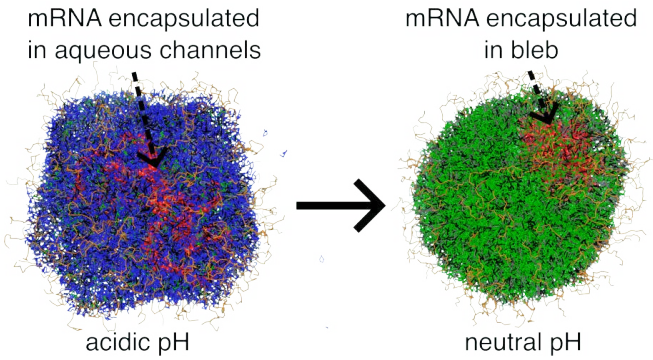
CASE STUDY

Characterizing lipid nanoparticle self-assembly and structure using coarse-grained simulations

mRNA/lipid nanoparticle (LNP) technology is the basis for the most successful Covid-19 vaccines and is being adapted for many other types of treatments. A detailed structural understanding of mRNA containing LNPs and their behaviors will aid in implementing and optimizing these therapeutics.

Summary

- Built and validated a coarse-grained model that accurately captures the self-assembly of an mRNA-encapsulating LNP starting from a homogeneous initial condition at low pH and on length-scales comparable with those currently used in therapeutics
- Demonstrated pH-dependent evolution in the distribution of LNP components that is consistent with experiment
- Observed spontaneously formed bleb structures in simulations of RNA-containing LNPs for the first time



Schrödinger

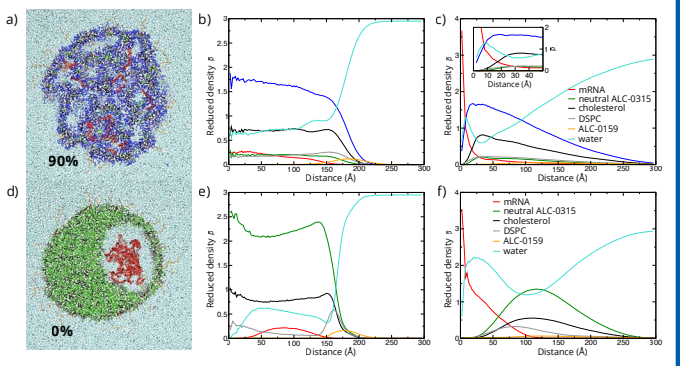
Approach

Schrödinger scientists carried out coarse-grained (CG) simulations using the Schrödinger Materials Science Suite, Desmond molecular dynamics engine, and OPLS4 force field, following the steps below:

1. Automated parameterization of CG model for mRNA-containing LNP components using a 1.5 microsecond atomistic reference simulation employing the OPLS4 force field
2. Constructed a homogeneous system containing CG mRNA, lipids (with molar composition 45.6/9.4/43.4/1.6 mol % of ALC-0315/DSPC cholesterol/ALC-0159), and water using the new CG model
3. Relaxed the system and conducted Langevin dynamics (LD) simulations to investigate evolution of LNP morphologies
4. Conducted LD simulations with progressively higher levels of ionizable lipid (ALC-0315) neutralization starting from the final self-assembled LNP, in order to study the changes in internal morphology as the pH rises from the acidic LNP formation conditions to the pH characteristic of blood

Outlook

This work by Grzetic et al. demonstrates that self-assembly of LNPs for nucleic acid delivery can be simulated. The predictive power of the presented model opens the possibility of simulating larger systems with longer RNA sequences and enables investigation of the dependencies of LNP structure on lipid composition and other factors, rapidly providing information that can complement both experimental efforts as well as atomistic simulations.



Characterization of the internal structure of the LNP with 90% of the ALC-0315 protonated at low pH (panels a-c) and with ALC-0315 completely neutralized at neutral pH (panels d-f). Panels b and e show radial density profiles measured from the LNP center, and panels c and f show radial density profiles measured from RNA backbone sites.*

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Publication

Grzetic DJ, et al. Coarse-Grained Simulation of mRNA-Loaded Lipid Nanoparticle Self-Assembly, *Mol. Pharmaceutics* 2024, 21, 4747-4753.

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