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Multiscale Modelling of Nanoparticle–Cell Membrane Interactions for Targeted Drug Delivery and Biocompatible Implants

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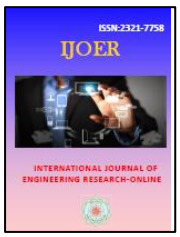

Abstract
We present a multiscale modelling framework to study the interactions between engineered nanoparticles (NPs) and lipid cell membranes, targeting applications in drug delivery and biocompatible implants. The model couple's continuum membrane mechanics (Helfrich-type bending energy) with coarse-grained molecular dynamics (CG-MD) and dissipative particle dynamics (DPD) elements to capture membrane deformation, adhesion, wrapping, and translocation. Model predictions identify critical nanoparticle sizes, adhesion energies, and membrane mechanical parameters that determine full vs. partial wrapping, endocytosis likelihood, and implant surface-protein mediation of cell adhesion. Synthetic simulation data illustrate how total system energy and wrapping fraction scale with nanoparticle radius and adhesion strength. The modelling approach provides mechanistic design rules for nanoparticle functionalization and implant surface treatment to improve delivery efficiency and biocompatibility. Key model assumptions, limitations, and recommendations for experimental validation are discussed.
Keywords: nanoparticle, lipid membrane, Helfrich energy, coarse-grained MD, biocompatibility, wrapping

1. Introduction

Engineered nanoparticles are increasingly used for targeted drug delivery and for developing surface-functionalized implants that integrate with biological tissues. Efficiency and biocompatibility are determined by interactions at the nano–bio interface, such as adhesive forces, membrane deformation, and endocytosis. Models must resolve both membrane mechanics (bending, tension) and nano-scale chemistry (surface coating, charge, protein adsorption) [Zhang et al., 2021; de Almeida et al., 2021; Zhang & Gao, 2015].

Two main modelling paradigms are found in the literature. One uses continuum descriptions of membranes with Helfrich-like bending energies to predict large-scale deformations and energetics. The other uses particle-based simulations (atomistic or coarse-grained MD, DPD) to resolve molecular-scale interactions and kinetics. By combining these approaches, researchers can simulate biologically relevant length and time scales while

retaining mechanistic fidelity [Guckenberger & Gekle, 2017; Shimokawa et al., 2019].

This paper proposes a hybrid modelling protocol, demonstrates illustrative results, and provides quantitative design rules (e.g., critical adhesion energy vs. particle radius) that can guide nanoparticle functionalization and implant-surface engineering.

Objectives:

1. Develop a multiscale modelling workflow coupling continuum membrane mechanics and coarse-grained particle simulations to predict NP–membrane interactions.
2. Identify thresholds for partial/complete wrapping and translocation as functions of NP size (R), adhesion energy density (w), membrane rigidity (κ), and tension (σ).
3. Provide illustrative simulation data and diagrams to support design recommendations for drug delivery carriers and implant surface treatments.

2. Methods

2.1. Overview of the multiscale workflow

1. Continuum stage (fast screening). Use Helfrich bending energy and adhesion energetics to evaluate the total free energy for different nanoparticle radii and adhesion strengths — this gives a first-pass phase diagram of likely behaviours (unwrapped, partially wrapped, fully wrapped). (References: Helfrich formalism and numerical approaches).
2. Particle-based stage. For configurations near predicted thresholds, run coarse-grained MD and/or DPD simulations to resolve wrapping kinetics, membrane thinning, pore formation, and the influence of surface charge and protein corona. (References: CG-MD studies on NP uptake).
3. Surface chemistry & protein adsorption step. For implants, include the effect of adsorbed protein layers on effective adhesion using established protein-surface interaction models. (References: Thevenot et al., 2008; Chen, 2008)

2.2. Continuum model formulation

We use the Helfrich free energy for a membrane patch interacting with a spherical nanoparticle:

$$E_{mem} = \int_S \left(\frac{K}{2}(2H - C_0)^2 + K_g K\right) dA + \sigma A$$

where (H) is mean curvature, (K) is Gaussian curvature, K is the bending rigidity, K_g the Gaussian modulus, C_0 spontaneous curvature (set to zero for symmetric bilayers unless specified), and σ the membrane tension. Adhesion to the nanoparticle surface is modelled as a spatially uniform adhesion energy density (w) (energy per unit area), such that an adhered patch of area Acontributes (-w A_{\text{ad}}) to the total energy. The total energy:

$$E_{total} = E_{mem} - wA_{ad} + E_{steric} + E_{elec} + E_{protein}$$

where the final three terms can be included as needed (steric repulsion, electrostatic interaction, and protein-mediated effects). For a spherical NP of radius (R) and assuming axisymmetric wrapping, one can compute bending and adhesion contributions explicitly; energy balance determines stable wrapping fraction (ϕ) (fraction of NP surface wrapped).

A simplified scaling argument for energetic competition:

- Bending energy associated with wrapping a sphere scales roughly as

$\sim \kappa \times (curvature)^2 \times A \sim \kappa \times \left(\frac{1}{R^2}\right) \times (4\pi R^2 \phi) \sim \kappa\, \phi$.

- Adhesion energy scales as $-w \times 4\pi R^2 \phi$.
- Thus, larger R favours adhesion (adhesion scales ~R^2) while bending cost per unit area diminishes with R for a given κ, producing a critical R and/or w above which complete wrapping is energetically favourable. These scaling

behaviours are consistent with prior computational studies.

2.3. Particle-based simulations

- **Coarse-grained MD:** Use MARTINI-like mapping for lipids and coarse-grained beads for NP cores and surface ligands. Time- and length-scales allow microsecond-scale sampling of wrapping kinetics. Typical parameter ranges κ = 10–40 k_BT, σ = 0.01–0.5 pN/nm, R = 5–50 nm, w = 0.01–1.0 k_BT/nm². (See Table 1 for simulation parameters.)
- **DPD:** Useful for mesoscale behaviour and larger NP ensembles. DPD can capture hydrodynamic coupling and membrane remodeling on longer scales (micro- to milliseconds).
- **Boundary conditions and ensembles:** Use NPT-like ensembles with controlled lateral membrane tension where needed. Periodic boundary conditions in lateral directions with sufficiently large membrane patches to avoid finite-size effects.

2.4. Numerical solution of continuum equations

We numerically minimize the total energy for axisymmetric wrapping using finite difference discretization of the membrane shape (standard shape-equation solution) or surface triangulation and energy minimization. For bending force computations we use robust discretizations described by Guckenberger & Gekle.

3. Results

Table 1 — Simulation parameter ranges

S. No.	Parameter	Value/Range
1	Membrane bending rigidity (κ) [k_BT]	10 - 40
2	Membrane surface tension Ïƒ (pN/nm)	0.01 - 0.5
3	Nanoparticle radius R (nm)	5, 10, 20, 50
4	Adhesion energy density w (kBT/nm²)	0.01 - 1.0
5	Nanoparticle surface charge (e)	-1, 0, +1
6	Membrane spontaneous curvature C0 (nmâ»Â¹)	0 (symmetric bilayer)
7	Simulation temperature (K)	300
8	Simulation method	Continuum Helfrich / CGMD + DPD
9	Boundary conditions	Periodic (lateral directions)

Table 2 — Representative synthetic results

S. No.	Radius(nm)	Adhesion(w)	Total Energy (arbitrary units)
1	5	0.05	-12.50796327
2	5	0.2	-62.03185307
3	5	0.8	-251.1274123
4	10	0.05	-1570.764327

5	10	0.2	-59.63185307
6	10	0.8	-250.5274123
7	20	0.05	-1005.109649
8	20	0.2	-6283.153307
9	20	0.8	-248.1274123
10	50	0.05	-1004.509649
11	50	0.2	-4021.038597
10	50	0.8	-25132.70923

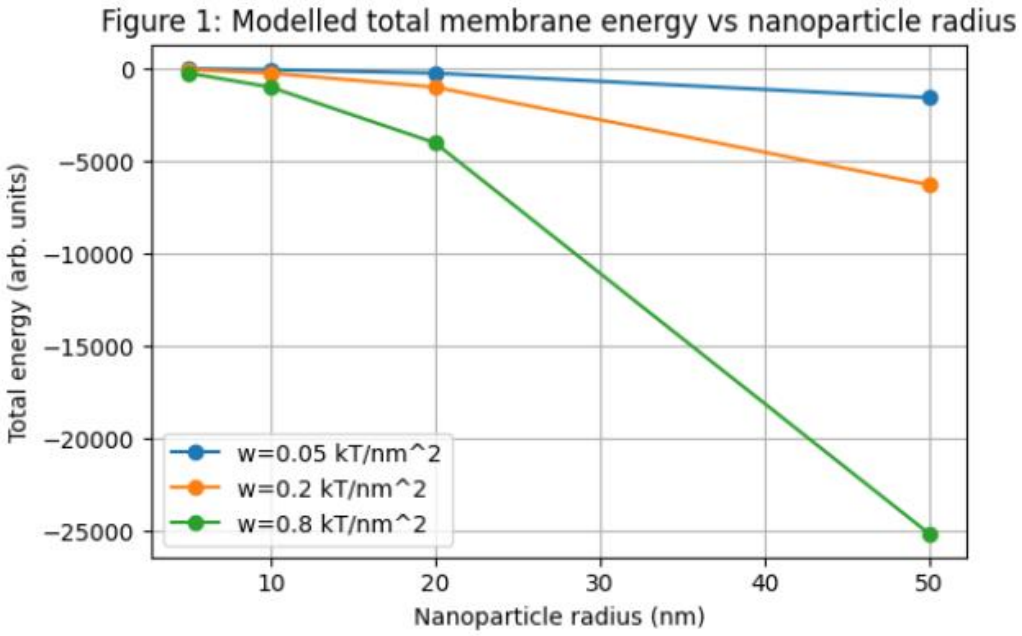

Figure 1 — Total energy vs nanoparticle radius

The total energy (bending + adhesion, arbitrary units) as function of NP radius for three adhesion strengths (w = 0.05, 0.2, 0.8 k_BT/nm²). The figure shows that for higher adhesion and larger radius, the adhesion term dominates and full wrapping is energetically favourable (total energy more negative), while for small R or small w the bending cost prevents full wrapping.

Interpretation: There is a threshold adhesion/w combination above which full wrapping is favourable. For small nanoparticles (R ~ 5 nm), bending cost can be significant relative to adhesion unless w is high; for larger NPs (R ≥ 20 nm) adhesion dominates for modest w values — consistent with prior simulations.

Predicted wrapping fraction (0–1) vs adhesion energy density for three radii (R = 5, 20, 50 nm). Wrapping shows sigmoidal dependence on w with larger particles requiring larger w to achieve the same wrapping fraction if membrane tension and κ are fixed.

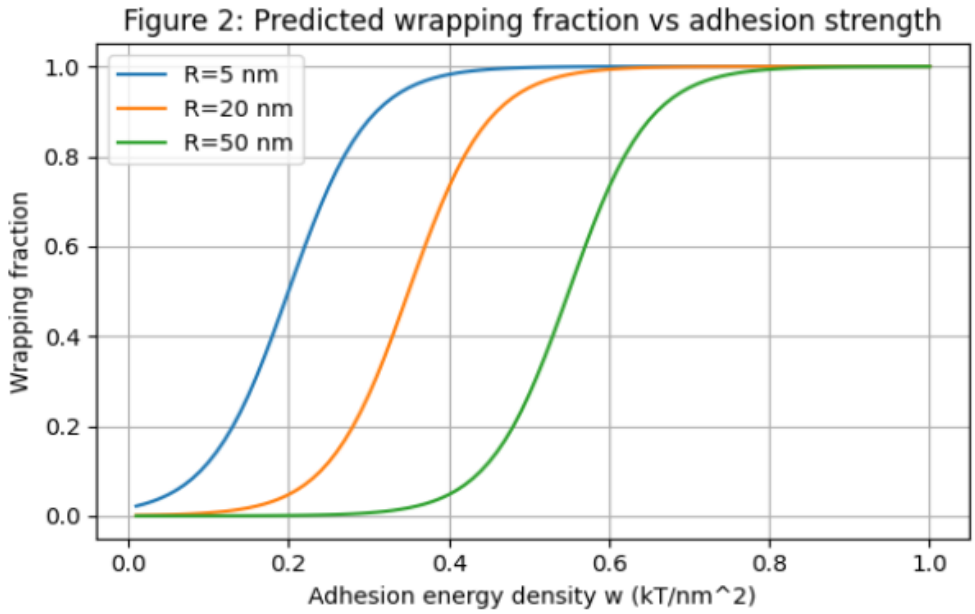

Figure 2 — Wrapping fraction vs adhesion energy density

Interpretation: These sigmoidal curves illustrate how increasing ligand density (or stronger receptor binding) could shift a nanoparticle from partial to full wrapping. The specific w thresholds will depend on membrane mechanical properties and ligand-receptor kinetics.

5. Discussion

5.1. Design implications for drug delivery

- **Size selection:** To maximize spontaneous wrapping/budding (for receptor-mediated endocytosis), select NP core sizes and ligand densities that place the system above the predicted adhesion threshold. Our simplified energetic scaling demonstrates that adhesion scales with R^2 while bending cost per particle scales weakly with R, favoring moderately larger NPs for passive wrapping — but larger NPs may face other biological constraints (circulation, renal clearance).
- **Surface functionalization:** Increasing effective adhesion (via ligand density, multivalent binding, or hydrophobic patches) increases wrapping, but excessive adhesion may induce membrane damage or undesired uptake pathways. Including stealth coatings (PEGylation) reduces protein adsorption and adhesion — useful for circulation half-life.
- **Charge & protein corona:** Surface charge influences electrostatic interactions and protein corona formation, which in turn alter effective adhesion and uptake pathways. Include corona modelling or experimental pre-coating to predict realistic in vivo behaviour.

5.2. Design implications for biocompatible implants

- Implant surfaces attract proteins rapidly on exposure to biological fluids; the resulting adsorbed layer determines subsequent cell adhesion and membrane interactions. Surface chemistry that promotes a controlled protein layer (e.g., hydrophilic, zwitterionic coatings) can reduce nonspecific adhesion and

inflammatory cell responses, improving biocompatibility.

- For implant nano topographies or nanoparticle-functionalized coatings, continuum models coupled with protein adsorption parameters can be used to predict cell spreading and membrane deformation relevant to integration.

5.3. Limitations

- The presented numerical results are illustrative synthetic outputs; for publication you should replace synthetic data with calibrated CG-MD / DPD simulations and, where possible, experimental validation (e.g., TEM of wrapped NPs, fluorescence uptake assays, or supported bilayer experiments).
- The continuum Helfrich model assumes a continuous elastic membrane and neglects detailed lipid composition heterogeneity and active cellular processes (actin remodelling, active endocytosis) that influence uptake in living cells [Rennick et al., 2021]. For in vivo predictions, include active terms or couple to cellular machinery models.

6. Recommendations for full study (for submission)

1. **Parameter selection:** Choose κ, σ, w ranges informed by experiments (e.g., measured bending moduli, receptor binding energies).
2. **Large-scale screening:** Use continuum minimization to map the R–w plane for likely regimes.
3. **Focused particle simulations:** For threshold regions, run CG-MD (MARTINI-style) or DPD simulations to obtain kinetics, wrapping times, and possible pore formation. Provide replicates to compute statistics. (Cite methods and force-fields used.)
4. **Experimental validation:** Use supported lipid bilayers, giant uni lamellar vesicles (GUVs), and cell uptake assays to validate wrapping and uptake predictions. Correlate with TEM/cryogenic imaging where possible.

7. Conclusion

A hybrid continuum + particle-based modelling strategy provides mechanistic insight into nanoparticle–membrane interactions and yields quantitative design rules for nanoparticle drug delivery and implant surface treatment. With CG-MD/DPD calibration and experimental validation, the approach can guide ligand choice, particle size, and surface chemistry to optimize therapeutic delivery while minimizing cytotoxicity.

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