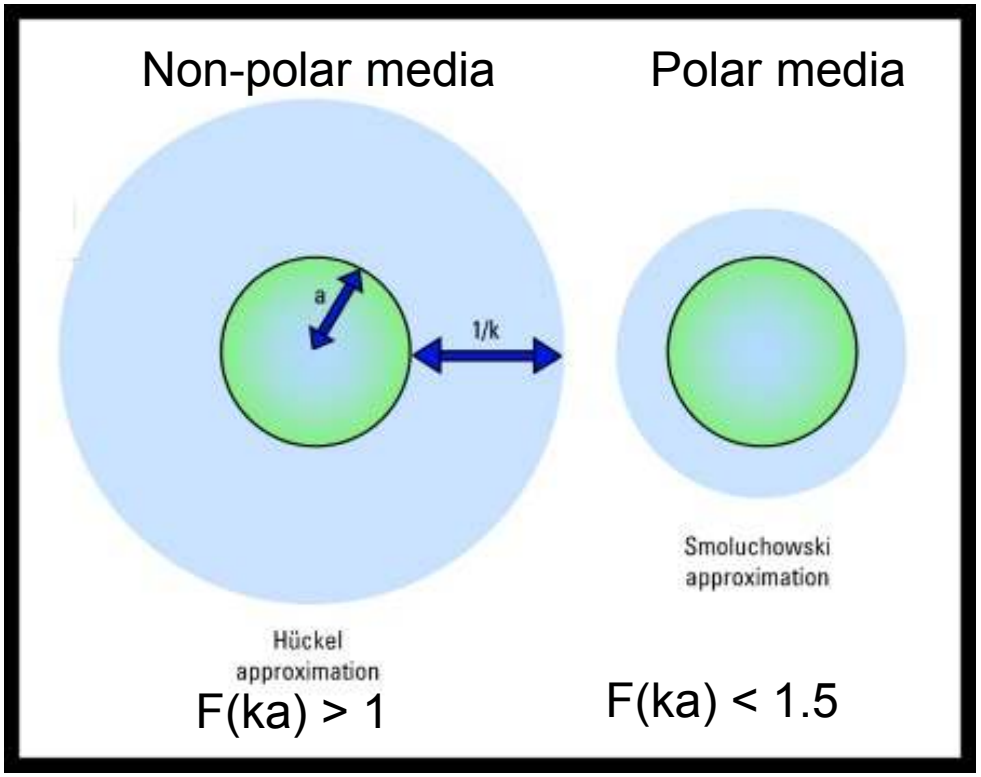
# By measuring the velocity of a nanoparticle in an electric field its zeta potential can be calculated

The velocity of a particle in a unit electric field is referred to as its electrophoretic mobility. Zeta potential is related to the electrophoretic mobility by the Henry equation:

$$U_E = \frac{2 \varepsilon z f(\kappa a)}{3\eta}$$

where UE = electrophoretic mobility, z= zeta potential, ε = dielectric constant, η = viscosity and f(κa) = Henry's function

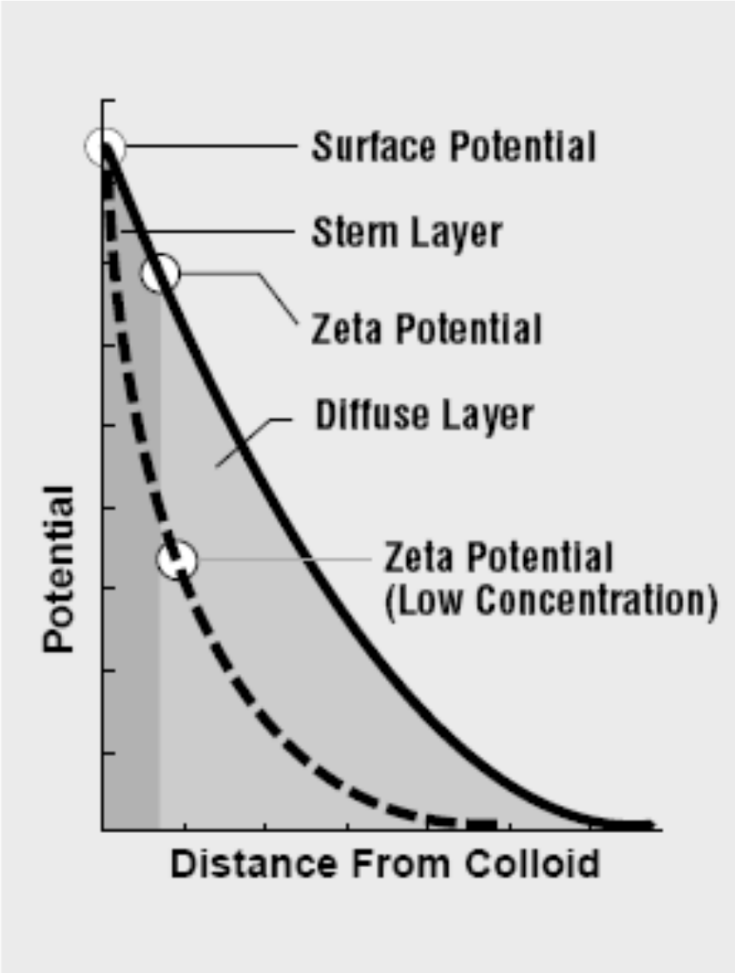
# Assumptions about slip layer diameter when calculating Henry's function for the zeta potential



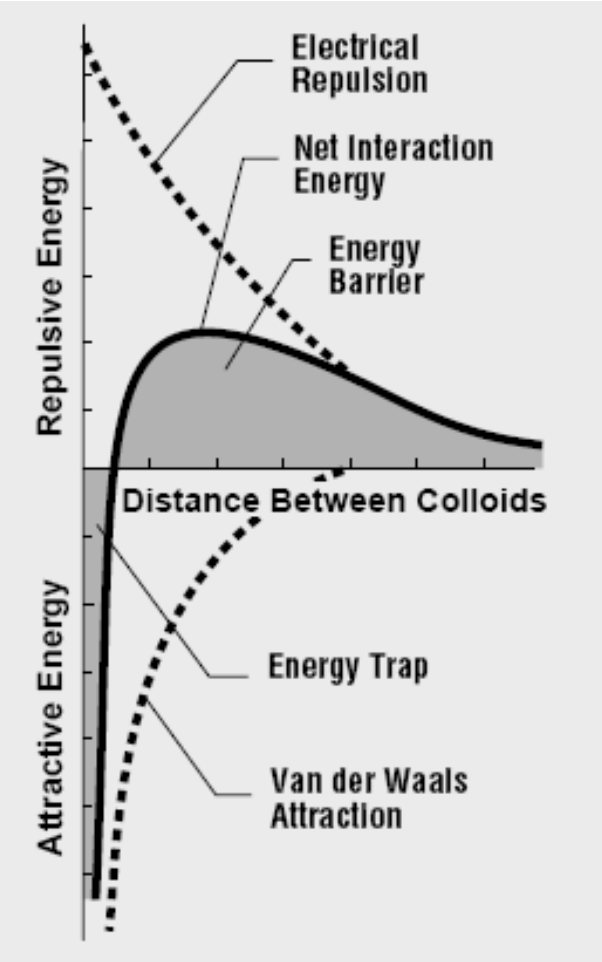

Schematic illustrating Huckel and Smoluchowski's approximations used for the conversion of electrophoretic mobility into zeta potential

*Adapted from http://www.silver-colloids.com/Tutorials/Intro/pcs21.html*

# Zeta potential represents the potential barrier to cell-nanoparticle interactions




**Zeta Potential vs. Surface Potential:** The relationship between zeta potential and surface potential depends on the level of ions in the solution.




**Interaction:** The net interaction curve is formed by subtracting the attraction curve from the repulsion curve.

*http://www.malvern.com*

# What is the best zeta potential to have for nanomedical systems?

That is not a simple question, but in general it is good to have a zeta potential of approximately -5 to -15 mV. Since most biological cells have zeta potentials in this range you want your nanomedical systems to also be slightly negative zeta potentials so that they do not stick non-specifically to cells but interact through a receptor-mediated interaction that allows binding of nanoparticles only when there is a receptor-ligand bond strong enough to overcome a modest electrical repulsion.*

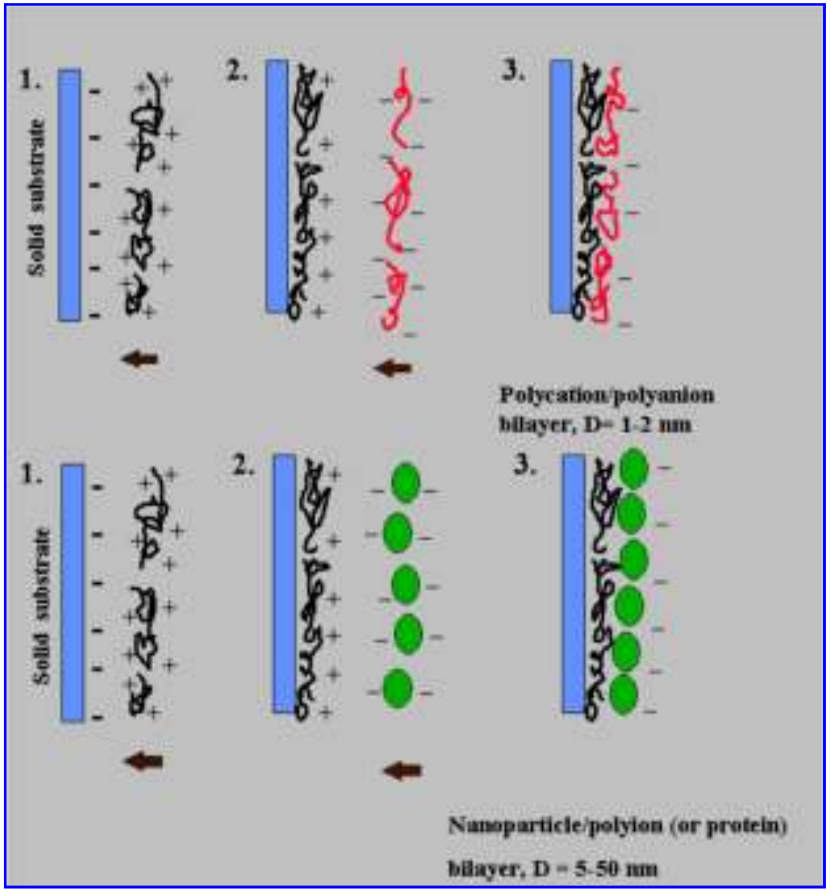
* If all you want is to have nanoparticles stick to cells in tissue culture for transfection, the zeta potential can be positive. Just pay attention to the zeta potential of the tissue culture surfaces!

# Some zeta potential experiences

Prow, T.W., Rose, W.A., Wang, N., Reece, L.M., Lvov, Y., Leary, J.F. "Biosensor-Controlled Gene Therapy/Drug Delivery with Nanoparticles for Nanomedicine" Proc. of SPIE 5692: 199 – 208, 2005.

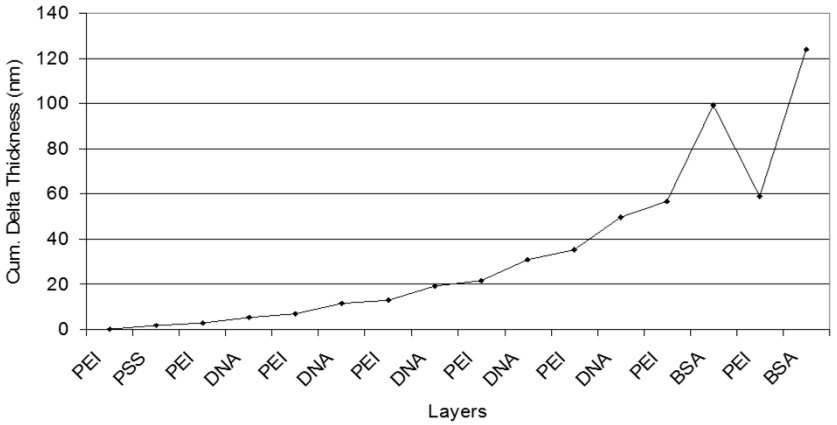
# Size and Zeta Potential Changes During LBL Construction of Nanoparticles

## Layer-by-layer (LBL) assembly of NP with charged polymers

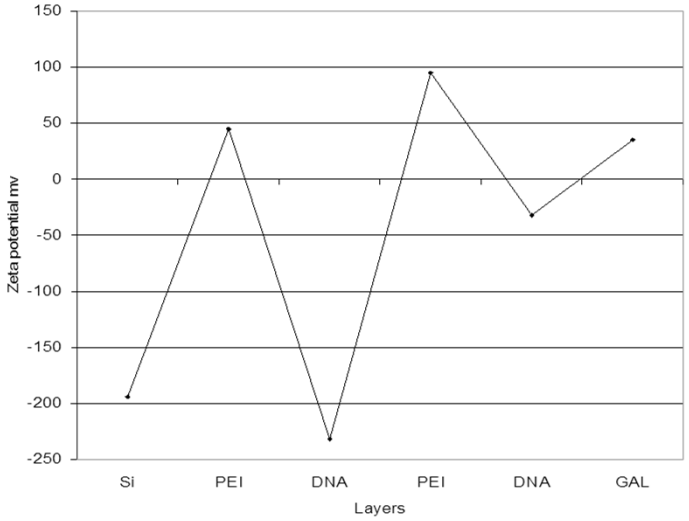



*Source: Prow et al. 2005.*

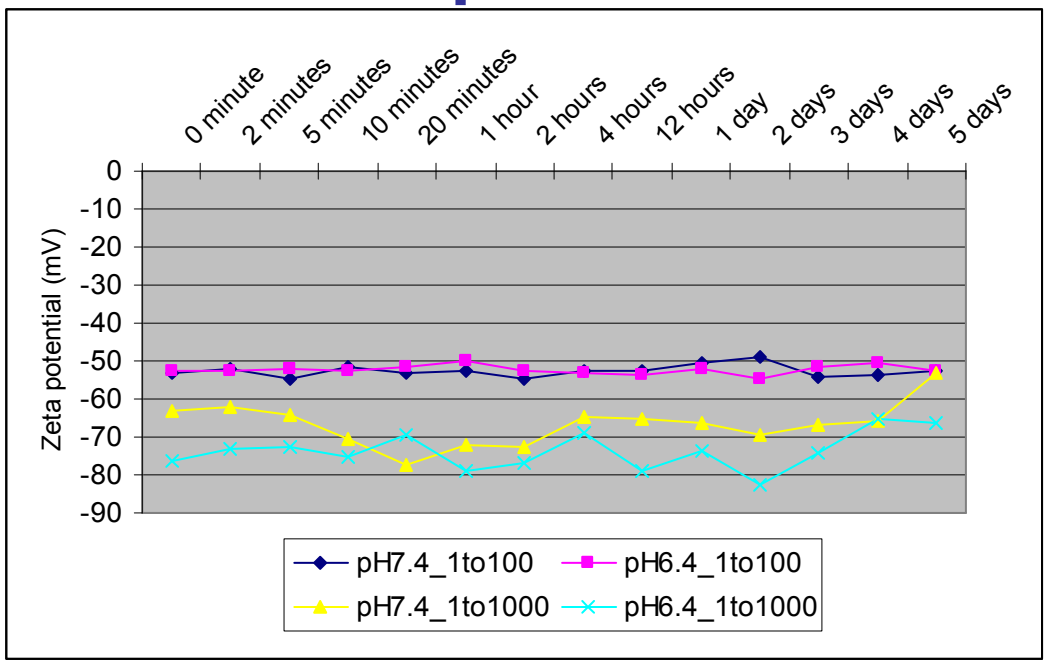
## Increase in NP size with layers

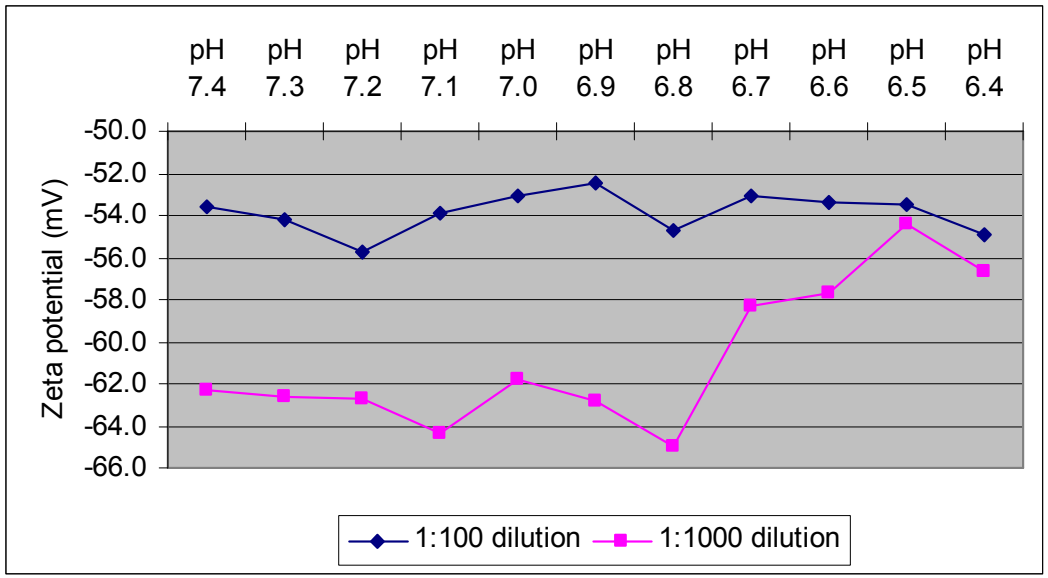



## Change in NP zeta potential with additions of layers



# Effects of pH and dilution on NP zeta potential

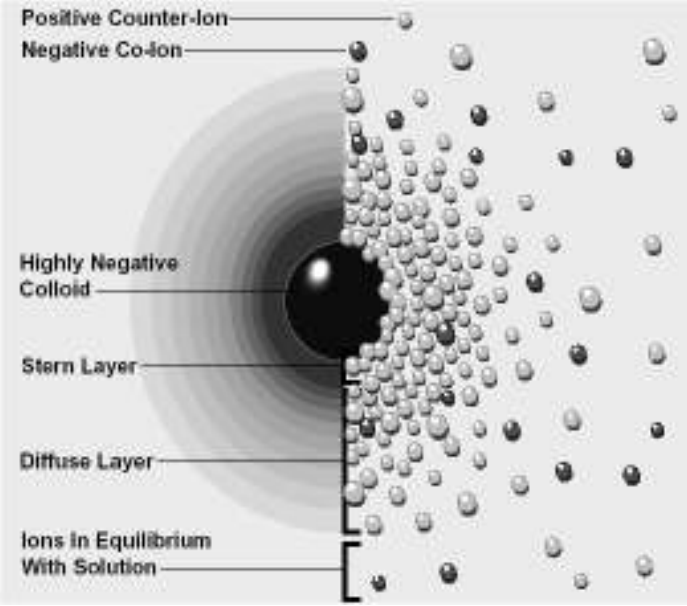


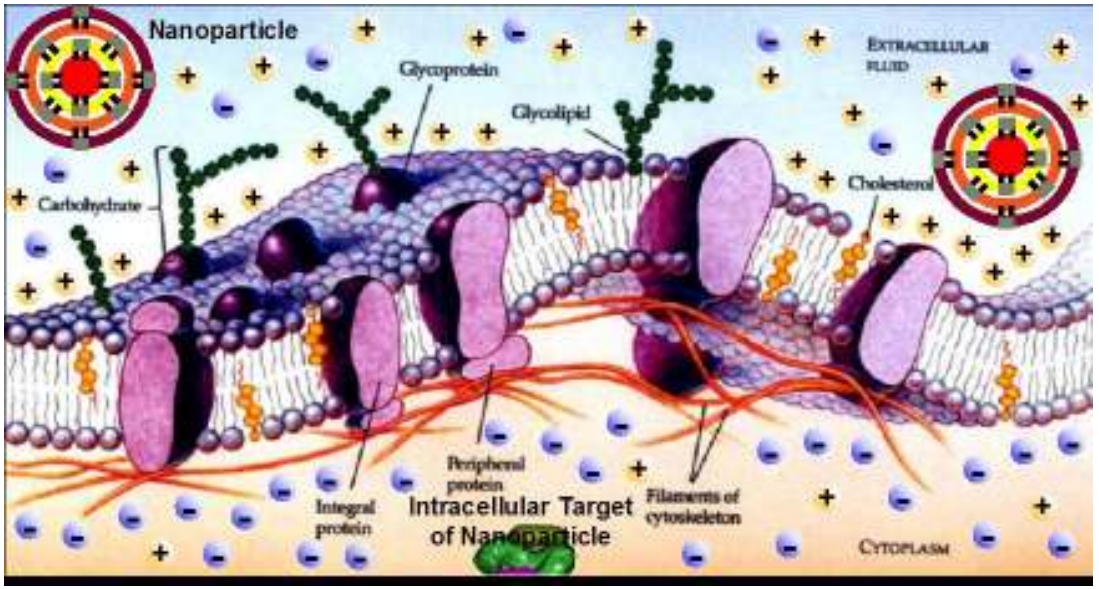




Zeta potential measurements of 40-50 nm silica particles tested over a 5 day time period at two different ph values and two different dilutions with distilled/ deionized water.

*Source: Prow et al. 2005.*

# Summary: Zeta Potential Properties of Nanoparticles




- The zeta potential is the electric potential at the shear plane, which is the boundary between the stern layer and the diffuse layer.
- This electrical property determines if a colloidal solution will agglomerate or remain a stable suspension.
- Zeta potential must be determined and controlled at each step in the construction of nanoparticles.
- Zeta potential of complete nanoparticle is important for controlling *in vivo* interactions.

Figure adapted from Zeta-Meter, Inc. Zeta-Potential: A Complete Course in 5 Minutes. Staunton: Zeta-Meter, Inc., 1997.

## V. "Zeta sizing" measuring size on a zeta potential instrument

# "DLS" (Dynamic Light Scattering) is an inexact measurement!

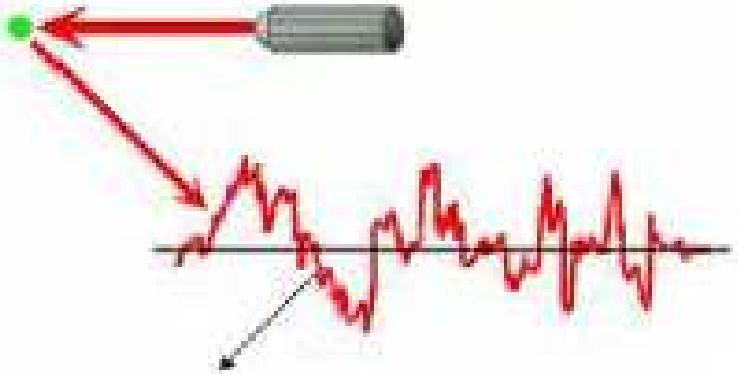
In typical dynamic light scattering (DLS) instrumentation, there is a single detector fixed at a single angle. The measured data in a DLS experiment is the intensity autocorrelation curve. Embodied within the autocorrelation curve is all of the information regarding the size distribution of the ensemble collection of particles in the solution.

Deconvolution of the intensity autocorrelation curve to an intensity distribution is an ill defined problem. As such, there is an inherent degree of uncertainty in DLS derived intensity size distributions. This inherent uncertainty translates into peak broadening or an apparent in the width of the intensity distribution.

For typical laboratory samples, this increase can amount to as much as a 10 – 15%. When Mie theory (or any other volume vs size algorithm) is applied to the DLS intensity distribution, the algorithm cannot distinguish this apparent increase in width from the true width. As such, all of the "size bins" in the intensity distribution are treated as though they are real, i.e. a fraction of the sample that has a slightly different size from that of the mean (see schematic shown in Figure 1).

# Dynamic Light Scattering (DLS)

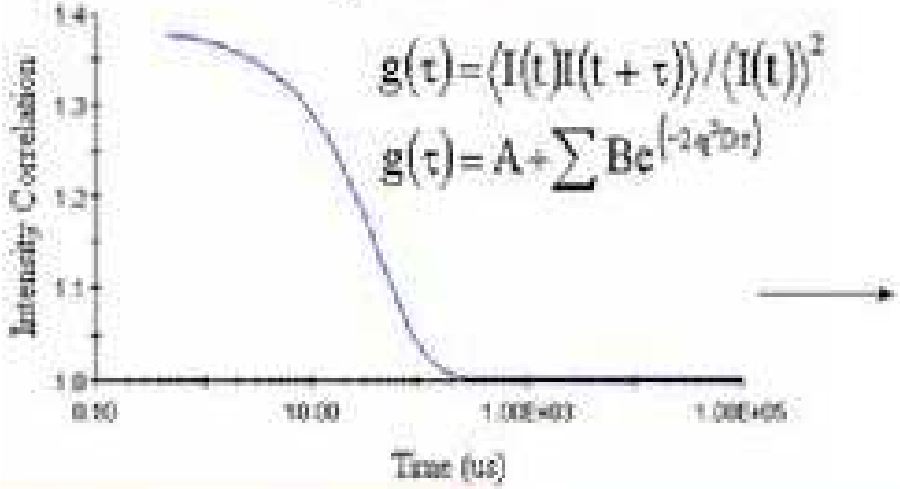
## Intensity correlation provides diffusion coefficient & hydrodynamic size



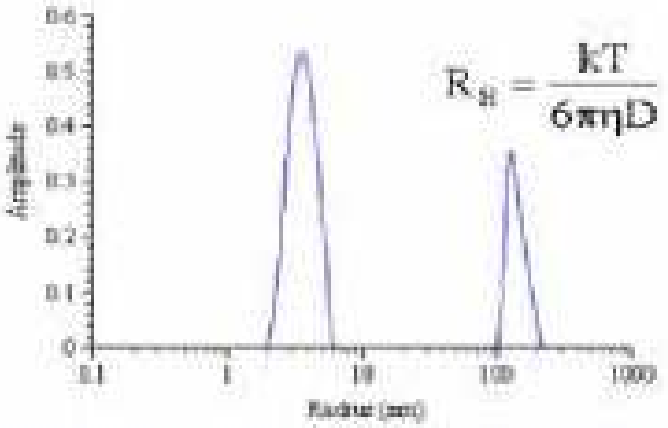
q = Scattering vector
$R_H$ = Radius
T = Temperature
D = Diffusion coefficient
k = Boltzmann constant
η = Solvent viscosity

$$g(\tau) = \langle I(t)I(t+\tau)\rangle / \langle I(t)\rangle^2$$

$$g(\tau) = A + \sum Be^{(-2q^2Dt)}$$




$$R_H = \frac{kT}{6\pi\eta D}$$




http://www.malvern.com

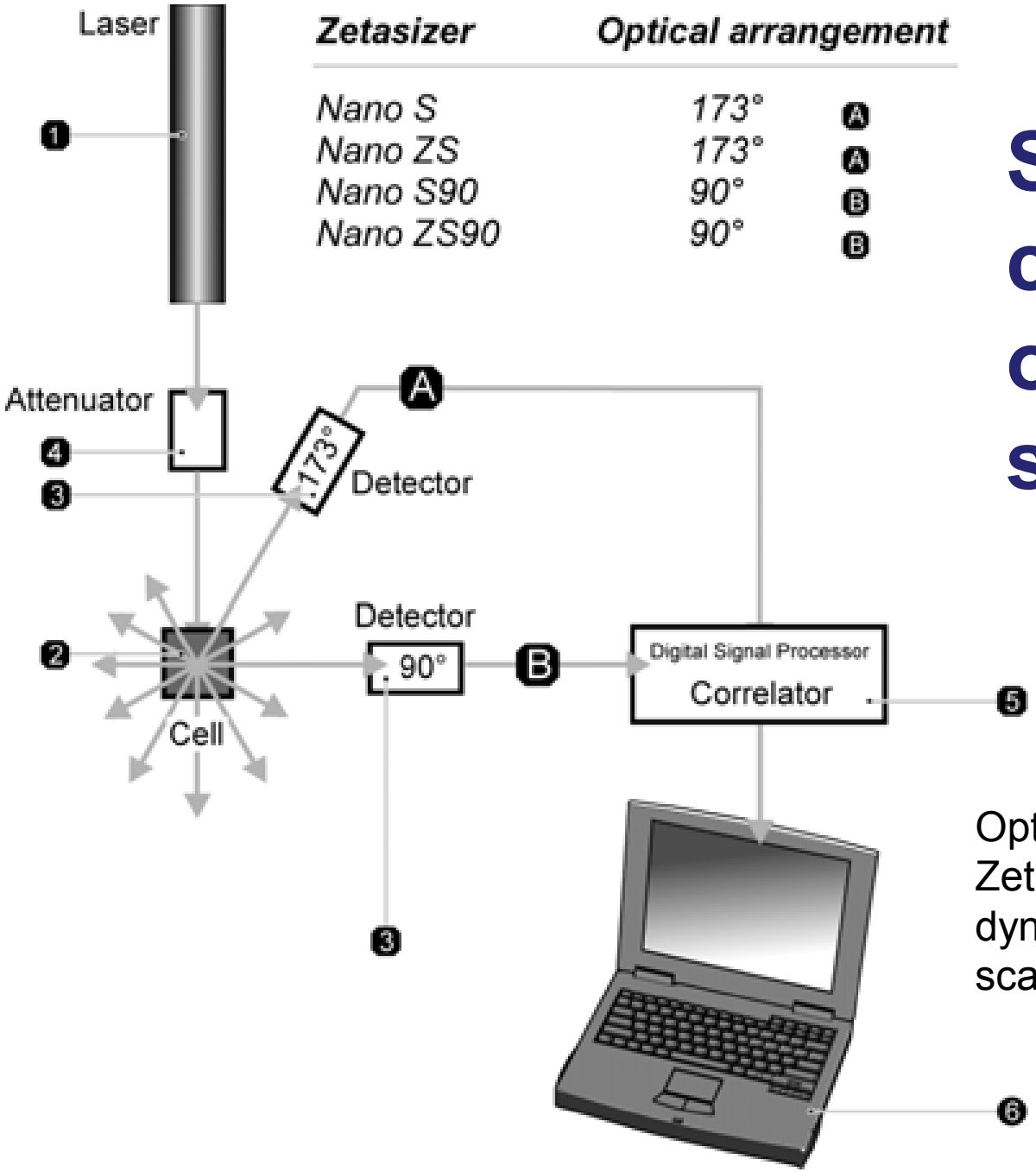
# DLS measurements compute the hydrodynamic diameter from the Stokes-Einstein Equation

## STOKES-EINSTEIN EQUATION

$$d(H) = \frac{kT}{3 \pi \eta D}$$

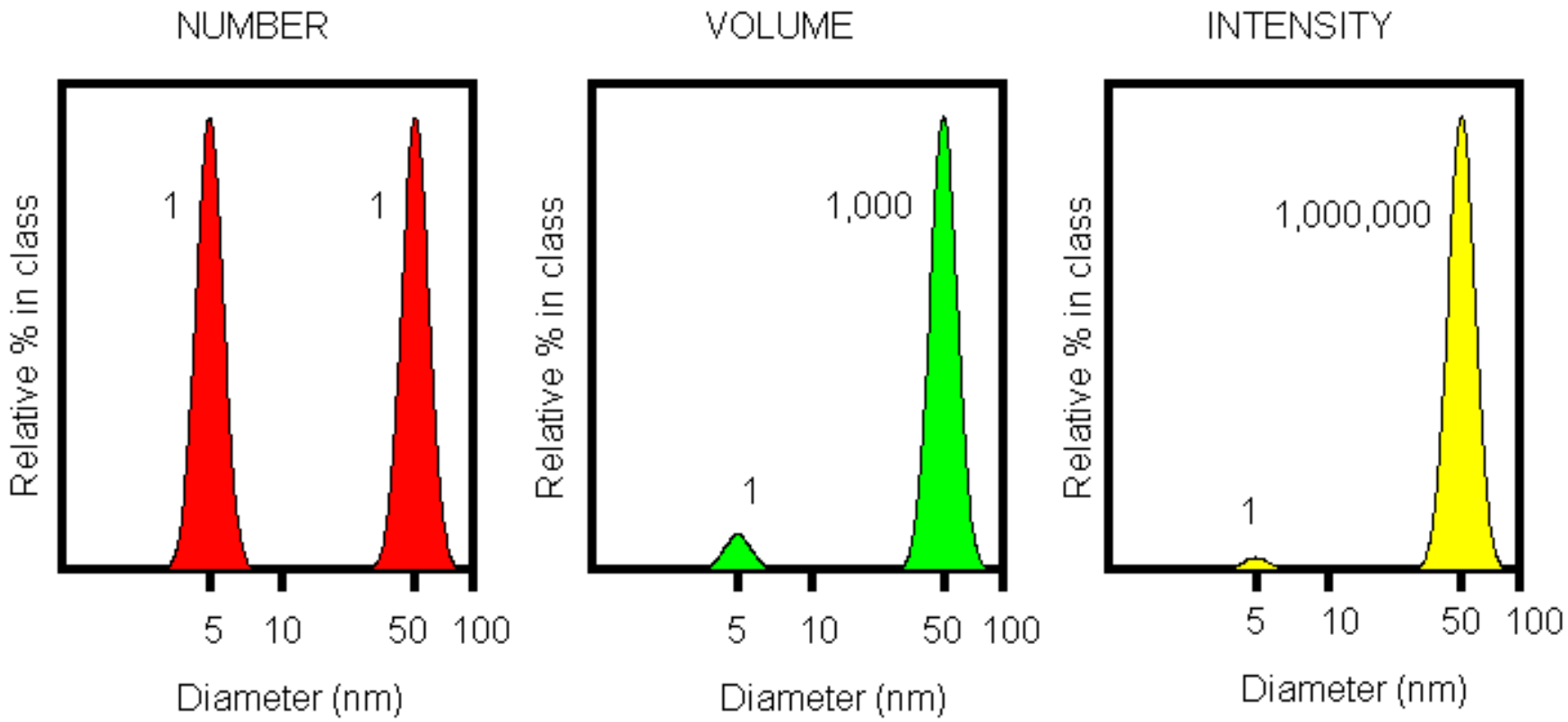
| | | |
|---|---|---|
| d(H) | = | hydrodynamic diameter |
| k | = | Boltzmann's constant |
| T | = | absolute temperature |
| $\eta$ | = | viscosity |
| D | = | diffusion coefficient |

# Some Different configurations of DLS systems




Optical configurations of the Zetasizer Nano series for dynamic light scattering measurements

# Types of data obtained from DLS measurements




Example: Number, volume and intensity distributions of a bimodal mixture of 5 and 50nm lattices present in equal numbers

## Actual NP size distributions are usually better than their Measured DLS distributions!

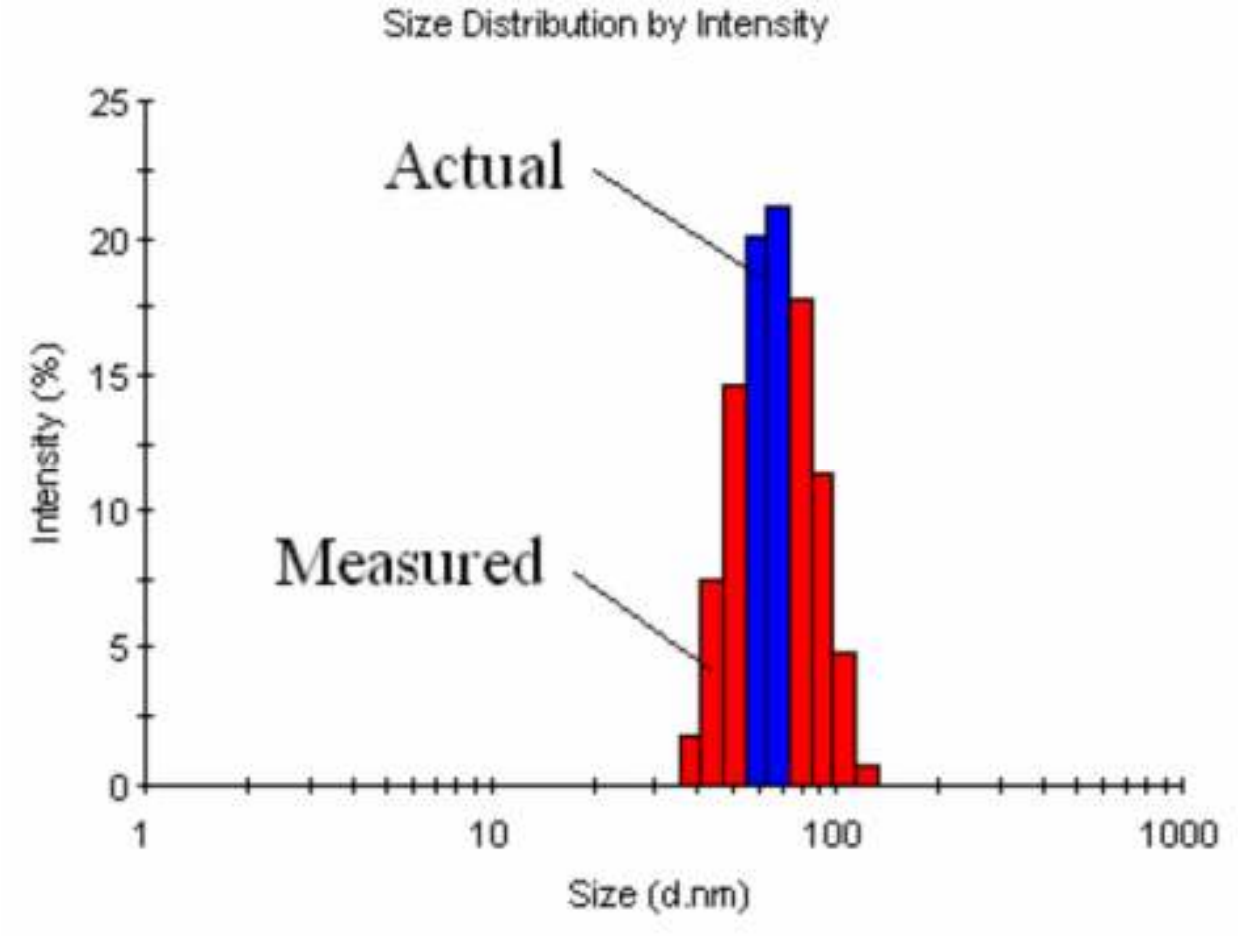



**Figure 1:** Schematic showing a comparison of a DLS measured intensity distribution to the number distribution for a 62 nm latex.

# References


"Zeta potential measurement using laser Doppler electrophoresis (LDE)":
**http://www.malvern.co.uk/LabEng/technology/zeta_potential/zeta_potential_LDE.htm**

"Why Measure Zeta Potential?": http://www.malvern.co.uk/malvern/ondemand.nsf/id/67126

"Zeta Potential: An Introduction in 30 minutes":
http://www.malvern.co.uk/malvern/kbase.nsf/0/26E2BC622DEE0CAC80256FBE00440C95/$file/MRK654-01%20An%20Introduction%20to%20Zeta%20Potential%20v3.pdf

Washington, C. "Zeta Potential in Pharmaceutical Formulation":
http://www.malvern.co.uk/malvern/kbase.nsf/allbyno/KB000022/$file/Zeta_potential_in_pharmaceutical_formulation_MRK036-03-low_res.pdf

Using zeta potential to assess protein adsorption to surfactant coated latex:
http://www.malvern.co.uk/malvern/kbase.nsf/0/AC284EC6076BF4D6802570D2005651E8/$file/MRK707-01%20Protein%20Adsorption%20to%20Surfactant%20Coated%20Latex.pdf

Prow, T.W., Rose, W.A., Wang, N., Reece, L.M., Lvov, Y., Leary, J.F. "Biosensor-Controlled Gene Therapy/Drug Delivery with Nanoparticles for Nanomedicine" Proc. SPIE 5692:199–208, 2005.

Zhang, Y., Yang, M., Portney, N.G., Cui, D., Budak, G., Ozbay, E., Ozkan, M., Ozkan, C.S., Zeta potential: a surface electrical characteristic to probe the interaction of nanoparticles with normal and cancer human breast epithelial cells" Biomed Microdevices 10:321–328, 2008.