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Drug release through liposome pores

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ABSTRACT

Electrical, ultrasound and other types of external fields are known to induce the formation of pores in cellular and model membranes. This paper examines drug release through field induced liposome pores using Monte Carlo simulations. We find that drug release rates vary as a function of pore size and spacing, as well as the overall fraction of surface area covered by pores: The rate of release from liposomes is found to increase rapidly with pore surface coverage, approaching that of the fully ruptured liposome at fractional pore areas. For a given pore surface coverage, the pore size affects the release rate in the limit of low coverage, but not when the pores cover a relatively high fraction of the liposome surface area. On the other hand, for a given pore size and surface coverage, the distribution of pores significantly affects the release in the limit of high surface coverage: The rate of release from a liposome covered with a regularly spaced array of pores is, in this limit, higher than the release rate from (most) systems where the pores are distributed randomly on the liposome surface. In contrast, there is little effect of the pore distribution on release when the pore surface coverage is low. The simulation results are in good agreement with the predictions of detailed diffusion models.

1. Introduction

The unique structure of lipid bilayers reduces their permeability to most hydrophilic molecules and ions. As a result, flux into (or out of) cells is dominated by active transport or diffusion through dedicated pores [1]: Biomedical or biotechnological processes based on the introduction of molecules such as nucleic acids or drugs into cells require, therefore, mechanisms that either mimic cellular transport, or increase membrane permeability [2–4]. A similar issue arises when utilizing liposomes (vesicles) for biomedical or biotechnological applications. Their biocompatible lipid bilayer is highly effective as a barrier that prevents leakage of encapsulated drugs and compounds, so that inducing release requires application of a membrane-disrupting mechanism [5,6].

Fields such as electric or ultrasound are known to increase the permeability of cellular [7–12], microbial [13] or model synthetic [14–19] membranes. Similar effects were obtained via thermal [20] or magnetic [21,22] fields. The advantage of such fields, especially for in vivo applications, is that they can be applied non-invasively to locally increase cellular uptake and/or trigger liposomal release. Understanding the mechanism by which fields enhance transport through lipid bilayers is therefore of both fundamental and practical interest.

The effect of applied fields on the complex, multi-component and highly variable cellular membranes is highly sensitive to system parameters, thereby obscuring general trends. Understanding the fundamentals of the applied fields' effect on membranes can be better understood through the study of model membranes, namely, liposomes.

Despite differences in the specific mechanisms, studies show that fields can increase lipid membrane permeability through several different methods (see Fig. 1): Strong fields can cause irreversible membrane rupture [6,14,18,23], where large sections of the bilayer are destroyed and the bilayer cannot heal even after the field is removed. Fields can also cause the formation of pores—either irreversible ones that remain once the field is removed, or reversible ones that heal [6,18,23]. Another mechanism is one where the membrane surface area increases (generally associated with liposome shape fluctuations as a result of the applied field) [14,18]. This reduces the lipid packing density and allows diffusion of small molecules through the bilayer.

The ability to utilize field-induced membrane permeation, especially for triggered drug delivery applications, requires understanding the parameters controlling the drug release profile. Studies show that the release rate depends on both the field properties and membrane composition [15–17,19,24,25]. In general, despite differences in the type of induced field and the suggested

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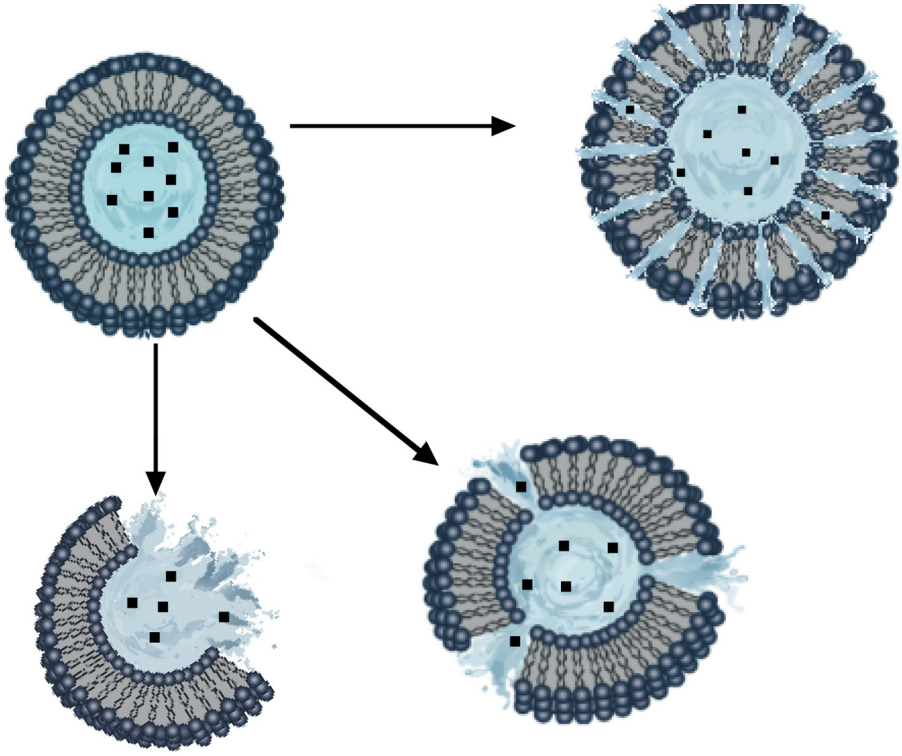

Fig. 1. Field-induced membrane permeation. The field can induce irreversible liposome rupture, or the formation of pores (permanent or transient). Alternately, the field can increase the surface area (causing 'dilation').

release mechanism, the rate of release (measured as the fraction of encapsulated compound that was released, as a function of time) could be fit using an exponential function, a common form for quantifying release of encapsulated compounds [26].

Does the specific mechanism for membrane permeation affect the release profile? The release from either ruptured liposomes or due to membrane stretching (see Fig. 1) where the membrane permeability is uniform, could be modeled using detailed diffusion models [26–28], or a 'lumped parameter' approach where concentration gradients within the liposome core are neglected (Fig. 2 bottom). Enden and Schroeder [29] applied a 'lumped parameter' model for liposomal release induced by low frequency ultrasound (LFUS), based on the assumption that the internal liposome volume is well mixed. The model examined the contributions due to liposomal rupture and those arising from transport throughout the uniform liposomal bilayer ('membrane stretching', as shown in Fig. 1). Fitting the data of Schroeder et al. [15] they conclude that approximately ¼ of the liposomes are destroyed, so that the release is largely dominated by diffusion through the membrane. Differences between different encapsulated drugs were accounted for through a membrane permeability parameter, which was obtained by fitting the profiles. It should be noted, however, that in large liposomes the encapsulated drug must diffuse through the liposome core until reaching the surrounding suspension (even if the membrane is ruptured), so that the 'lumped parameter' approximation may be inaccurate. Small et al. [19] developed a model similar to that of Enden and Schroeder [29] that included the spatial distribution of the encapsulated drug in the liposome. As a result, the model accounted explicitly for the radius of the liposome (which defined the lengthscale for diffusion in the core) and the diffusion coefficient of the drug in the aqueous core medium. The model yielded functionally similar profiles for the release from ruptured liposomes to that through permeable membranes [19], so fitting release profiles for LFUS-induced release could not determine the role of each mechanism.

While the release profiles due to liposome rupture vs membrane stretching are of interest, experimental studies clearly show that field-induced release may be attributed in many cases to the formation of transient or permanent pores [6,18,23] (note that pore formation may be even more prevalent, but not explicitly identified due to their small size and temporary nature). Yet, few

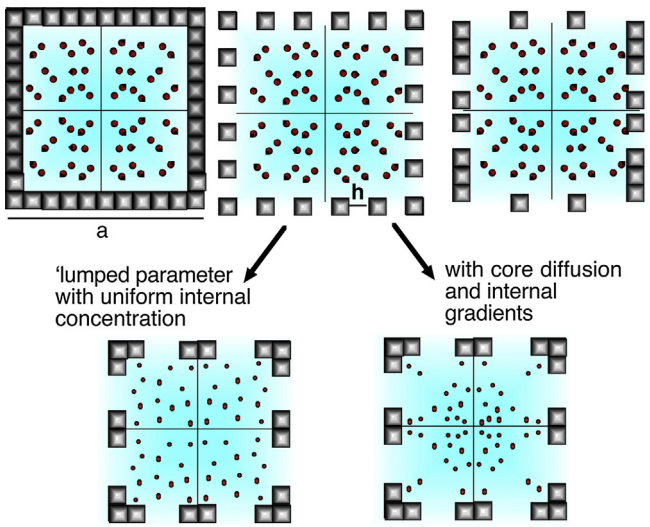

Fig. 2. The MC simulations set up. Liposomes are modeled as an $(a \times a)$ core enclosing M randomly distributed drug molecules (top left). The membrane contains n pores of size h, which may be uniformly distributed in an ordered array (top center) or randomly distributed (top right). Previously, two types on analytical models were proposed for transport in these systems: 'Lumped parameter' where the distribution of the drug molecules in the core is assumed to be uniform at any time (bottom left), or detailed diffusion models that account for transport in the core (bottom right). In this model, the distribution of the drug molecules becomes non-uniform, with depletion regions developing near pores, and regions with higher concentration in the center or near intact membrane sections.