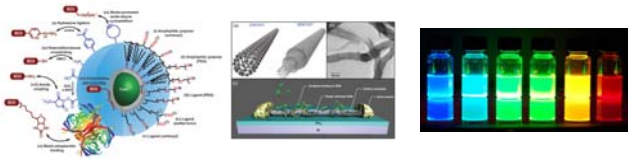
Introduction to BioMEMS & Medical Microdevices

Nanotransducers – Quantum Dots & Nanoparticles

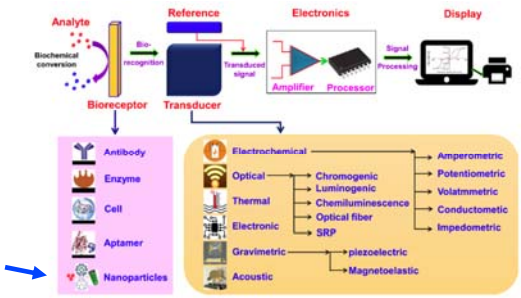
Prof. Steven S. Saliterman, http://saliterman.umn.edu/



Topics

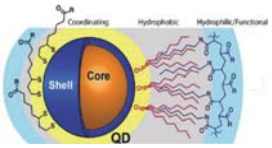
- Nanoparticle transducers:
  - Quantum dots.
  - Carbon dots.
  - Lanthanide nanoparticles.
  - Gold nanoparticles.
- Label free transducers
  - Nanowires
  - Nanotubes
  - Nanocantilevers

Sposito AJ, Kurdekar A, Zhao JQ, Hewlett I. Application of nanotechnology in biosensors for enhancing pathogen detection. *Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology*. 2018;10(5).



Naresh V, Lee N. A Review on Biosensors and Recent Development of Nanostructured Materials-Enabled Biosensors. *Sensors*. Feb 2021;21(4):1109. doi:10.3390/s21041109

Quantum Dots



- Semiconductors nanocrystals of 10-50 atoms, 2-10 nm diam.
- "Tunable" colloidal, meaning they are synthesized in a liquid solution so that their size, shape and surface properties can be controlled.
- Core/shell construction with organic ligand shell for bioconjugation

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Core/Shell Materials…

- The core of a quantum dot is the central part, and it's usually composed of a semiconductor material like cadmium selenide (CdSe), cadmium sulfide (CdS), or indium phosphide (InP).
- The shell is a layer surrounding the core, and it's typically made of a semiconductor with a larger band gap than the core material. Common shell materials include zinc sulfide (ZnS).
- The shell helps to improve the quantum dot's stability and efficiency by passivating surface states and reducing non-radiative recombination.
- There are other materials that can be used for both core and shell materials, such as:

  Core: CdTe, InAs, ZnSe

  Shell: CdS, ZnSe, HgSe, HgTe

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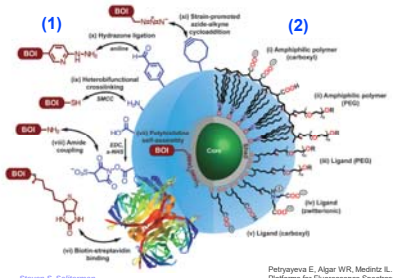
Two Strategies for Bioconjugation…



Two Possible Surface coatings:

1) "Cap exchange" with hydrophilic ligands via the thiol-affinity of the ZnS shell.
2) Encapsulation with amphiphilic polymers.

Petryayeva E, Algar WR, Medintz IL. Quantum Dots in Bioanalysis: A Review of Applications Across Various Platforms for Fluorescence Spectroscopy and Imaging. *Applied Spectroscopy*. 2013;67(3):215-252.

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Cap-Exchange…

- Original hydrophobic stabilizing surface of quantum dots (QDs) is replaced with hydrophilic ligands to make them water soluble and biocompatible.
  - Hydrophilic ligands have strong anchoring groups (such as dihydrolipoic acid, DHLA).
  - Hydrophilic segments (such as polyethylene glycol, PEG) promote water affinity.

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https://chem.fsu.edu/~mattoussi/Pub%20PDF/Susumu%20JACS%202007.pdf
https://www.mdpi.com/1424-8220/11/12/11036

Use as Biosensors…

- QDs are coated with organic molecules and macromolecules to provide aqueous solubility and opportunities for bioconjugation.
  - These coatings can be broadly classified as ligand-based (e.g., mercaptopropionic acid and dihydrolipoic acid) or polymer-based (e.g., polyethylene glycol).
- Multiple QD labels can be excited by a single light source and emit light with minimal spectral overlapping.
  - This allows for multi-target assays without the added cost of filtering excitation light.
- QDs offer better spectral properties than traditional fluorescent dues, including broad excitation spectrum, negligible photobleaching, and a tunable, symmetric and narrow emission spectrum.

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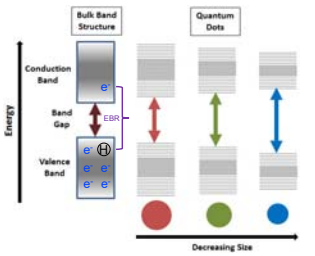
Sposito AJ, Kurdekar A, Zhao JQ, Hewlett I. Application of nanotechnology in biosensors for enhancing pathogen detection. *Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology*. 2018;10(5).

Discrete, Quantized Energy Levels…

- EBR – Exciton Bohr Radius.
- As the size of the crystal decreases, the difference in energy between the highest valence band and the lowest conduction band increases.
- More energy is then needed to excite the dot, and concurrently, more energy is released when the crystal returns to its ground state, resulting in a color shift from red to blue in the emitted light.



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Millipore-Sigma https://www.sigmaaldrich.com/technical-documents/articles/materials-science/nanomaterials/quantum-dots.html

Definition of Exciton Pair & Bohr Radius…

- "Exciton Pair" is defined as an electron and the hole that it leaves behind when it is excited up to the conduction band.
- "Exciton Bohr Radius" is the average distance between the electron in the conduction band and the hole it leaves behind in the valence band.
- Electrons in quantum dots are confined in a small space called a quantum box.
- When the radii of the semiconductor nanocrystal is smaller than the Exciton Bohr Radius there is quantization of the energy levels according to Pauli's exclusion principle (no two identical fermions - like electrons - in a quantum system can occupy the same quantum state simultaneously).

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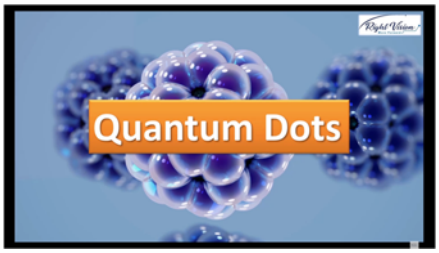
Millipore-Sigma https://www.sigmaaldrich.com/technical-documents/articles/materials-science/nanomaterials/quantum-dots.html

Quantum Dots…



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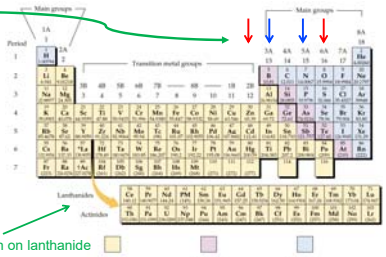
https://youtu.be/0EokkhdppgE

Elements for Quantum Dots…

Inorganic semiconductor crystals composed of members from groups: **2B & 6A** (e.g. **CdTe**, **CdSe**, **ZnS**) or **3A & 5A** (e.g. **InP**) elements.

Diameters from 2 to 10 nm (10-50 atoms).

Cd cadmium
Te tellurium
Se selenium
In indium
P phosphorus
S sulfur
Zn zinc



Later discussion on lanthanide nanoparticles.

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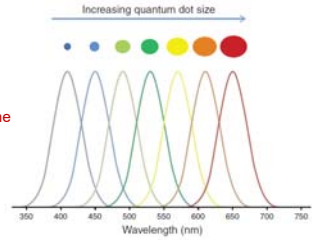
Image courtesy of Prentice Hall, Inc.

Quantum Confinement…

- For a given material, the color can be tuned continuously across a broad spectral range through quantum confinement and control of nanocrystal size.
- Quantum confinement is the term used to describe changes in electronic properties as the number of atoms in a crystal becomes small.
- The onset of quantum confinement coincides with crystal dimensionality below the Exciton Bohr Radius, which is the preferred electron-hole separation, for a semiconductor material (~5 nm for CdSe).



Algar WR, Susumu K, Delehanty JB, Medintz IL. Semiconductor Quantum Dots in Bioanalysis: Crossing the Valley of Death. *Analytical Chemistry*. 2011;83(23):8826-8837.
Sposito AJ, Kurdekar A, Zhao JQ, Hewlett I. Application of nanotechnology in biosensors for enhancing pathogen detection. *Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology*. 2018;10(5).

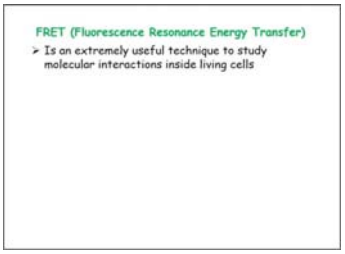
Efficiency and Brightness…

- Growing shells of another *higher band gap* semiconducting material improves efficiency and brightness.
- *Alloyed semiconductor quantum dots* allow tuning of the optical and electronic properties by merely changing the composition and internal structure without changing the crystallite size.

Millipore-Sigma https://www.sigmaaldrich.com/technical-documents/articles/materials-science/nanomaterials/quantum-dots.html

FRET – Fluorescence Resonance Energy Transfer

Movie:



FRET is also called *Förster Resonance Energy Transfer*

https://youtu.be/qwMdtqgdap0

Requirements for ET…

- The ability of QDs to engage in FRET, FRET-based biosensing, and other forms of energy transfer depend on:
  - Type and quality of QD material used.
  - Photophysical properties.
  - How the QD was colloidally stabilized in aqueous media and made biocompatible (which, in turn, reflects the choice of surface ligand type utilized).
  - How the QD was modified with it; and how the bioconjugate structure was formed along with its intrinsic physicochemical properties.

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Hildebrandt N, Spillmann CM, Algar WR, et al. Energy Transfer with Semiconductor Quantum Dot Bioconjugates: A Versatile Platform for Biosensing, Energy Harvesting, and Other Developing Applications. *Chemical Reviews*. 2017;117(2):536-711.

Carbon Quantum Dots

- Carbon dots are small carbon nanoparticles, whereas quantum dots are small semiconductor particles.
- Fluorescent labels for DNA, aptamers, proteins, glucose, phosphate, metal ions, etc.
- Size <10 nm.
- No toxic heavy metals.
- Classified based on the carbon cores – nanodot, graphene quantum dots and polymer dots.

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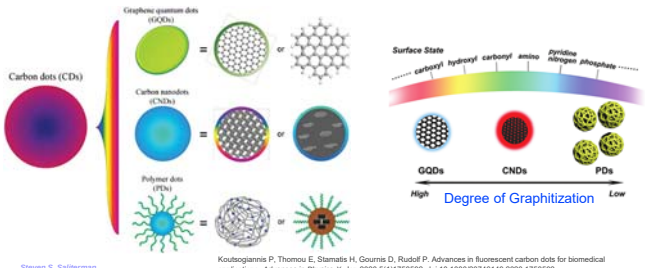
Degree of Graphitization Changes Surface State…



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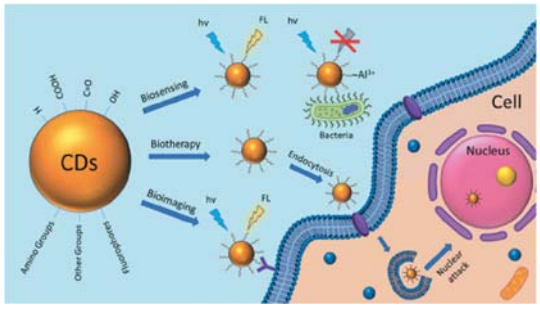
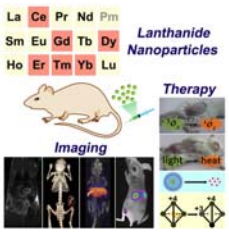
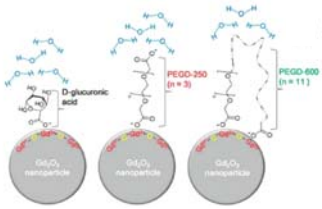
Koutsogiannis P, Thomou E, Stamatis H, Gournis D, Rudolf P. Advances in fluorescent carbon dots for biomedical applications. *Advances in Physics-X*. Jan 2020;5(1)1758592. doi:10.1080/23746149.2020.1758592



Koutsogiannis P, Thomou E, Stamatis H, Gournis D, Rudolf P. Advances in fluorescent carbon dots for biomedical applications. *Advances in Physics-X*. Jan 2020;5(1)1758592. doi:10.1080/23746149.2020.1758592

Lanthanide Nanoparticles





D-glucuronic acid, PEGD-250, and PEGD-600 on the ultrasmall Gd_2O_3 NPs

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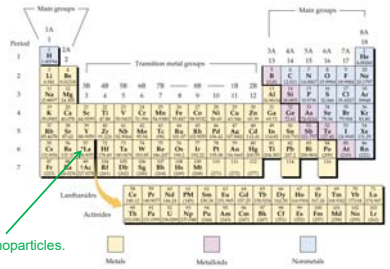
Dong H, Du SR, Zheng XY, et al. Lanthanide Nanoparticles: From Design toward Bioimaging and Therapy. *Chemical Reviews*. Oct 2015;115(19):10725-10815. doi:10.1021/acs.chemrev.5b00091

Lanthanide Luminescent Nanoparticles…

Lanthanide luminescent nanoparticles are composed of ions from elements located in the sixth period and IIIB group in the periodic table.



Lanthanide nanoparticles.

Image courtesy of Prentice Hall, Inc.

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- The key feature of lanthanide luminescence is that lanthanide ions have exceedingly long-lived luminescence (μs to ms range), as opposed to conventional dyes that luminesce on the nanosecond scale.
- Enhanced sensitivity of lanthanide materials makes them popular alternatives to conventional fluorescent dyes for use in diagnostics.

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- Lanthanide-based labels have the unique ability to be probed after the extinction of luminescence from background noise.
  - This leads to improved ability to resolve analyte signal at lower concentrations where back-ground noise would normally suppress that signal.
  - Done with Time Resolved Fluorometry (TRF) - a fluorescence detection technique that measures the intensity decays and delayed emission signals of fluorophores
- Lanthanide based probes also exhibit excellent photostability, large Stokes shift (>150 nm), and sharp-band emissions (<10 nm full width at half-maximum).

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Gold Nanoparticles (Noble Metals)

- Gold nanoparticles (AuNPs) are small gold particles with a diameter of 1 to 100 nm which, once dispersed in water, are also known as colloidal gold.
  - Gold and silver nanoparticles have been studied extensively for use with local surface plasmon resonance (LSPR).
- This appears as an absorption peak in the visible spectra .
- Nanoclusters show superior biocompatibility.
  - Yet comparable to QDs in terms of their size dependent emissions, strong photoluminescence, and photostability.

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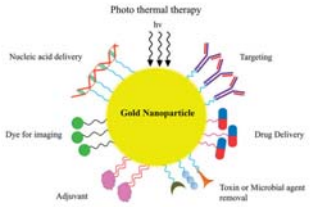
Applications…



AuNP	Size	Application
Nanocages	40×60nm	Drug loading
Nanoshell	50nm	Toxic drug delivery and Bioimaging
Nanostars	45-120 nm	Bioconjugation
Nanorods	10×40 nm	Immunomagnetic separation and Particle Diffusion

Examples of AuNPs used in phototherapy.

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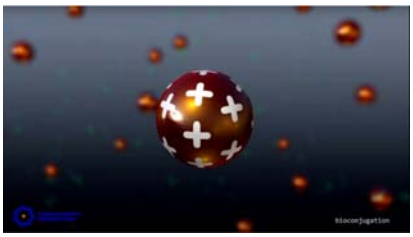
Bagheri S, Yasemi M, Safaie-Qamsari E, et al. Using gold nanoparticles in diagnosis and treatment of melanoma cancer. *Artificial Cells Nanomedicine and Biotechnology*. 2018;46:S462-S471. doi:10.1080/21691401.2018.1430585

Gold Nanoparticle Bioconjugation…



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https://www.youtube.com/watch?v=-0qfa65hI8M

Features…

- Nobel metal nanoparticles can have a metal core consisting of one element, or be composed with a shell of a different metal (i.e., gold-silver core-shell nanoparticles).
  - These bimetallic nanoparticles have the advantage of taking properties from both metals to enhance their optical and electronic properties over monometallic nanoparticles.
- At sizes smaller than 3 nm noble metal nanoparticles are called nanoclusters.
  - Nanoclusters do not display SPR absorption in the visible region, but possess fluorescence emission in the near-infrared to visible region.
  - The wavelength of emission can be tuned by controlling the size of the cluster, making nanoclusters very useful fluorescent biosensor labels.

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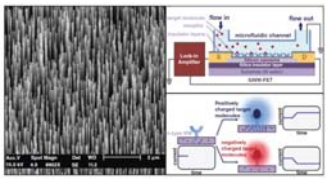
Label-Free Transduction

- Nano wires
- Nanotubes
- Nanocantilevers

Nanowires

- Silicon nanowires (SiNWs) are high aspect ratio wires that typically have a diameter of <100 nm, and have been employed recently in highly sensitive microfluidic detection platforms for nucleic acids. Recall FETs:

SEM image of the nitrogen-doped ZnO nanowire array.



SiNW-FET integrated into a microfluidic device for biosensing.

Shen, M.-Y., Li, B.-R., & Li, Y.-K. (2014). Silicon nanowire field-effect-transistor based biosensors: From sensitive to ultra-sensitive. Biosensors and Bioelectronics, 60, 101–111. https://doi.org/10.1016/j.bios.2014.03.057.

Attachment Options…

1. Electrostatic Absorption
   - Employs electrostatic attraction to absorb ionic species onto oppositely charged absorbents and has been successfully applied for capturing DNA with negatively charged oligo probes linked to an amine-terminated layer on the nanowire.
2. Covalent Bonding
   - Silane chemistry is used to introduce amino terminal groups on the SiNW surface that react with aldehyde, carboxylic acid, and epoxy groups present on proteins and other biomolecules

Sposito AJ, Kurdekar A, Zhao JQ, Hewlett I. Application of nanotechnology in biosensors for enhancing pathogen detection. *Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology*. 2018;10(5).

Features…

- Charged biomolecules bind to the surface of the nanowire and alter its electric field.
- Quantum confinement is possible with diameters less 2.2 nm.
- A single binding event may cause sufficient charge leading to *depletion or accumulation* of carriers throughout a much larger percentage of the conducting channel cross-section.
- *Dopants or addition of Au or Ag nanoparticles increases sensitivity.*

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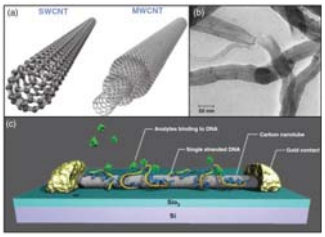
Sposito AJ, Kurdekar A, Zhao JQ, Hewlett I. Application of nanotechnology in biosensors for enhancing pathogen detection. *Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology*. 2018;10(5).

Nanotubes

Hollow cylindrical tubes made up of carbon atoms.

a) Single-walled carbon nanotube (SWCNT) and multiwalled carbon nanotube (MWCNT).
b) TEM images of MWCNTs.
c) A graphic of a DNA functionalized CNT field effect transistor.

Dimensions from 1-100 nm x centimeters



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a) Gajewiczet et al. (2012).; b) Abbasi, Zebarjad, Baghban, and Youssefi (2015); c) Johnson (2017).

Features…

- High aspect ratio, high conductivity, high mechanical strength, and biocompatibility make them excellent electrode materials for use in biosensors.
- SWCNTS can act as either semi-conducting, or metallic in nature depending on the chirality of the structure, while MWCNTS will exhibit metallic behavior if only a single layer within is metallic.
- *Fabricated by three techniques: laser ablation, electric arc discharge, and chemical vapor deposition.*

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Sposito AJ, Kurdekar A, Zhao JQ, Hewlett I. Application of nanotechnology in biosensors for enhancing pathogen detection. *Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology*. 2018;10(5).

- The most common functionalization strategy is to treat the CNTs with *acids to expose oxides* on the surface.
  - These carboxylates can be linked to the amino groups on nucleotides or proteins using a carbodimide procedure.
    - This reduces van der Waals interactions, improving dispensability and solubility.
    - Also leads to decreased electron transport critical to biosensor sensitivity.
- Often integrated into FETs and used as electrochemical sensors for DNA, proteins, cells, and other pathogen biomarkers.

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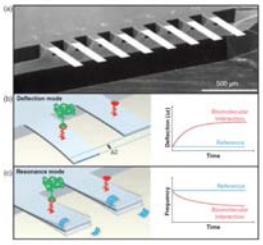
Sposito AJ, Kurdekar A, Zhao JQ, Hewlett I. Application of nanotechnology in biosensors for enhancing pathogen detection. *Wiley Interdisciplinary Reviews-Nanomedicine and Nanobiotechnology*. 2018;10(5).

Nanocantilevers

- Nanocantilevers are flexible beams typically constructed of silicon, silicon nitride, or quartz that are clamped on one side.
  - Cantilever array based artificial nose.
  - Cantilever deflection mode of biomolecule detection.
  - Cantilever resonance mode of biomolecule detection.



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a) Baller, M. K., Lang, H. P., Fritz, J., Gerber, C., Gimzewsk, J. K., Drechsler, U., ... Guntherodt, H. J. (2000). A cantilever array-based artificial nose. Ultramicroscopy, 82(1–4), 1–9. https://doi.org/10.1016/S0304-3991(99)00123-0
b, c) Hwang, K. S., Lee, S. M., Kim, S. K., Lee, J. H., & Kim, T. S. (2009). Micro- and nanocantilever devices and systems for biomolecule detection. Annual Review of Analytical Chemistry, 2,77–98. https://doi.org/10.1146/annurev-anchem-060908-155232.

Features…

- Beams are functionalized with biorecognition elements to absorb target analytes if they are present in sample.
  - The analyte adds mass to the beam which affects the beams conformational or *resonant* properties.
- Nanoscale dimensions results in better sensitivity and increased surface-to-volume ratio which enhances the target capture efficiency.

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Types of Cantilevers…

- Static Devices
  - An analyte binds to the beam causing surface stress that deflects the beam up or down proportional to the amount of target. Detectable by reflected laser light or piezoelectrically.
  - Able to operate in a variety of buffers.
- Dynamic Excitation Devices
  - the cantilever is *actuated* and the added mass of captured target will produce a shift in the cantilever's resonant frequency.
  - Lower limits of detection compared to static.
  - Aqueous buffers dampen the signal.

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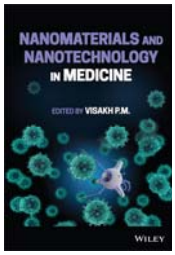
Further Reading…



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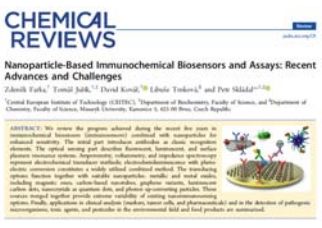
Wongkaew N, Simsek M, Griesche C, Baeumner AJ. Functional Nanomaterials and Nanostructures Enhancing Electrochemical Biosensors and Lab-on-a-Chip Performances: Recent Progress, Applications, and Future Perspective. *Chem Rev*. Jan 2019;119(1):120-194. doi:10.1021/acs.chemrev.8b00172
Sheikh FA, Sheikh FA. *Application of Nanotechnology in Biomedical Sciences*. Springer; 2020.
Visakh PM. Nanomaterials and nanotechnology in medicine medical applications: Challenges and opportunities. 2022:1-25.

More Reading…



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Farka, Z. et al., Nanoparticle-based immunochemical biosensors and assays: Recent advances and challenges. Chemical Reviews, 2017;117(15) 9973-10042.
Hildebrandt N, Spillmann CM, Algar WR, et al. Energy Transfer with Semiconductor Quantum Dot Bioconjugates: A Versatile Platform for Biosensing, Energy Harvesting, and Other Developing Applications. *Chem Rev*. Jan 2017;117(2):536-711. doi:10.1021/acs.chemrev.6b00030

Key Points

- Quantum dots are colloidal semiconductor nano-crystals with core and shell structure that can be modified with biological moieties.
  - They consist of 10-50 atoms, with a diameter of 2-10 nanometers.
  - They can be coupled with other molecules and nanomaterials through both bioconjugation and energy transfer (ET) processes.
  - When the radii of the semiconductor nanocrystal is smaller than the Exciton Bohr Radius there is quantization of the energy levels according to Pauli's exclusion principle.
  - For a given material, the color can be tuned continuously across a broad spectral range through quantum confinement and control of nanocrystal size.

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- Multiple QD labels can be excited by a single light source and emit light with minimal spectral overlapping.
- Surface coating strategies include encapsulation with amphiphilic polymers and cap exchange with hydrophilic ligands.
- Semiconductor QDs engage in both Förster resonance energy transfer (FRET) and electron/charge transfer (ET & CT).
- The ability of QDs to engage in FRET, FRET-based biosensing, and other forms of ET directly depend on type of QD, photophysical properties, method of colloidal stabilization, and the bioconjugate structure.

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- Carbon nanotubules are small carbon nanoparticles (<10 nm) used as fluorescent labels for DNA, aptamers, proteins, glucose, phosphate, metal ions, etc.
- Lanthanide luminescent nanoparticles have exceedingly long-lived luminescence (μs to ms range) and enhanced sensitivity, compared to conventional dyes.
- Gold and silver nanoparticles have been studied extensively for use with local surface plasmon resonance (LSPR). Show superior biocompatilbity.
- Label-free transducers include nanowire, nanotubes and nano cantilevers.

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