Multiscale approach to nanocapsule design

Z. Shreif and P. Ortoleva

Center for Cell and Virus Theory, Department of Chemistry,

Indiana University, Bloomington, Indiana, USA, ortoleva@indiana.edu

ABSTRACT

The design of nanocapsules for targeted delivery of therapeutics presents many, often seemingly contradictory, constraints. Considering the variation in the nature of the payload and surrounding medium, software for predicting the rate of drug release for given nanocapsule structure under specific conditions in the microenvironment would be a valuable asset. An algorithm for such software using a novel all-atom, multiscale technique is presented. The method takes into consideration the atomistic effects; a necessary condition to obtain a realistic model. Other advantages of this method include the ability to (1) develop a model that doesn't require recalibration with each new application and (2) predict the supra-nanometer scale behavior such as timed payload release. Multiscale techniques are used to derive equations for the stochastic dynamics of therapeutic delivery. Application to liposomal doxorubin release is presented.

Keywords: nanomedicine; nanocapsule; therapeutic delivery; computer-aided nanocapsule design

1 INTRODUCTION

The delivery of drugs, siRNA, or genes via a functionalized nanocapsule (e.g. viral capsides and liposomes) is of great interest. Requirements for therapeutic delivery nanocapsules include (1) the ability to deliver payload at the target site while minimizing release at non-target tissues in order to reduce toxicity and increase efficacy, (2) the ability to control release of the payload over a long period of time with constant concentration, and (3) have a sufficient circulation time.

Considering the variation in the nature of the payload and the thermal and chemical environments that nanocapsules must address, it would be a great advantage to have a general physico-chemical simulator that can be used in computer-aided nanocapsule therapeutic delivery. For example, the prediction of the rate of drug release for given nanocapsule structure and conditions in the microenvironment based on a parameter-free model of supra-molecular structures that would optimize payload targeting would be a valuable asset. Some theoretical work has been presented previously [1-6] which provided some insights to certain aspects of the problem. These models are either empirical or mechanistic. Empirical models [3-4] only take into consideration the overall order of the payload release rate law, while mechanistic ones [5-6] take into account the specific processes involved such as diffusion, swelling, and erosion. However, these models are macroscopic and, therefore, do not take into consideration atomistic effects and, furthermore, require recalibration with each new application.

Release of payloads is a phenomenon that occurs over long and wide timescales; while release takes seconds to hours, atomic collisions/vibrations take place on the 10^{-12} second scale. Molecular dynamics codes, while powerful at the small scale, are impractical when it comes to dealing with nanometer scale problems spanning a timescale of a millisecond and more. An all-atom multiscale approach has been developed recently for simulating the migration and structural transitions of nanoparticles and other nanoscale phenomena [7-10]. This formulation allows for the use of an interatomic force field, making the approach universal, avoiding recalibration with each new application. In this work, this multiscale approach is applied to the nanocapsule delivery problem. The presented computational method preserves key atomic-scale behaviors needed to make predictions of interactions of functionalized nanocapsules with the cell surface receptors, drug, siRNA, gene, or other payload.

In this study, we introduce novel technical advances that capture key aspects of the nanoscale structures needed for therapeutic delivery analysis. In section 2, a variety of order parameters (characterizing nanoscale features of the capsule and its surroundings) are introduced to enable a multiscale analysis of a complex system. The final result is a Fokker-Planck (FP) equation governing the rate of stochastic payload release and structural changes and migration accompanying it. In section 3, key parameters which minimize the need for calibration are identified and

predicted drug release scenarios are presented. Conclusions are drawn in section 4.

2 DERIVING THE STOCHASTIC MODEL

The specific aim of this study is to provide a starting point for a computer-aided nanocapsule design strategy. Consider a system consisting of the nanocapsule, payload, and host medium. We introduce four order parameters and their conjugate momenta which we prove to be slowly varying via Newton's equations. These order parameters are the center of mass position of the nanocapsule, $\vec{R}$, that of the drug, $\vec{R}_d$, a measure of the capsule dilatation, Φ, and the dispersal (i.e. spatial extent of the cloud of payload molecules), Λ:

$$\vec{R} = \sum_{i=1}^{N} \frac{m_i \vec{r}_i}{m^*} \Theta_i \tag{1}$$

$$\vec{R}_d = \sum_{i=1}^{N} \frac{m_i \vec{r}_i}{m_d^*} \Theta_i^d \tag{2}$$

$$\Phi = \sum_{i=1}^{N} m_i \vec{s}_i \bullet \vec{\vec{X}} \hat{s}_i^0 \Theta_i \Big/ m^* \tag{3}$$

$$\Lambda = \sum_{i=1}^{N} m_i s_i^d \Theta_i^d \Big/ m_d^* \tag{4}$$

where m_i and $\vec{r}_i$ are the mass and position of the i^{th} atom; $m^* = \sum_{i=1}^{N} m_i \Theta_i$, and $m_d^* = \sum_{i=1}^{N} m_i \Theta_i^d$ are the total mass of the nanocapsule and payload; $\Theta_i = 1$ when i is in the nanocapsule and zero otherwise, and similarly with Θ_i^d for the payload; $\vec{s}_i$ is the position of atom i relative to $\vec{R}$; $\vec{\vec{X}}$ is a length-preserving rotation matrix that depends on a set of three Euler angles specifying nanocapsule orientation; $\hat{s}_i^0 = \vec{s}_i^{\,0} / s_i^0$ where s_i^0 is the length of $\vec{s}_i^{\,0}$ and the superscript 0 indicates a reference nanocapsule structure; $\vec{s}_i^{\,d}$ is the position of atom i relative to $\vec{R}_d$, and s_i^d is its length. Newton's equations imply $d\vec{R}/dt = -\mathcal{L}\vec{R}$, $d\vec{R}_d/dt = -\mathcal{L}\vec{R}_d$, $d\Phi/dt = -\mathcal{L}\Phi$, and $d\Lambda/dt = -\mathcal{L}\Lambda$, where $\mathcal{L}$ is the Liouville operator

$$\mathcal{L} = -\sum_{i=1}^{N} \left[\frac{\vec{p}_i}{m_i} \bullet \frac{\partial}{\partial \vec{r}_i} + \vec{F}_i \bullet \frac{\partial}{\partial \vec{p}_i} \right] \tag{5}$$

With this, and introducing a smallness parameter ε, such that $\varepsilon^2 = m/m^* = m_d/m_d^*$ (m is the typical mass of a capsule atom, and $m_d \equiv m m_d^*/m^*$ is on the order of the mass of a typical payload atom), we get

$$d\vec{R}/dt = \varepsilon \vec{P}/m \tag{6}$$

$$d\vec{R}_d/dt = \varepsilon \vec{P}_d/m_d \tag{7}$$

$$d\Phi/dt = \varepsilon \Pi/m \tag{8}$$

$$d\Lambda/dt = \varepsilon \Pi_d/m_d \tag{9}$$

where $\vec{P}$, $\vec{P}_d$, Π, Π_d are the conjugate momenta of $\vec{R}$, $\vec{R}_d$, Φ, and Λ, and are defined as $\vec{P} = \varepsilon \sum_{i=1}^{N} \vec{p}_i \Theta_i$, $\vec{P}_d = \varepsilon \sum_{i=1}^{N} \vec{p}_i \Theta_i^d$, $\Pi = \varepsilon \sum_{i=1}^{N} \vec{\pi}_i \bullet \vec{\vec{X}} \hat{s}_i^0 \Theta_i$, $\Pi_d = \varepsilon \sum_{i=1}^{N} \vec{\pi}_i^d \bullet \hat{s}_i^d \Theta_i^d$

where $\vec{\pi}_i$ and $\vec{\pi}_i^d$ are the relative velocities of the capsule and payload atoms. The conjugate momenta are also found to be slowly varying. Applying Newton's equation, we get

$$\frac{\mathrm{d}\vec{P}}{\mathrm{d}t} = \varepsilon \vec{f}, \quad \vec{f} = \sum_{i=1}^{N} \vec{F}_i \Theta_i \tag{10}$$

$$\frac{\mathrm{d}\vec{P}_d}{\mathrm{d}t} = \varepsilon \vec{f}_d, \quad \vec{f}_d = \sum_{i=1}^{N} \vec{F}_i \Theta_i^d \tag{11}$$

$$\frac{\mathrm{d}\Pi}{\mathrm{d}t} = \varepsilon g, \quad g = \sum_{i=1}^{N} \vec{F}_i \bullet \vec{\vec{X}} \hat{s}_i^0 \Theta_i \tag{12}$$

$$\frac{\mathrm{d}\Pi_d}{\mathrm{d}t} = \varepsilon h, \quad h = \sum_{i=1}^{N} \vec{F}_i \bullet \hat{s}_i^d \Theta_i^d \tag{13}$$

where $\vec{f}$ and $\vec{f}_d$ are the net force on the nanocapsule and that on the payload, g is the "dilatation force", and h is the "dispersal force".

We suggest that this set of order parameters constitutes a minimal description capturing many nanocapsule delivery phenomena. With this, we follow the multiscale approach of Refs [7-11] to derive an FP equation of stochastic dynamics for the order parameters. Starting from the Liouville equation describing the evolution of the *N*-atom probability density, we arrive at an FP equation describing the evolution of the reduced probability density, *W*

$$\frac{\partial W}{\partial t} = \varepsilon \mathcal{D}' W \tag{14}$$

where

$$\mathcal{D}' = \mathcal{D} - \left[\frac{\vec{P}}{m} \bullet \frac{\partial}{\partial \vec{R}} + \vec{f}^{\,th} \bullet \frac{\partial}{\partial \vec{P}} + \frac{\Pi}{m} \frac{\partial}{\partial \Phi} + g^{th} \frac{\partial}{\partial \Pi} + \frac{\vec{P}_d}{m_d} \bullet \frac{\partial}{\partial \vec{R}_d} + \vec{f}_d^{\,th} \bullet \frac{\partial}{\partial \vec{P}_d} + \frac{\Pi_d}{m_d} \frac{\partial}{\partial \Lambda} + h^{th} \frac{\partial}{\partial \Pi_d} \right]$$

$\vec{f}^{\,th}$, g^{th}, $\vec{f}_d^{\,th}$, h^{th} are the thermal average of the forces, which is also equivalent to the long-time average though Gibbs hypothesis, and

$$\begin{aligned}\mathcal{D} = {} & \bar{\bar{\gamma}}_{ff} \frac{\partial}{\partial \vec{P}} \left(\beta \frac{\vec{P}}{m} + \frac{\partial}{\partial \vec{P}} \right) + \bar{\gamma}_{fg} \bullet \frac{\partial}{\partial \vec{P}} \left(\beta \frac{\Pi}{m} + \frac{\partial}{\partial \Pi} \right) + \bar{\bar{\gamma}}_{ff_d} \frac{\partial}{\partial \vec{P}} \left(\beta \frac{\vec{P}_d}{m_d} + \frac{\partial}{\partial \vec{P}_d} \right) \\ & + \bar{\gamma}_{fh} \bullet \frac{\partial}{\partial \vec{P}} \left(\beta \frac{\Pi_d}{m_d} + \frac{\partial}{\partial \Pi_d} \right) + \bar{\gamma}_{gf} \bullet \frac{\partial}{\partial \Pi} \left(\beta \frac{\vec{P}}{m} + \frac{\partial}{\partial \vec{P}} \right) + \gamma_{gg} \frac{\partial}{\partial \Pi} \left(\beta \frac{\Pi}{m} + \frac{\partial}{\partial \Pi} \right) \\ & + \bar{\gamma}_{gf_d} \bullet \frac{\partial}{\partial \Pi} \left(\beta \frac{\vec{P}_d}{m_d} + \frac{\partial}{\partial \vec{P}_d} \right) + \gamma_{gh} \frac{\partial}{\partial \Pi} \left(\beta \frac{\Pi_d}{m_d} + \frac{\partial}{\partial \Pi_d} \right) + \bar{\bar{\gamma}}_{f_d f} \frac{\partial}{\partial \vec{P}_d} \left(\beta \frac{\vec{P}}{m} + \frac{\partial}{\partial \vec{P}} \right) \\ & + \bar{\gamma}_{f_d g} \bullet \frac{\partial}{\partial \vec{P}_d} \left(\beta \frac{\Pi}{m} + \frac{\partial}{\partial \Pi} \right) + \bar{\bar{\gamma}}_{f_d f_d} \frac{\partial}{\partial \vec{P}_d} \left(\beta \frac{\vec{P}_d}{m_d} + \frac{\partial}{\partial \vec{P}_d} \right) + \bar{\gamma}_{f_d h} \bullet \frac{\partial}{\partial \vec{P}_d} \left(\beta \frac{\Pi_d}{m_d} + \frac{\partial}{\partial \Pi_d} \right) \\ & + \bar{\gamma}_{hf} \bullet \frac{\partial}{\partial \Pi_d} \left(\beta \frac{\vec{P}}{m} + \frac{\partial}{\partial \vec{P}} \right) + \gamma_{hg} \frac{\partial}{\partial \Pi_d} \left(\beta \frac{\Pi}{m} + \frac{\partial}{\partial \Pi} \right) + \bar{\gamma}_{hf_d} \bullet \frac{\partial}{\partial \Pi_d} \left(\beta \frac{\vec{P}_d}{m_d} + \frac{\partial}{\partial \vec{P}_d} \right) \\ & + \gamma_{hh} \frac{\partial}{\partial \Pi_d} \left(\beta \frac{\Pi_d}{m_d} + \frac{\partial}{\partial \Pi_d} \right).\end{aligned}$$

The γ factors account for the cross frictional effects, expressions for which are to be presented in a following paper [12].

3 SIMULATING PAYLAOD RELEASE

The FP equation (14) is equivalent to a set of Langevin equations wherein the forces and the friction coefficients can be calculated using MD code. Here, we try to illustrate our method by adopting a simplified model wherein the capsule is at the target site and ready for release. With this, only two Langevin equations remain:

$$\frac{d\Lambda}{dt} = \frac{\Pi_d}{m_d} \tag{15}$$

$$\frac{d\Pi_d}{dt} = h^{th} - \gamma_{hh}\Pi_d + A(t) \tag{16}$$

where $A(t)$ is a random force.

The dispersal is related to the concentration profile, $C(r)$, by

$$C(r,\tau) = C_0(\tau) e^{-(r/a\Lambda)^2} \tag{17}$$

where r is the distance from the center of mass of the nanocapsule, α is a constant, and C_0 is the payload concentration at the center of mass of the nanocapsule. In the above equation, payload release is assumed to be spherically symmetric, and the concentration to be a maximum at the center of mass. h^{th} is minus the derivative of the potential energy, U, with respect to the dispersal. The latter is related to the concentration profile by the phenomenological expression

$$U = 4\pi \int_0^\infty uCr^2 \mathrm{d}r \ , \ u = \begin{cases} \bar{u} & R_c \le r \le R_o \\ 0 & \text{otherwise} \end{cases} \tag{18}$$

where R_c and R_o are the inner and outer radius of the nanocapsule, respectively.

Table 1 Values used for the simulation

atoms	R_0 (nm)	R_c (nm)	m^* (g)	m_d^* (g)
6.7×10^5	100	92	7.208×10^{-17}	9.01×10^{-18}

In what follows, we show release profiles for different values of friction coefficient (Fig. 1). Values for the radii, masses, and number of atoms (Table 1) are chosen to be consistent with experimental observations on a typical liposome loaded with doxorubicin [13].

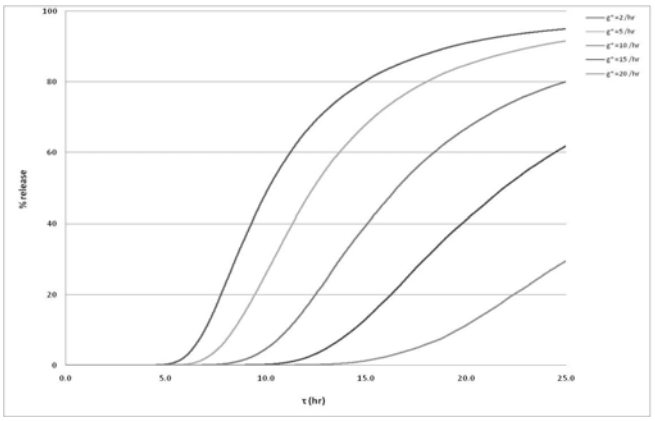

Fig. 1 Release profile simulated using equations (15) and (16) for parameter values as in Table 1

The g^* value indicated in the graphs is a calibrated coefficient that is related to the maximum friction value in the inner shell of the nanocapsule, γ_{max}, via $\gamma_{max} = g^* e^{\bar{u}/RT}$. Thus, changes in γ_{max} can be induced either through changes in the barrier height or friction coefficients, both of which can be modified via temperature changes or interaction with the cell membrane. From Fig. 1, we see

that as the barrier height or friction inside the shell increases, the rate of release of drug from the nanocapsule decreases. This is consistent with the fact that increasing the length and/or saturation of the fatty acyl chains comprising a liposome leads to slower release rates. Increasing γ_{max} also leads to longer residence time in the nanocapsule, as shown from the simulation results summarized in Fig. 2.

As can be seen in Figs. 1 and 2, the nature of payload/nanocapsule/medium dictates how long a nanocapsule's membrane can sequester the paylaod. Before the nanocapsule reaches the target site, the barrier height should be larger than the fluctuating forces. Once at the target site, release can be enhanced by lowering the barrier height and friction, or increasing the amplitude of fluctuations. This can be done by either applying an external field such as heat, light, or ultrasound, or by changes in the medium, i.e. the trigger is intrinsic to the system.

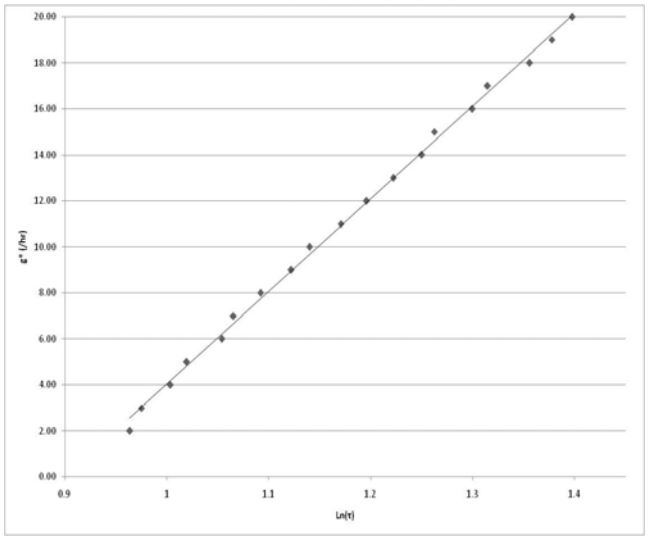

Fig. 2 Residence time in the nanocapsule simulated with different g^* values

4 CONCLUSIONS

An all-atom, multiscale approach for modeling nanocapsule therapeutic delivery systems has been presented. This method allows for the use of an interatomic force field, thereby avoiding the need for recalibration with each new application. Order parameters were introduced to characterize special features of these systems. These order parameters are the center of mass of the payload and nanocapsule, the state of the capsule (a measure of dilatation), and the dispersal (extent of release of the payload). We believe that these order parameters constitute the minimal set needed to describe such systems. Additional order parameters can readily be introduced to account for the presence of a cell surface and other nanoobjects; include other system-specific effects such as externally applied heat, magnetic forces, and ligand properties; or provide a more detailed description of the nanocapsule (i.e. shape, orientation, or distribution of small-scale structure across the nanocapsule). A reduced equation for the stochastic dynamics of these parameters was derived. To illustrate the approach, the time-course of liposomal doxorubicin delivery was simulated for a simplified case wherein the fully loaded capsule starts at the target zone and ready for release. In ongoing work, we are developing modules for estimating friction coefficients and thermal average forces based on statistical mechanical formulas and a universal interatomic force field; the goal being to avoid recalibration with each new application.

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