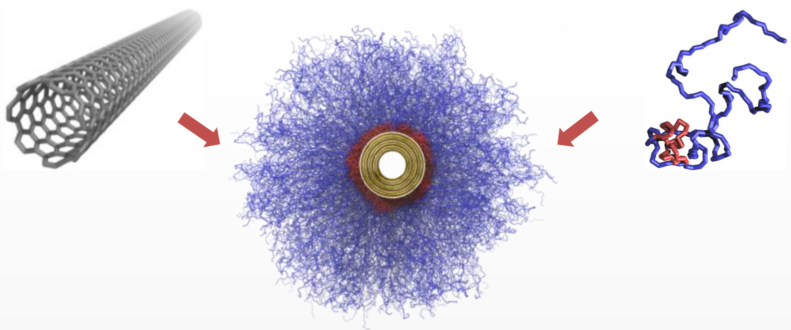
Pluronics and CNTs: Modeling and Toxicity

SRC-ERC Teleseminar Series, July 26th 2012

Part I

Computer Modeling of Pluronic:CNT Composites

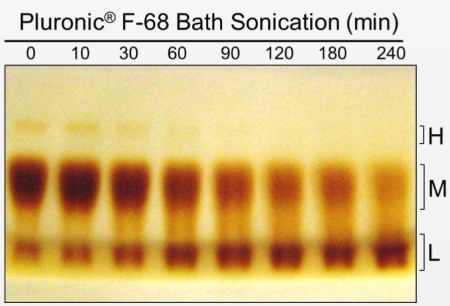
R. J. K. Udayana Ranatunga



Part II

Sonication of Pluronic Polymers Induces Toxic Degradation Products

Ruhung Wang

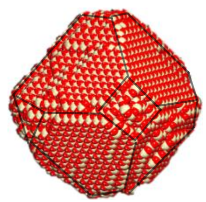


The University of Texas at Dallas
BioNanosciences Group

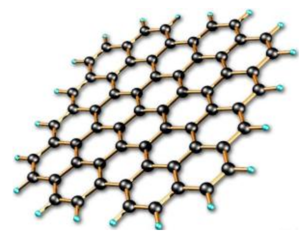
Dispersion, Bioaccumulation, and Mechanisms of Nanoparticle Toxicity

Nanoparticle(NP) Material: Varying shapes and surface chemistries

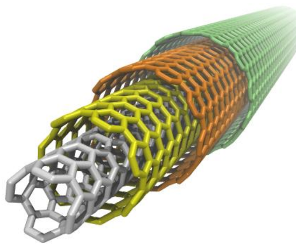
Spherical C_{60}



Faceted Ceria



Planar Graphene Oxide



Cylindrical MWCNTs

- Focuses
  1. Dispersant mechanism / effectiveness
  2. Correlation of NP aggregation state and toxicity
  3. Tracking cellular uptake and concentration of NPs

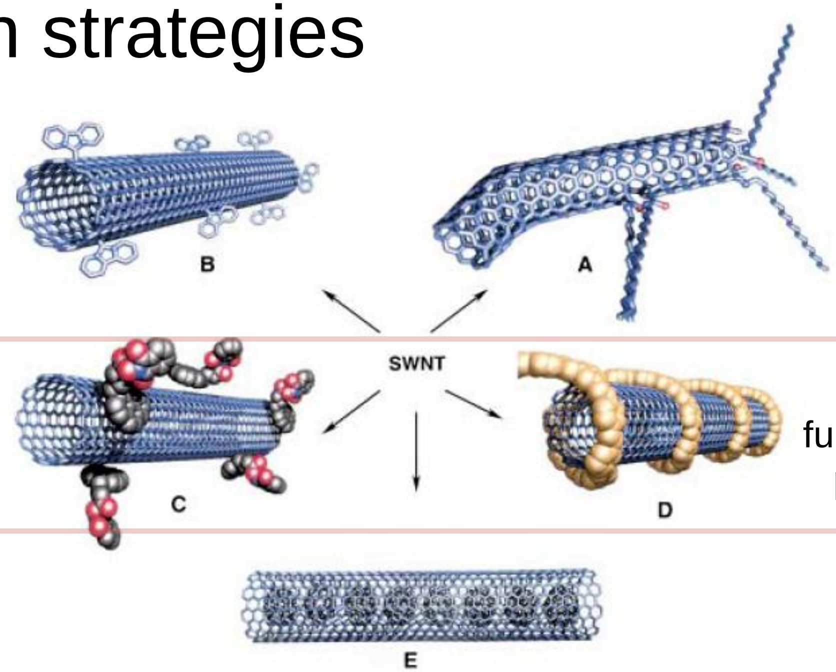
Characterization ⟷ **Modeling** ⟷ **Biological Testing**

The Bundling of Nanotubes

- Carbon nanotubes (CNTs) aggregate in water
  - Hinders processing, controlled assembly
  - Aggregation implicated in toxicity
- Dispersion strategies

covalent sidewall functionalization

defect-group functionalization



Noncovalent functionalization with surfactants

Noncovalent functionalization with polymers/ peptides

endohedral functionalization

Hirsch A. Angew. Chem. Int. Ed. 2002, 41, No. 11; 1853-1859

Dispersion of CNT with Pluronic Polymer

- Dispersing agents promote separation of particle aggregates / clumps
  - Improve processability, handling of material
  - Aid in nanomaterial remediation
- Pluronics are an amphiphilic tri-block copolymer which can be used as a nanotube dispersant

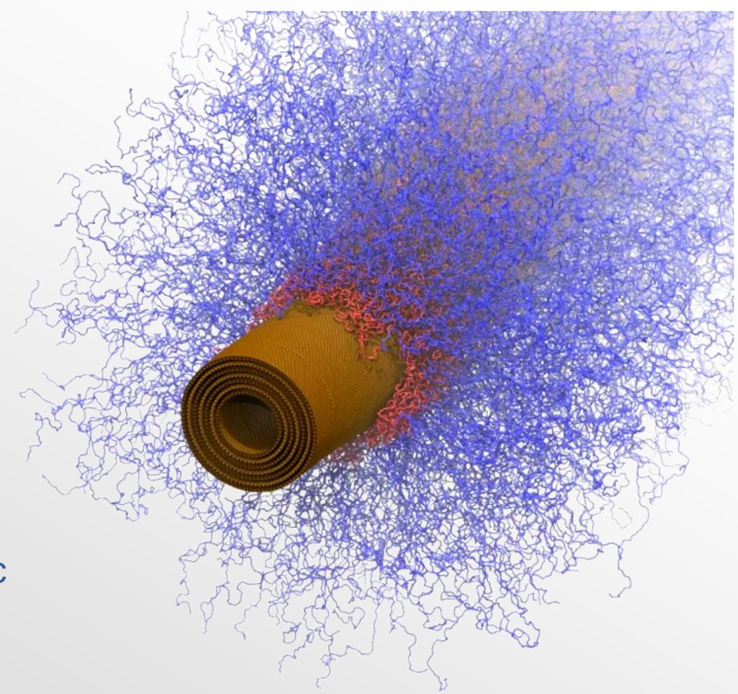
Pluronics®

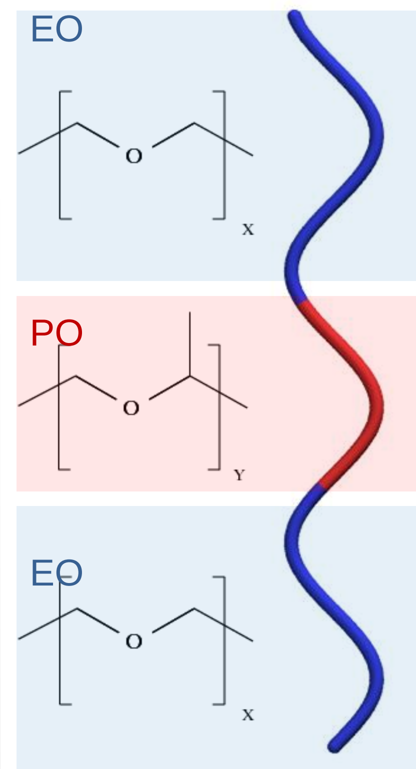
- Commercially available
- FDA approved
- Block lengths vary

naming convention

F68

- F: physical state
- 6: hydrophobic block mass
- 8: x10 = % hydrophilic



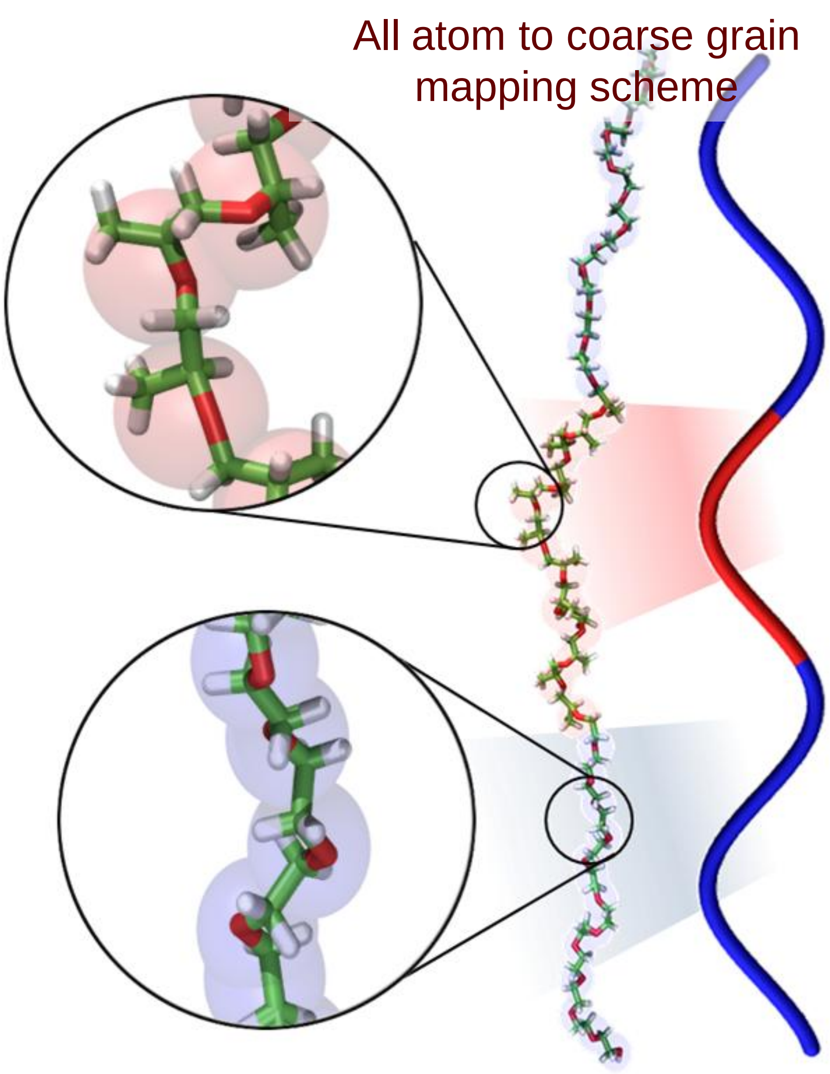


Modeling Pluronics

- Interested in modeling Pluronic:CNT composites

- **Existing Pluronic models**
  - All atom representation
  - Too detailed!
  - Cannot simulate adequate sizes

- **Need to create a coarse grained (CG) model**
  - All atom simulations used to set bonded interactions
  - Experiment data (density, surface energies) used to tune non-bonded interactions

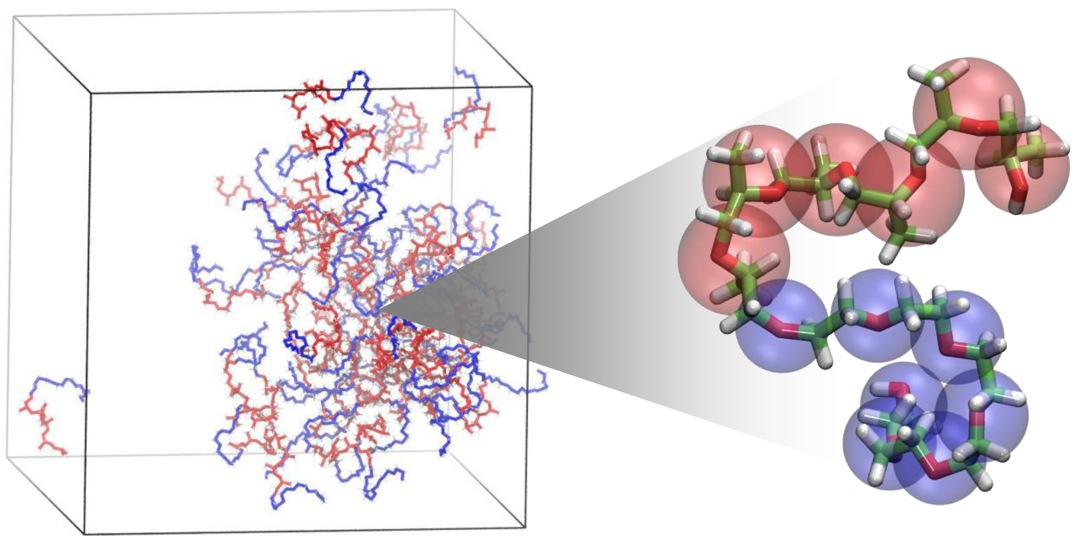


Bonded Parameters

- **Bonded parameters**
  - Dictate the vibrations and flexibility of a molecule

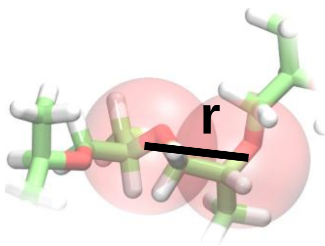
- **Parametrization strategy**
  - Carry out all atom simulations to obtain target data for CG model
  - Iteratively tune CG model parameters to arrive at target data

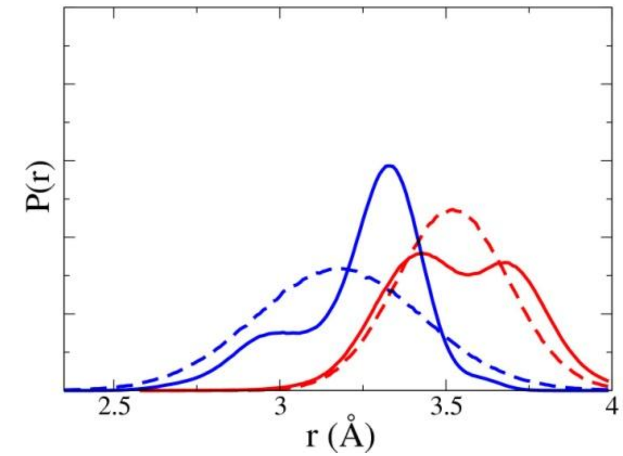
All atom simulation



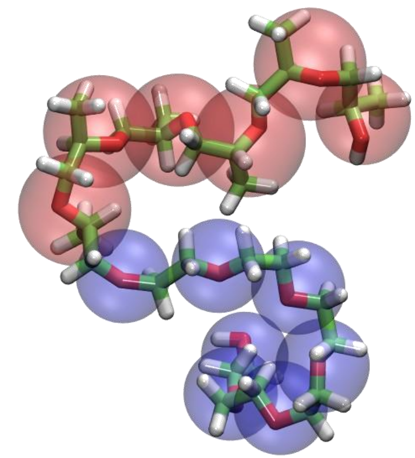
Bonded Parameters

Bond stretching

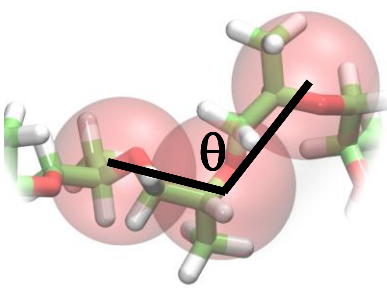


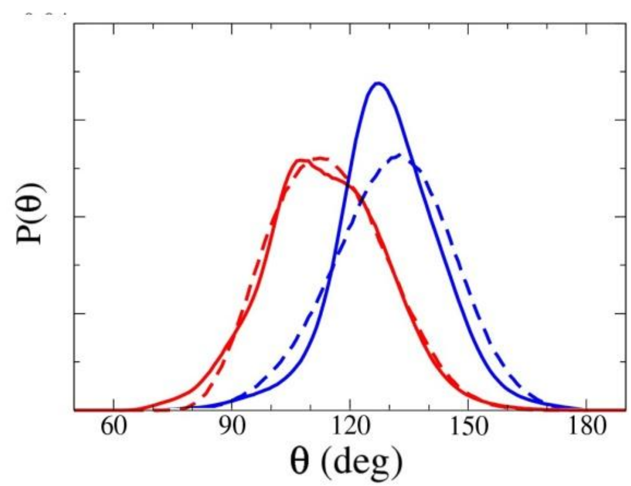


$$U(r) = \tfrac{1}{2} k_r \left(r - r_0\right)^2$$



Bond bending





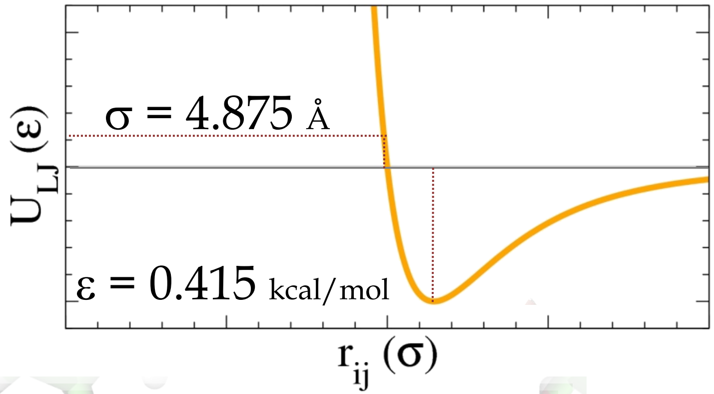
$$U(\theta) = \tfrac{1}{2} k_\theta \left(\theta - \theta_0\right)^2$$

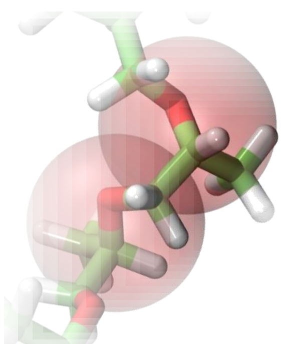
— Target all atom data

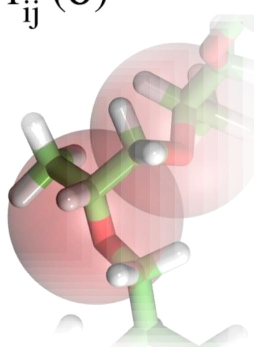
- - CG model data

Non-bonded Parameters

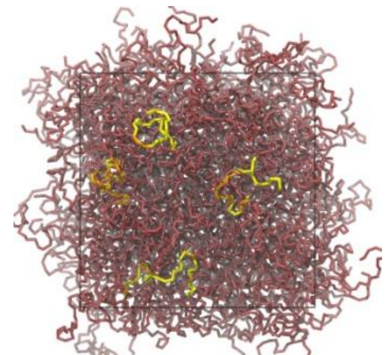
$$U_{lj}(r) = \frac{27}{7}\varepsilon\left\{\left(\frac{\sigma}{r_{ij}}\right)^9 - \left(\frac{\sigma}{r_{ij}}\right)^6\right\}$$

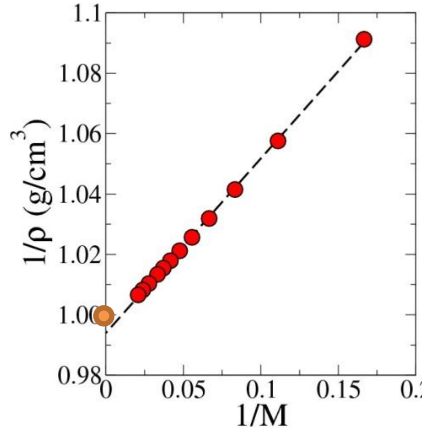






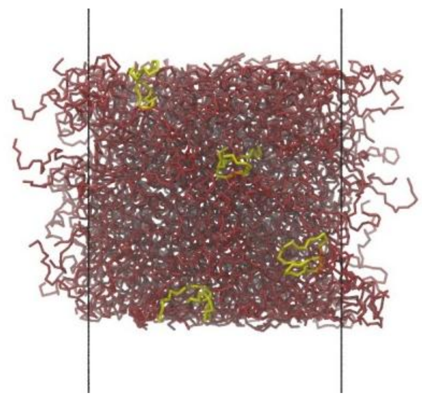
Density

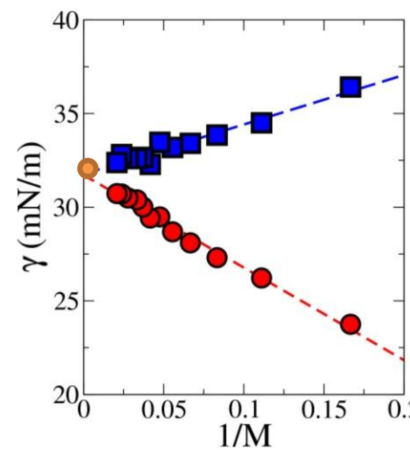




$$\rho(M) = \left(\frac{1}{\rho_\infty} + \frac{2V_e}{M}\right)^{-1}$$

Surface Tension





$$\gamma = \gamma_\infty - \frac{k_0}{M_n}$$

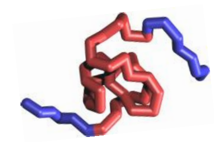
- Density depends mostly on σ
- Surface tension depends mostly on ε

Pluronics in Water

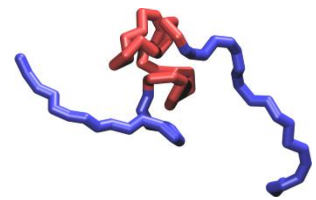
- Focus on three specific Pluronics,
  - **L62 : $(EO)_6(PO)_{35}(EO)_6$**

  - **P65 : $(EO)_{19}(PO)_{29}(EO)_{19}$**

  - **F68 : $(EO)_{77}(PO)_{29}(EO)_{77}$**

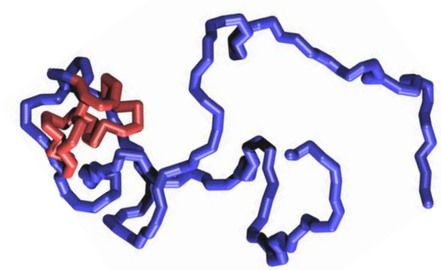


L62



P65

F68

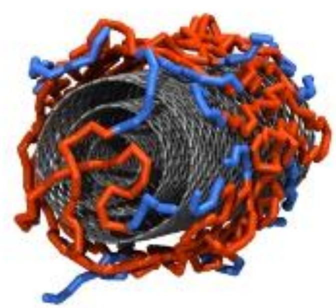


- Hydrophobic length remains constant, hydrophilic length increases:

  L62, P65, F68

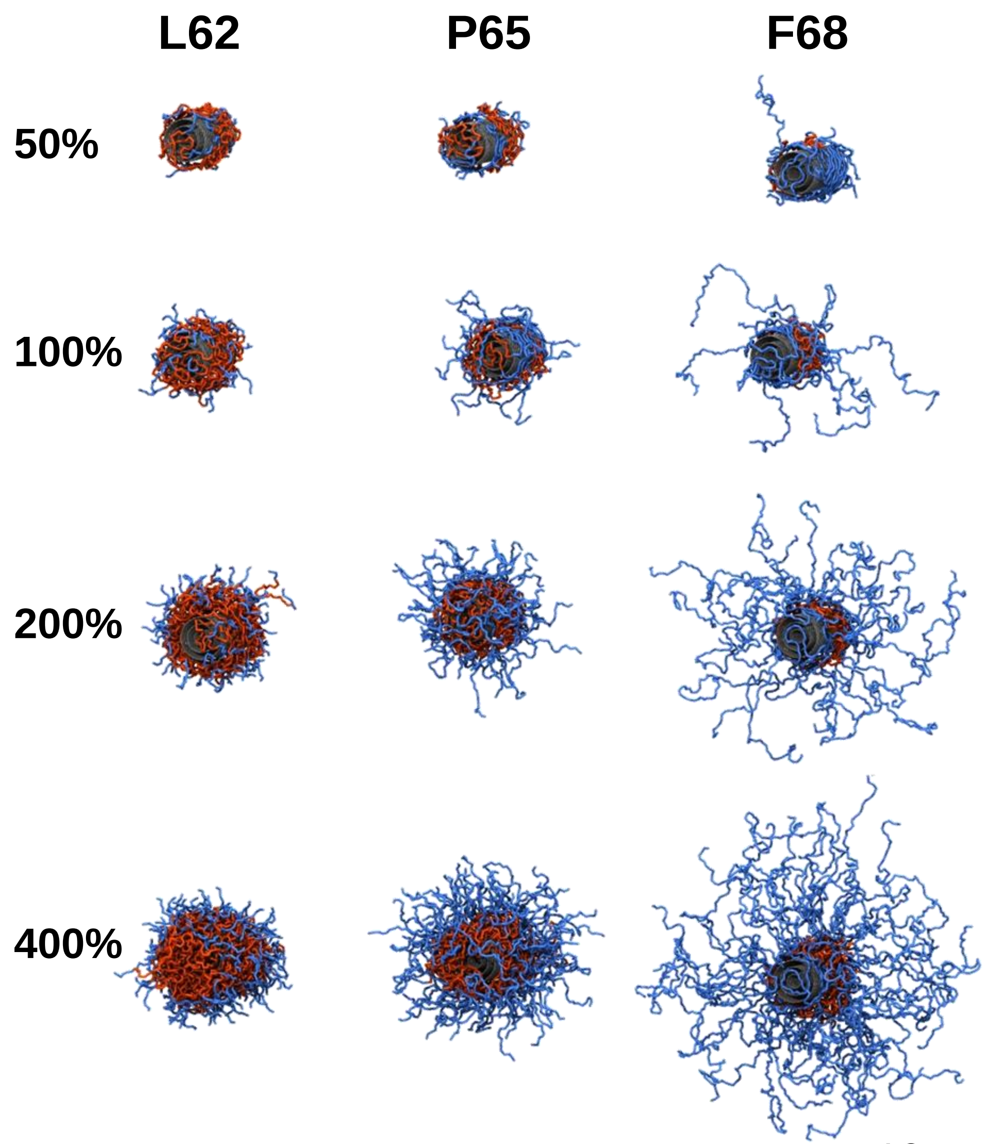
Pluronic:Nanotube in Water

- Study Pluronics coating Multi-Walled CNT



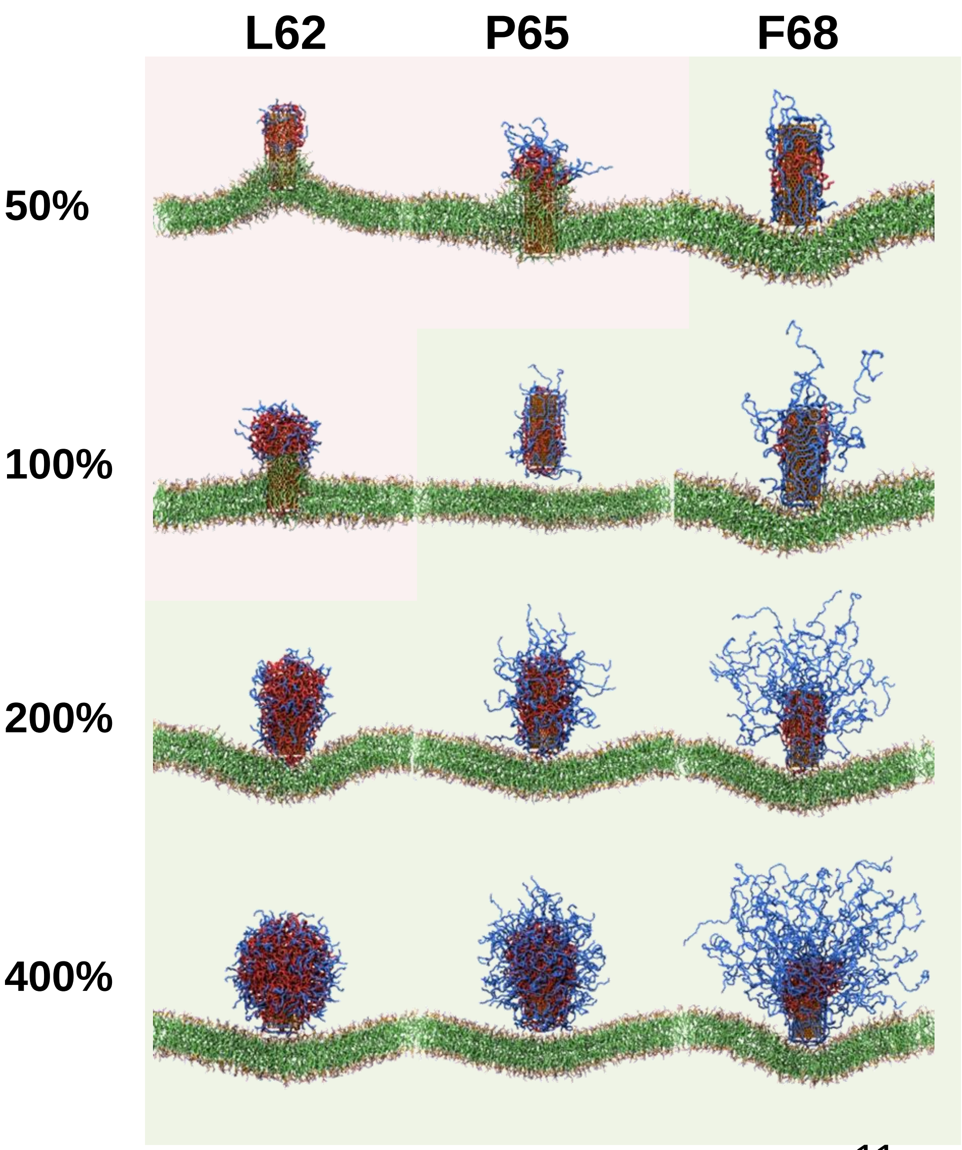
  - Outer radius = 2.9 nm
  - Length = 7.0 nm

- For each Pluronic species study 4 different mass loadings

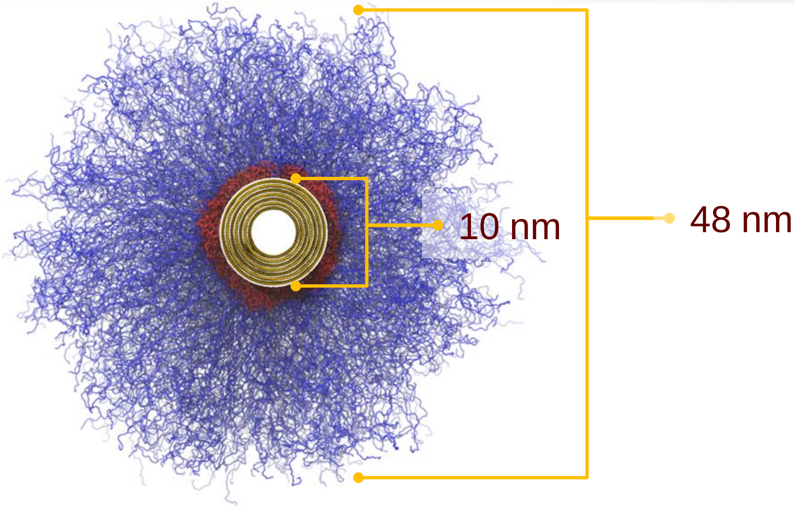


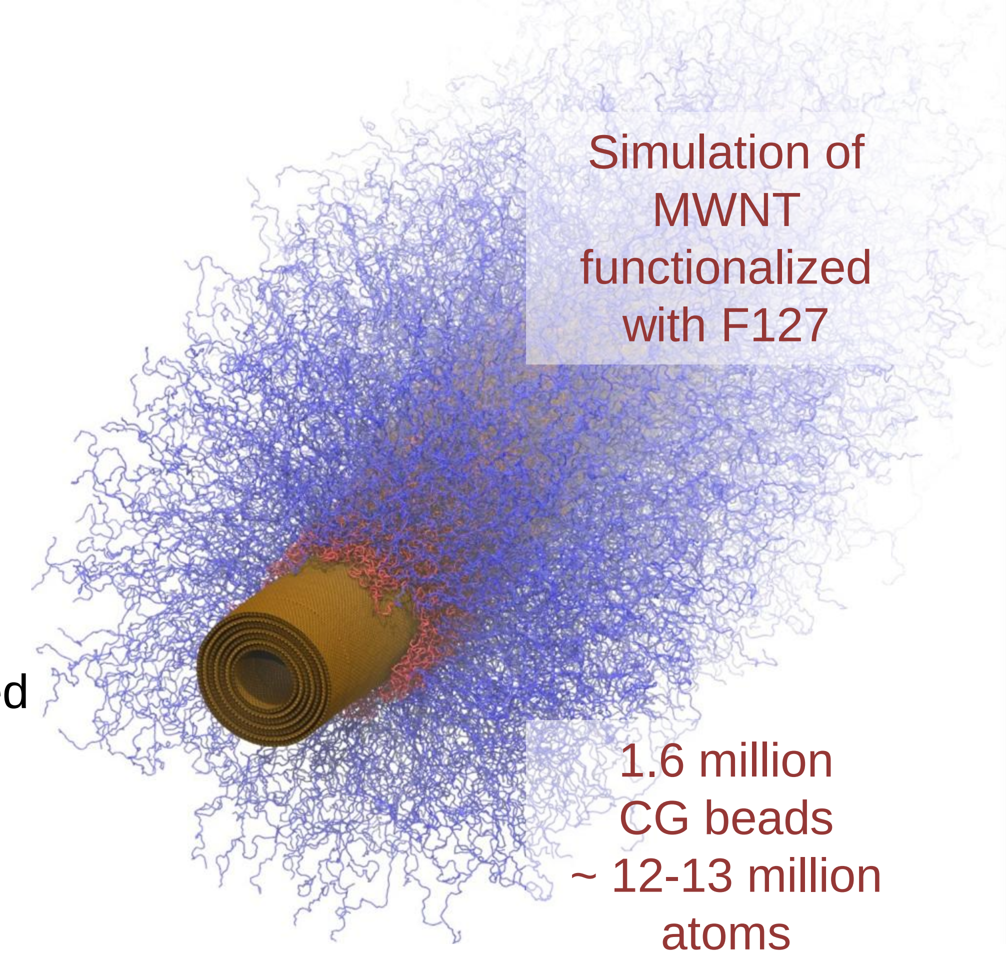
Interaction of CNT:PLN with Lipid Bilayer

- Insertion of CNTs into lipid bilayers → biological implications
- Bare nanotube spontaneously enters lipid bilayer
- Most Pluronic coated CNTs require external force
- Qualitatively, F68 > P65 > L62 in raising insertion energy barrier



Simulating Pluronic:MWCNTs





- **Simulations are too CPU intensive**
  - Diameter of experimentally used MWNT ~10-20 nm
  - Too many atoms to simulate!
  - Developing a new approach
- **Phenomenological model:**

  \- Explicitly include free energy terms involved in formation of Pluronic: MWNT composite structures

Conclusions from Simulation Studies

- Successfully constructed a coarse grained model of Pluronics
- Pluronics with higher % hydrophilic mass are suitable for dispersing carbon nanotubes
  - Larger corona → barrier towards aggregation
  - Higher barrier towards membrane insertion
- Simulating experimentally relevant Pluronic-functionalized MWNTs leads to the development of new computational methodology

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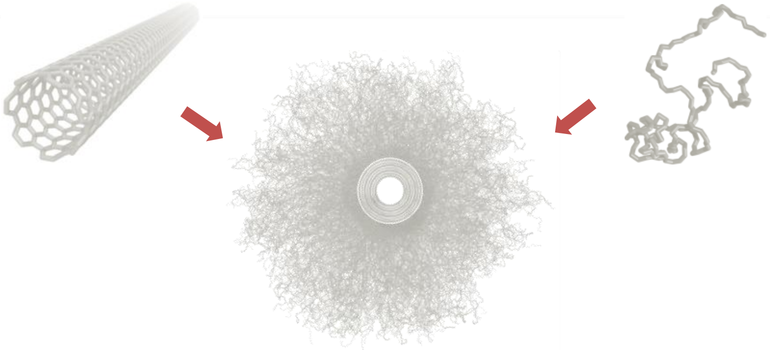
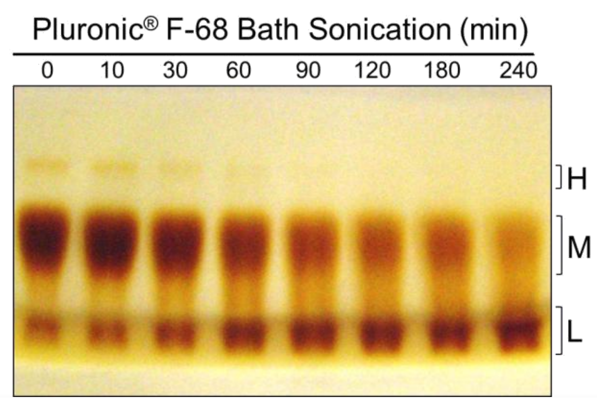


Part II

Sonication of Pluronic Polymers Induces Toxic Degradation Products

Ruhung Wang



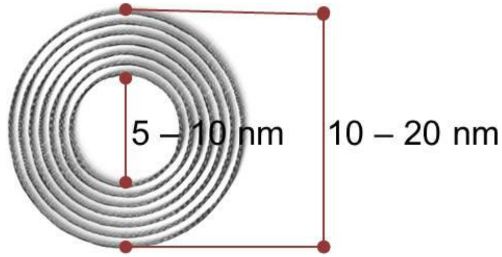
Generation of Toxic Degradation Products by Sonication of Pluronic® Dispersants: Implications for Nanotoxicity Testing

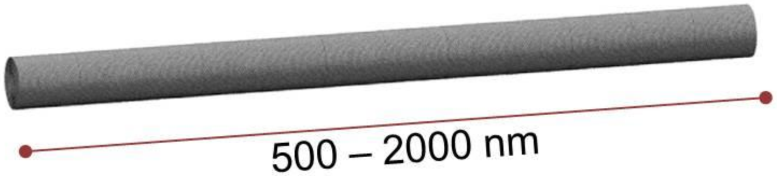
RUHUNG WANG[1,2], TYLER HUGHES[1], SIMON BECK[1], SAMEE VAKIL[1], SYNYOUNG LI[1], PAUL PANTANO[2], AND ROCKFORD K. DRAPER[1,2,*]

[1]Department of Molecular & Cell Biology and
[2]Department of Chemistry,
The University of Texas at Dallas, Richardson, TX 75080

MWNTs and Bio-compatible Dispersants

- MWNTs

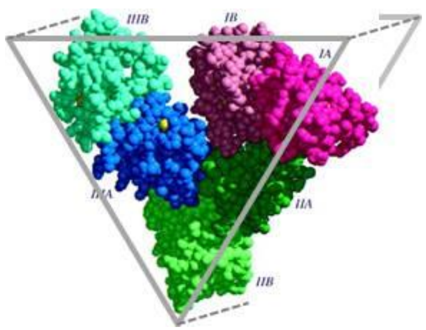




- Three dispersants

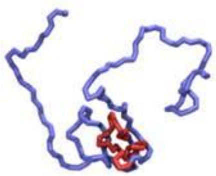
BSA : 67 kDa protein

(8 nm x 8 nm x 8 nm) x 4 nm



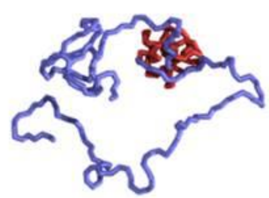
F-68 : 8.4 kDa tri-block copolymer

$(EO)_{77}(PO)_{29}(EO)_{77}$

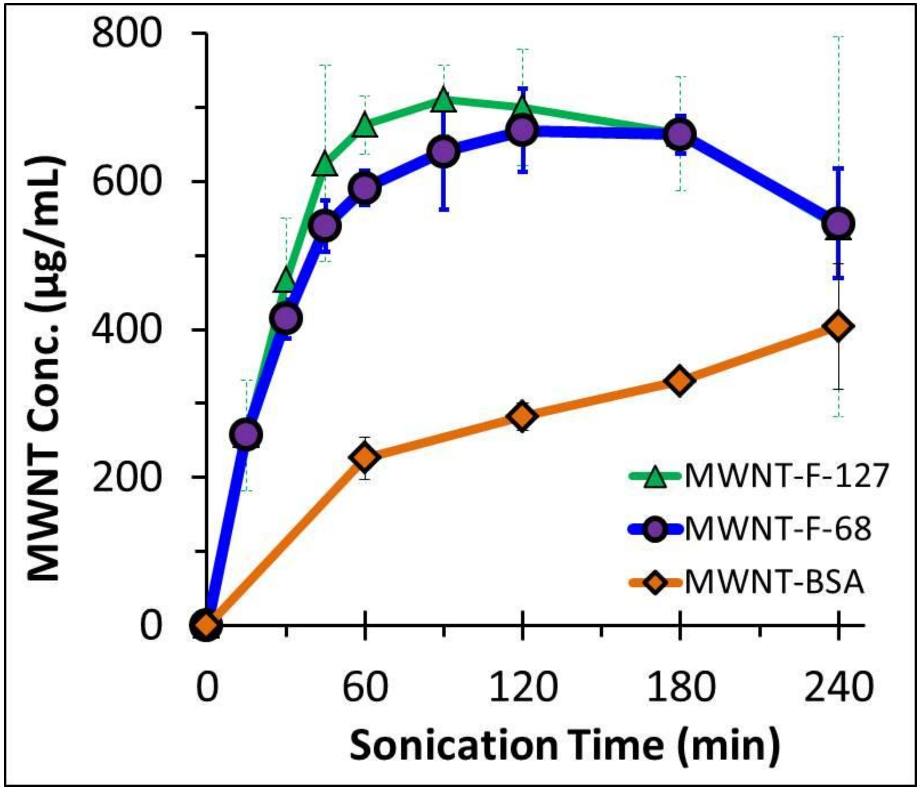


F-127 : 12.6 kDa tri-block copolymer

$(EO)_{101}(PO)_{56}(EO)_{101}$

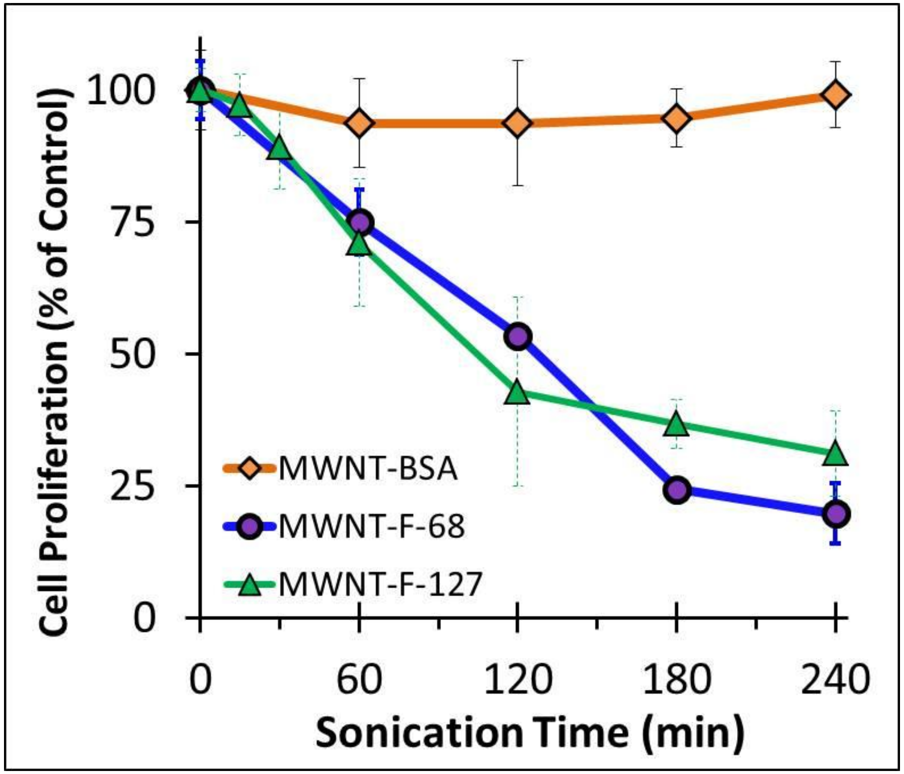


Effectiveness of F-68, F-127, or BSA in dispersing MWNTs using bath sonication at 37 kHz and 120 W.



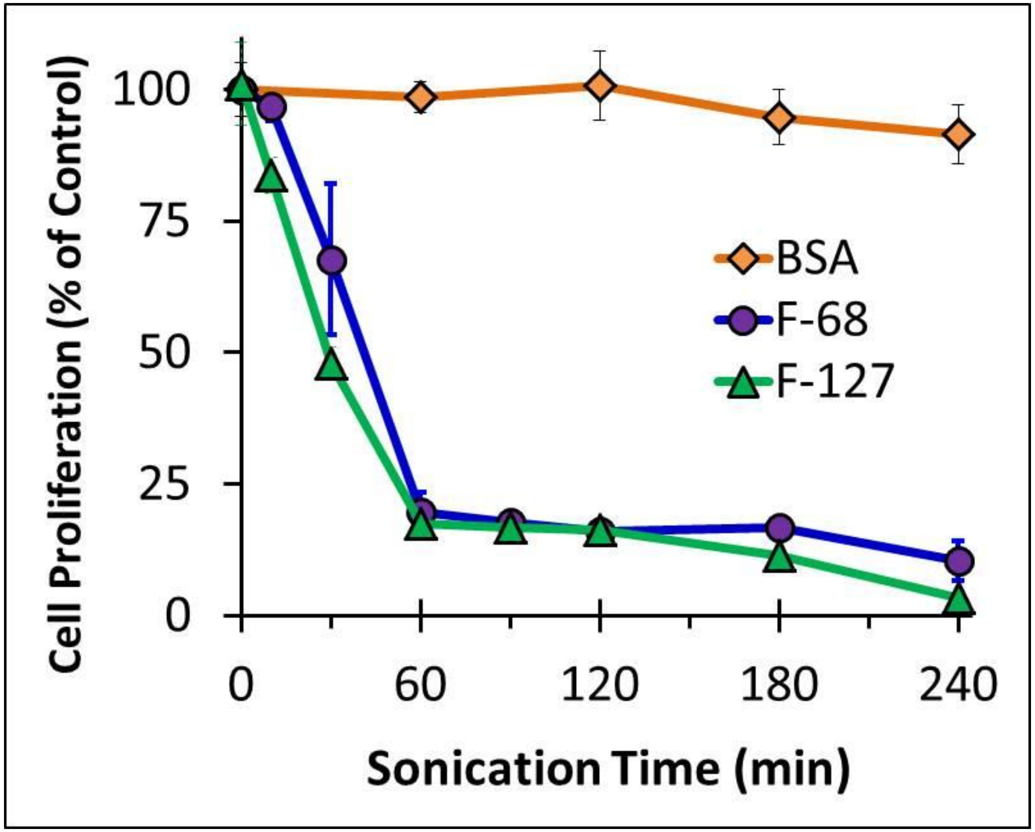
- Pluronic® F-68 and F-127 are better dispersants than BSA for MWNTs.

Cytotoxicity of MWNTs suspended in F-68, F-127, or BSA as a function of bath sonication time.



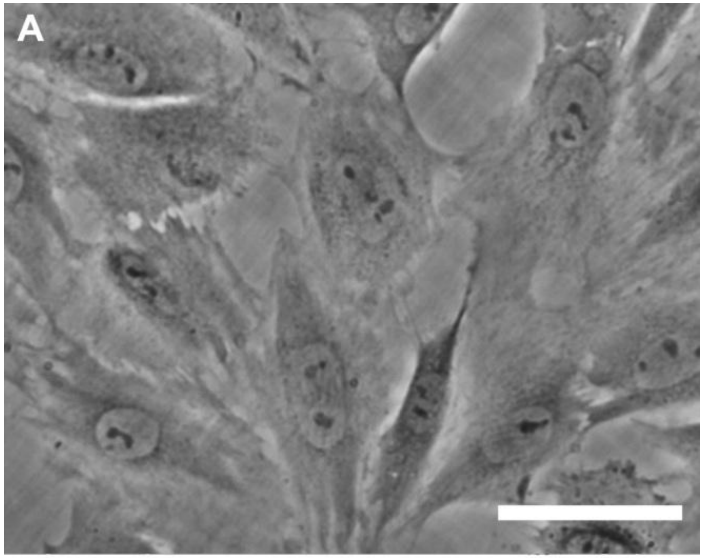
- MWNT-F-68 and MWNT-F-127 suspensions become toxic after sonication.
- MWNT-BSA suspensions are not toxic to NRK cells.

Cytotoxicity of F-68, F-127, and BSA as a function of bath sonication time in the absence of MWNTs.

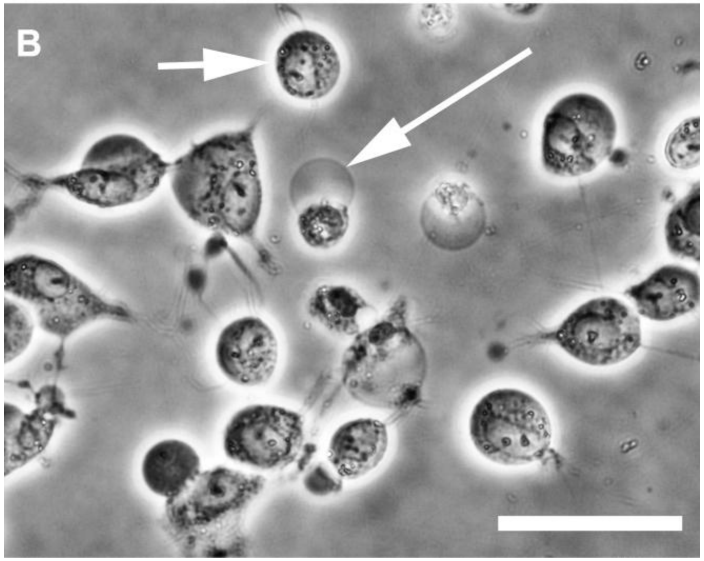


- Pluronic® F-68 and F-127 solutions become highly toxic after sonication
- BSA solutions are not toxic.

Morphology of NRK cells after 12 h exposure to non-sonicated or sonicated F-68.



Non-sonicated F-68 (0.1 mM)



4 h-sonicated F-68 (0.1 mM)

- Cell death was apparent after 12 h exposure to sonicated F-68.
- No morphological changes were observed in cells exposed to non-sonicated F-68.

IC_{50} of sonicated F-68 and F-127 for NRK cells after 24 h exposure.

Pluronic®	F-68		F-127	
Sonication Time (h)	1	4	1	4
IC_{50} (μM)	53.2	16.5	18.3	6.9

- The longer the sonication time, the more toxic the Pluronic polymers become.

* IC_{50}: The half maximal inhibitory concentration

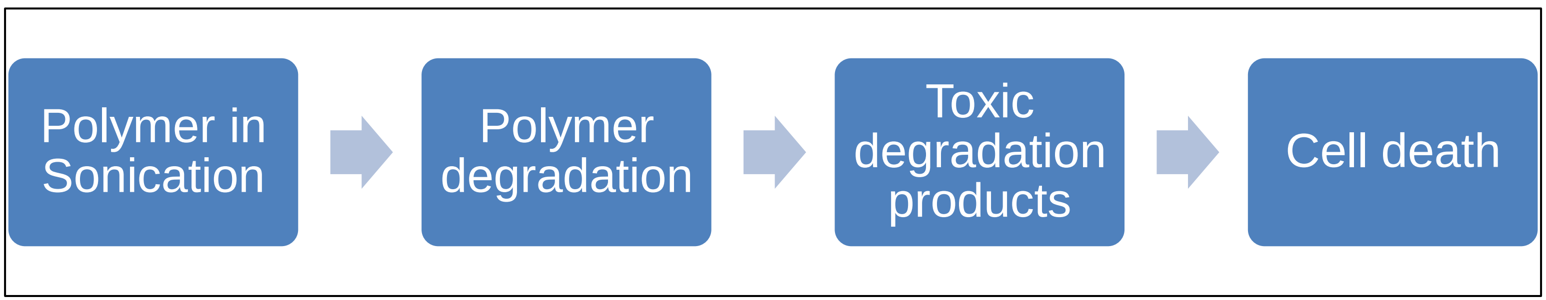
Sonication induces degradation in F-68 and F-127

Sonication is known to degrade various polymers

- ❖ Sonication ➔ cavitation bubbles ➔ heat, pressure, and shear forces
- ❖ Sonication ➔ H_2O_2 ➔ free radical attacks

Many degradation products of polymers are toxic to cells

- free radicals
- reactive oxygen species (ROS)
- organic acids
- alcohols
- aldehydes

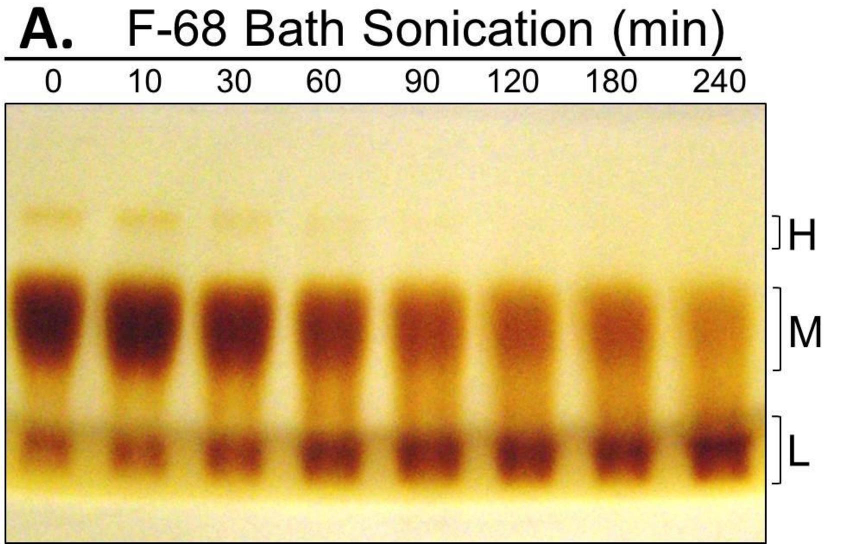


Does sonication induce polymer degradation?

Monitor changes in polymer size as a function of sonication time by

- Dynamic Light Scattering (DLS)
- SDS-PAGE

Degradation of F-68 as a function of bath sonication time at 37 kHz and 120 W.

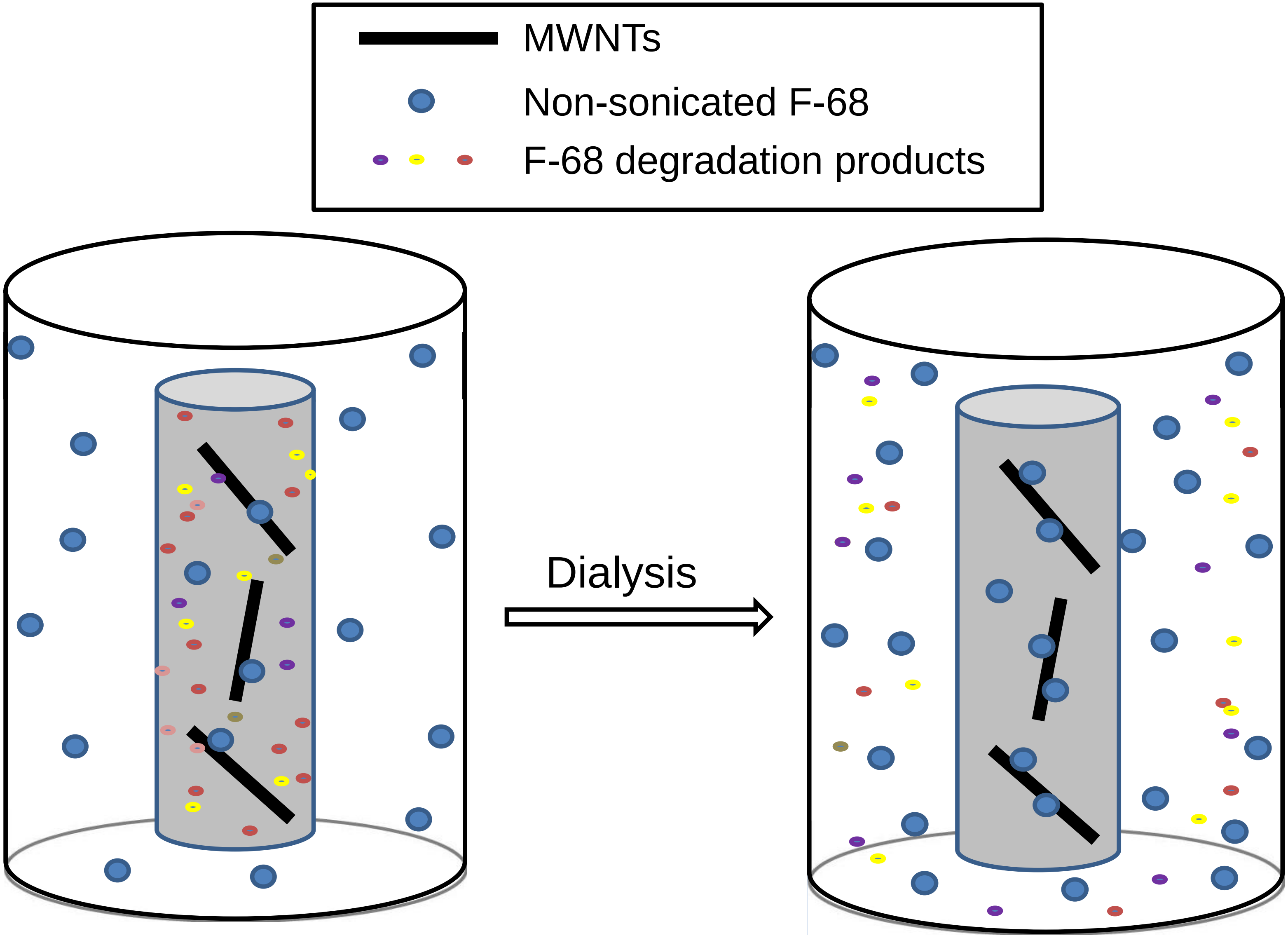


- Degradation of F-68 polymers were detected in BaI_2 stained SDS-PAGE gels as a function of sonication time.

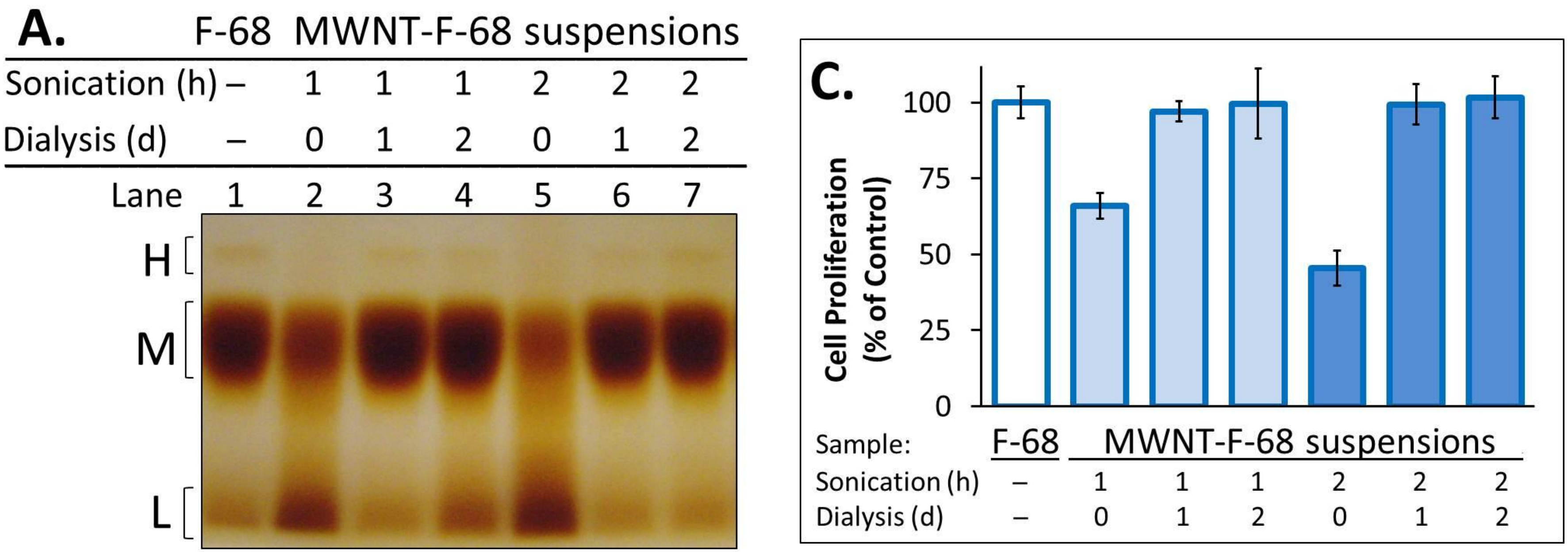
- Similar results were found in F127.

- Established the correlation between polymer degradation and toxicity; both are sonication dependent.

Removing toxic degradation products in MWNT-F-68 and MWNT-F-127 suspensions by dialysis.



Effects of dialysis on the removal of toxic degradation products in MWNT-F-68 suspensions.



- Degradation products of F-68 and F-127 polymers in MWNT suspensions were removed by dialysis.
- MWNTs remained in high concentrations and stable in suspension after dialysis against intact non-sonicated F-68 or F-127.

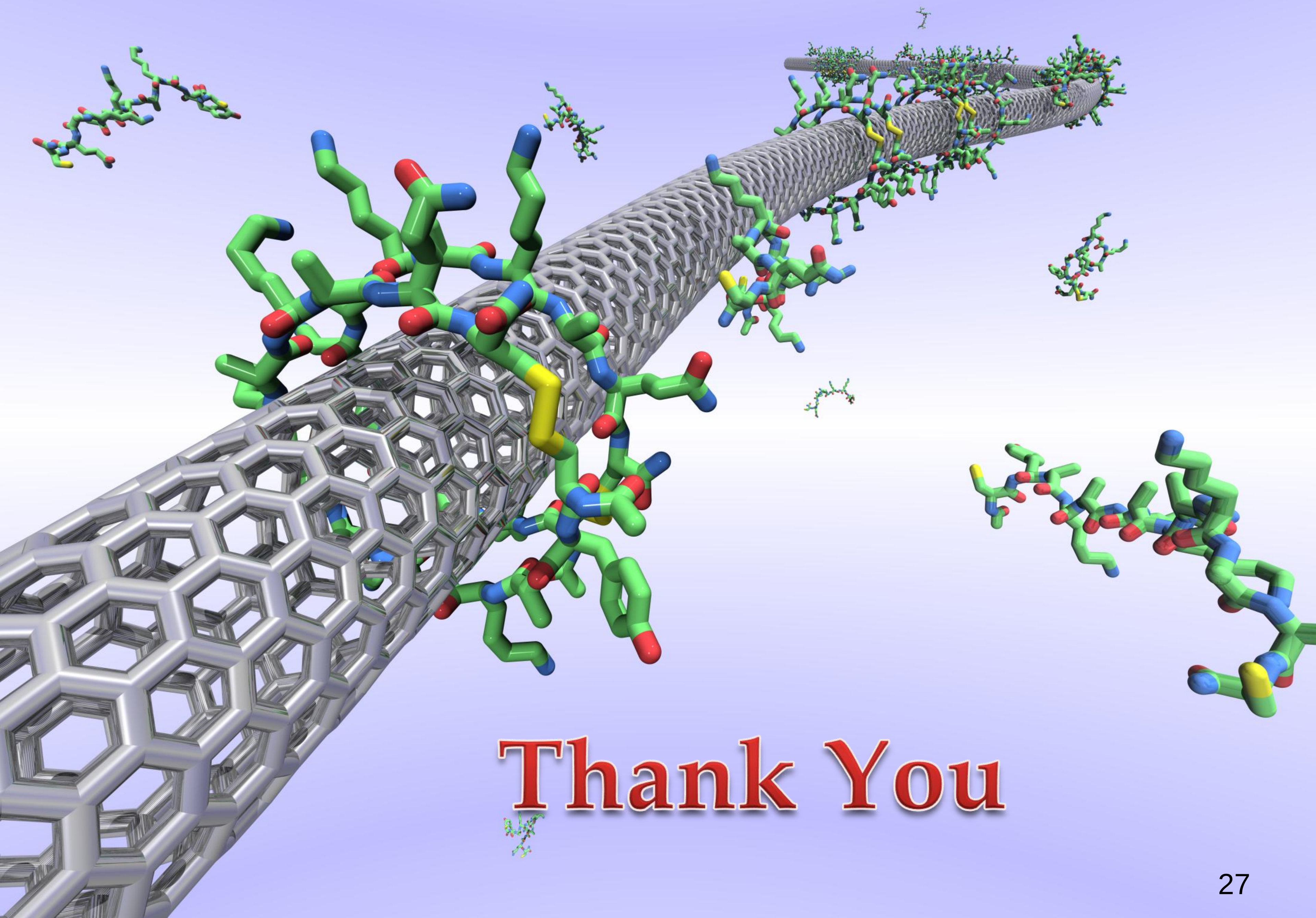
Conclusions from MWNT-Pluronic Suspension Toxicity Studies

- Pluronic® tri-block copolymers F-68 and F-127 are better dispersants compared to BSA in suspending MWNTs in biocompatible solutions.

- F-68 and F-127 become highly toxic after sonication in the presence or absence of MWNTs; polymer toxicity correlate with degradation, both are sonication time dependent.

- Caution should be used in interpreting the results of nanotoxicity studies where the sonolytic degradation of dispersants has not been controlled.

- Dialyzing MWNT-F-68 or MWNT-F-127 suspensions against non-sonicated F-68 or F-127 replaced the degraded materials and eliminated toxicity while retaining the MWNTs in suspension at high concentration.


Thank You