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ORIGINAL PAPER

Hybrid coarse-grained/atomistic model of "chitosan + carbon nanostructures" composites

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Abstract We present a new hybrid molecular dynamics model of chitosan oligomers which is constructed specifically for studying chitosan + carbon nanostructures composites, their structure and mechanical properties. The model is derived for application within the modified molecular mechanics force field AMBER. Method of virtual sites mapping allowed to retain hexagonal rings of chitosan backbone. Mass and structural disposition of virtual atoms has been found as function of joined groups' atoms masses and coordinates. Geometrical parameters (e.g., bond length, valence angles, torsional angles and van der Waals distances) were found using semi-empirical methods. Parameters of interaction within the AMBER force field were estimated according to structural and energy characteristics of chitosan dimers and oligomers. Model has successfully passed multilevel verification based on comparison of its behaviour with atomistic chitosan within the same force field. It appeared that the model reproduces structural and energy characteristics of chitosan and its composites with carbon nanostructures. Moreover, it allows estimation of their mechanical properties. Dynamical characteristics of composite components are also well reproduced.

Keywords Composite · Chitosan · Carbon nanostructures · Molecular dynamics · Atomistic model · Hybrid model

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Introduction

Recently the so-called biopolymers became extremely popular in various spheres of production since nowadays only they are applicable within the framework of ecological requirements. In comparison with more cheap and strong synthetic polymers, biopolymers are biodegradable and biocompatible [1]. One of the most widely produced biopolymers is polysaccharide chitosan. It is one of the most unique substances, and novel materials, based on it, could be applied in many areas of production [2] and medicine [3–5].

It is well-known that pure chitosan fibres and membranes are not strong enough to be applied in production of, for example, biodegradable packaging. In order to improve their properties new nanostructured composites are being developed [6]. It was demonstrated that the most efficient way to construct strong and biodegradable composites is to add reinforcing fillers based on carbon nanostructures [7]. For example, carbon nanotubes and graphene flakes have significantly improved chitosan mechanical properties [7–9]. It should be mentioned that structural characteristics of chitosan composites affect their mechanical properties [10].

Unfortunately, most of such composites are being constructed with help of experiments, and this increases the cost of their production. In order to manage the properties of newly developed materials, it is nowadays possible to predict their characteristics *in silico* with help of mathematical modeling at various levels of their structure. Nanocomposites properties are primarily based on their atomistic structure and interaction between components. One of the most efficient ways to study such characteristics of composites are molecular modelling methods, such as molecular dynamics. Here, a material is studied at a nano-level, as molecules and atoms, interaction between the latter is described through potential energy gradient within the so-called atom-atomic potential force fields. In order to study the real-time dynamical characteristics of a structure, the classical Newtonian equations of motion are solved. Unfortunately, when one needs to study a polymer or biological macromolecules, there appears a complexity due to the number of atoms in the structure and, therefore, a too large number of equations to be solved. Recently, a way to simplify the calculations and reduce the number of equations was developed. It is based on replacement of typical groups of atoms by a large virtual one with all the characteristics of a real group. The so-called coarse-grained (CG) models were constructed for biological macromolecules (phospholipids, proteins, ets.) [11–14]. Polysaccharides, such as chitosan, are not being modelled widely [15] although their successful application in various areas of production and medicine depends on molecular modelling of composites and pure compounds. Unfortunately, although the coarse-grained models of macromolecules are extremely efficient in terms of structure and dynamical properties reproduction, they usually do not allow estimation of mechanical properties of materials. In order to avoid such restrictions of CG models, new methodology of hybrid multiscale molecular dynamics was developed. It is based on all-atom (AA) and CG modelling with various methods of coupling between the latter [16–20]. Such models are constructed to more accurately reproduce additional quantitive characteristics of polymeric and biological structures under study along with computational time and cost efficiency of CG modelling. Unfortunately, such methodology has been more often applied in simulations of biological macromolecules [17, 21] rather than for polymeric structures. It should be mentioned that nowadays the area of multiscale modelling of polymers [22] widens because application of the aforementioned methodology of studies may become a basis of management of polymer and novel functional materials mechanical properties. Therefore, the aim of the paper is to construct a new hybrid multiscale model of ”chitosan + carbon nanostructures” composites. The model should allow studying structural, energy and mechanical properties of the aforementioned compounds.

Table 1 Masses of virtual sites of hybrid model

Type of virtual site	Mass, amu
C2O	44
CO	30
CN	29
CH	13

Hybrid CG+AA model of chitosan+carbon nanostructurescomposites

In the current work we consider biocomposites based on chitosan with carbon nanostructures fillers which usually occupy 0.1–5 % of the total product mass. Therefore, in order to reduce number of equations and calculation time (within the molecular dynamics method) we propose to introduce virtual atoms only for chitosan oligomers involved in composites.

It should be mentioned that structure of chitosan chains is very important in terms of interaction with carbon nanotubes, their derivatives, and also graphene, since all of them have hexagonal elements. It was found that chitosan backbone rings tend to reproduce the shape of carbon nanostructure when interacting with it, and this affects chitosan mechanical structures [23]. Therefore, in order to reproduce such behaviour of the polysaccharide, we need to take into

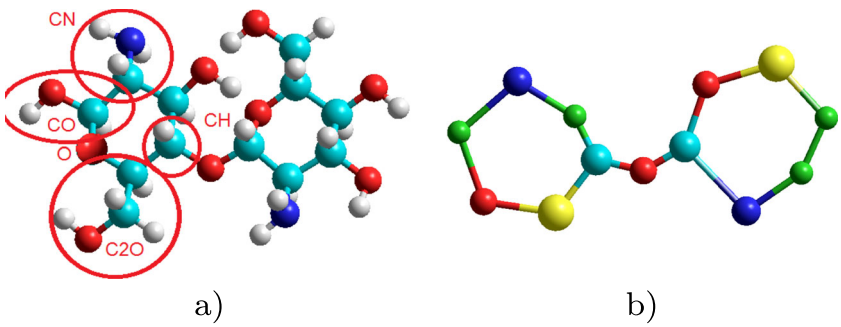

Fig. 1 Hybrid chitosan model construction: **a** atomistic model; **b** hybrid model

Table 2 Bond parameters for a hybrid CG/atomistic model of chitosan

Bonded atoms	K_r, kcal/(mol*Å^2)	r_{eq}, Å
O—C2O	126.83	2.05
O—CO	136.06	1.83
O—CH	87.63	1.83
C2O—CO	322.85	2.38
C2O—CH	276.73	2.38
CO—CO	345.91	2.23
CO—CN	161.42	2.25
CO—CH	345.91	2.229
CN—CH	161.42	2.25

account structural characteristics of the macromolecules such as backbone hexagon rings.

Model construction was divided into 3 steps: at first step we chose geometrical structure and decided which groups should be reduced to virtual atoms. Model consists of four virtual atoms: C2O, CO, CN and CH, as shown in Fig. 1. Coordinates of virtual atoms are coordinates of mass centres for each of the joined groups. Mass of each virtual atom was chosen to be a sum of grouped atom masses and is presented in Table 1. In order to reproduce the hexagonal backbone of chitosan, oxygen atoms were left to remain in the ring and as a link atom between the monomers (Fig. 1b). It should be mentioned that such a geometrical organization allows reproducing interactions and structural features between chitosan backbone and carbon hexagonal lattice,

Table 3 Angle parameters for a hybrid CG/atomistic model of chitosan

Bonded atoms	K_θ, kcal/(mol*deg^2)	θ_{eq}, deg
C2O—O—CO	88.32	180
C2O—O—CH	65.26	180
CH—O—CH	67.33	120
O—C2O—CO	253.66	122
O—C2O—CH	205.24	122
O—CO—CN	205.24	150
C2O—CO—CO	232.91	150
CO—CO—CN	196.01	145
CN—CO—CH	149.89	145
CO—CN—CO	145.28	120
CO—CN—CH	32.97	120
O—CH—O	73.79	120
O—CH—CO	59.96	145
O—CH—C2O	145.28	145
O—CH—CN	172.95	145
C2O—CH—CO	145.28	145
CO—CH—CN	140.66	145

Table 4 van der Waals interaction parameters

Type of virtual site	r_i^0, Å	ε_i, kcal/mol
C2O	1.81	0.24
CO	1.94	0.91
CN	1.82	1.27
CH	1.58	0.23

which is extremely important in estimation and managing of chitosan mechanical properties [23].

The next step in hybrid model construction was to choice of potential force field. In the current work we use the AMBER force field [24]. This potential is widely applied in modelling of biological molecules and takes into account various levels of interatomic interactions. Note that in the work we use a modified AMBER potential where we neglect the Coulomb interaction term (see Eq. 1) in order to reduce the computational costs. This is justified since carbon nanostructures are neutral molecules whereas the positively charged chitosan chains form a neutral electric field interaction, which is mostly defined by van der Waals term.

$$E_{\text{potential}} = \sum_{\text{bonds}} K_r \left(r - r_{eq}\right)^2 + \sum_{\text{angles}} K_\theta \left(\theta - \theta_{eq}\right)^2 + \sum_{\text{torsions}} \frac{1}{2} V_n \left(1 + \cos\left(n\phi - \phi_{eq}\right)\right) + \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \varepsilon_{ij} \left(\left(\frac{r_{0ij}}{r_{ij}}\right)^{12} - 2\left(\frac{r_{0ij}}{r_{ij}}\right)^{6}\right), \quad (1)$$

where $r_{0ij} = r_i^0 + r_j^0$ is the equilibrium Van der Waals distance between interacting atoms, defined as a sum of Van der Waals radii of atoms, $\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$.

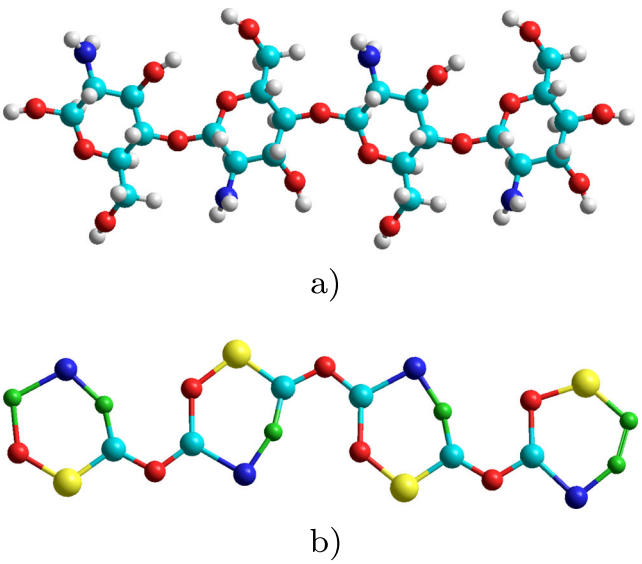

Fig. 2 Chitosan chain (4 links): **a** atomistic model, **b** hybrid model

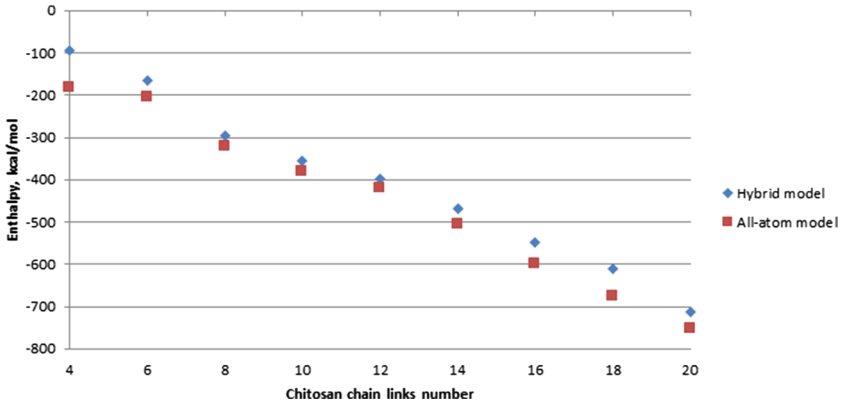

Fig. 3 Chitosan chain formation enthalpy

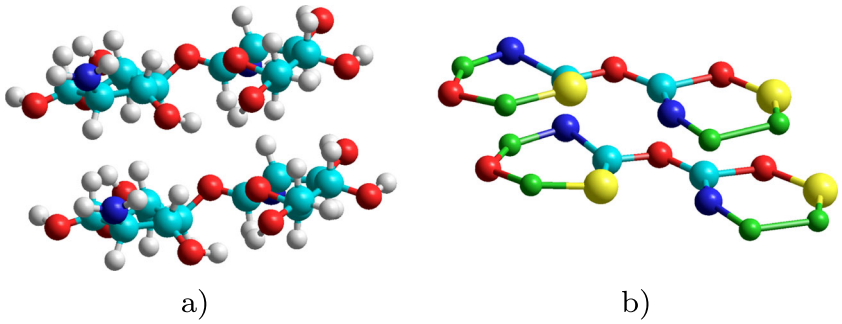

Fig. 4 Non-bonded interaction between chitosan dimers: **a** atomistic model; **b** hybrid model

Parameter set for the model within the framework of AMBER force field was calculated on a basis of geometrical and energy characteristics of chitosan dimer. Such characteristics were found using the DFT calculations by the Gaussian 09 software [25]. We solved a minimax problem similar to the one described in [26] for parameters set estimation for carbon nanostructures. The methodology presented in [26] consists of the following steps:

1. We pick the parametrisation of the force field as a set $A = \left\{K_r, K_\theta, V_n, \varepsilon_i, r_i^0\right\}$.
2. The parameter set was found by solving a minimax problem in form

$$S(A) = \min_A \max \sum_{i=1}^{4} \left| r_i - r_i^{eq} \right|, \tag{2}$$

where $\{r_i\}$ is the set of all (dimensionless, normalized by their equilibrium prototypes) geometrical parameters of the structure (bond-length, angle, torsional angle, Van der Waals distances) as function of atoms coordinates, $\left\{r_i^{eq}\right\}$ is the set of equilibrium parameters found by DFT calculations of the structure (also dimensionless). The problem was solved for the whole molecules considered in the model, the geometrical parameters deviation was considered less or equal to 10^{-6}. Geometrical parameters $\{r_i\}$ were found by Eq. 1 by substitution of the set A and minimization of Eq. 1 over the total energy of the molecule. The set $A = \left\{K_r, K_\theta, V_n, \varepsilon_i, r_i^0\right\}$ was constructed by building the 4D surface of the total energy (1) and estimation of local profile maxima depending on A.
3. Modification of method presented in [26] was based on one additional restriction of coincidence of potential energies of the molecules under study found by atomistic modelling within AMBER force field without Coulomb interaction and found by solving of problem (2).

$$\left| E_{\text{potential}} - E_{\text{potential}}^{\text{AT-AMBER}} \right| < \varepsilon, \tag{3}$$

where $\varepsilon < 0.001$.

In order to achieve the best accuracy in our calculations we considered chitosan dimers and chains consisting of 4, 6 and 8 backbone rings.

Table 5 Chitosan dimer adsorption on graphene nanoparticle

Graphene nanoparticle (height × width), Å	ΔE (atomistic model), kcal/mol	ΔE (hybrid model) kcal/mol
20.5×12.7	−20.75	−35.974
25×15	−21.216	−37.589
29.3×17.8	−21.216	−35.974
34×20	−20.524	−40.125

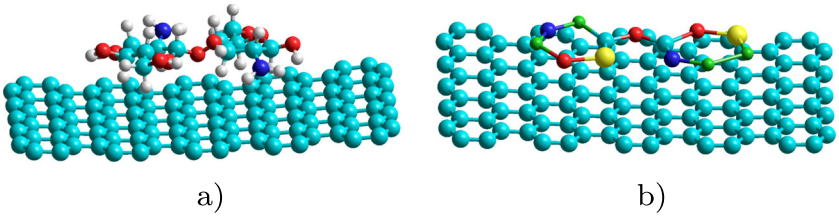

Fig. 5 Placement of chitosan dimer on graphene nanoparticle: **a** atomistic model; **b** hybrid model

The results of parameters estimation is presented below. Table 2 defines the bond parameters for the hybrid model, Table 3 is dedicated to angle parameters.

Torsional parameters were found to be equal for each of the group: $V_n = 0.415$ kcal/mol, $n = 2$, $\phi_{eq} = 180\,^\circ$.

Parameters for non-bonded van der Waals interaction are presented in Table 4.

Such methodology of parameters estimation allowed reduction of reparametrization of the AMBER force field for non-bonded interactions between new virtual sites and existing atomistic models, for example, for carbon nanostructures. This will be shown below in verification section.

Model verification

We verified the constructed model by comparing its behaviour with atomistic chitosan behaviour. To this end we used a software LAMMPS [27, 28] which allows user-defined parametrisation of force fields.

Chitosan dimer Geometrical characteristics of the models (see Fig. 1) demonstrated that coordinate deviation between the atomistic and hybrid model has not exceeded 5 %. Total molecule energy for atomistic model was 404.021 kcal/mol whereas for the hybrid model it is 406.788 kcal/mol, therefore, the difference is less than 1 %.

Chitosan chain formation We have studied the processes of chain formation. Total free energy of, for example, chains consisting of four monomers, was close: 805.274 kcal/mol for atomistic and 802.507 kcal/mol for hybrid models (see Fig. 2). Similar values were observed for structures consisting of 4, 6, 8, 10, 16 and 20 links.

Values for enthalpy of chain formation were calculated for standard conditions. Change of enthalpy of formation ΔH was found according to the following law:

$$\Delta H = \Delta E_{potential} + \Delta H_{bond} + p\Delta V, \tag{4}$$

where $\Delta E_{potential}$ is a change of free energy between initial and final structures, ΔH_{bond} is a heat of bond breaking/formation (calculated as a sum of bond breaking and bond formation heats), $p = 1$ atm is a constant pressure of the compounds and ΔV is a change of volumes between initial structures formed by chitosan monomers and the final chain. The results are presented in Fig. 3. It is obvious that the reaction characteristics are well-reproduced by the constructed hybrid model. The results clearly demonstrate the exothermic properties of reaction, although the absolute values of enthalpy differ due to inaccuracy of volume change term calculations based on the model.

Non-bonded interactions Next, we considered molecular dynamics simulation of chitosan dimers non-bonded interaction. Simulation was performed for atomistic and hybrid

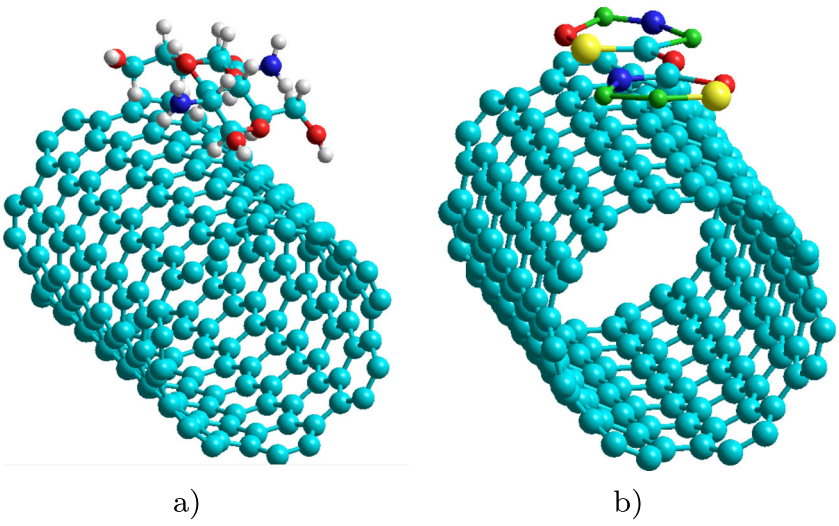

Fig. 6 Example of chitosan dimer positioning when interacting with carbon nanotube: **a** atomistic model, **b** hybrid model

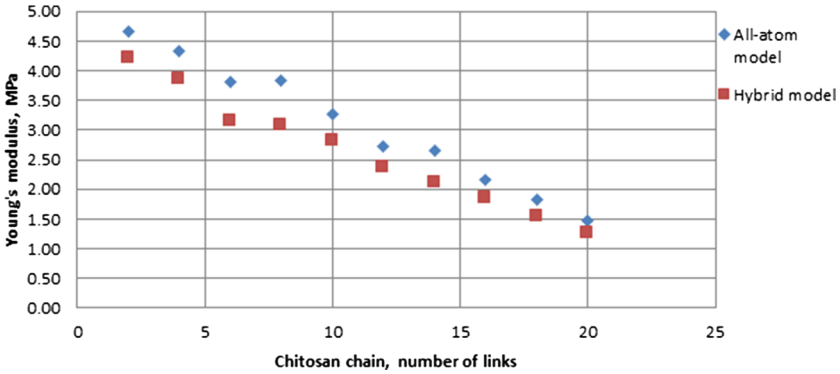

Fig. 7 Youngs modulus of chitosan chains

models in vacuum. Temperature was kept at the level of 300 K. In order to keep the temperature of simulation at the aforementioned value, a Berendsen thermostate algorithm was used. Time of simulation was 1 ns. Integration time step was 1 fs because of atomistic representation of several elements of molecules. Therefore, the proposed model does not allow enlarging of integration time steps.

Atomistic and hybrid models demonstrated the same behaviour and formed a structure shown in Fig. 4.

Bulk density of space distribution of chitosan molecules was also computed and compared with atomistic and experimental calculations. It appeared that the density found by the hybrid model and atomistic model are average of 205 kg/m^3 and 198 kg/m^3, respectively. The experimental estimations vary between 150 and 300 kg/m^3, which proves accuracy of the modeling.

We conclude that the constructed hybrid model of chitosan is successfully reproducing its energy, structural and dynamical characteristics.

Interaction with carbon nanostructures First we considered adsorption process of chitosan dimer on graphene nanoparticles (graphene sheets which linear dimensions are lower than 40 $\AA$). To this end we considered a non-bonded interaction between the aforementioned molecules. Results concerning stability of such compounds are presented in Table 5. The molecular dynamics simulations were performed at the same conditions as mentioned before for chitosan-chitosan interaction. The adsorption energy presented in Table 5 was calculated as a difference of total potential energies (1) of equilibrated complex $E^{\text{complex}}_{\text{potential}}$ and components located infinitely far away from each other as a sum $E^{\text{chitosan-dimer}}_{\text{potential}} + E^{\text{graphene}}_{\text{potential}}$ (see Eq. 5).

$$\Delta E = E^{\text{complex}}_{\text{potential}} - \left(E^{\text{chitosan-dimer}}_{\text{potential}} + E^{\text{graphene}}_{\text{potential}}\right). \quad (5)$$

It should be noted that atomistic and hybrid models demonstrate similar topological position of chitosan dimer on graphene (see Fig. 5).

Interaction of chitosan with carbon nanotubes demonstrated a similar behaviour (see Fig. 6).

We conclude that the constructed hybrid model successfully represents structural and energy characteristics of composites ”chitosan + carbon nanostructures”.

One of the most important characteristics of the composites under study is their mechanical strength. The aim of hybrid model construction is to develop a new simple method of composites characteristics estimation. We found Youngs modulus for various single chitosan chains (using atomistic and hybrid models). Method of elastic modulus calculation for various structures is described in paper [26] and is based on estimation of potential energy gradient as a result of deformation of the structure, and also on geometrical parameters of the molecule under study. Results are demonstrated in Fig. 7 and show that the hybrid model is successfully reproducing mechanical behaviour of chitosan.

Finally, it should be mentioned that the methodology of model construction allowed a significant decrease of calculation time within molecular dynamics method not less than two times due to reduction of number of interacting cites. This depends on the amount of atomistically represented cites, for example, the size of carbon nanostructures within the chitosan compound.

Conclusions

In the paper we demonstrate a new hybrid CG/atomistic model of ”chitosan + carbon nanostructures” composites. The model represents structural, dynamical, energy and mechanical properties of composites and chitosan itself while 2 times reducing the number of atoms in system.

The main properties of the model are:

1. a well-known popular potential force field AMBER is used to model the atom-atomic interaction;
2. model not only reproduces structural, dynamical, energy and mechanical characteristics of composites but also their stability.

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References

1. Ramakrishna S, Mayer J, Wintermantel E, Leong KW (2001) Biomedical applications of polymer-composite materials: a review. Compos Sci Technol 61:1189–1224. doi:10.1016/S0266-3538(00)00241-4
2. Goosen MFA (1996) Applications of Chitin and Chitosan. CRC Press
3. Kossovich LY, Salkovskiy YE, Kirillova IV (2010) Electrospun chitosan nanofiber materials as burn dressing. IFMBE Proceedings 31:1212–1214. doi:10.1007/978-3-642-14515-5_307
4. Baldrick P (2009) The safety of chitosan as a pharmaceutical excipient. Regul Toxicol Pharmacol 56(3):290–299. doi:10.1016/j.yrtph.2009.09.015
5. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM (2004) Recent advances on chitosan-based micro- and nanoparticles in drug delivery. J Control Release 100(1):5–28. doi:10.1016/j.jconrel.2004.08.010
6. Liang D, Hsiao BS, Chu B (2007) Functional electrospun nanofibrous scaffolds for biomedical applications. Adv Drug Deliver 59:1392–1412. doi:10.1016/j.addr.2007.04.021
7. Li Q, Zhou J, Zhang L (2009) Structure and properties of the nanocomposite films of chitosan reinforced with cellulose whiskers. J Polym Sci Part B Polym Phys 47:1069–1077. doi:10.1002/polb.21711
8. Thostenson ET, Li C, Chou T-W (2005) Nanocomposites in context. Compos Sci Technol 65:491–516. doi:10.1016/j.compscitech.2004.11.003
9. Fan H, Wang L, Zhao K, Li N, Shi Z, Ge Z, Jin Z (2010) Fabrication, mechanical properties, and biocompatibility of graphene-reinforced chitosan composites. Biomacromolecules 11:2345–2351. doi:10.1021/bm100470q
10. Manchado MAL, Valentini L, Biagiotti J, Kenny JM (2005) Thermal and mechanical properties of single-walled carbon nanotubes-polypropylene composites prepared by melt processing. Carbon 43:1499–1505. doi:10.1016/j.carbon.2005.01.031
11. Marrink SJ, de Vries AH, Mark AE (2004) Coarse grained model for semiquantitative lipid simulations. J Phys Chem B 108:750–760. doi:10.1021/jp036508g
12. Tozzini V (2005) Coarse-grained models for proteins. Curr Opin Chem Biol 15:144–150. doi:10.1016/j.sbi.2005.02.005
13. Nielsen SO, Lopez CF, Srinivas G, Klein ML (2004) Coarse grain models and the computer simulation of soft materials. J Phys Condens Matter 16:481–512. doi:10.1088/0953-8984/16/15/R03
14. Rudnicki WR, Bakalarski G, Lesyng B (2000) A mezoscopic model of nucleic acids. Part 1: Lagrangian and quaternion molecular dynamics. J Biomol Struct Dyn 17:1097–1108. doi:10.1080/07391102.2000.10506595
15. Ahmad S, Johnson BF, Mackay SP et al. (2010) In silico modeling of drug-polymer interactions for pharmaceutical formulations. J R Soc Interface 7(4):423–433. doi:10.1098/rsif.2010.0190.focus
16. Voth GA (2008) Coarse-graining of condensed phase and biomolecular systems. CRC Press
17. Izvekov S, Voth GA (2005) A multiscale coarse-graining method for biomolecular systems. J Phys Chem B 109:2469–2473. doi:10.1021/jp044629q
18. Liwo A, Czaplewski C, Pillardy J, Scheraga HA (2001) Cumulant-based expressions for the multibody terms for the correlation between local and electrostatic interactions in the united-residue force field. J Chem Phys 115:2323–2347. doi:10.1063/1.1383989
19. Izvekov S, Parrinello M, Burnham CJ, Voth GA (2004) Effective force fields for condensed phase systems from ab initio molecular dynamics simulation: A new method for force-matching. J Chem Phys 120:10896–10913. doi:10.1063/1.1739396
20. Rzepiela A, Louhivuori M, Peter C, Marrink S (2011) Hybrid simulations: combining atomistic and coarse-grained force fields using virtual sites. Phys Chem Phys 13:10437–10448. doi:10.1039/c0cp02981e
21. Predeus AV, Gul S, Gopal SM, Feig M (2012) Conformational sampling of peptides in the presence of protein crowders from AA/CG-Multiscale simulations. J Phys Chem B 116(29):8610–8620. doi:10.1021/jp300129u
22. Theodoru D (2005) Multiscale modeling of polymers. In: Yip S (ed) Handbook of materials modeling. Springer, Netherlands, pp 2757–2761
23. Glukhova OE, Kirillova IV, Kolesnikova AS, Kossovich EL, Ten GN (2012) Strain-hardening effect of graphene on a chain of the chitosan for the tissue engineering. Proc SPIE 8233:82331E. doi:10.1117/12.907032
24. Cornell WD, Cieplak P, Bayly CI, Gould IR, Merz Jr KM, Ferguson DM, Spellmeyer DC, Fox T, Caldwell JW, Kollman PA (1995) A second generation force field for the simulation of proteins, nucleic acids, and organic molecules. J Am Chem Soc 117:5179–5197. doi:10.1021/ja00124a002
25. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE et al (2009) Gaussian 09, Revision A.02. Gaussian Inc., Wallingford CT
26. Glukhova OE (2009) Study of mechanical properties of peapod-like carbon nanotubes based on molecular-mechanics model. Physika volnovih processov i radiotehnicheskie systemi 12(1):69–75. (in Russian)
27. Plimpton S (1995) Fast parallel algorithms for short-range molecular dynamics. J Comp Phys 117:1–19. doi:10.1006/jcph.1995.1039
28. http://lammps.sandia.gov