Molecular Modeling Strategies for Predicting the Toxicity of Nanomaterials

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MOLECULAR MODELS

Background Information

What is Nanotechnology? Technologies that have functionality at sub-micron scales (10-100 nm), about the size of macromolecules.

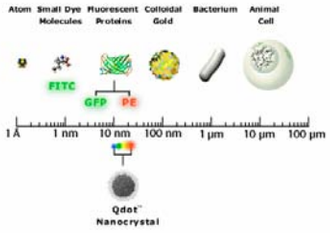

Image taken from: http://www.nanotech-now.com/2003-Awards/

Materials based on nanotechnology (i.e., nanomaterials) are designed and fabricated from molecules that have interesting functional properties on the nanometer length scale. Nanotechnology can be utilized to create or improve the properties of advanced materials and devices, with applications in a broad range of areas:

- Textiles
- Electronics
- Medical diagnostics
- Tissue engineering
- Paints and coatings
- Therapeutic vehicles

Due to their miniscule size, nanotechnologies have the potential to provide both novel applications and challenging risks to the environment and human health.

Physicochemical Characteristics

Nanotechnologies have functional properties that *distinctly differ* from bulk properties, such as biological, chemical, electrical, mechanical, optical, and/or magnetic. In addition, the following characteristics make them unique[1]:

- **Size and shape:** The nanometer dimensions enable innovative applications for the technologies
- **Surface structure:** Chemical reactivity, surface area effects, surface groups, functionalized coatings
- **Chemical composition and morphology:** purity, crystallinity, porosity
- **Interactions:** solubility, aggregation

Challenges with Computational Nanotoxicology

- Current understanding of potential toxicity of nanomaterials is limited
- The same characteristics that make nanotechnologies unique might also impact biological activity and kinetics
- Differential molecular aspects of the mode of toxicity: getting "lodged" in fibrous materials such as lung tissues, different binding regions on proteins or DNA
- Current molecular modeling methods may not be sufficient

Goals

We are devising computational strategies for assessing the potential risks of nanomaterials. We are currently focusing our studies in two main areas:

(1) Predicting the potential health risks, such as skin sensitization, that can occur from prolonged exposure to functional textiles that are derived from nanotechnology.

(2) Developing inverse virtual screening tools that predict potential biological targets for nanotechnologies that might lead to adverse health effects.

Contact Information

We are currently seeking collaborative opportunities!

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References

1) A. Nel, T. Xia, L. Mädler, N. Li, *Science* 311:622 (2006). K.W. Powers, S.C. Brown, V.B. Krishna, S.C. Wasdo, B.M. Moudgil, S.M. Roberts, *Toxicol. Sci.* **90:** 296-303 (2006).

2) J.P. Ryman-Rasmussen, J.E. Riviere, N.A. Monteiro-Riviere, *Toxicol. Sci.* **91:** 159-165 (2006). G.J. Nohynek, J. Lademann, C. Ribaud, M.S. Roberts, *Crit. Rev. in Tox.* **37:** 251-277 (2007).

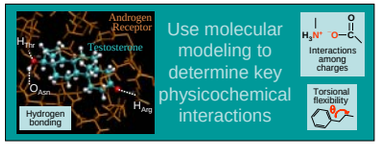
3) Z.L. Ji, Y. Wang, L. Yu, L.Y. Han, C.J. Zheng, Y.Z. Chen, *Tox. Lett.* **164:** 104-112 (2006).

Methodology

These computational strategies utilize molecular modeling methods to calculate the physicochemical interactions between nanomaterials and potential targets that can lead to a toxic outcome.

Link Structure, Dynamics, and Function

Relate the structure and dynamics of macromolecules (proteins and polymers) to their function



Calculate essential dynamics modes from molecular dynamics simulations

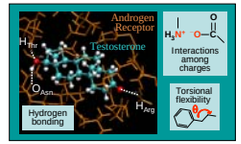
Tools for Predicting Health Effects

The physicochemical interactions and the structural and dynamical information that is pertinent to the function of nanomaterials is being used to develop quantitative structure-activity relationships (QSAR).

We are utilizing these QSAR models and the partial coarse-grained models to predict the potential health risks of nanomaterials, and we are currently focusing on skin sensitization.[2]

Computational Strategies for Interacting Molecules

We are developing a partial coarse-grained model for macromolecules that contains the pertinent structural, dynamical, and chemical characteristics and is thermodynamically sound. These models can be used to study a system of interacting molecules.



Physicochemical interactions and structural and dynamical information

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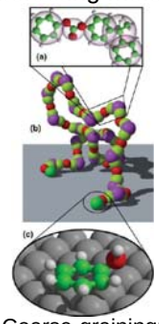
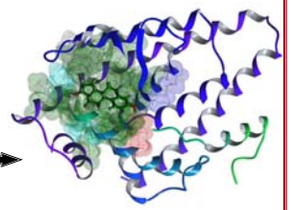


Coarse-graining: Each "bead" represents a structural unit



Partial coarse-grained model for macromolecules contains atomic detail in key regions (such as active site), and the rest of the structure is coarse-grained

Inverse Virtual Screening Tools

Inverse virtual screening tools enable potential targets of toxicity to be identified.[3] We will be utilizing the partial coarse-grained model for macromolecules in order to develop inverse virtual screening strategies. The advantage to using this approach is that pertinent structural and dynamical information will be included during the screening, and hence lead to improved accuracy.