The Development of a Systematic Coarse-Grain Model for Polymer Drug Encapsulation

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1 - Nanoprecipitation

• Polymers can be used to encapsulate drug molecules for delivery *in vivo*.

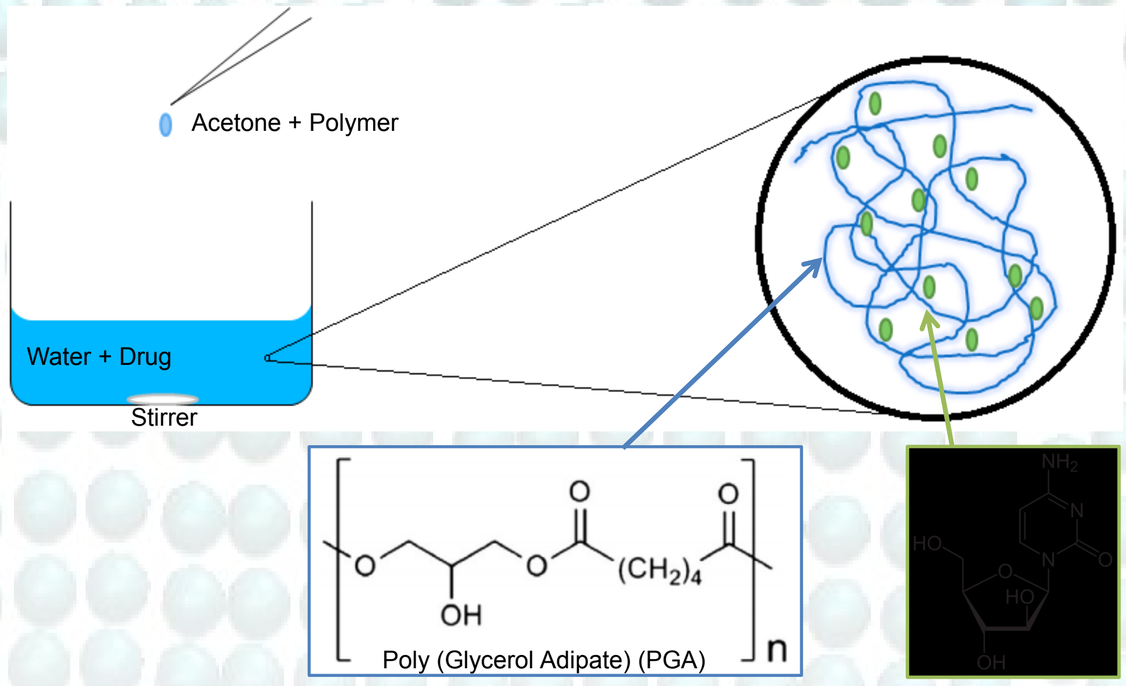
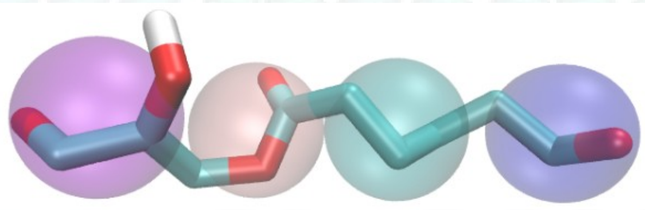


Fig. 1 – Polyglycerol adipate in acetone is added dropwise to water containing propofol. The hydrophobic polymer aggregates entrapping any drug molecules present in solution.

• Good: Polymers provide increased circulation time, targeting and reduce drug side effects.
• Bad: Sufficient drug loading is difficult to achieve and compatibility between drug and polymer is unpredictable.

3 - Systematic Coarse-Graining



• A simplification of the model by grouping the atoms into “superatoms” or “coarse-grains” is one technique to allow the simulation of multiple polymers on realistic time scales.

• However, it is vital to maintain a high level of accuracy for the molecular interactions in the model. The most accurate interactions come from atomistic simulations. These can be used as a “gold standard” for parameterising the coarse-grain model.

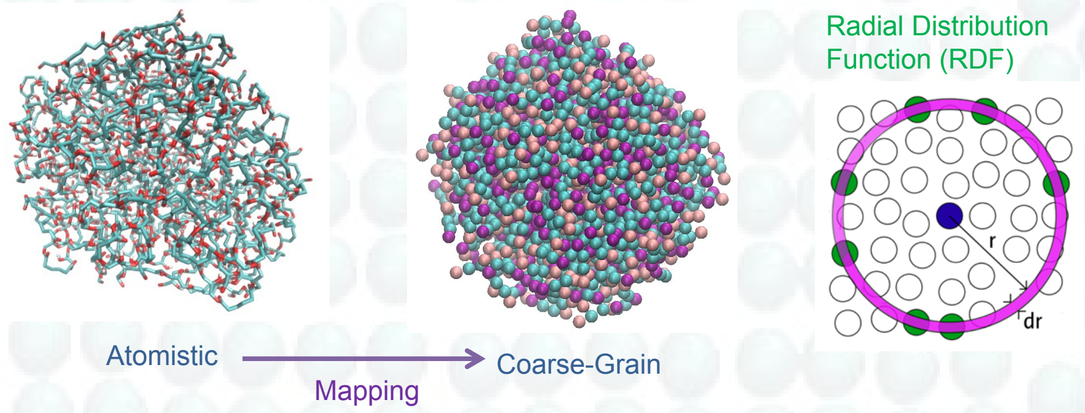


Fig. 3 – The atomistic simulation can be mapped to a coarse-grain one using a mapping scheme. We can calculate a radial distribution function (RDF) for the four different polymer coarse-grains with respect to each other.

• The RDF generated can be used to create a potential of mean force (PMF) for how the coarse-grains interact. This potential can be refined through iterative boltzmann inversion.

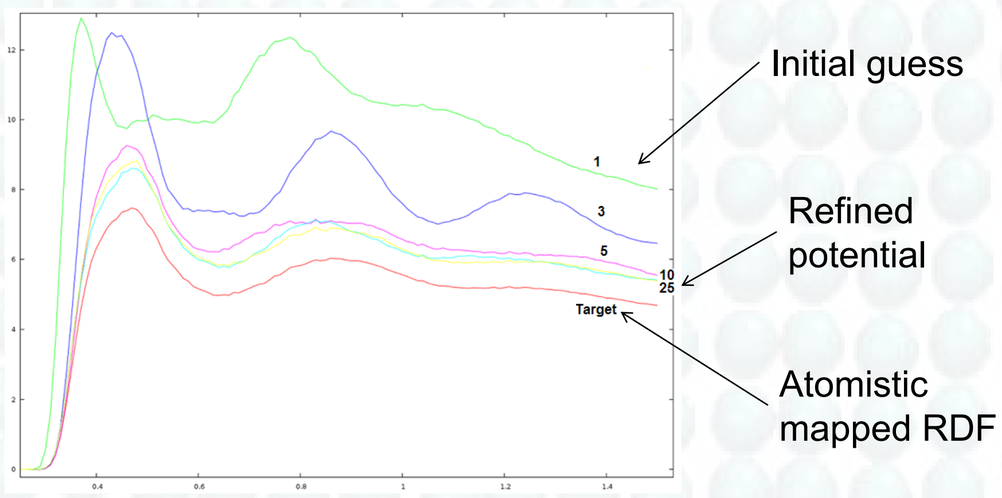


Fig. 4 – The PMF for two coarse-grains in PGA is refined. Over 25 iterations the radial distribution of these grains in the simulation more closely resembles the RDF from the atomistic simulation.

2 - Molecular Dynamics

• Molecular dynamics is a simulation method for observing/analysing molecular behaviour. A computer can calculate Newton’s equations of motion on thousands of atoms simultaneously.

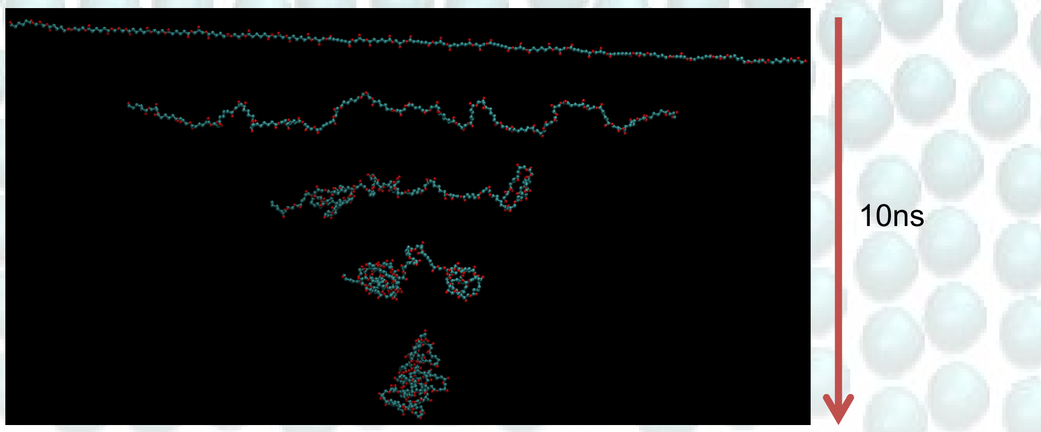


Fig. 2 – 10ns molecular dynamics simulation of poly(glycerol adipate) (PGA) in water. The polymer aggregates as it does during nanoprecipitation due to forces acting on the polymer by the surrounding water.

• This atomistic simulation a single polymer took around 2 days, for multiple polymers these simulations are not feasible. We need to simplify the model to speed it up without sacrificing interaction detail.

4 - A Nanoprecipitation Model

• *in silico* we can design a model that has a droplet of acetone (containing three PGA molecules) surrounded by water.

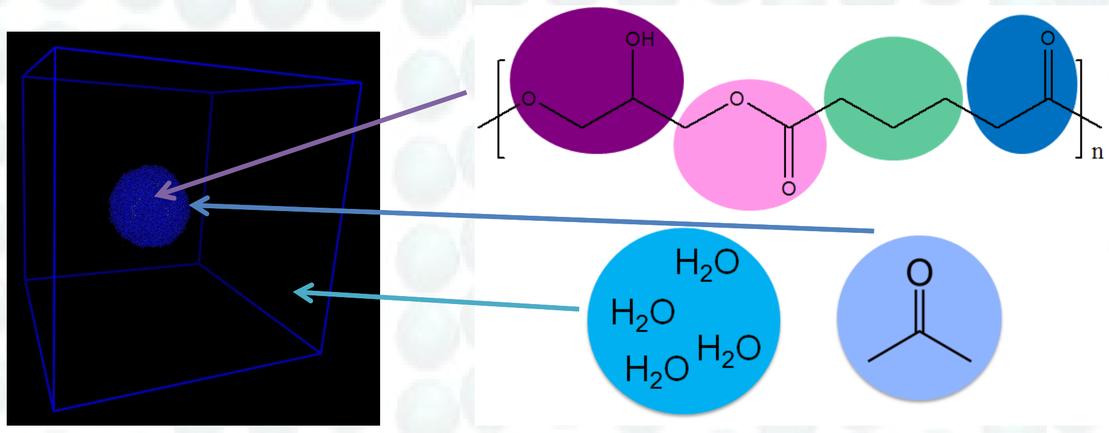


Fig. 5 – A simulation box containing coarse-grain acetone, PGA and water. Note the water is not shown for clarity. The MARTINI force-field is used to model the interactions for water and acetone.

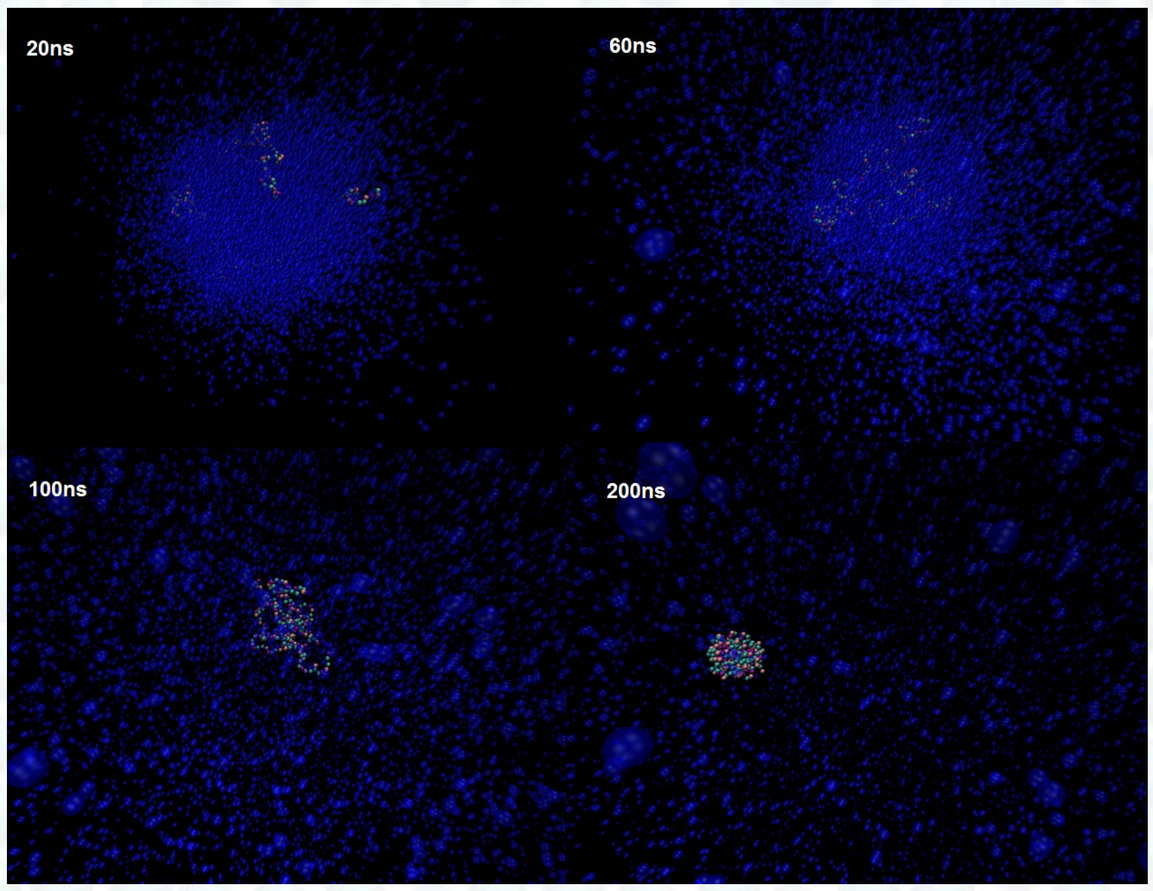


Fig. 6 – Four snapshots from a simulation showing the nanopreciptation of PGA. As the blue coarse-grain acetone diffuses into the surrounding water , the polymer is exposed to the water and aggregates into a cluster.

• This dual-solvent model allows the PGA to aggregate over a slower time frame. We believe this is important when it comes to drug encapsulation as the drug molecules have more time to become closely associated with the polymer before it aggregates.

• Drug molecules have been coarse-grained similarly to the polymer. However it is difficult to parameterise the interactions between drug and polymer.
• Current work involves the use of a hybrid model where the most important interactions, i.e. drug and polymer, can be done atomistically and interactions with the solvent are coarse-grained.