Development of Quantitative Structure-Activity Relationship for Prediction of Biological Effects of Nanoparticles Associated with Semiconductor Industries (*Task Number: 425.025)*

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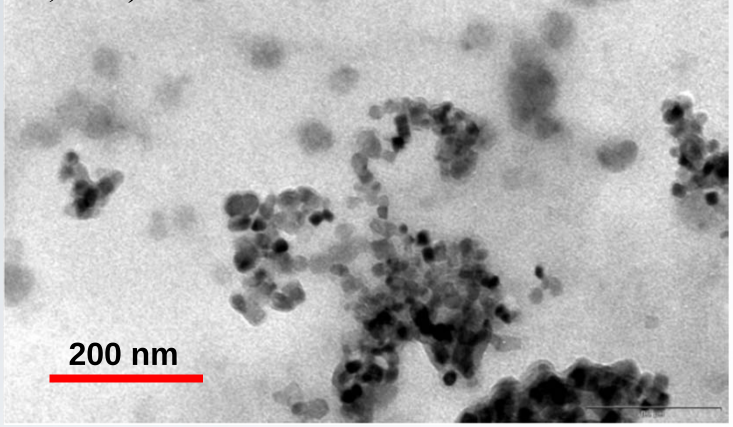
Trevor J. Thornton, ASU

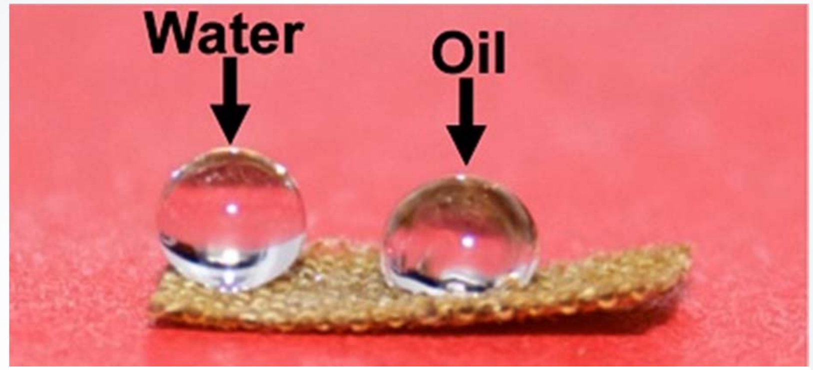
Date: 10 March 2011

Georgia Institute of Technology®
School of Civil and Environmental Engineering

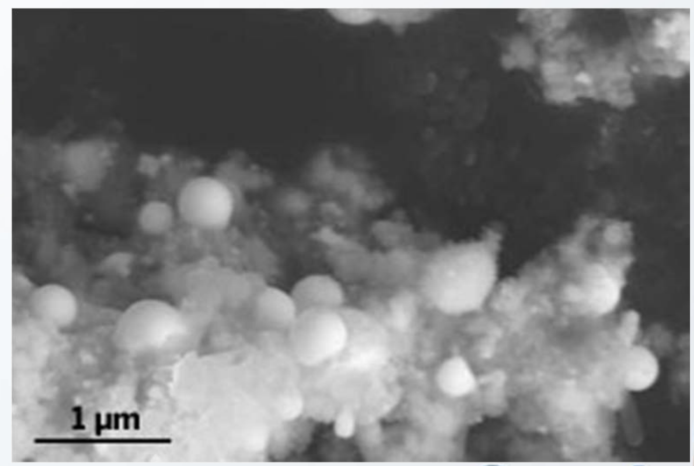
Manufactured nanomaterials: invisible but existing

Transmission-electron-microscope image of 25nm TiO_2nanoparticles in a diluted cream. (Popov et al, 2009)





Simultaneous water and oil repellency (iFyber, LLC.)



Troy Benn, et al. 2008

Nano Health Silver (Fight against virulent stomach flu)

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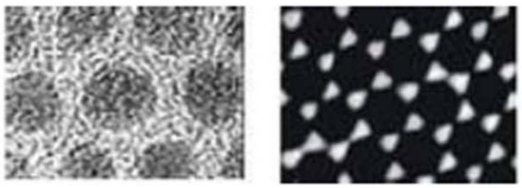
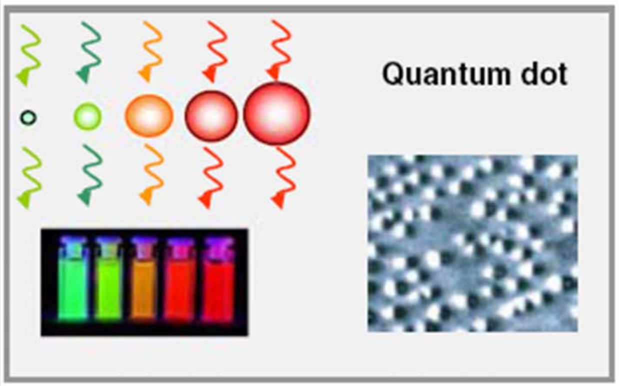
Fast and wide applications (est. 70%) in semiconductor industries

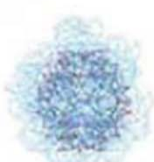
Metal and metal oxide nanoparticles

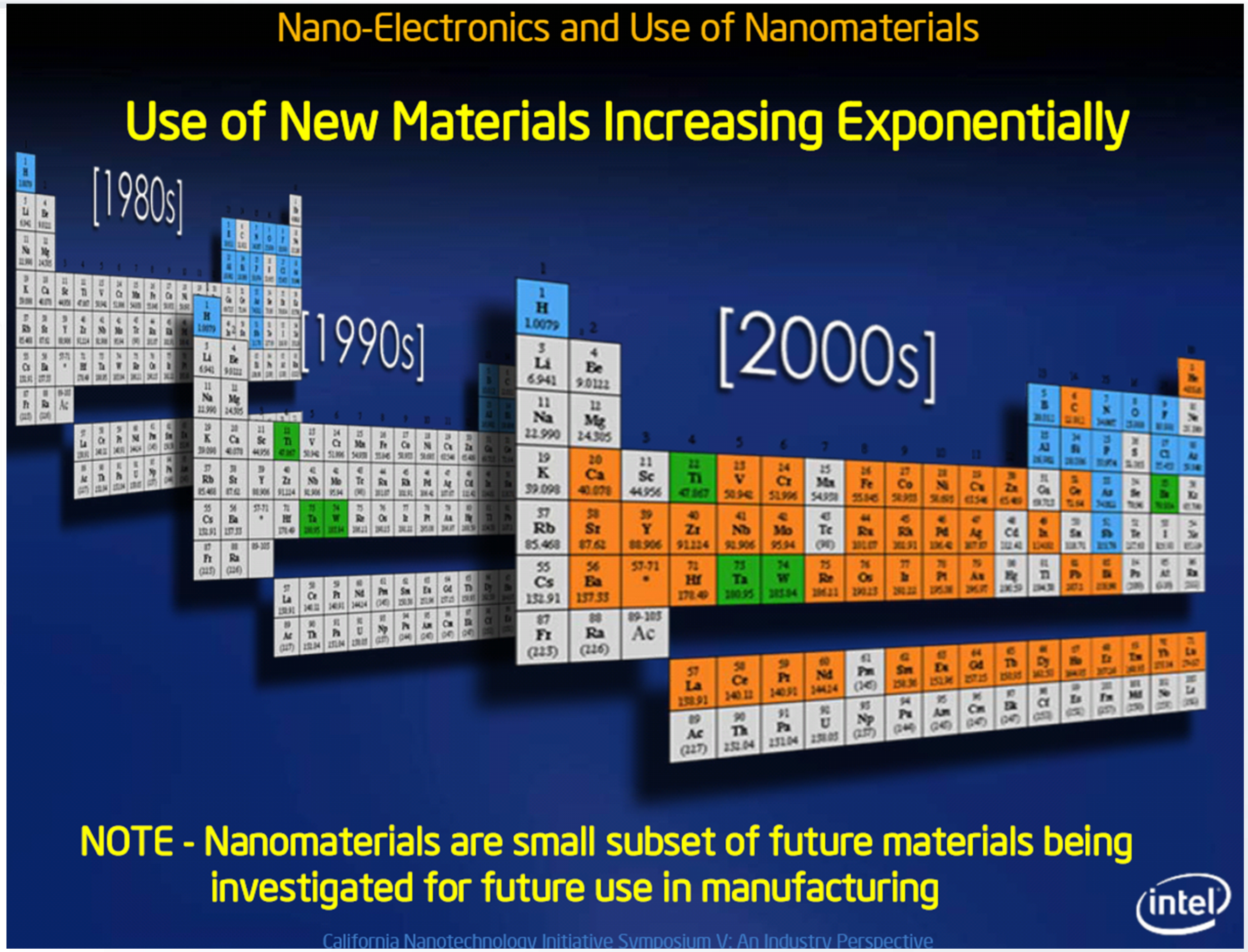




Carbon based nanomaterials

Dendrimers





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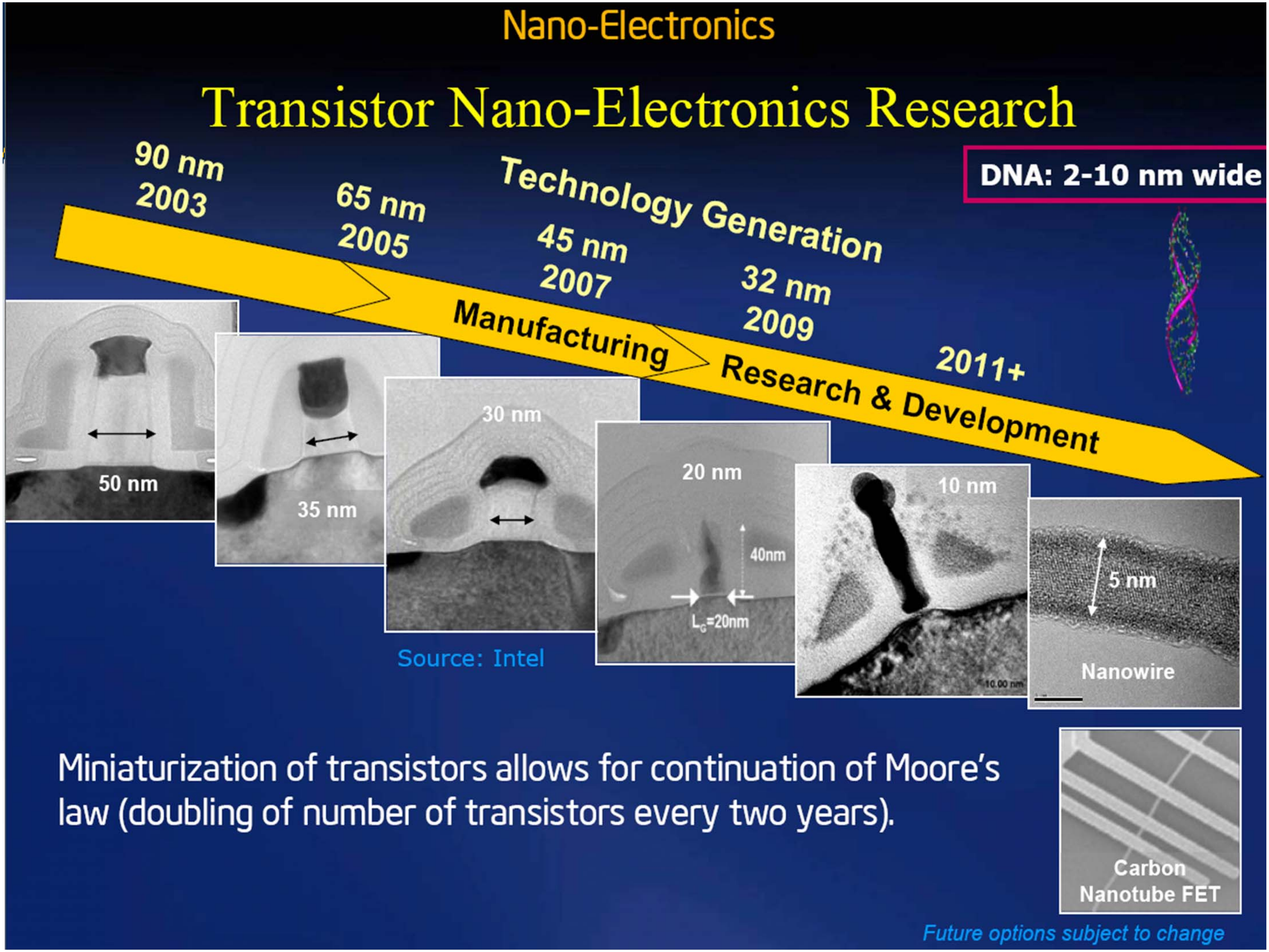
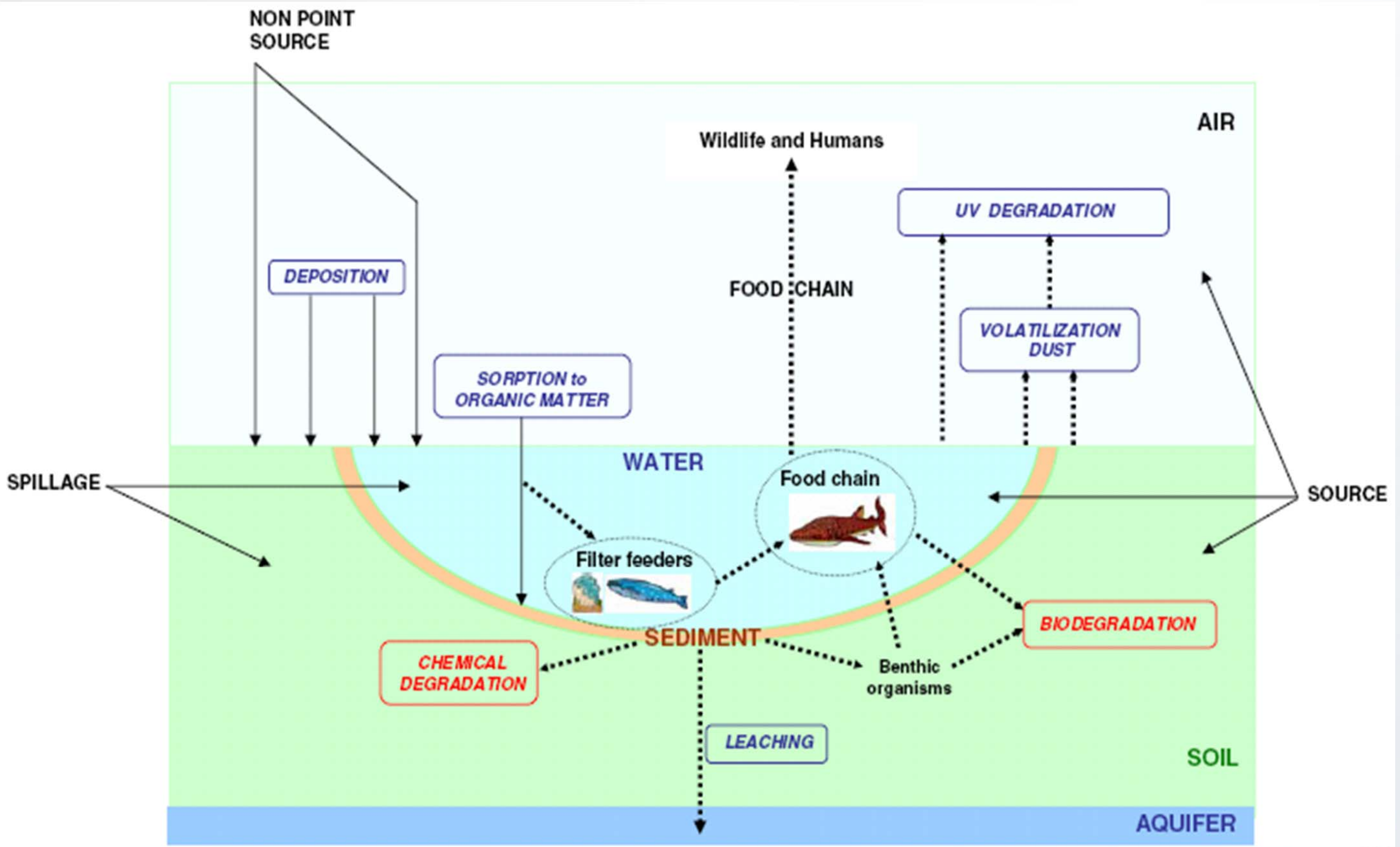


Nano-Electronics
Transistor Nano-Electronics Research
DNA: 2-10 nm wide
90 nm
2003
65 nm
2005
Technology Generation
45 nm
2007
32 nm
2009
2011+
Manufacturing
Research & Development
50 nm
35 nm
30 nm
20 nm
40nm
L_G=20nm
10 nm
5 nm
Nanowire
Source: Intel
Miniaturization of transistors allows for continuation of Moore's law (doubling of number of transistors every two years).
Carbon Nanotube FET
Future options subject to change

Environmental fate and biological interactions



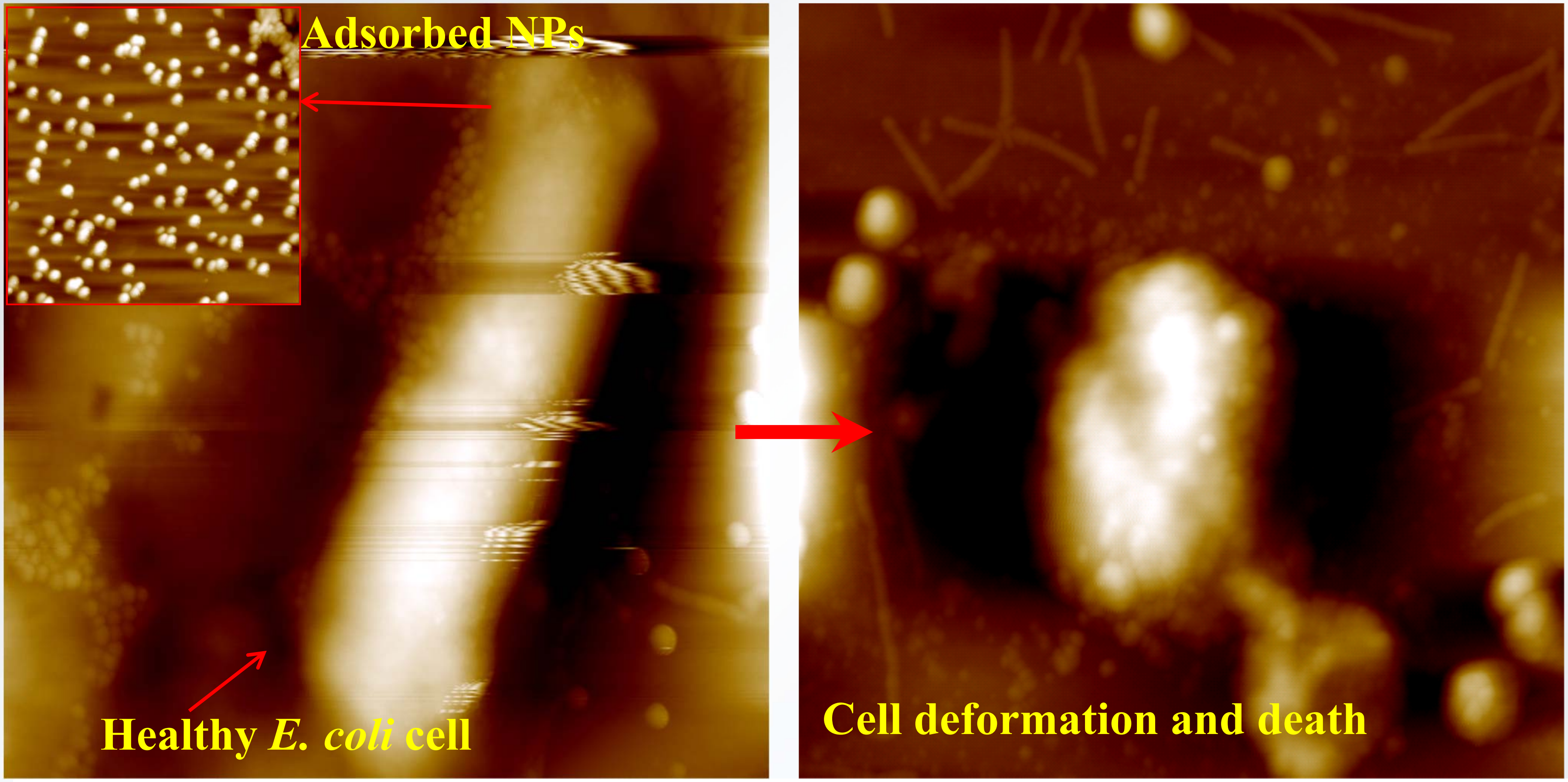
Cited from M Farré et al., Ecotoxicity and analysis of nanomaterials in the aquatic environment, *Analytical and Bioanalytical Chemistry*. 2009

Infrastructure of our research

- **Semiconductor nanomaterials**
  - **Biological interactions**
    - Interfacial forces
    - Adsorption kinetics on cells
    - Adsorption onto lipid bilayers
  - **Environmental fate**
    - Aggregation kinetics
    - Ion release kinetics

Hematite (α-Fe_2O_3)
CeO_2
TiO_2
ZnO
Al_2O_3
CuO
SiO_2
QDs
Au
Ag

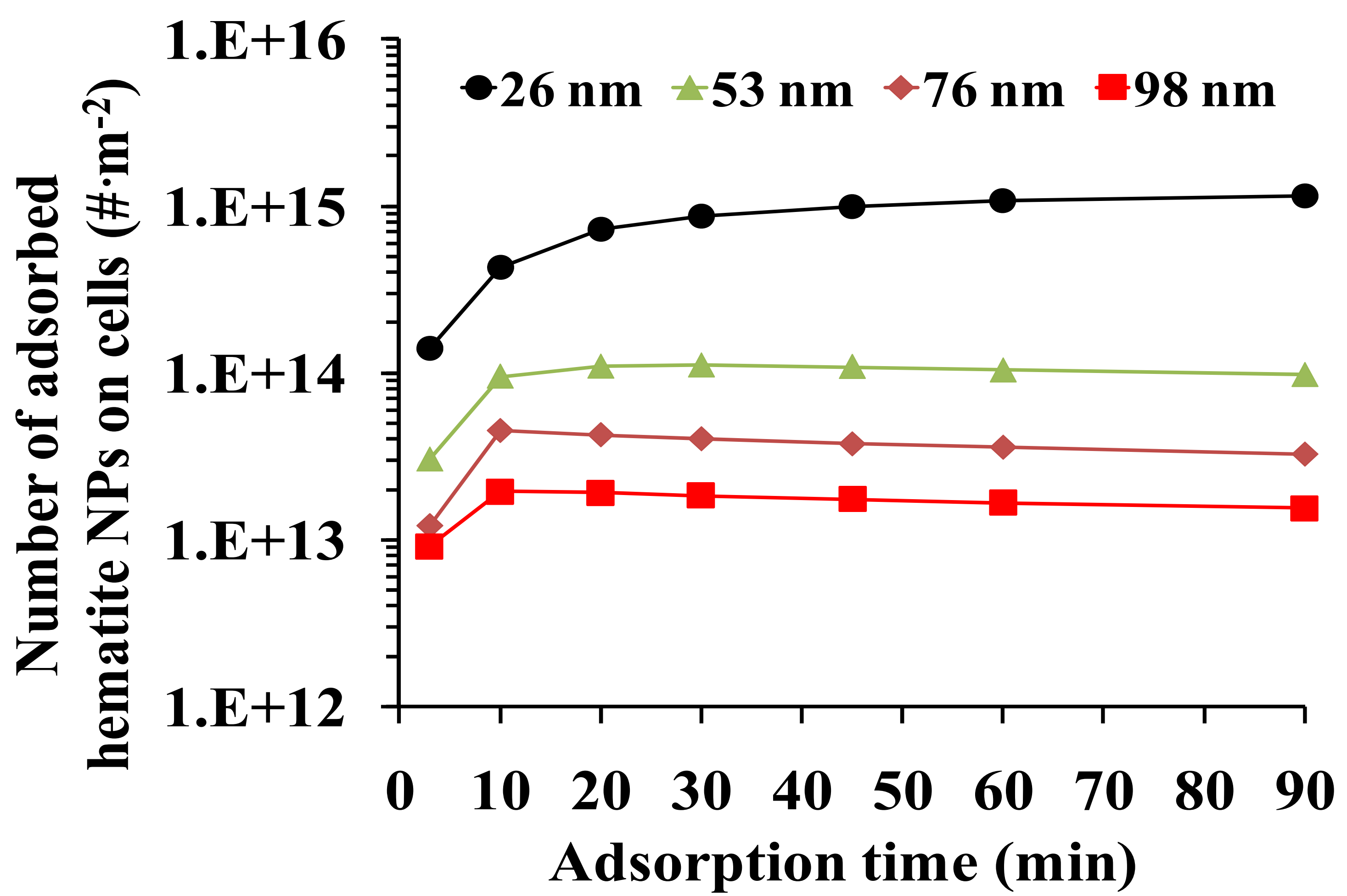
Adsorption, surface disruption, and adsorption kinetics modeling of hematite NPs on *E. coli* cells



Exposure impairment of hematite NPs on *E. coli* cells.

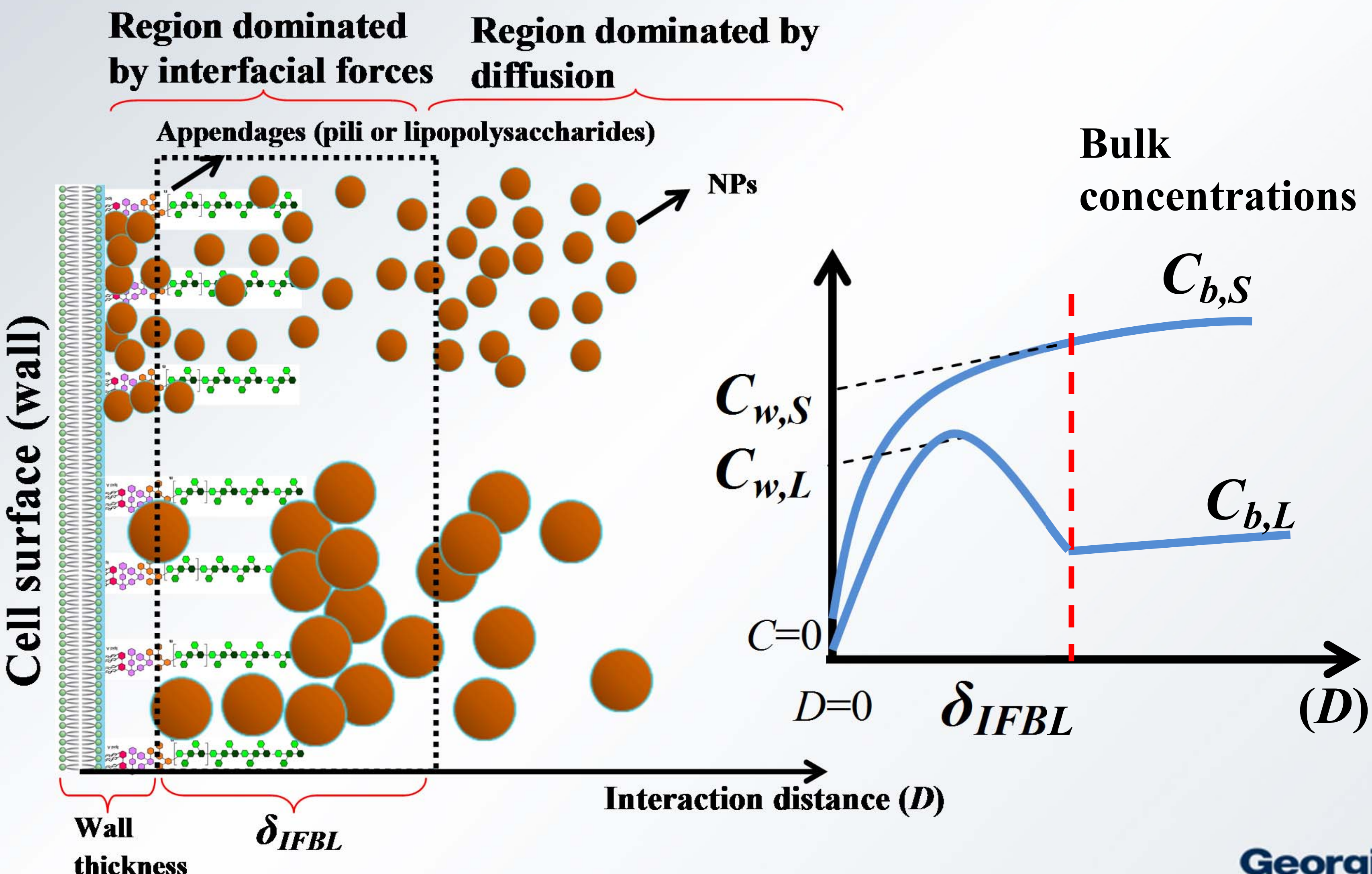
Wen Zhang, Joe Hughes, and Yongsheng Chen. Surface impact of *E. coli* cells upon exposure to hematite NPs. In preparation.

Adsorption, surface disruption, and adsorption kinetics modeling of hematite NPs on *E. coli* cells



They have size-dependent transport behaviors toward biological interface.

Adsorption, surface disruption, and adsorption kinetics modeling of hematite NPs on *E. coli* cells



Wen Zhang, Bruce Rittmann, and Yongsheng Chen. Size effects on adsorption kinetics of hematite NPs on *E. coli* cells. *Environmental Science and Technology.* Accepted

Technical data that are to be presented in detail

1. **Ion release and aggregation kinetics of AgNPs: size and concentration effects.**
2. **Aggregation kinetics and its predictive modeling of metal oxide or metal NPs in aqueous environments;**
3. **Subcellular interactions (QDs vs DNA).**

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Fate and transformation in environmentally relevant water chemistries: the case of AgNPs

1. **AgNPs has wide applications in food packaging, clothing and other household products (antibacterial and sterile purposes); AgNPs of less than 10 nm in diameter are utilized in the semiconductor industry and printed electronic products due to their lower melting point (Kashiwagi et al., 2006).**
2. **AgNPs exhibit size- and shape-dependent toxicity;**
3. **The ratio of silver particles to silver ions plays critical roles in cytotoxicity;**
4. **Citrate-coated AgNPs are one of the most widely used nanoparticles in commercial products and are recommended by the Organization for Economic Co-operation and Development (OECD) for standard use in toxicology;**

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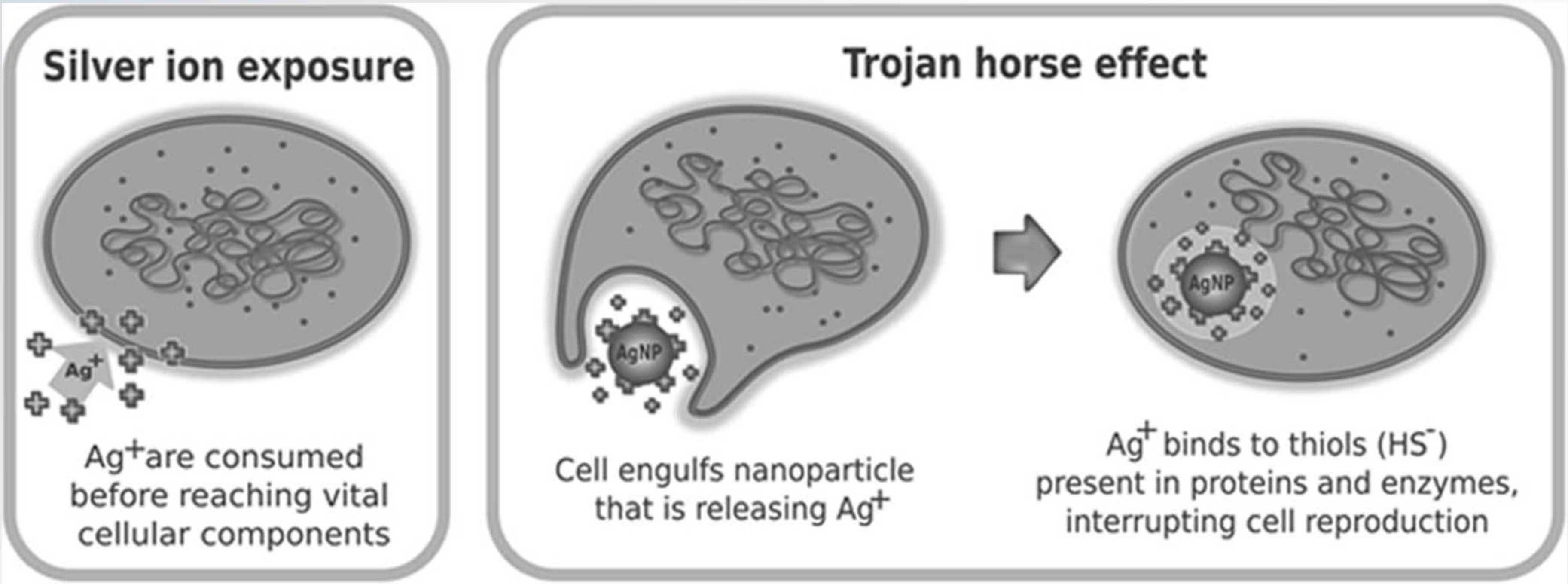
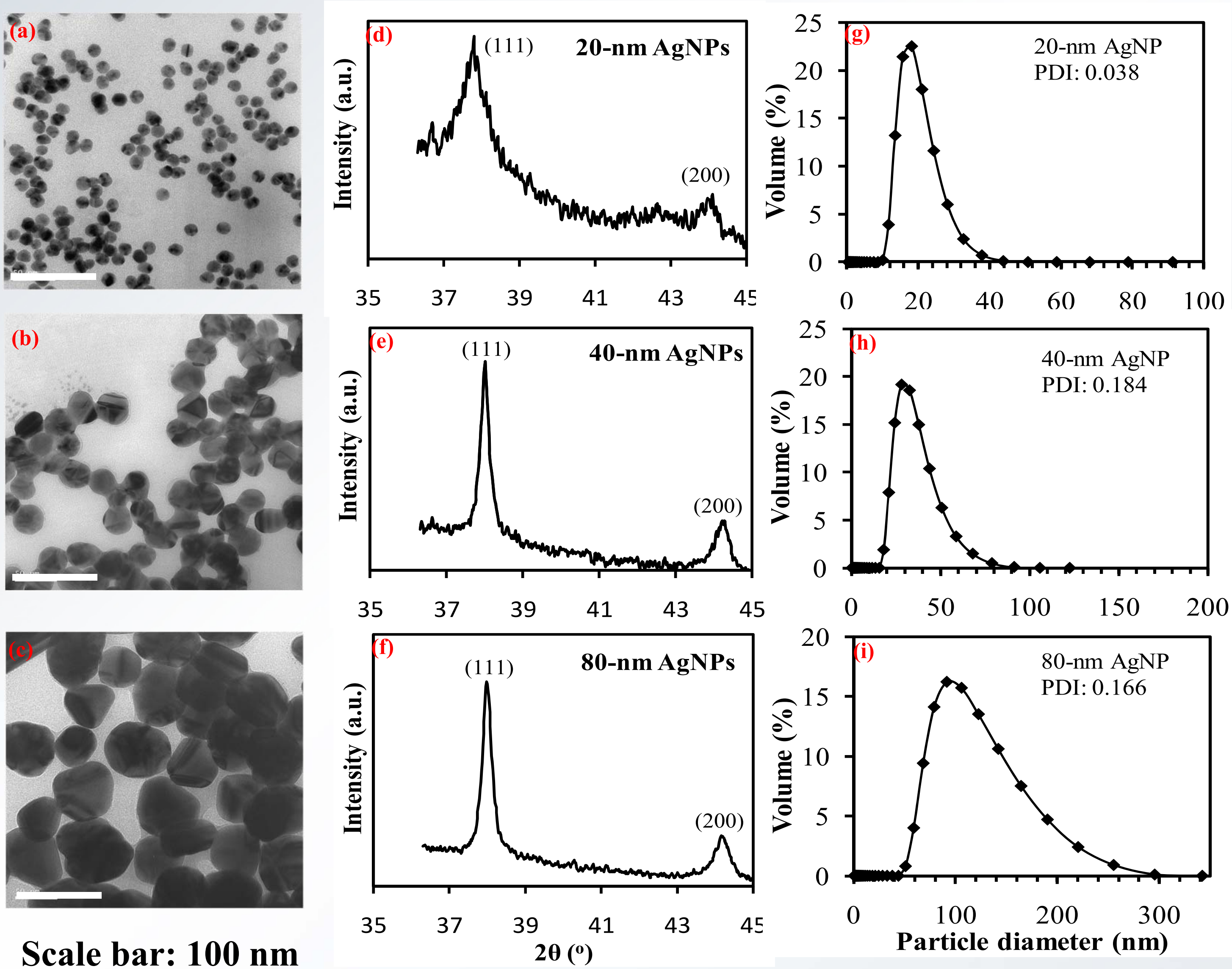
Silver ion release and aggregation kinetics of citrate-coated silver nanoparticles in aqueous environments



Park et al., Toxicology in Vitro, 2010; Quadros et al., Journal of the Air & Waste Management Association, 2010

$Ag^+ \rightleftharpoons$ **Adsorbed by negatively charged naturally occurring colloids, cell surfaces, and complexation or speciation with typical anions, fluoride (F^-), chloride (Cl^-), sulfate (SO_4^{2-}), hydroxide (OH^-), or carbonate (CO_3^{2-}), sulfhydrate (AgSH or HS-Ag-S-Ag-HS).**

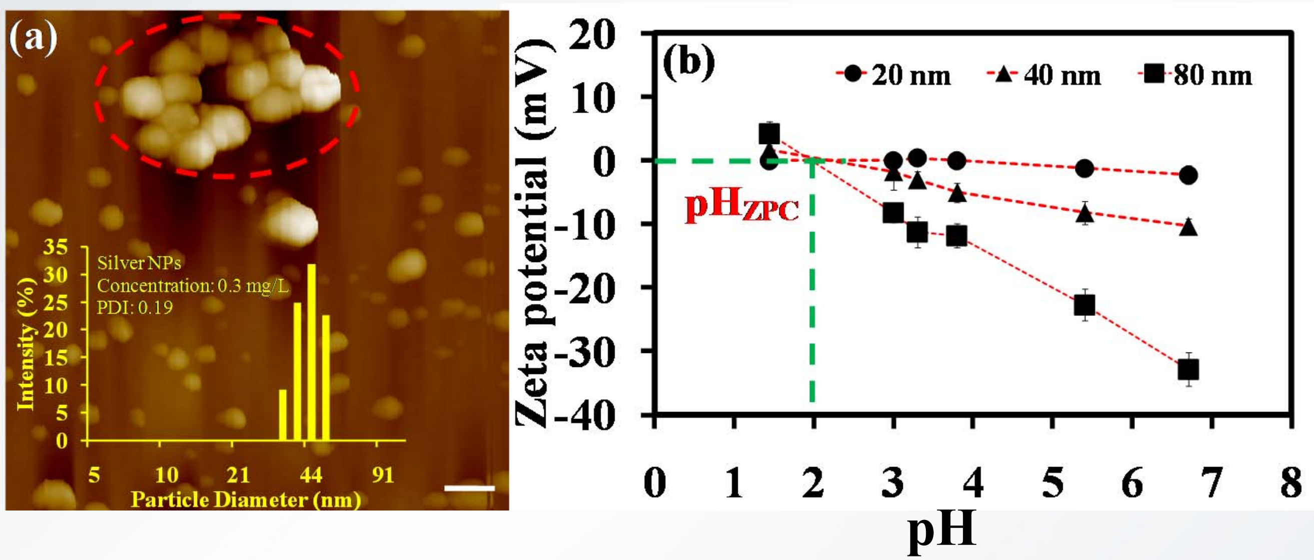
Characterizations of AgNPs with TEM, XRD, and DLS



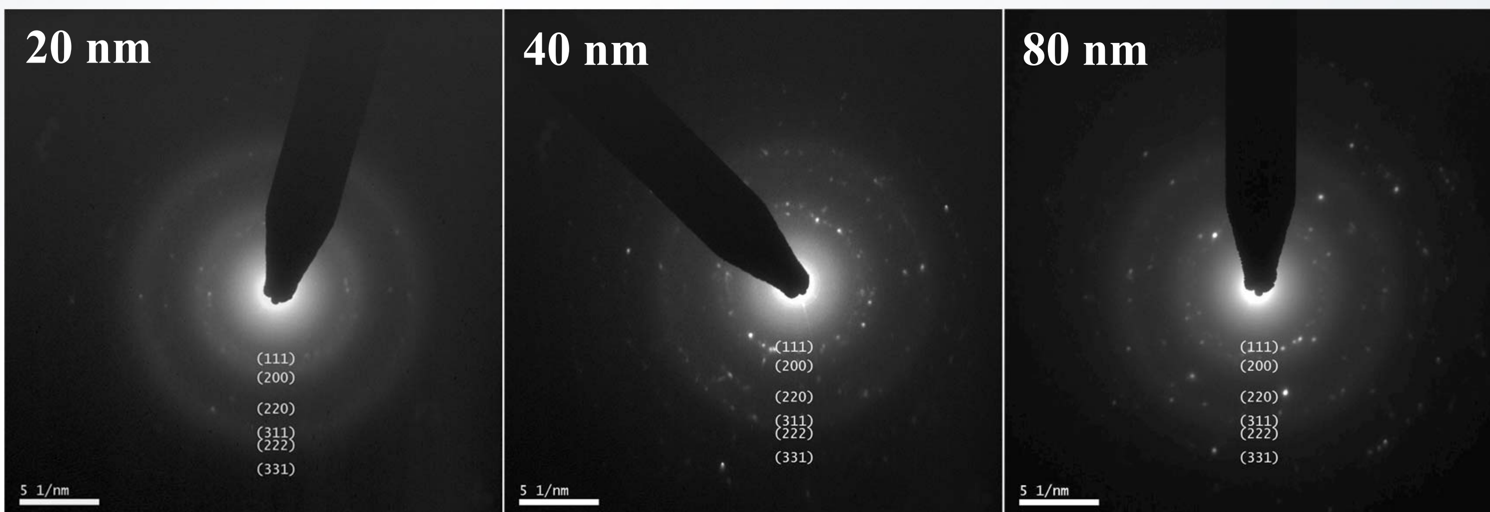
Scale bar: 100 nm

Characterizations of AgNPs with AFM, DLS, and Electron diffraction

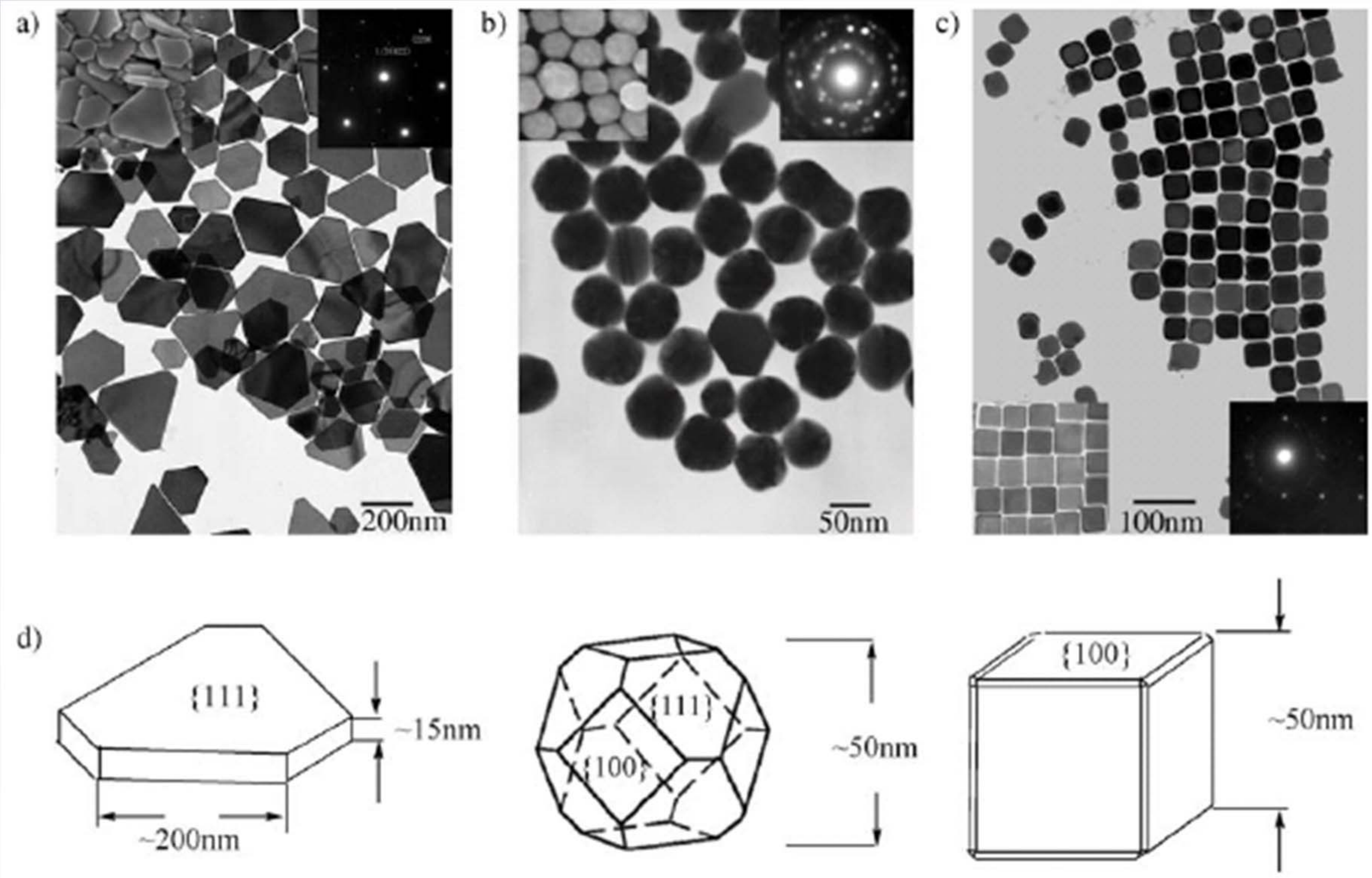
Morphology, size distribution, and zeta potential.



Crystallinity: Fused structure (fused small single crystals), or polycrystalline

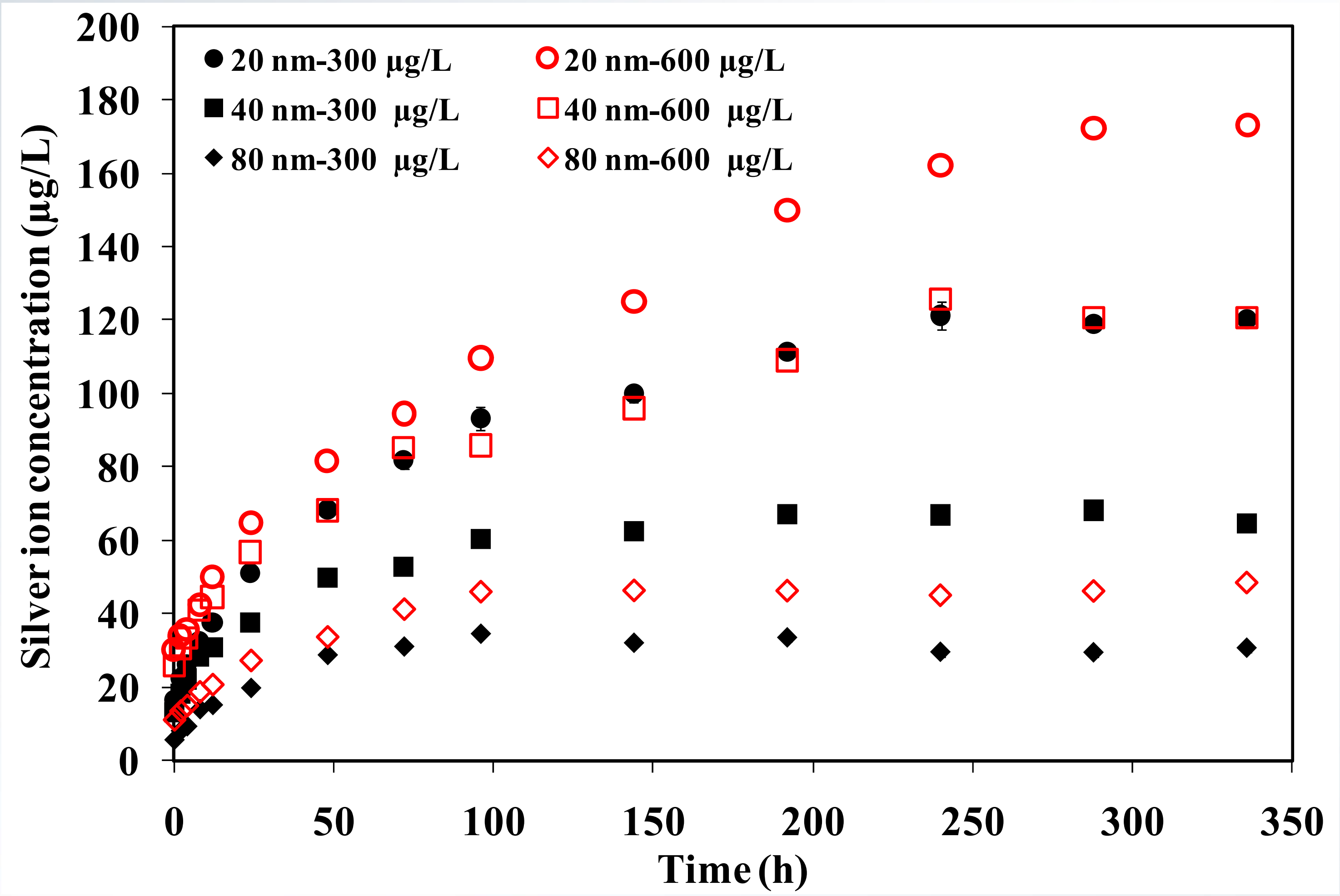


Effects of crystallinity, shape, crystal plane on environmental and toxicological activity of AgNP



TEM image of (a) truncated triangular nanoplates, (b) near-spherical silver nanoparticles, and (c) nanocubes, and d) their structural models. The insets show the scanning electron microscopy image (left) and the selected area electron diffraction pattern (right). Xu et al., *Chem. Asian J.* 2006

Ion release kinetics of AgNPs: primary particle size and concentration effects



Wen Zhang, Ying Yao, Nicole Sullivan, Yongsheng Chen. Kinetics modeling of ion release silver NPs in the environment. ***Environmental Science and Technology.*** Revision submitted.

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Ion release kinetics of AgNPs: primary particle size and concentration effects.

Reaction stochiometry:

$$Ag_{(s)} + \frac{1}{2}O_{2(aq)} + 2H^{+}_{(aq)} \leftrightarrow 2Ag^{+}_{(aq)} + H_2O_{(l)}$$

Hard sphere theory and Arrhenius equation are used to derive the silver ion release rate:

$$\gamma_{Ag^{+}} = \frac{3}{4}\left(\frac{8\pi k_B T}{m_B}\right)^{1/2} \cdot \rho^{-1} \cdot \exp\left(\frac{-E_a}{k_B T}\right) \cdot [Ag] \cdot r^{-1} \cdot [O_2]^{0.5} \cdot [H^{+}]^{2}$$

$$[Ag^{+}]_{released} \approx \frac{1}{6}a^3t^3 + \left(\frac{1}{2}a^2bt^2 - \frac{1}{2}a^2t^2\right) + \left(at - abt + \frac{1}{2}ab^2t\right) + \left\{[Ag^{+}]_{initial} - 1 + b - \frac{1}{2}b^2 + \frac{1}{6}b^3\right\}$$

Released silver ion concentration is a function of time, particle size, oxygen and proton concentrations, temperature and "activation energy".

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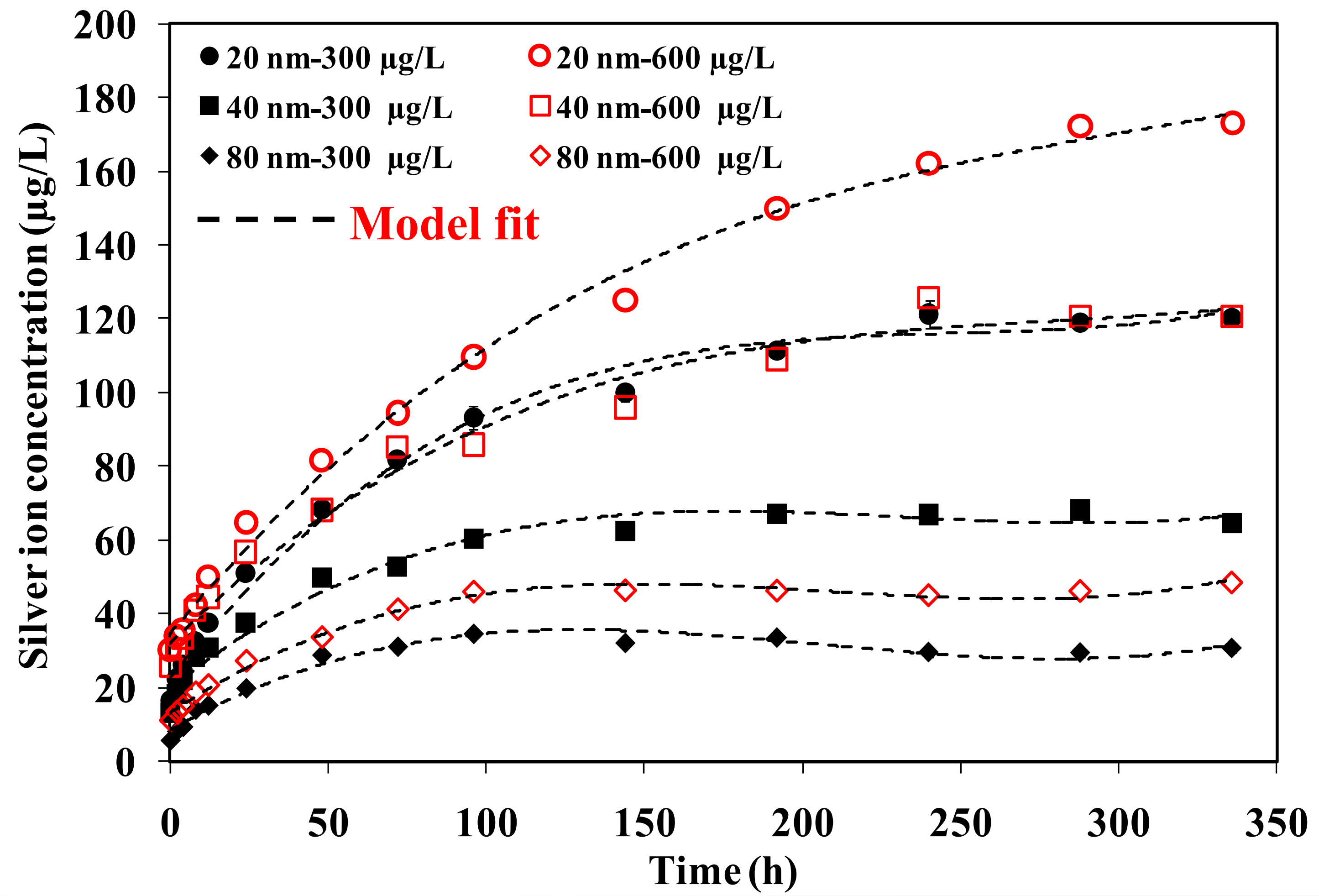
Ion release kinetics of AgNPs: primary particle size and concentration effects



Wen Zhang, Ying Yao, Nicole Sullivan, Yongsheng Chen. Kinetics modeling of ion release silver NPs in the environment. ***Environmental Science and Technology.*** Revision submitted.

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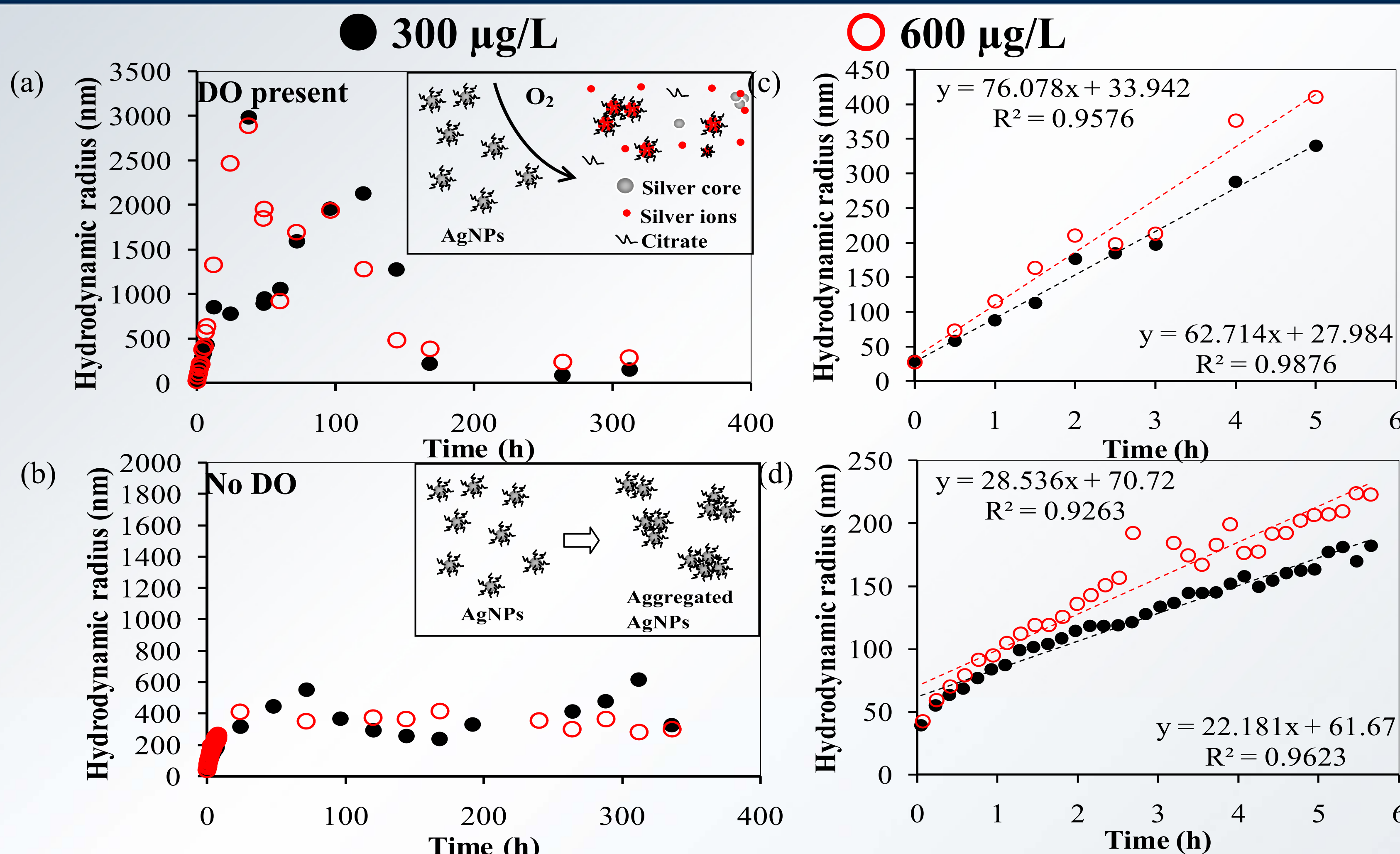
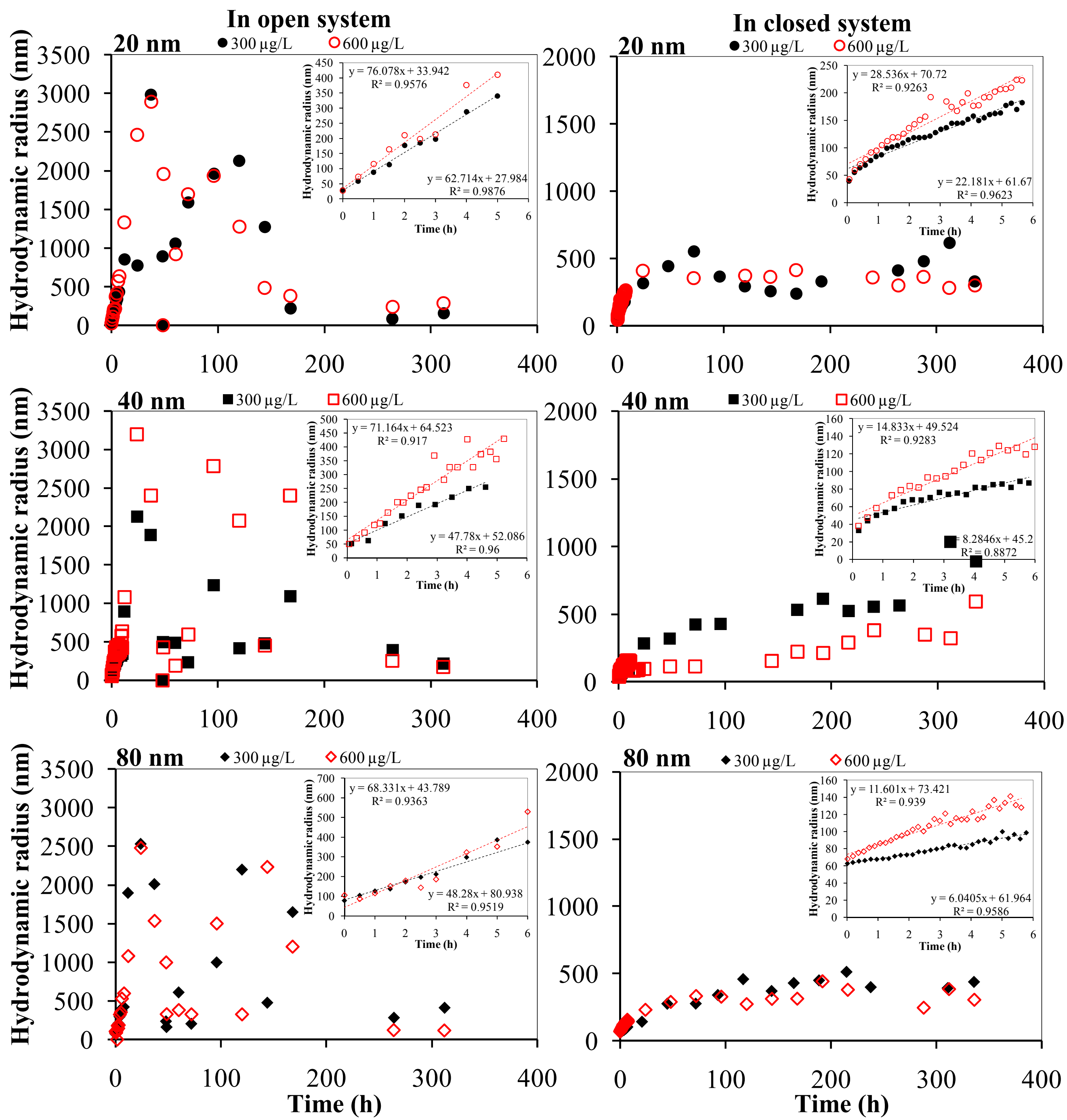
Effects of aggregation on ion release kinetics



Aggregates may still preserve most of the surface area available for the heterogeneous reaction with oxygen within the aggregated particles (Liu et al. 2010).

Aggregation kinetics of AgNPs

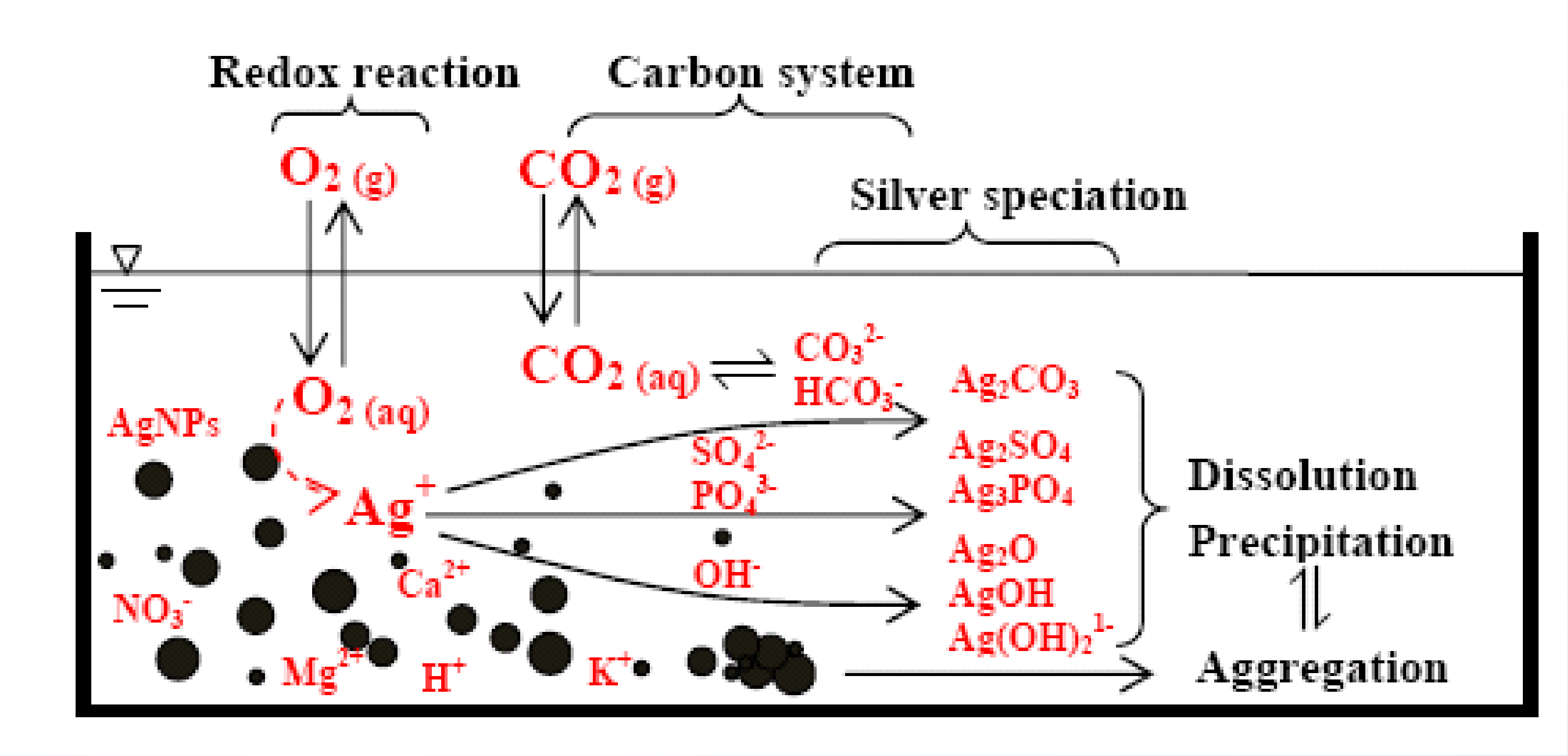
- ➢Size effects;
- ➢Concentration effects;
- ➢Linear growth feature;
- ➢Random distribution with DO present in the medium.



Wen Zhang, Ying Yao, Kungang Li, Ying Huang, Yongsheng Chen. Aggregation kinetics of silver nanoparticles in open and close systems. *In preparation*.

Potential physiochemical processes occurred to AgNPs in open system

Ionic strength and components influence colloidal stability (DLVO theory)



The presence of DO and CO_2 have significant impacts on the environmental fate and transformations.

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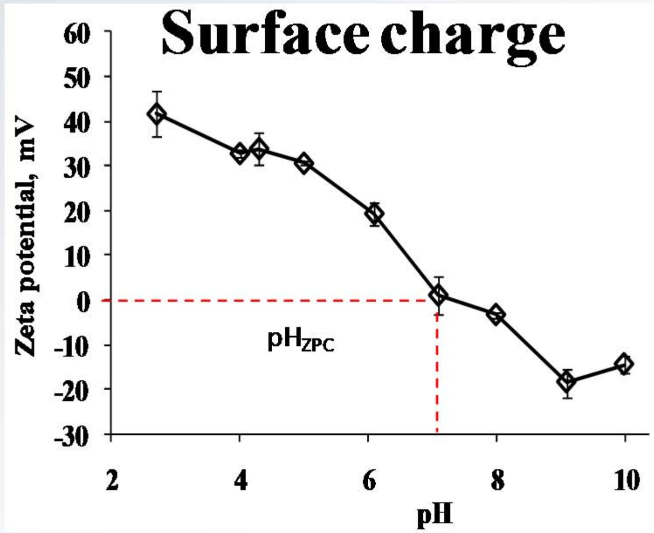
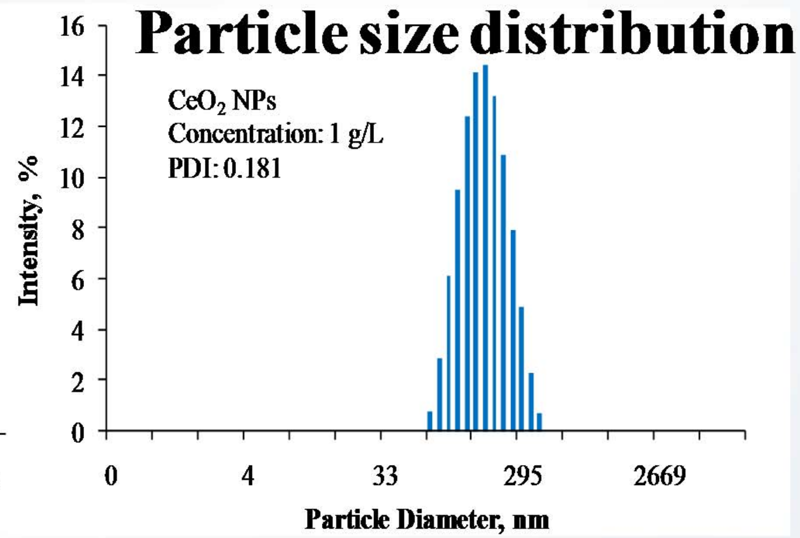
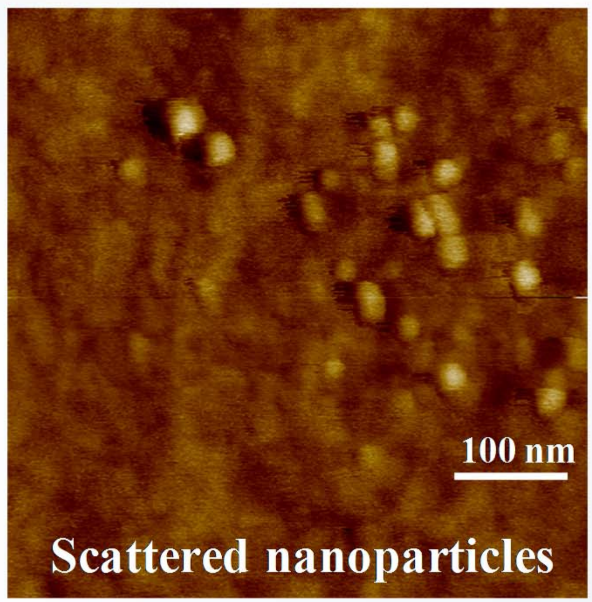
Aggregation kinetics of CeO_2 NPs in aqueous environments and modeling

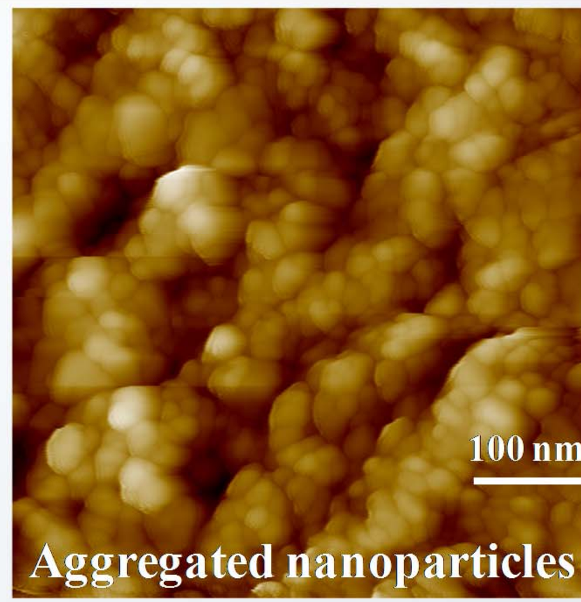
Stability

bioavailability









Kungang Li, Wen Zhang, Ying Huang, and Yongsheng Chen, Modeling the aggregation kinetics of CeO_2 nanoparticles in monovalent and divalent electrolytes with EDLVO theory, *Colloids and Surfaces A*, Under review.

Aggregation kinetics of CeO_2 NPs in aqueous environments and modeling

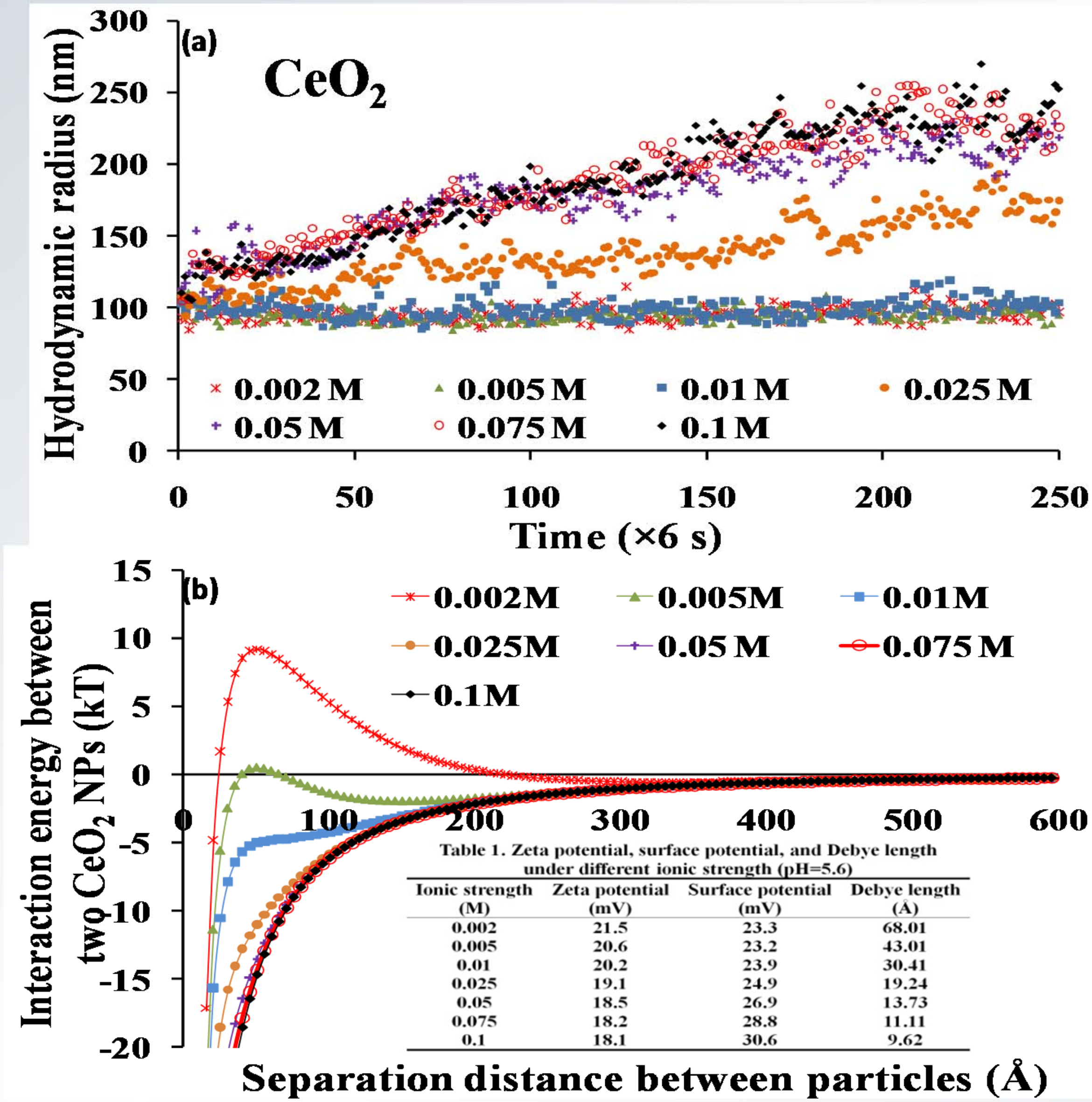


Table 1. Zeta potential, surface potential, and Debye length under different ionic strength (pH=5.6)

Ionic strength (M)	Zeta potential (mV)	Surface potential (mV)	Debye length (Å)
0.002	21.5	23.3	68.01
0.005	20.6	23.2	43.01
0.01	20.2	23.9	30.41
0.025	19.1	24.9	19.24
0.05	18.5	26.9	13.73
0.075	18.2	28.8	11.11
0.1	18.1	30.6	9.62

Ionic strength

Interaction energy

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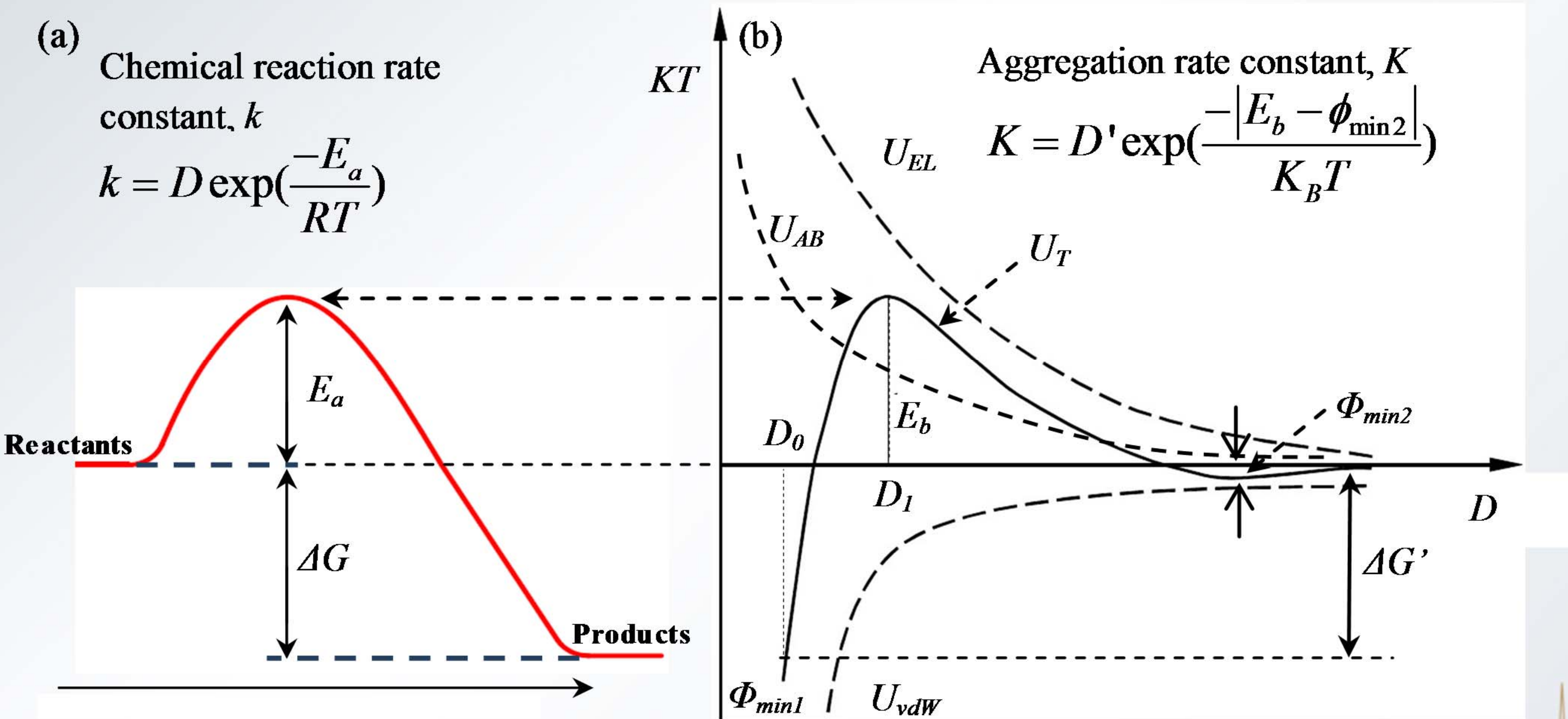
monovalent and divalent electrolytes with EDLVO theory,

Aggregation kinetics of CeO_2 NPs in aqueous environments and modeling

Aggregation may be a pseudo-2nd reaction kinetics and the rate constant has an Arrhenius form at low particle concentration.

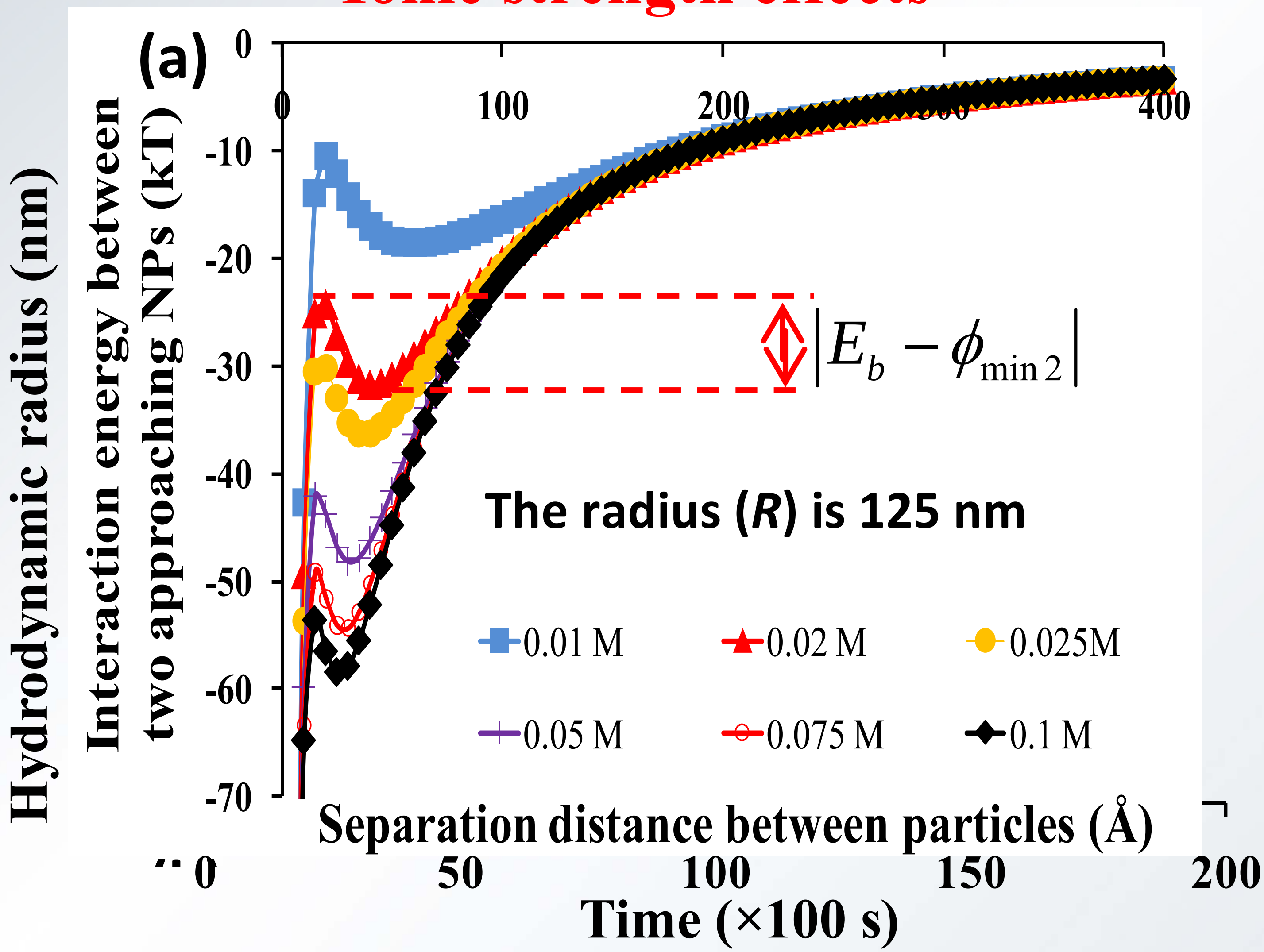


Kungang Li, Wen Zhang, Ying Huang, and Yongsheng Chen, Modeling the aggregation kinetics of CeO_2 nanoparticles in monovalent and divalent electrolytes with EDLVO theory, *Colloids and Surfaces A*, Under review.

Aggregation kinetics of CeO_2 NPs in aqueous environments and modeling

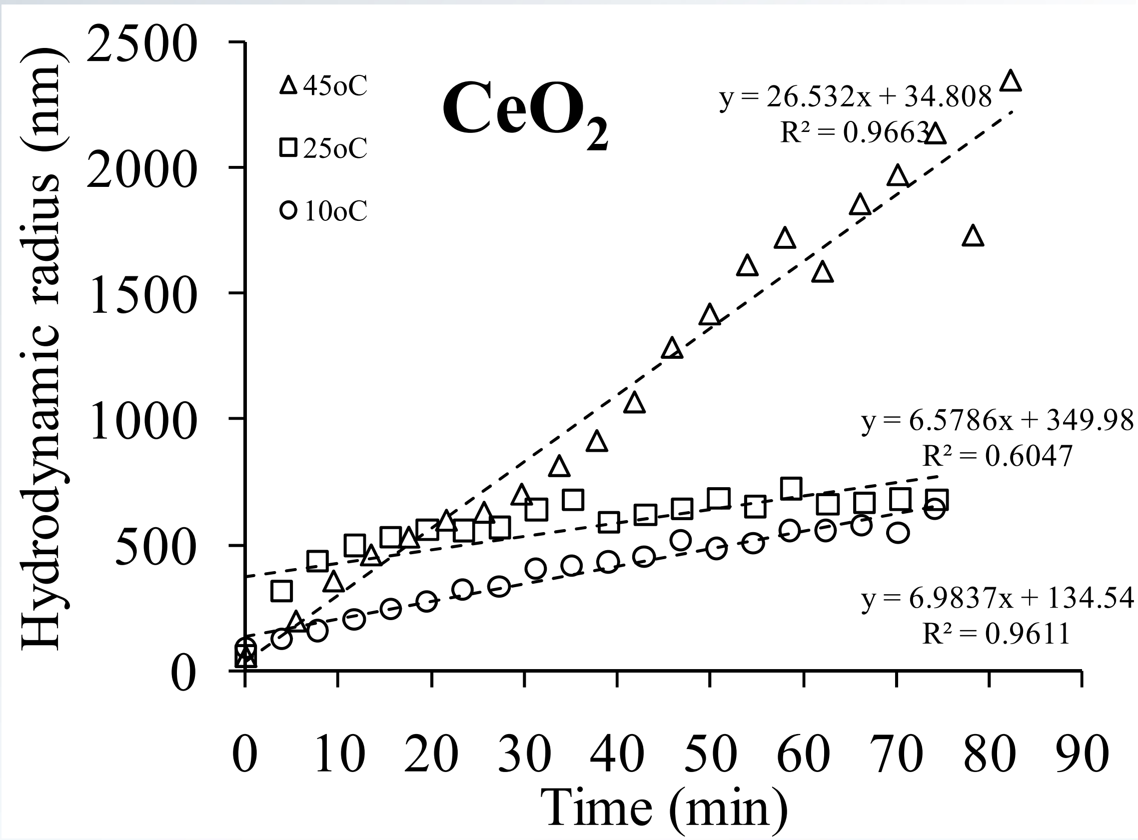
Ionic strength effects

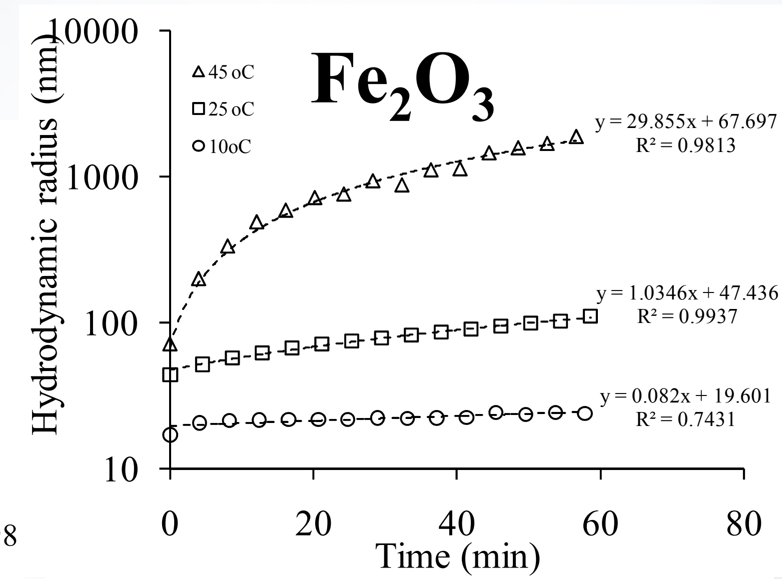
Size effects

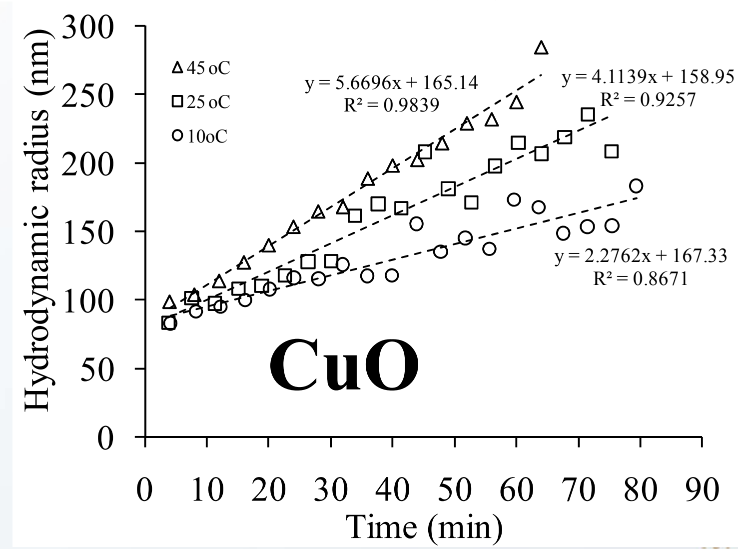


Aggregation kinetics of CeO_2 NPs in aqueous environments and modeling

Temperature effect





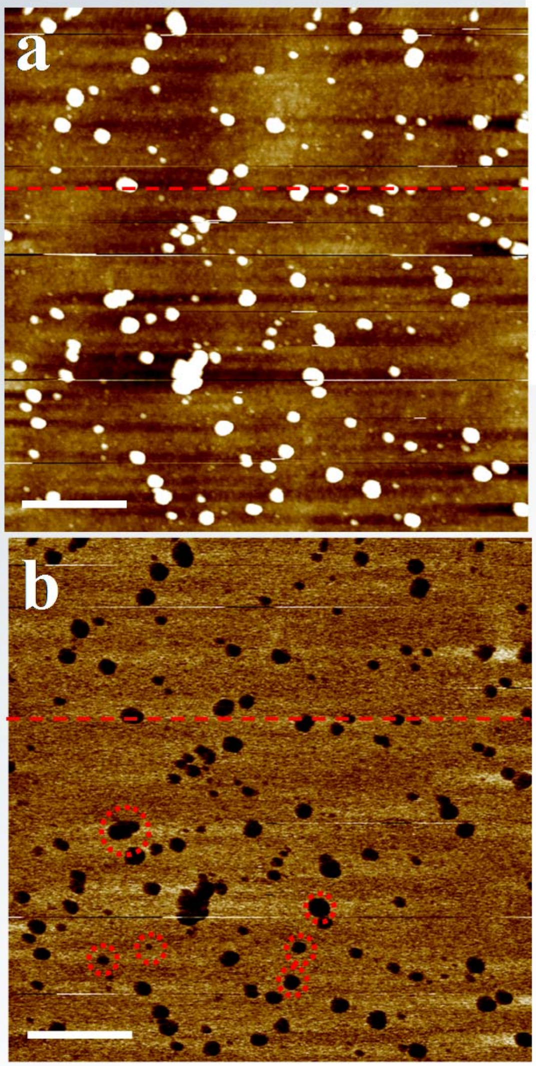


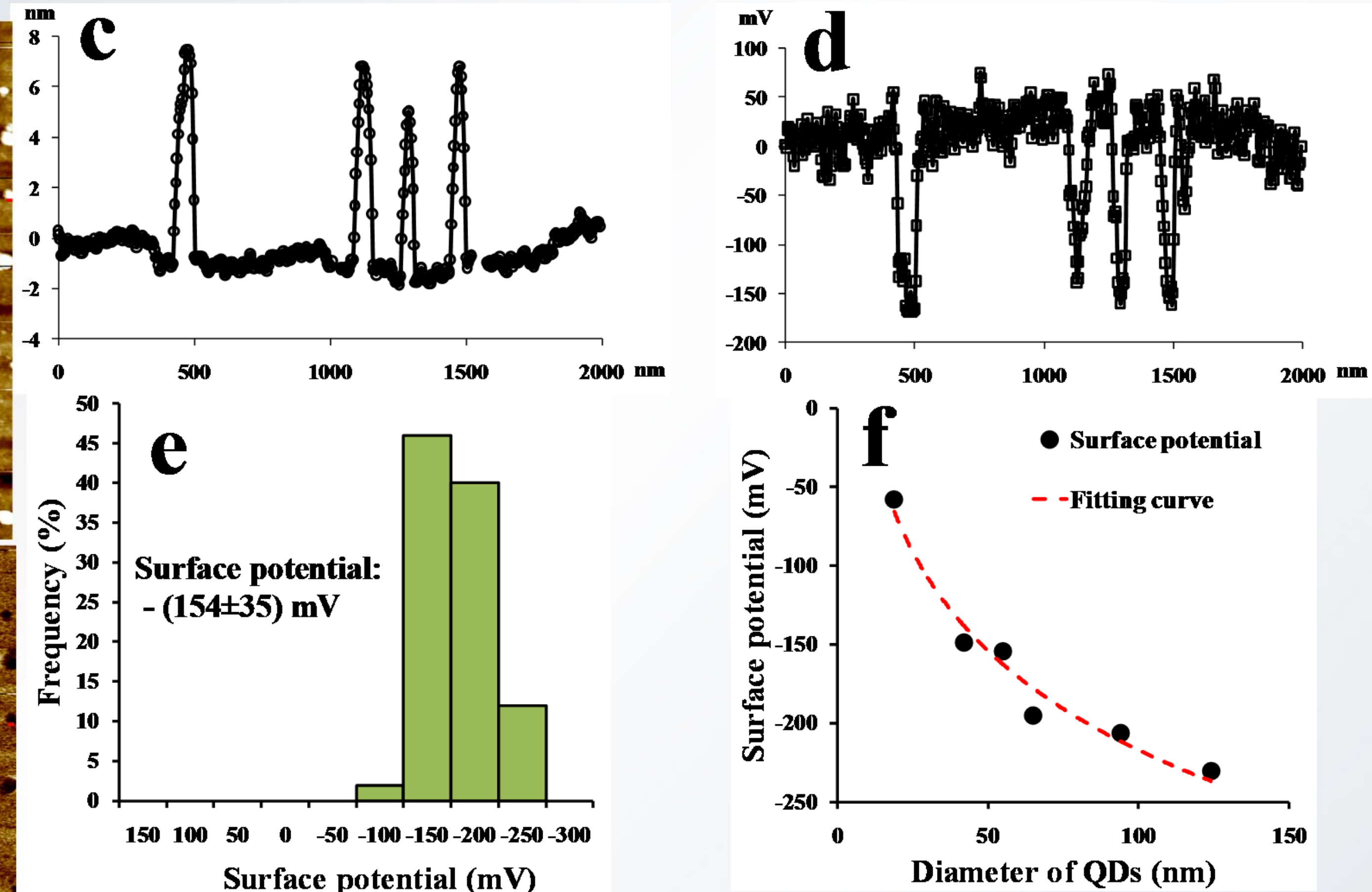
Kungang Li, Wen Zhang, Ying Huang, and Yongsheng Chen, Modeling the aggregation kinetics of CeO_2 nanoparticles in monovalent and divalent electrolytes with EDLVO theory, *Colloids and Surfaces A*, Under review.

Cellular and subcellular impairment by exposure to NPs

Caco-2 cells	• Hematite NPs of different sizes • Surface disruption and cell penetration
E. Coli cells	• Hematite NPs of different sizes • Surface adsorption, and surface disruption
E. Coli cells	• QDs • Cell growth inhibition, DNA binding and visualization

Permeation of QDs into *E. coli* cells and binding with DNA





CdSe-ZnS core-shell, 15-25 nm in diameter, Citrate coated.

Wen Zhang, Ying Yao, and Yongsheng Chen Quantifying and Imaging the Morphology and Nanoelectric Properties of Soluble Quantum Dot Nanoparticles Interacting with DNA. *Journal of Physical Chemistry C*. DOI: 10.1021/jp107676h.

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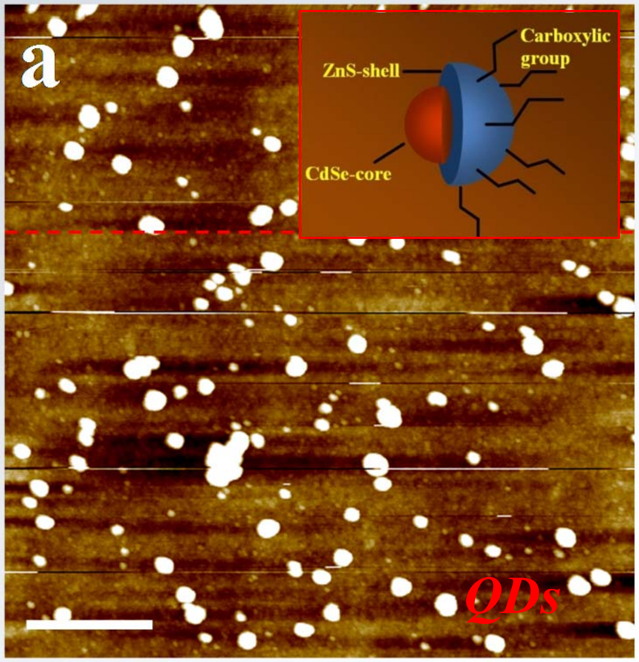
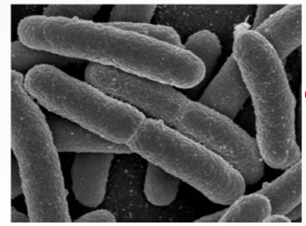
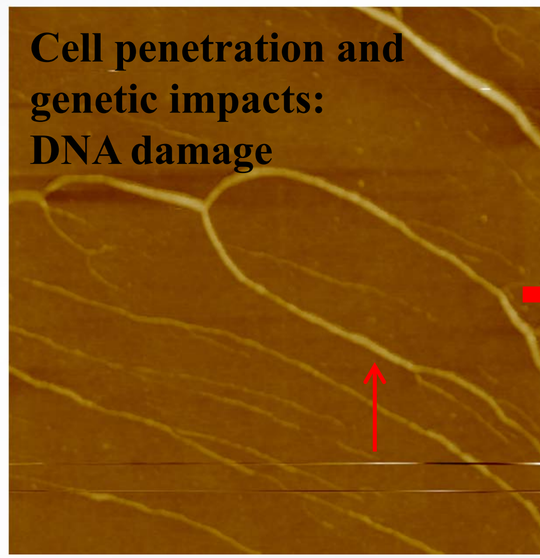
Permeation of QDs into *E. coli* cells and binding with DNA

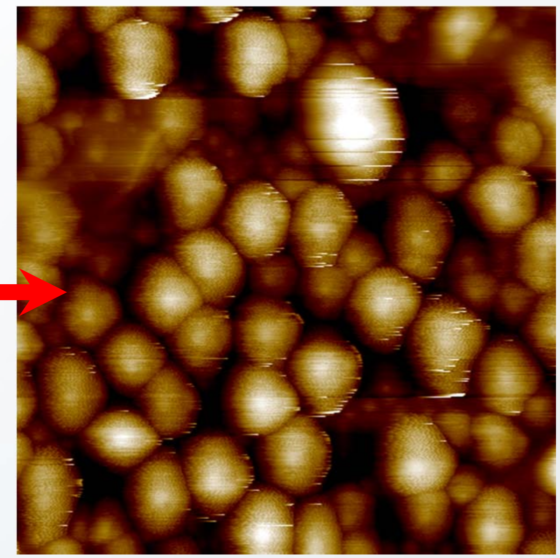


Permeate into



Bind with





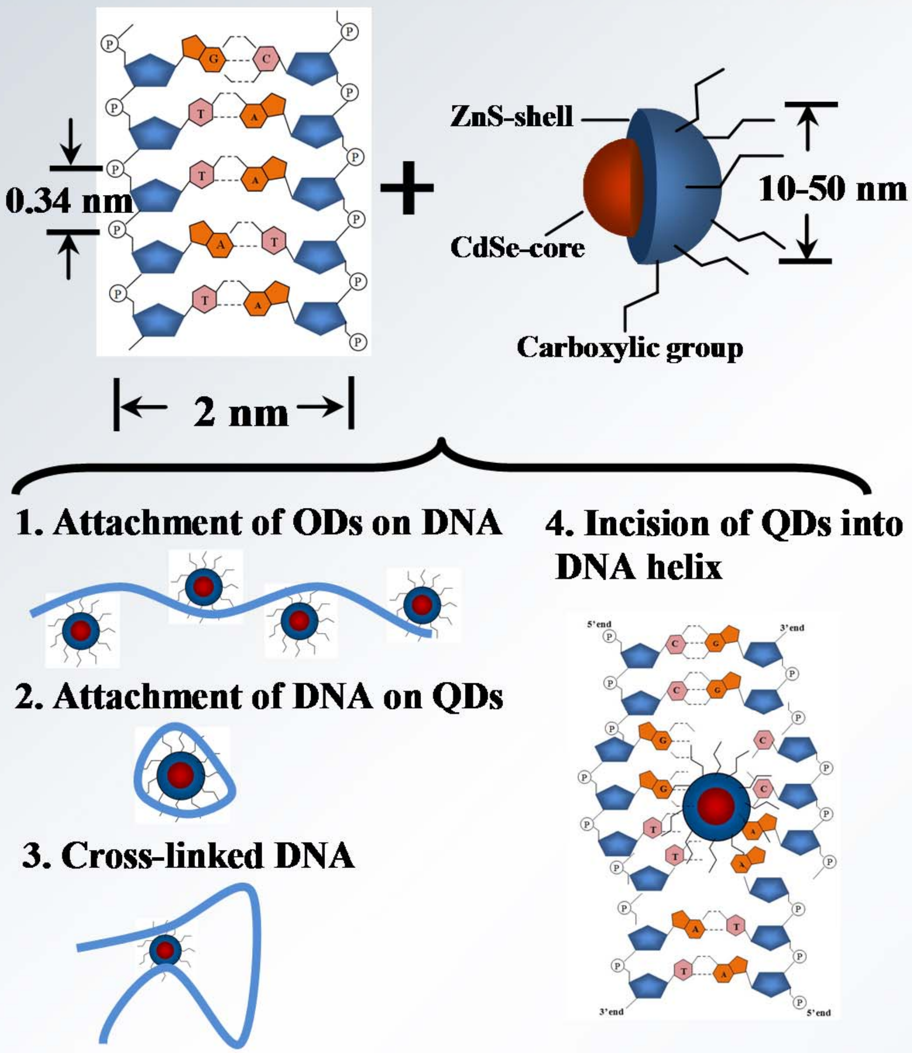
Ultrasmall QDs (CdSe-ZnS) can permeate into *E. coli* cells and unintentionally bind with DNA

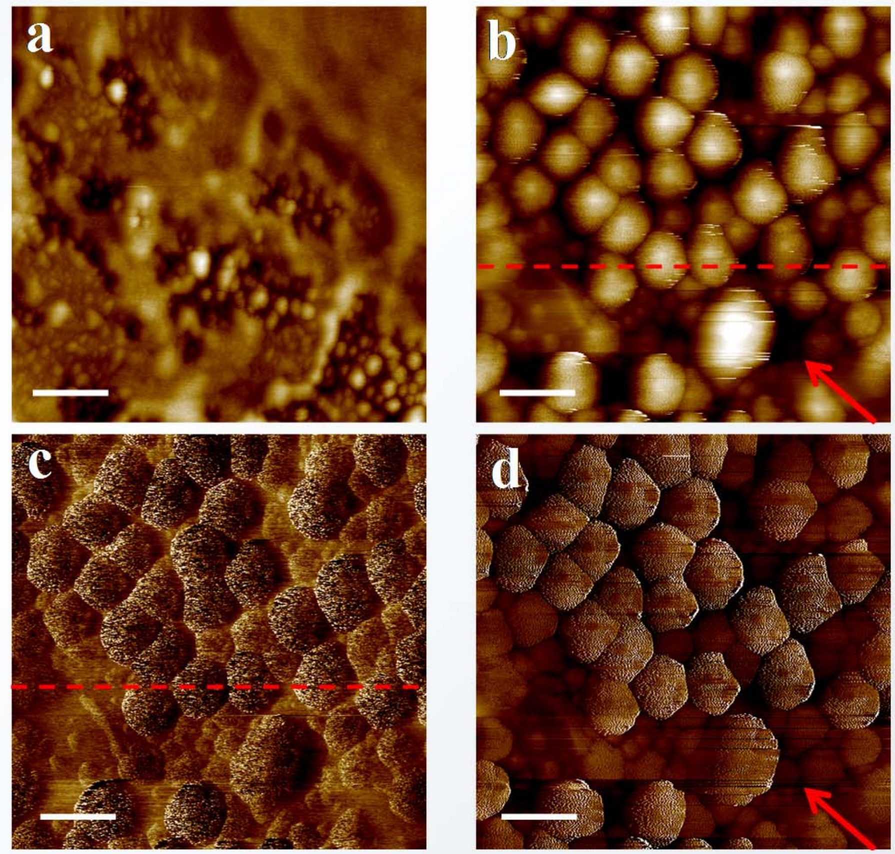
Tangled DNA extracted from *E. coli*

DNA binding with QDs and form sphere shapes

Wen Zhang, Ying Yao, and Yongsheng Chen Quantifying and Imaging the Morphology and Nanoelectric Properties of Soluble Quantum Dot Nanoparticles Interacting with DNA. *Journal of Physical Chemistry C*. DOI: 10.1021/jp107676h.

Permeation of QDs into *E. coli* cells and binding with DNA





Sphere-shaped DNA conformation after binding with QDs.

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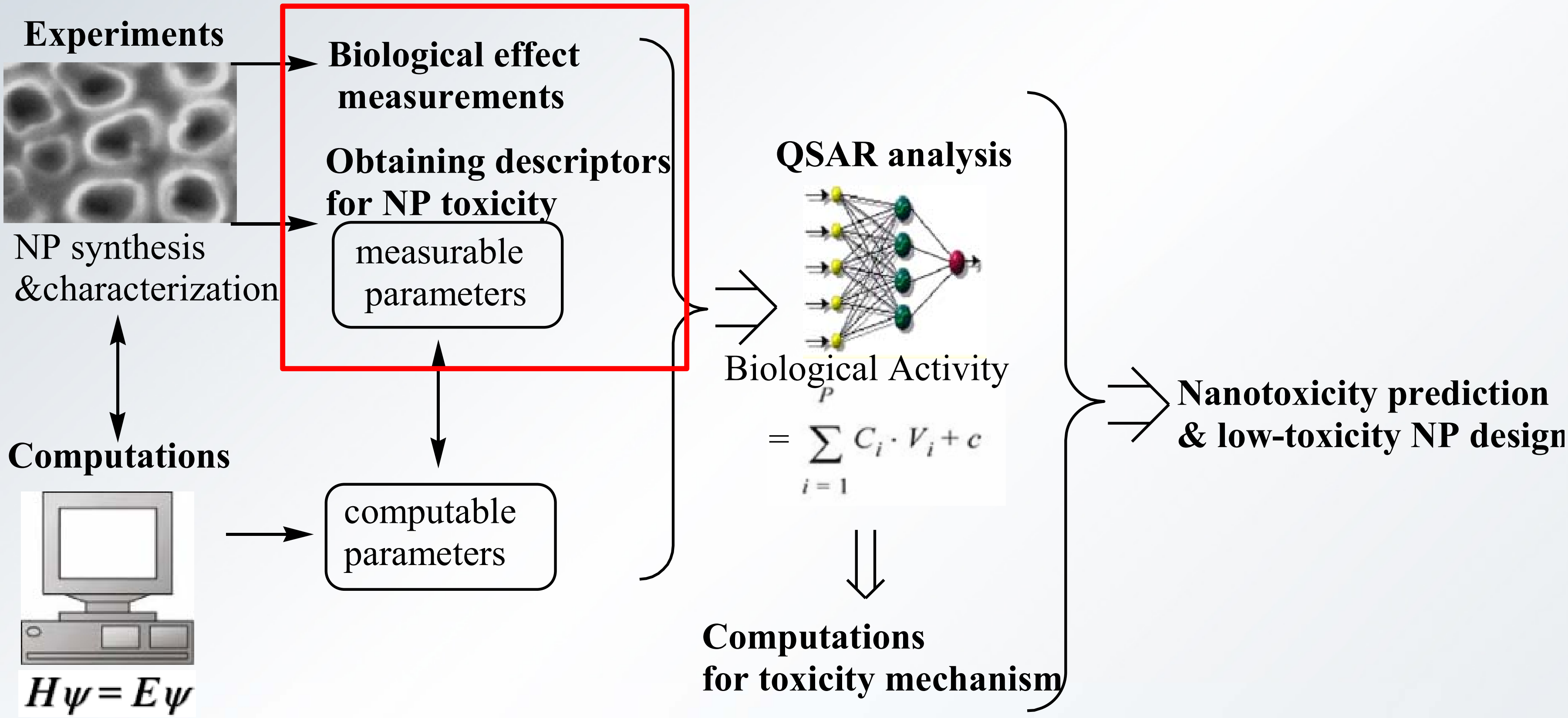
Wen Zhang, Ying Yao, and Yongsheng Chen Quantifying and Imaging the Morphology and Nanoelectric Properties of Soluble Quantum Dot Nanoparticles Interacting with DNA. *Journal of Physical Chemistry C*. DOI: 10.1021/jp107676h.

Quantitative Structure-Activity Relationship (QSAR) Model



Relates particle properties(direct or indirect) to biological effect (toxicity, bioaccumulation)

Correlation between ion release and aggregation kinetics and toxicokinetics- semiconductor NPs

Generalized descriptors for NP toxicity:

Input descriptor in QSAR	Kinetics
Particle size	Aggregation kinetics
Particle size distribution	
Released ion concentration	Ion release kinetics
Ratio of released ions over total concentration of NPs	Evolution of the ratio between ionic and particle components
Surface charge	Surface energy
Surface functionalization	
Shape	
Crystallinity on exposure surfaces	

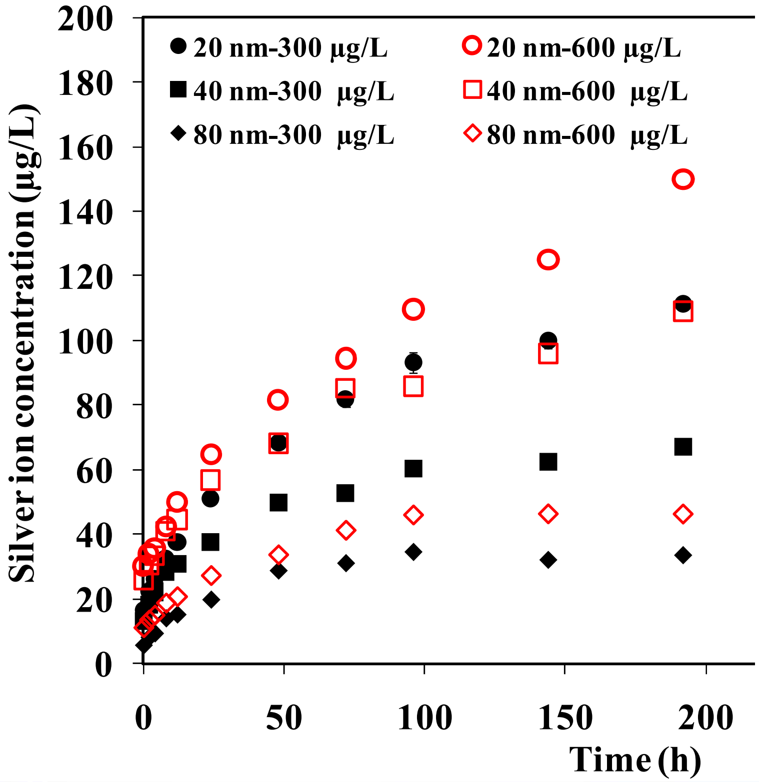
Toxicokinetics

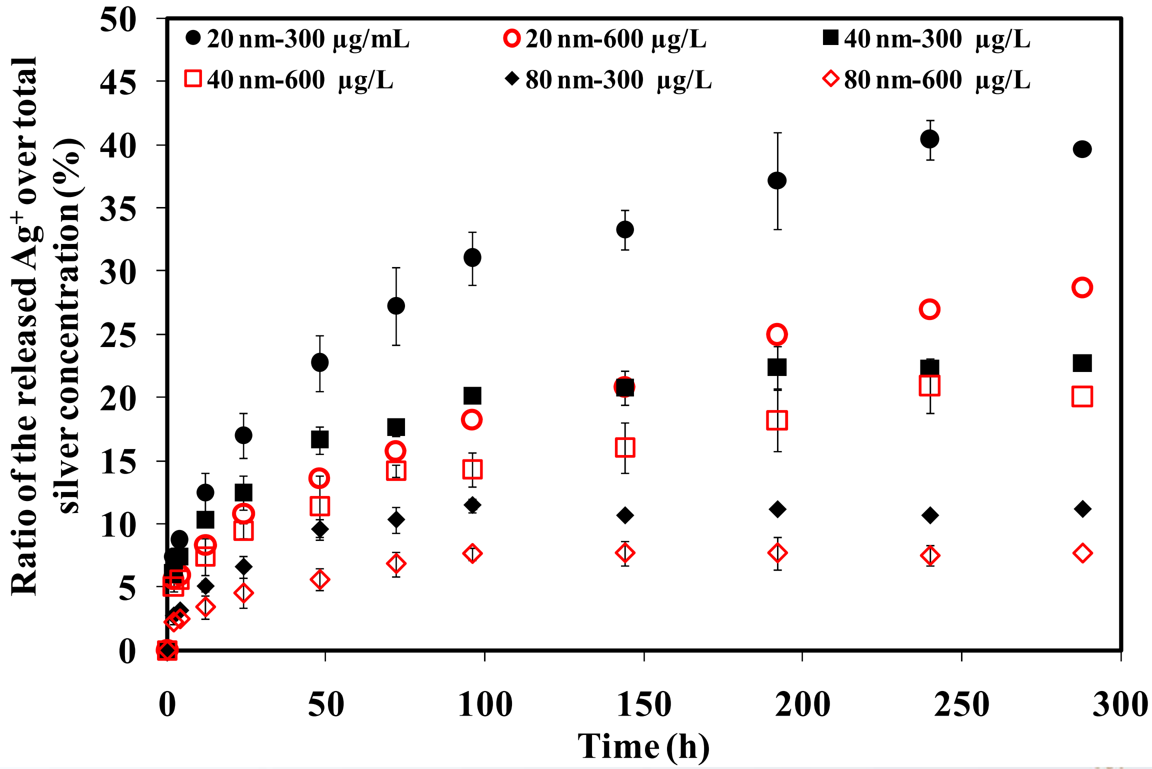
Adsorption;
Membrane disruption;
Internalization;
Cellular integrity;
DNA damage;
Cellular death (viability);

Correlation between ion release and aggregation kinetics and toxicokinetics- AgNPs

Hypothesis:

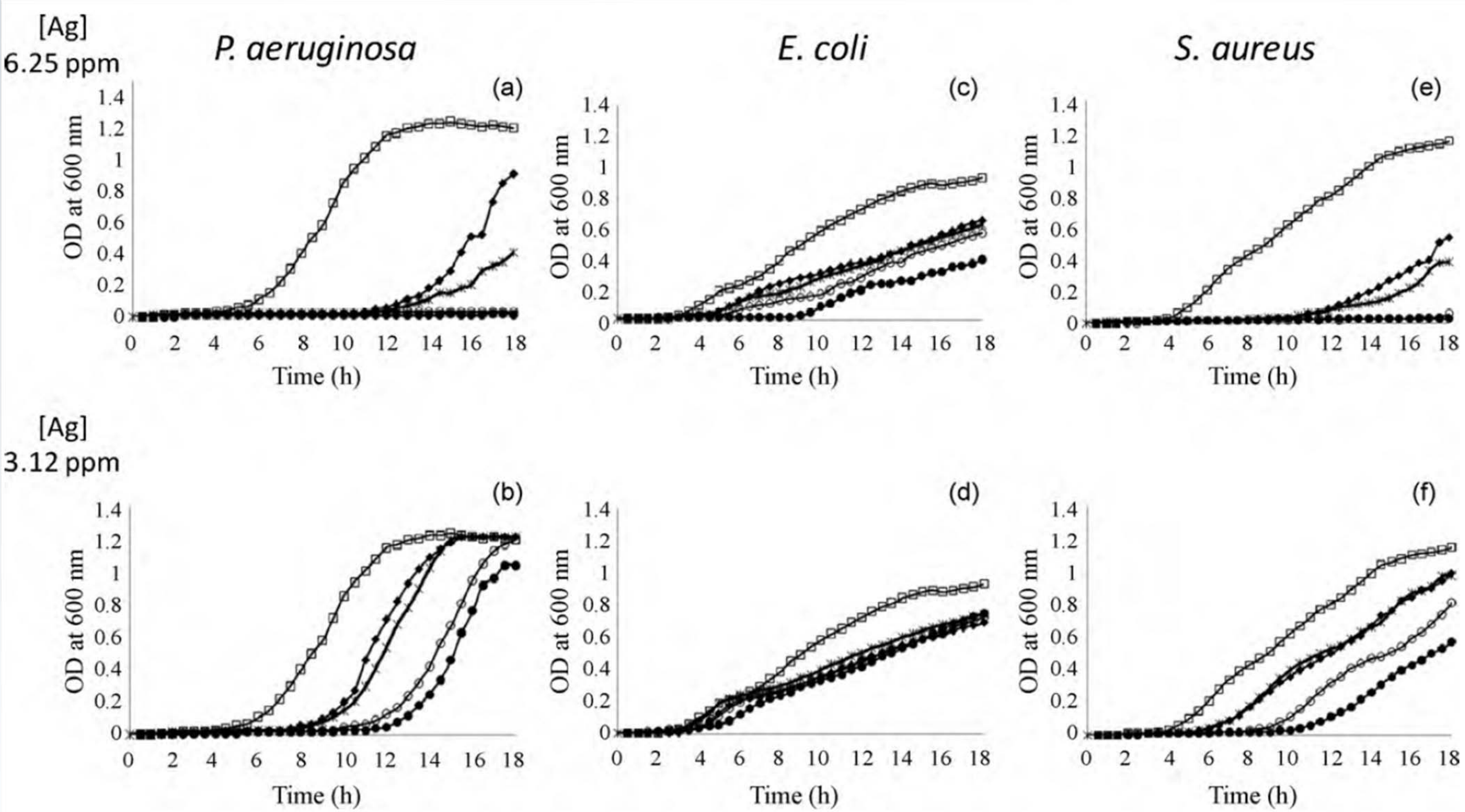
1. Ionic silver inactivates vital cellular enzymes (attacking thiol groups);
2. Trojan-horse mechanisms (internalization and intracellular damages);
3. Oxidative radicals (most generic cytoxic mechanism);
4. Capping ligand-assisted cellular surface attack;





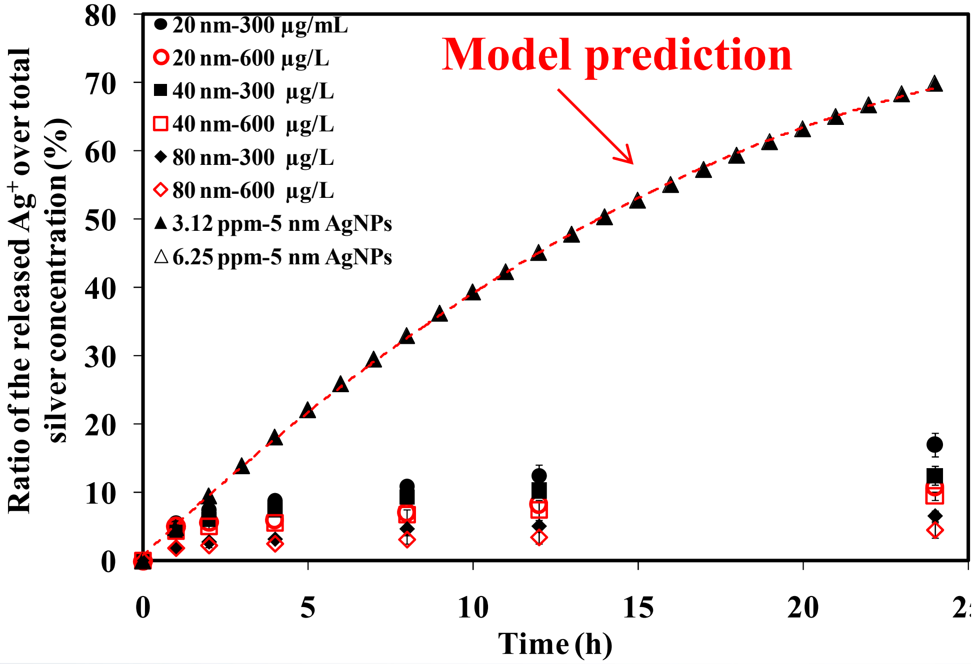
Correlation between ion release and aggregation kinetics and toxicokinetics- AgNPs

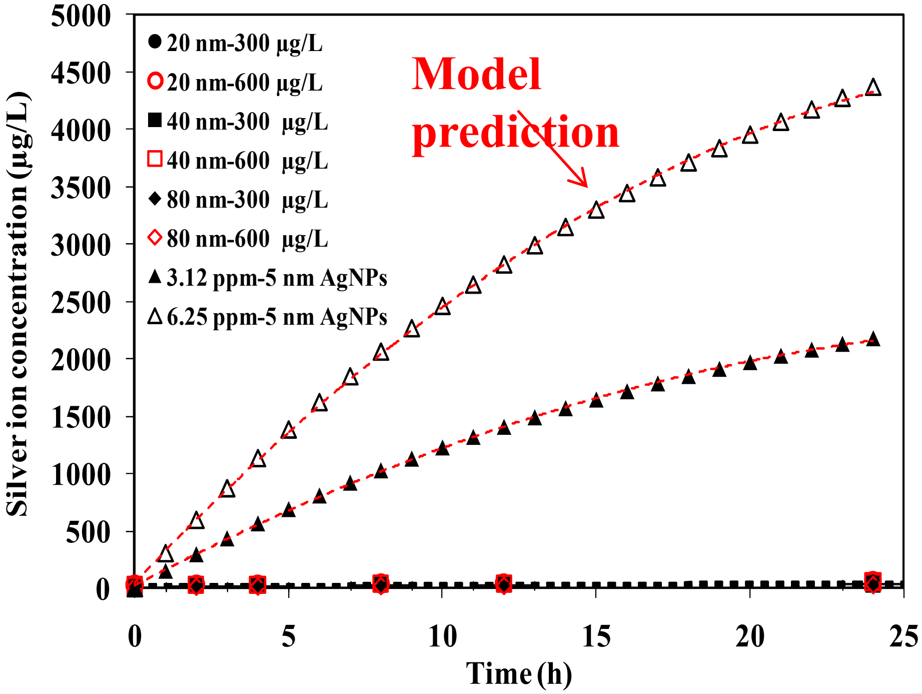
Diameter: 4-6 nm

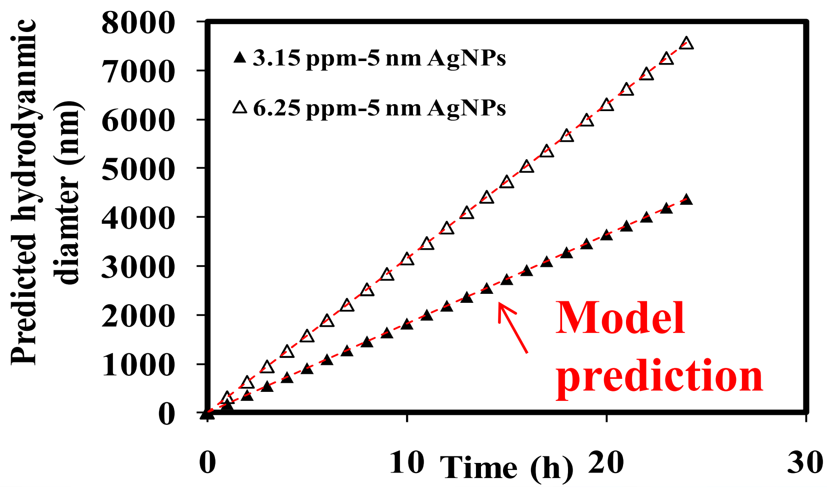


Jaiswal, S.; Duffy, B.; Jaiswal, A. K.; Stobie, N.; McHale, P. Enhancement of the antibacterial properties of silver nanoparticles using beta-cyclodextrin as a capping agent. *International Journal of Antimicrobial Agents 2010, 36 (3), 280-283.*

Correlation between ion release and aggregation kinetics and toxicokinetics- AgNPs







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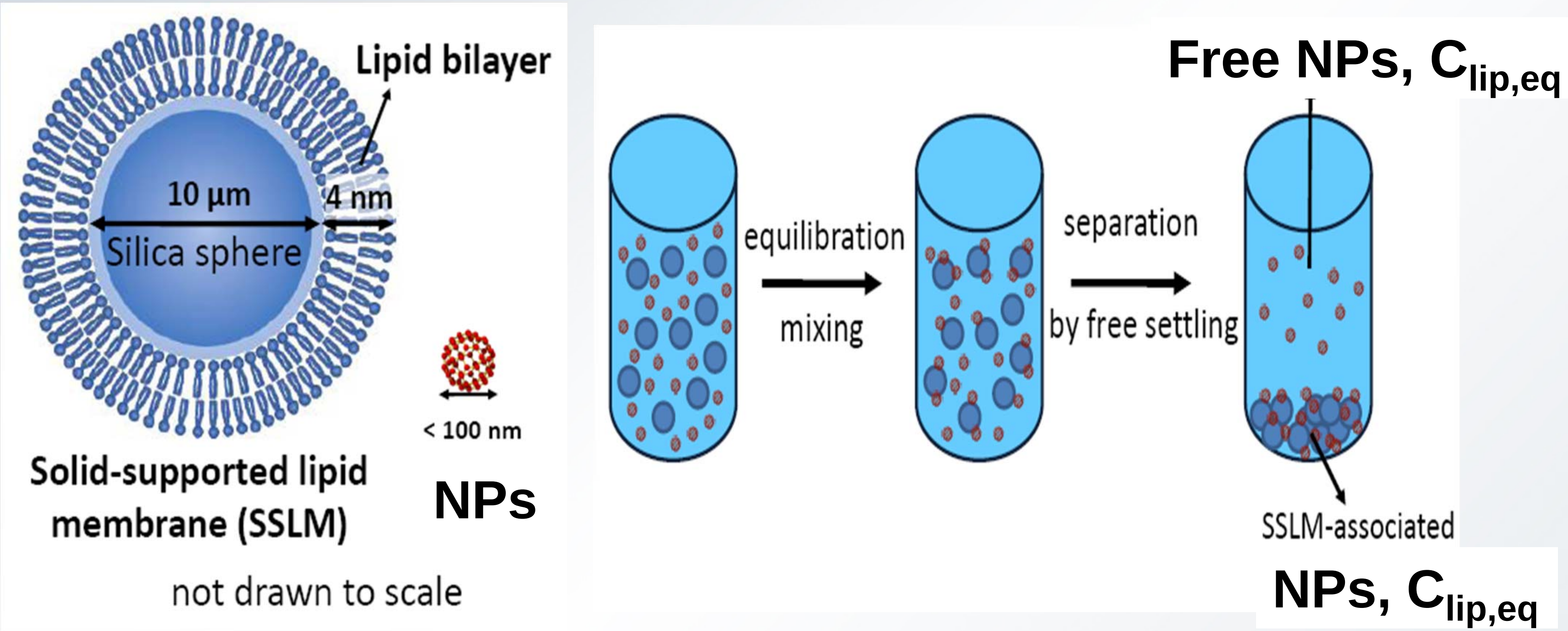
Adsorption kinetics of NPs to lipid bilayers, partial work from Jonathan Posner group



Schematic of adsorption of NPs to lipid bilayers supported on 10 micron silica spheres. These commercially available solid-supported lipid membranes (SSLM) greatly improve the speed and accuracy of measurements and enable the quantification of lipid surface area. Varied concentrations of SSLM and ENMs are placed in glass vials and mixed on a rotary mixer in an end-over-end action. At equilibrium, vials will be sit quiescently, allowing the SSLM beads to settle to the bottom and the supernatants containing free ENMs will be drawn for analysis of concentrations.

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Future Plans

Next Year Plans

- Systematical study of important relevant physiochemical properties of semiconductor nanomaterials, specifically on size, shape and surface properties on biological and environmental interactions.
- Continue cytotoxicity tests with various typical cells (e.g., *E. coli*) at cellular and genetic levels and semiconductor nanoparticles of high interest (e.g., CeO_2);
- Predictive QSAR modeling;
- Development AFM-based imaging tools for visualization of cellular disruption by exposure to NPs;

Long-Term Plans

- Accumulating sufficient data to categorize and prioritize relevant nanoparticles and their characteristics that are used for establishing robust and accurate predictive QSAR models.
- Provide fundamental information for manufacturing environmental benign semiconductor nanomaterials for industries.

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Publications, Presentations, and Recognitions/Awards from GeorgiaTech

➢ Publication

1. Wen Zhang, Madhavi Kalive, David G Capco, and Yongsheng Chen, Adsorption of hematite nanoparticles onto Caco-2 cells and the cellular impairments: effect of particle size. *Nanotechnology.* 2010, 21, 355103.
2. Wen Zhang, Andrew Stack, and Yongsheng Chen, Interaction force measurement between E. coli cells and nanoparticles immobilized surfaces by using AFM. *Colloids and Surfaces B: Biointerfaces.* 10.1016/j.colsurfb.2010.09.003.
3. Wen Zhang, Ying Yao, and Yongsheng Chen Quantifying and Imaging the Morphology and Nanoelectric Properties of Soluble Quantum Dot Nanoparticles Interacting with DNA. *Journal of Physical Chemistry C*. DOI: 10.1021/jp107676h.
4. Wen Zhang, Bruce Rittmann, and Yongsheng Chen. Size effects on adsorption kinetics of hematite NPs on *E. coli* cells. *Environmental Science and Technology.* accepted.
5. Wen Zhang, Ying Yao, Nicole Sullivan, Yongsheng Chen. Kinetics modeling of ion release silver NPs in the environment. *Environmental Science and Technology.* Revision submitted.
6. Kungang Li, Wen Zhang, Ying Huang, and Yongsheng Chen, Modeling the aggregation kinetics of CeO2 nanoparticles in monovalent and divalent electrolytes with EDLVO theory, *Colloids and Surfaces A*, Under review.

➢ Presentation

During year 2008-2010, I attended and made oral presentations in 8 national conferences, including ASM, ACS, USEPA grantees meetings, ICEIN, SRC, IENC, and etc.

➢ Recognitions/Awards

News report for our research: http://nanotechweb.org/cws/article/lab/43670

Acknowledgements

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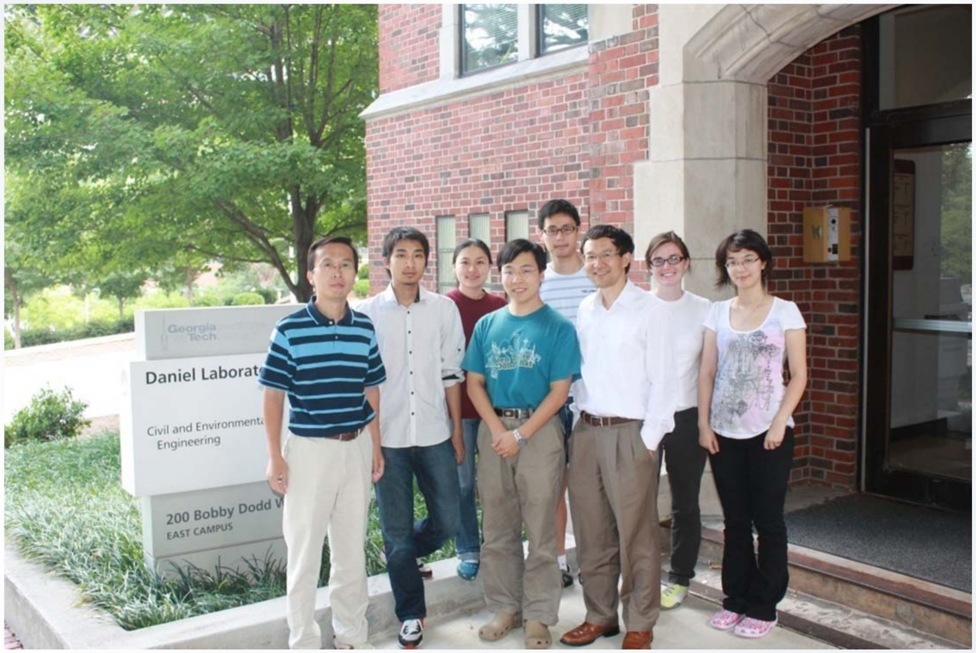

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