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# Encapsulation of the anticancer drug cisplatin into nanotubes

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**Abstract**—One important application of nanotechnology is that of drug delivery, and in particular the targeted delivery of drugs using nanotubes. A proper understanding of the encapsulation behavior of drug molecules into nanotubes is vital for the development of nanoscale drug delivery vehicles. Furthermore, there are many other materials which may form single-walled nanotubes, such as carbon, boron carbide, boron nitride and silicon, and it is also important to understand their advantages and disadvantages. This paper presents a synopsis of the recent work in which boron nitride, boron carbide and silicon nanotubes are examined as drug delivery vehicles, and their encapsulation behavior is compared to previous work of the authors on carbon nanotubes.

**Keywords**—nanotubes; drug delivery; cisplatin; suction; acceptance

## I. INTRODUCTION

The idealized ‘magic bullet’ concept [1], first proposed at the beginning of the 20<sup>th</sup> century is now becoming a reality due to the advent of nanotechnology, and in particular the use of nanoparticles and nanotubes as delivery vehicles. In principle, an ideal drug carrier is injected into the body and transports itself to the correct target, such as a tumor, and delivers the required dose at this target. Due to their precise targeting nature and their protective environment, these nanoscale drug carriers enable a stronger drug to be used at a lower dose, resulting in fewer of the adverse side effects which exist for current methods, such as the highly toxic chemotherapeutic cancer treatments. Also, nanocapsules offer improvements to drug delivery methods for infections, metabolic diseases, autoimmune diseases, and pain treatment as well as for gene therapy [1].

To date, nanoparticles have been used for drug delivery and cosmetics and it has only been recently that nanotubes have gained significant attention. Nanotubes offer a number of advantages which suggest that they may provide an improved result [2]. Namely, they have a larger inner volume which allows more drug molecules to be encapsulated, and they have distinct inner and outer surfaces for functionalization. In addition, the volume and surfaces of the nanotube are more readily accessible since the end caps can be easily removed. Both nanoparticles and nanotubes have been shown to be readily taken up by cells [3, 4], and nanotubes have been found

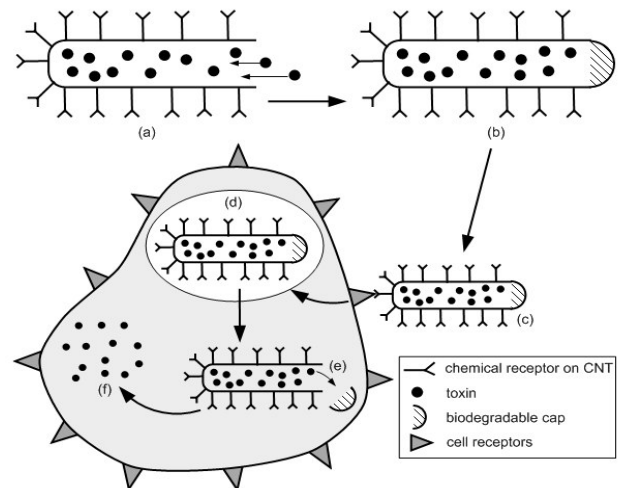


Figure 1. Outline of the proposed drug delivery process. (a) Nanotube surface is functionalized with a chemical receptor and the drug molecules are encapsulated, (b) open end is capped, (c) nanocapsule is ingested and locates to target site due to functionalized surface, (d) cell internalizes the capsule for example by receptor mediated endocytosis, (e) cap is removed or biodegrades inside cell, and (f) drug molecules are released [7].

to enter cell nuclei [5] suggesting another advantage in that they may be useful in gene therapy. The general proposed drug delivery process using nanotubes, in this case in the form of nano test tubes [6], is illustrated in Fig. 1.

Ultimately, we want to design a nanotube carrier such that prior to delivery it is energetically favorable for the drug molecule to be encapsulated, and once inside the desired cell it is energetically favorable to be ejected. Thus, the contents are deposited to the target site. Understanding the encapsulation and expulsion of drug molecules from nanocarriers is vital for the development of nanoscale drug delivery. As stated by Ferrari [8] “Novel mathematical models are needed, in order to secure the full import of nanotechnology into oncology.”

Motivated by recent research into the suction of fullerenes into carbon nanotubes [9], we investigate the encapsulation behavior of a particular anticancer drug molecule entering a nanotube using applied mathematical modeling techniques and elementary mechanics. In particular, we determine the minimum radius of nanotube that will accept the anticancer drug cisplatin into its interior, and we determine the tube radius

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that provides the maximum drug uptake. Cisplatin is a platinum based anticancer drug which is used to treat a wide range of tumors, despite its adverse side effects. It is expected that this form of targeted nanoscale drug delivery will significantly reduce these adverse side effects.

Single-walled nanotubes may be formed from a range of materials, such as carbon, boron nitride, boron carbide and silicon [10], and the list of possible materials is constantly growing [11]. Since their discovery, carbon nanotubes have generated considerable research and development for nanomechanical devices due to their demonstrated remarkable and unique electrical, mechanical, and optical properties. Nanotubes formed from alternative materials may be more biocompatible and be better for use in nanomedical devices, and as such it is important to understand the various advantages and disadvantages of these alternative materials. For example, boron nitride nanotubes share many of the excellent properties of carbon nanotubes because they share the same structure [12]. However, compared to carbon nanotubes, boron nitride nanotubes offer improved performance, through their high chemical stability, and high resistance to oxidation at high temperatures [13]. Furthermore, boron nitride tubes have already shown improvement over carbon nanotubes in the area of gigahertz oscillators [14, 15], in which boron nitride based oscillators generate higher oscillatory frequencies. Due to their biocompatibility [16, 17] boron nitride nanotubes may be particularly suitable for nanomedical applications. Similarly, silicon, with proven biocompatibility [18], has been widely used in the development of biomedical devices, such as neural prostheses and biochips, and therefore may also be a good material for nanomedical devices.

This paper provides a synopsis of recent work by the authors [19], in which the encapsulation behaviors of the anticancer drug cisplatin entering a boron nitride, boron carbide and silicon nanotube are compared to earlier work investigating the encapsulation of cisplatin into carbon nanotubes [20]. Our aim is to determine if there is an improved encapsulation behavior for the alternative nanotube materials. The technique presented here may be applied to any particular drug molecule, provided that the atom coordinates are known. However, the drug cisplatin is chosen in the interest of drawing a direct comparison to our earlier work [20]. We comment that this paper draws on a mathematical formulation proposed in an earlier paper by the authors [21].

## II. METHOD

### A. Interaction energy, acceptance and suction

The intermolecular forces between two interacting molecules is typically evaluated using either the discrete atom-atom approach or by the continuum approach whereby the atoms are assumed to be uniformly distributed over the surface of each molecule. These approaches have their disadvantages, the discrete atom-atom formulation can be time consuming especially for large molecules, and the continuum approach is mostly applicable to highly symmetric structures. This paper utilizes the hybrid discrete-continuous approach [21] in which one molecule is represented discretely and the other

continuously, thereby enabling irregular shaped molecules, such as drugs, to be represented whilst maintaining the time saving advantage of the continuous approach. Using the hybrid discrete-continuous approach [21], the interaction energy is given by

$$E = \sum_i \eta \int \nu(\rho_i) dS, \quad (1)$$

where  $\eta$  is the mean surface density of atoms on the continuously modeled molecule,  $\nu(\rho_i)$  is the potential function, and  $\rho_i$  is the distance between atom  $i$  on the discretely modeled molecule and a typical surface element  $dS$  on the continuously modeled molecule. The hybrid model has been shown to compare well to the typically used, discrete atom-atom and continuous, methods [21]. Note that the various components of the interaction force are determined by the negative gradient of the interaction energy (1). In particular, due to symmetry, of specific interest is the axial force, which is given by  $F = -dE/dZ$  and illustrated in Fig. 2.

In this paper the potential function  $\nu(\rho_i)$  is described by the Lennard-Jones potential which applies to non-bonded, non-polar atomic interactions, and is given by

$$\nu(\rho) = -A\rho^{-6} + B\rho^{-12}, \quad (2)$$

where  $A$  and  $B$  are the attractive and repulsive constants, respectively. In some cases, such as in this investigation, the force constants for the interaction between two atoms is unavailable, and the empirical combining rules [20, 22] may be used to determine approximate constants. Typically, a solvent medium is used to deliver drug molecules, and although this is not specifically addressed in this paper it may be incorporated by adjusting the Lennard-Jones constants by a factor of the dielectric constant of the solvent [20, 22].

To understand the encapsulation behavior of a particular drug molecule as it enters a nanotube the concepts of an acceptance condition and the suction energy [23] are used. With reference to Fig. 2, a particular molecule (located at negative  $Z$  and with no initial velocity) will be accepted into the nanotube interior (positive  $Z$ ) by van der Waals forces alone provided that the work done or acceptance energy  $W_a$  from  $-\infty$  to  $Z_0$  (the positive root of the interaction force, as shown in Fig. 2) is positive. Fig. 3 illustrates the typical behavior of the acceptance energy against nanotube radius  $a$ , noting that the point where the curve crosses the  $x$ -axis, labeled  $a_0$ , is the minimum radius of nanotube that will accept a particular molecule by van der Waals forces alone.

Similarly, the suction energy  $W$  is the work done generated by van der Waals interactions acquired by a particular molecule as a consequence of being sucked into the nanotube interior. Fig. 4 illustrates a typical suction energy, which crosses the  $x$ -axis at  $a_{min}$  and has a maximum at a nanotube radius  $a_{max}$ . Note that when the nanotube radius is equal to  $a_{min}$  it is energetically favorable for the molecule to be inside the nanotube. However, when the radius is in the range  $a_{min} < a < a_0$ , an additional energy is required for the molecule to be encapsulated. For further details the reader is referred to Hilder and Hill [20].

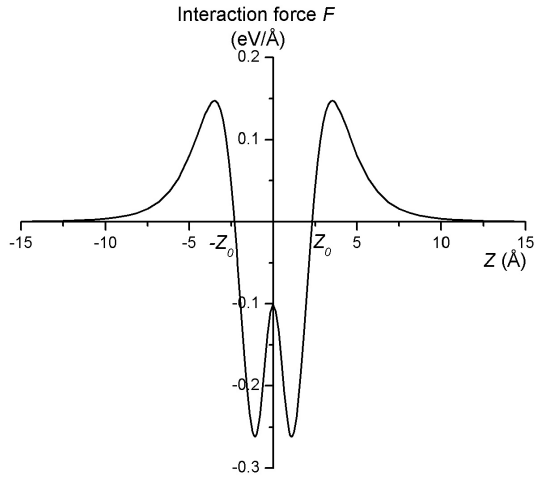


Figure 2. Typical interaction force between a drug molecule and a nanotube. Note that negative  $Z$  is outside the nanotube and positive  $Z$  is inside.

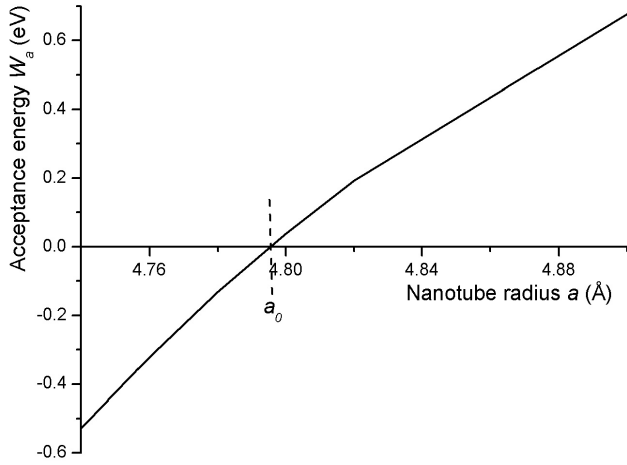


Figure 3. Typical acceptance energy for a drug molecule entering a nanotube of radius  $a$ , with the minimum radius of acceptance  $a_0$  indicated.

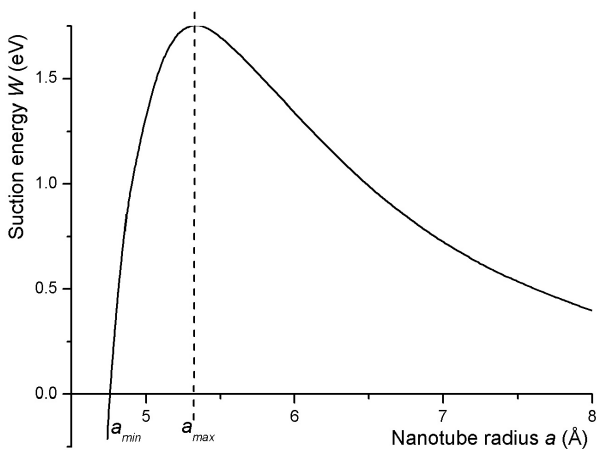


Figure 4. Typical suction energy for a drug molecule entering a nanotube of radius  $a$ , with the energetically favorable radius  $a_{min}$ , and the maximum uptake radius  $a_{max}$  indicated.

## B. Nanotube materials

A carbon nanotube can be thought of as a sheet of graphite rolled up into a seamless hollow cylinder. Similarly, boron nitride, boron carbide and silicon can all form graphite-like nanotubes [11, 12, 24-31]. However, silicon nanowires have been observed much more readily [32] due to the preference of  $sp^3$  bonding [33], despite this, silicon nanotubes have been reported experimentally [30, 31]. By use of the empirical combining rules [20, 22], the Lennard-Jones constants are determined and are summarized in Table I [19, 20]. For further details of the method used we refer the reader to [19-21].

TABLE I. LENNARD-JONES CONSTANTS

Atom	$A$ ( $eV \times \text{\AA}^6$ )	$B$ ( $eV \times \text{\AA}^{12}$ )
Boron-boron	27.91	47304
Nitrogen-nitrogen	36.48	52955
Carbon-carbon	19.96	34792
Silicon-silicon	436.91	2742630
Chlorine-chlorine	612.76	3445961
Hydrogen-hydrogen	10.51	5363
Platinum-platinum	287.85	1044434

## III. RESULTS AND DISCUSSION

Following Hilder and Hill [20], three orientations of cisplatin are examined. Table II outlines approximate values for the nanotube radii which provide acceptance  $a_0$ , maximum suction  $a_{max}$ , and the energetically favorable radius  $a_{min}$ . More specifically, to accept all three orientations of cisplatin the nanotube must have a radius of at least 4.895 Å, 4.875 Å, 4.894 Å and 5.226 Å for carbon (CNT), boron nitride (BNNT), boron carbide (BCNT) and silicon (SiNT) nanotubes, respectively [19]. The boron nitride nanotube has the smallest radius for acceptance, and thus the smallest radius to be efficiently filled with cisplatin. Accordingly, the boron nitride nanotube requires the least amount of material to deliver the drug, and as a result provides the least toxicity. Once the drug is ejected inside the cell the remaining nanocapsule may either slowly clear from the body or may remain, thus it is vital to reduce the amount of material required for efficient encapsulation. Alternatively, a silicon nanotube requires the largest radius for acceptance.

Comparing the magnitude of the suction energy at the maximum suction location illustrates a notable difference between all four materials, and the order from the lowest to the highest magnitude is boron carbide, boron nitride, carbon and silicon. In particular, the magnitude for the silicon nanotube is significantly larger than the other three materials. For encapsulation this is a positive result, since a larger suction energy results in a more efficient encapsulation. However, upon expulsion there will be a higher energy barrier for the encapsulated molecule to overcome. Therefore, the smaller suction energies are preferable as they provide efficient encapsulation in addition to minimizing the barrier upon expulsion.

TABLE II. RADIUS OF NANOTUBE AT ENERGETICALLY FAVORABLE VALUE  $a_{min}$ , ACCEPTANCE  $a_0$ , AND MAXIMUM SUCTION  $a_{max}$

	Orientation and corresponding radii (Å)								
	(i)			(ii)			(iii)		
	$a_{min}$	$a_0$	$a_{max}$	$a_{min}$	$a_0$	$a_{max}$	$a_{min}$	$a_0$	$a_{max}$
CNT <sup>a</sup>	4.76	4.80	5.34	4.76	4.90	5.34	4.74	4.79	5.27
BNNT <sup>b</sup>	4.76	4.77	5.3	4.76	4.88	5.3	4.71	4.75	5.23
BCNT <sup>b</sup>	4.78	4.79	5.34	4.78	4.89	5.34	4.74	4.78	5.27
SiNT <sup>b</sup>	5.12	5.13	5.73	5.12	5.23	5.73	5.08	5.13	5.67

a. Hilder and Hill [20], b. Hilder and Hill [19]

#### IV. CONCLUSIONS

In summary, the boron nitride nanotube provides the most ideal delivery capsule in terms of minimizing the amount of material required for encapsulation, thus providing the least toxicity. This technique, used to represent the encapsulation of cisplatin entering carbon, boron nitride, boron carbide and silicon nanotubes, can be extended to any number of drug molecules or alternative nanotube materials. It may be used to provide overall guidelines to assist in future experimental and molecular dynamics studies. It is hoped that in future work the expulsion of the drug molecule, once the nanocapsule is inside the cell, may be investigated. However, the expulsion occurs in an extremely complicated environment and presents challenges in terms of how best to model this environment.

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