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An artificial neural network model for investigating the dynamics of regulatory T cells in cancer immunotherapy

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Abstract

The immunosuppressive activity of regulatory T cells (REGTs) has been recognized as an obstacle to the success of cancer immunotherapy. Despite the intensive in-vivo and in-vitro researches on the role of these cells, the dynamics of their suppressive mechanisms are poorly understood. Computational modeling of the immune system opens the way for in-silico analysis of these dynamics. Research on the subject has been mostly restricted to equation based models, which describe cellular interactions, employing deterministic immunological knowledge. This paper examines the use of artificial neural networks (ANNs) to model the competing roles of REGTs and effector T cells (EFFTs) in tumor-immune interactions. Due to the learnability of ANNs from input data, no a priori immunological knowledge of the modeler is needed. Data for this study were collected from experiments in which the amount of tumor size, REGTs, and EFFTs were measured in tumor-bearing mice under immunotherapy. A multilayer perceptron was trained to model the tumor growth rate (TGR) using the inputs: (1) tumor size, (2) REGTs, and (3) EFFTs. Monte Carlo simulation was employed to estimate the sensitivity of TGR to REGTs and EFFTs. The trained ANN was able to mimic the dynamics in the data with a low validation error. The sensitivity of the model to REGT was much greater than EFFT, which suggests that fighting the suppressive functions of REGTs is more important than enhancing the cytotoxicity of EFFTs. This finding must be taken into account when defining immunotherapy strategies. Visualization of TGR as a function of REGT and EFFT indicates that the relationship between the two inputs REGT and EFFT with TGR is highly nonlinear and there are conflicting behaviors in different regions. This suggests that the design of treatment protocols should be personalized for each patient based on his/her REGT-EFFT area.

Keywords: Artificial neural network; Tumor; Immunotherapy; Regulatory T cell; Modeling; Immunosuppression.

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An individual-based spatial model for the role of suppressor T cells in tumor growth

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Abstract

Computational modeling is a handy tool for simulating and analyzing biological systems, and has been extensively used in quantitative description of tumor-immune system (IS) interplay. Once validated, these models can be used for prediction of tumor size in presence or absence of various treatments. The models presented on the subject to date has been mostly limited to non-spatial ones and rely on the assumption that cells are well-mixed. On the other hand the existing spatial models haven't considered the immunosuppressive elements of the IS, especially the regulatory T cells (REGTs). This study therefore seeks to present an individual-based model (considering both space and time) that describes the conflicting roles of REGTs and cytotoxic T cells (CYTTs) in tumor-IS interplay. In the present study, in conformance with recent models that assume the cells of the IS alter their motion type after activation by tumor antigen, two types of motion are employed for REGTs, CYTTs, and dendritic cells (DCs): (1) a free search if they are not triggered yet, and (2) a Brownian motion if they are activated. The simulations were run assuming a 2-D 100×100 lattice representing a 1 mm^2 area of the body, containing 10000 empty or cell-occupied spaces. In addition to parameters such as tumor antigenicity and cytotoxicity of CYTTs suggested in previous studies, simulations of the proposed model introduce two other critical parameters of the IS to be considered as possible targets in DC-based treatments; firstly the rate of REGT activation by DCs must be reduced with the aid of proper materials for DC maturation, and secondly the immunosuppressive condition provided by REGTs, which cause inhibitory effects on CYTTs, must be minimized. In summary, this study calls attention to the importance of employing spatial structures in quantitative description of tumor-IS interplay.

Keywords: Individual based modeling; Agent based modeling; Tumor; Immunotherapy; Regulatory T cell; Immunosuppression.

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Drug Modeling

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Abstract
Although the advent of nano-engineered drug delivery systems has revived optimisms for better administration of a wide range of pathologies, we describe a theoretical modeling framework as influential tools to furnish future design and development of DDSs. Albert and Gernaat (1984) [1] collected data on the levels of ibuprofen (sold under the name Motrin) in the blood of patients being treated for arthritis. We used these data to construct our model. By using Two-Compartment Model for Drug Metabolization [2], we can compatible the model to these data, that is, approximation the parameters and that make the mathematical model match experimental quantities to control how uickly the ibuprofen enters and leaves a patient's blood. The mechanisms of creativity are the same, i.e., incremental (plodding from darkness to dawn) or sudden (the "Eureka" effect) realization, but both are poorly understood. Creativity remains a human characteristic, but it is directly related to the tools available, especially computer software and hardware [3]. In this article, we analyzed the flow of a medication from a patient's gut to their blood. We analyzed the model assuming the rate of elimination of medication from the patient's blood is the same as the rate at which medication passes from the gut into blood. We showed that the function of the amount of drug enters the patient's blood from the gut, is the exponential function. We solve for the amount of the drug in the patient's blood and sketch the graph of it against time. We find the maximum level of medication in a patient's blood, if the passage of medication through the patient's body is modeled by the equations.

Keywords: Two-compartment model, dynamical system, equilibria points, local extrema, , Classify extrema. separation of variables

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Epidemic mode

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Abstract

Mathematical models can be used to analysis disease eruptions. Models for the spread of sickness can provide critical information for efforts to control a disease. Fishman, Khoo, and Tuite (2014) [1] built a mathematical model to predict the rate of growth of an EHF epidemic in West Africa, and to show that the control measures in place at that time were not enough to stop the disease from continuing to spread.
Mathematical models are used throughout epidemiology (the science of how diseases spread). They are used both to predict the future growth of emerging disease outbreaks like Ebola [1]. And vaccination strategies to eliminate or control diseases like measles [2], [3].
We will model how a disease spreads through a population of N people (or organisms). In [4] we considered a two-state model for the disease. That is, we divided the population into two classes; individuals who have the disease and individuals who do not have it. In that model after recovering from the disease, an individual is immediately returned to the population that does not have the disease, which means that they can immediately catch the disease again. This assumption may be a good model for the cold virus, which evolves quickly and has many different variants.
However, for many diseases like measles, after a person recovers their immune system adapts to the disease, which makes them immune to it for some period of time (though this immunity can also be lost). To model the progression of such a disease we will use a model that was created by Kermack and McKendrick [5].
We will divide the population into three classes: susceptible individuals who do not have the disease, but who could catch it; infected individuals who currently have (and can also transmit) the disease; and recovered individuals who had the disease but who have since recovered from it, and are now immune to the disease. Denote by S(t) the number of susceptible individuals, I(t) the number of infected individuals, and R(t) the number of individuals in the recovered class all at time t.
Individuals start off in the susceptible class (S). After contact with an infected individual, they too may become infected (I). An individual will remain infected until their immune system fights off the disease. Then they enter the recovered class (R).
After some time, an individual's immunity to the disease may wear off, returning them to the susceptible class.
In this article we introduced a mathematical model we used the graphical method to sketch the behaviors of the solution for different values of S and I.

Keywords: Dynamical Systems, Differential Equations, Equilibrium point, stability, unsuitability, Vector Field.

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Bioinformatic analysis of miRNA-mRNA interactions and related biological pathways in platinum-resistant epithelial ovarian cancer cells

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Abstract

Introduction: Epithelial ovarian cancer (EOC) is one of the most lethal gynecologic cancers. Chemoresistance of tumor cells and disease relapse often result in treatment failure and death of patients. Since better understanding the molecular mechanism of chemoresistancy could led to increasing the efficiency of treatment methods, in this study we aimed to evaluate the molecular pathways that regulate chemoresistancy. **Methods:** miRNA profiling dataset was retrieved from the NCBI Gene Expression Omnibus (GEO) database by accession number GSE93794. This dataset demonstrated 3 Epithelial Ovarian Cancer cell lines Platinum-resistant vs. their parental. Initial bioinformatics analyses were performed using GEO2R. Top 5 up-regulated miRNAs were assessed by miRwalk web-tool to find their target mRNAs. Moreover related pathways and biological processes were explored using enrichr bioinformatics tool.
Results: Our result showed that miR-365a-3p, miR-299-3p, miR-24-1-5p, miR-361-5p and miR-29b-1-5p are 5 top up-regulated miRNAs. Moreover studying the mRNA targets such as FAM166B, FAM214B, TESK1, ARHGEF39 and so on indicated that these microRNAs mostly involved in cell-cell communication, cell-extracellular communication, extracellular remodeling, cell mobility and metastasis related processes that are followed by chemoresistance and tumor relapse. **Discussion:** These findings specified that in concordance with previous reports metastasis related processes could be correlated to different responses to platinum in ovarian cancer cells. So molecular targeting of these biological processes could be effective in better outcome of ovarian cancer therapy.

Keywords: Bioinformatics; Cancer; miRNA-mRNA interaction; Molecular pathway; Chemoresistancy, Metastasis

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Urinary metabolomics and prostate cancer biomarkers

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Abstract

Introduction: Prostate cancer is the fifth leading cause of cancer-related mortality in male worldwide. Current biomarkers for this cancer such as prostate serum antigen (PSA) have not sufficient specificity and sensitivity. So, finding novel effective biomarkers is so important. **Results:** Accumulating evidences have indicated the efficacy of metabolomics in identifying novel cancer biomarkers. Tumor metabolism significantly differs from normal tissue and it is extremely informative about the biological condition. Urinary metabolomics has recently appeared as a potentially accurate method to cancer biomarker discovery. Noninvasive sampling properties, less sample preparation, higher amounts of metabolites and lower protein content are advantages of this sample compared with other biological fluids. Urinary metabolomics could be analyzed via multiple technological developments in mass spectrometry, nuclear magnetic resonance, gas and liquid chromatography and capillary electrophoresis and studies have been shown that alteration in glycolysis, amino acids, organic acids, tricarboxylic acid cycle, choline, carbohydrates and fatty acid metabolism have been observed in prostate cancer patients. **Discussion:** in conclusion, urinary metabolomics could be proposed as reliable and powerful tool to find novel biomarkers for prostate cancer. However, further investigations are required to identify inexpensive, noninvasive, sensible and specific biomarkers in urinary metabolomics for prostate cancer.
Keywords: Prostate cancer, Urinary metabolomics, Biomarkers

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Molecular investigation on the interaction of curcumin with serum albumin by multispectroscopic techniques and molecular simulation studies

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Abstract

Curcumin, Built from Curcuma longa, Was used as spice, preservative and food coloring for centuries[1]. Curcumin has proven to be one of Most effective natural remedies for inhibiting multiple signals and for preventing cell proliferation, invasion, metastasis and angiogenesis [2]. Curcumin was recognized to enjoy anti-inflammatory, antioxidant, and anti-tumor activity[3]. Serum albumin, specifically human serum albumin (HSA), is a protein that is applyed chiefly in drug-binding trials. [4]. The interaction of serum albumin binding with drugs is crucial for grasping the delivery, safety, toxicity, and dispensation of drugs during the chemotherapy procedure [5]. Spectroscopic and analytical methods have been used in the Study of todayto investigate the impact of Curcumin on the HSA structure. UV–Vis absorption curve increased with increasing Curcumin concentration, indicating a non-covalent Interaction amongst Curcumin and HSA. Increasing the emission intensity has caused a static decrease. Quenching fluorescence demonstrat the polarization of the residues of Trp and Tyr. DSC studies demonstarted that with the participation of Curcumin, the amount of T_M decreased. Molecular docking outcome indicate that HSA binding to Curcumin is correlated with hydrophobic interactions and with negative Gibbs free energy. Docking tests also demonstarte that HSA amino acid residues organize at drug sites I interact by hydrophobic force with Curcumin. The molecular dynamics simulation revealed HSA leaves more unstable in attendance of Curcumin. The mean RMSF of HSA in attendanceof Curcumin demonstarted that this system flexibility increased during the simulation. The RG outcome demonstart that the structural density of the protein decreased during the simulation. ASA values of Trp and Tyr were measured and demonstarte that several of these residues more exposed to polar solvent.

Keywords: HSA, Curcumin, fluorescence quenching, DSC, molecular docking, molecular dynamics simulation

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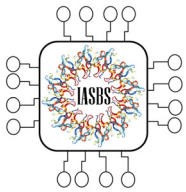

Multi-spectroscopic and molecular modeling studies of The interaction between Naringenin with serum albumin

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Abstract

Flavonoids are a wide group of phenolic blends with broader therapeutic properties [1]. Naringenin is one of Most important flavonoids derivative from certain eatable fruits, such as citrus[2]. Naringenin was used to improve human health and treat adiposity, diabetes, hypertension, metabolic syndrome, osteoporosis, cancer and, cardiovascular diseases in various medication formulations[3]. Serum albumin is a protein that It widespread used as a bearer for drug binding studies[4]. In this study, the Spectroscopic and computational approaches applied to peruse the effect of naringenin on the structure of the HSA. Analyzes of fluorescence demonstrated the static quenching mechanism. Results from the different experiments have shown that naringenin binds to HSA. Methods of spectroscopy demonstarted that naringenin induces a transition in the HSA structure. At three temperatures, the number of binding sites, the binding constant, and the thermodynamic parameters (somewhere between ΔH°, somewhere between ΔS°, and somewhere between ΔG°) calculated. The experiences of Van der Waals and bonding hydrogen considered to be the main forces. The results of molecular dynamics simulation and thermal denaturation demonstarte that naringenine increases the stability of HSA and decreases its flexibility. Due to the decline in Rg in attendance of naringenin, the gyration radius (Rg), protein folded and firmer. The amount of RMSD decreases in attendance of naringenin, indicating that HSA leaves more stable by binding to naringenin. The mean RMSF HSA in attendance of naringenin demonstarted a decrease in protein flexibility during the simulation. ASA values were extented from Trp and Tyr and demonstarted that most of these residues moved outward from the protein (more polar medium).

Keywords: Flavonoid, Naringenin, fluorescence quenching, molecular docking, molecular dynamics simulation

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Comparative studies on the interaction of spermidine with lysozyme by multi-spectroscopic, activity measurements and molecular modelling methods

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Abstract
Lysozyme (E.C.3.2.17) also known as N-acetyl-muramic-hydrolase is a naturally occurring globular protein and is a lytic enzyme [1, 2]. Polyamines are basics molecules in cell cycling and replication and crucial also for cell growth and differentiation [3, 4]. Spermidine is combine from putrescine and applied as a pioneer of spermine [5]. We used UV-Vis spectros, copy simulation method and kinetic assay to understand the effect of polyamine (such as spermidine) on conformation, stabilisation, and lysozyme function. Structural lysozyme variability was experiment at several spermidine concentrations. Spermidine connection switches enzyme mixture. UV – Vis absorption curve increased with increased spermidine concentration, showing van der Waals and the interaction between spermidine and lysozyme in the hydrogen bond. UV- Vis measurement display the lysozyme changes in tertiary structure as an action of the concentration of spermidine. The consequences of molecular simulation well illustrate that spermidine could spontaneously interconnect and modify the lysozyme structure, thus corroborating the tentative consequences. Additionally, kinetic test display that these spermidines reduced the condensation-affiliate activity of lysozyme enzymes.
Keywords: Lysozyme, Polyamine, spermidine, UV- Vis spectroscopy, kinetic

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Dynamical behavior of HIV virus in the presence of synaptic transmission

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Abstract

HIV is a retrovirus that destroys immune cells (the target cells CD4+ T that known commonly as T-helper cells). The virus can live in the body for many years without any symptoms. After treatment the virus will not be removed from the body. Studies in recently years have sought to explain why the disease has not been eradicated. In the mathematical model we will consider effect of Virological synapse and proliferation target cells with a logistic form. $T(t)$, $I(t)$, $V(t)$ and $L(t)$ denote the concentrate of uninfected CD4+ T cells, productively infected cells, free virus and latent infected cells at time t, respectively.

$$\dot{T} = \lambda - d_T T + rT\left(1 - \frac{T}{T_{max}}\right) - \beta_f TV - p(s)\beta_s TI,$$
$$\dot{I} = (1-\rho)\beta_f TV - d_I I + \alpha(s)\beta_s TI + a_L L + \omega LV,$$
$$\dot{L} = \rho\beta_f TV - d_L L - a_L L + \eta(s)\beta_s TI - \omega LV - \beta_s LI,$$
$$\dot{V} = kI - s\beta_s(T+I+L)I - d_V V,$$

$T(0) = 700, I(0) = 0, L(0) = 0$, $V(0) = 10$ and $s = 2000, \alpha(s) = 0.0001, \eta(s) = 0.0001,$ in the diagram, amount of virus initially rises to the peak and then decreases and remains at a relatively constant level during chronic infection, but target cells initially decreases and then increases and remains constant level. Latent infected cells increases with $\beta_f TV$ and synaptic transmission ($\eta(s)\beta_s TI$) and decreases by coefficient of d_L, ωLV and $\beta_s LI$. Infected cells increases with $\beta_f TV, a_L L, \omega LV$ and synaptic transmission ($\alpha(s)\beta_s TI$) and decreases by rate of $d_I I$, therefor initially rises to the peak and then decreases and remains different constant level. Virus levels increases with kI and decreases by rate of $s\beta_s(T+I+L)I$ and d_V. Target cells increases by rate of λ and logistic form ($rT\left(1 - \frac{T}{T_{max}}\right)$) and decreases by rate of $\beta_f TV$ and $p(s)\beta_s TI$. Considering virological synapse make us a more realistic model of the disease.

Keywords: mathematical model, virological synapse, latent reservoir, logistic growth, HIV.

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Experimental and Computational studies on the binding of β-carotene to pepsin enzyme

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Abstract
Carotenoids are a class of isoprenoids, which exist as natural pigments in different sources.β-carotene is an antioxidant carotenoid, and can therefore be protected against cancer and cardiovascular diseases. Pepsin is a digestive enzyme in the stomach. This paper proposes the interactions between β-carotene and pepsin. The binding potential was measured using the spectroscopic and circular dichroism techniques (CD), molecular docking, and molecular dynamics (MD) simulation methods. UV-Vis results indicating that β-carotene will bind to pepsin and form a β-carotene-pepsin complex. The fluorescence analyses explained that the addition of β-carotene resulted in the gradual reduction of fluorescence intensity and this reached up to 11.5 and ~10% quenching respectively at 25°C and 35°C. This result is according to the ASA result. Results show that KSV values increased with higher temperature, but Kq is more than 2.0×10^{10} $mol^{-1}s^{-1}$; thus the quenching mechanism is the static mode. From the thermodynamic parameters calculated according to the van't Hoff equation, positive enthalpy (ΔH°) and entropy (ΔS°) values of the interaction of β-carotene-pepsin show that the binding is mainly for the hydrophobic forces. The Stability of pepsin in the absence and presence of multiple concentrations of β-carotene was increased that also agrees with the results of MD simulation. The interaction between β-carotene and the polypeptide chain of pepsin causes the β-sheet content of pepsin to increase from 33.8% to 40.6% and the α-helical content to decrease from 11.7% to 8.7%. The β-carotene-pepsin complex showed average RMSD (0.651nm) lower than that the free pepsin system (1.214nm). The result of RMSF shows that the residues involved in the complex contacting are less flexible. The gyration radius (Rg) decreases, which means a more compact. These studies are beneficial for understanding the safety and biological action of foodstuffs in the body.

Keywords: β-carotene, Pepsin, Fluorescence quenching, Circular dichroism, Molecular docking, Molecular dynamics (MD) simulation.

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A molecular simulation and spectroscopic approach to the binding affinity between pepsin with catechin hydrate

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Abstract

In recent years, greater attention has been paid to the use of natural antioxidant sources in the prevention of different diseases. This paper focuses on the interactions between catechin hydrate, one of the polyphenols compounds with potent antioxidant properties in green tea, with pepsin as a digestive enzyme in the stomach. The impact of these interactions will be described by using the spectroscopic technique, circular dichroism technique (CD), molecular docking and molecular dynamics (MD) simulation methods. Increased absorption in the UV–Vis spectrophotometry results suggested that catechin–pepsin complexes were formed. The fluorescence analyses explained that emission intensity decreases significantly (≈85 %), with a small red-shift to 342 nm in the emission maximum of pepsin. Positive enthalpy (ΔH°) and entropy (ΔS°) values of the interaction of catechin-pepsin show that the binding is mainly for the hydrophobic forces. According to the thermal stability result, in the absence and presence of catechin, Tm was decreased that also agrees with the results of MD simulation. The CD result shows that the amount of α-helix and β-sheets decreased thus reducing the compression. The docking analysis shows that catechin binds to pepsin in the hydrophobic pocket. The average RMSD catechin-pepsin complex (2.76 nm) was larger than the free pepsin system (1.44 nm). It could be noted that the pepsin gyration radius (Rg) increases after the simulation when the catechin is bound, which means a less compact structure and partial unfolding of the protein. The RMSF result shows that the residues present in the contacting of polyphenols are more stable. These studies give essential results of the binding mechanism of catechin in living organisms, which are useful in determining the therapeutic effectiveness and biological activity potential such as antioxidant and stomach inhibitory behaviors.

Keywords: Catechin hydrate, Pepsin, Fluorescence quenching, Circular dichroism, Molecular docking, Molecular dynamics (MD) simulation

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Theoretical design of a new peptide for binding to HLA-A*03- KLIETYFSK complex as a potential drug for multiple sclerosis disease

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Abstract

The brain and spinal cord are chronically demyelinated by inflammatory multiple sclerosis. The human leukocyte antigen is included in a growing immune response. The HLA class I resides on virtually all cells, with endogenous antigens presenting cytotoxic T cells. HLA-A*03 is a Category I HLA alleles closely associated with MS. We have engineered in this work a new peptide to Contract with Identified complex as a possible drug for multiple sclerosis disease. This peptide will prevent the Identified complex from Contracting to particular cytotoxic T cells. To Engineering 14 new helical peptides we used the PEP-FOLD peptide structure Forecast server first. Then docking of the Engineering peptides on the Identified complex was performed by the HADDOCK web server. To improve the Contracting affinity of the engineered peptide, a systematic mutation approach was done by the BeAtMuSiC server. After applying mutations that increase Contracting affinity, the docking of the individually engineered peptide was repeated by the HADDOCK server. Finally, the obtained complexes of docking were simulated via AMBER18 software for 40 ns. MM/GBSA and MM/PBSA Contracting free energy and other analysis were performed for engineered peptide- HLA complexes. The simulation results showed that out of 14 engineered peptides, WRYWWKDWAKQFRQFYRWF peptide has the best Contracting affinity to the Identified complex. The results of MD simulation may be used for the engineered of a more specific treatment for multiples sclerosis diseases.

Keywords: multiples sclerosis; HLA-A*03; peptide design; T cell receptor; molecular dynamics simulation; MM/GBSA energy

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Studies of Ascorbyl Palmitate bonded to Human Serum Albumin by Spectroscopic method and molecular docking

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Abstract

Introduction: Ascorbic acid (AA) as antioxidants' is suggested to have antitumor potential against certain cancer types but has the limitation of requiring high doses for treating cancer, and high water solubility. To get over this problem, AA has been esterified with different fatty acids to make the function ascorbyl esters and obtain new compounds with antioxidant as well as surfactant properties. Ascorbyl Palmitate (AP) is an ester derivative of ascorbic acid with comparable potent apoptotic activity. The present study was aimed to develop a Nanocarrier system for intelligent delivery of AP. Human Serum Albumin (HSA) can bind to different classes of ligands at multiple sites. For this principle, Binding of AP to Albumin has been studied using UV-vis absorption spectroscopy in combination with molecular docking studies. **Methods:** Different ratios of AP to HSA were examined by spectroscopic studies. As a result, the final formulation has shown a high encapsulation efficiency of AP on HSA. To find out the interaction between AP and HSA, we have applied molecular docking. Additionally, different concentration of AP was investigated by in vivo and in vitro studies based on 4T1 breast cancer cell line. **Results:** The results of UV-Vis spectra stand for a decline in HSA absorption; this decreasing signifies the interaction of AP with HSA. So, HSA can be considered as carrier for the delivery of AP to the target tissue. Also, the $0 > \Delta G$ were obtained by docking exhibited that AP binds to HSA at the favorable conformation. The Log plot result was shown AP connects with HSA through hydrophobic forces and hydrogen bonding. **Conclusion:** HSA can be considered as the best Nanocarrier to deliver AP to specific cells also it promotes its anticancer efficiency by synergic effects because of the antioxidant properties of HSA that is related to its ligand-binding capacities.

Keywords: Ascorbyl palmitate, human serum albumin, UV-Vis spectroscopic, hydrophobic forces, molecular docking

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Robust Analysis of the Effects of an Anticancer Drug on Temporal Patterns of Gene Expression Using Type-2 Fuzzy Logic

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Abstract

Introduction. Computational study of time-course gene expression data reveals significant patterns such as the effects of drugs on cell dynamics. Fuzzy logic is a robust scheme for analyzing the omics data in the presence of uncertainty [1-3]. **Methods.** In this paper, a novel type-2 fuzzy approach is proposed for studying the effects of a CDK inhibitor R547 on the temporal transcriptomic profile in HCT116 human colon cancer cells. The dataset GSE15395 was taken from GEO [4]. Eight genes have been introduced as important biomarkers in the literature [5]. In the present paper, several computational metrics are designed, using type-2 fuzzy computing, to consider the transient and steady-state responses of the expression patterns to the treatment agents. **Results.** The results revealed that an inverse relationship exists between the similarity of expression patterns and drug dose. The most correlated genes (above 70% similarity) were CCNB1 and MKI67. The transcription of these two cases was downregulated, while EGR1 and JUN was upregulated. For these four genes, there was a direct relation between the dose and the intensity of regulation. PFAAP5 expression was enhanced in a nonlinear manner with respect to the drug concentration. Transcription of CD86 was inhibited at lower concentrations. The inhibition decreased with increasing the concentration, where upregulation was observed at the higher doses. The expression of HEXIM1 and FLJ44342 was upregulated at lower concentrations. For the first case, there was an inverse relation between activation intensity and dose. But for the second case, the relationship was nonlinear. For both cases, the activation decreased and changed to inhibition at the higher concentrations. **Discussion.** This technique can robustly extract the transient and steady-state patterns of transcriptomic data in response to treatment agents.

Keywords: Gene Expression, Anticancer Drug, Pharmacodynamics, Human Colon Cancer, Type-2 Fuzzy Logic, Gene Regulation.

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The Impact of Genetic and Epigenetic Alterations on the Attractors of a Network of Interacting Genetic Toggle Switches

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Abstract

Introduction. A network of interacting genetic toggle switches is an applied type of synthetic biological circuits that can be practically realized inside a cell with the aid of biotechnology to perform logical functions at subcellular level [1-5]. **Methods.** In this paper, an efficient approach is proposed for considering the nonlinear behavior of the above-mentioned process based on the notion of stochastic differential equations with uncertain components. In this model, two basic kinds of subcellular variations including genetic and epigenetic alterations are considered, and they are mathematically modeled as 'structural uncertainty' and 'parametric uncertainty and external disturbance', respectively. **Results.** The Waddington landscape of the circuit was quantified and the phase plane trajectories were precisely computed in the presence of noise and uncertainty. Analysis of these signals revealed that the number, type, and the position of the attractors are very sensitive to these basic changes. Bifurcations and multi-stability were observed. Computer simulation confirmed that genetic alterations can drastically change the equilibrium states, and even in some cases depending on the mutation intensity, the dimension of the equilibrium state may be varied. Also, epigenetic alterations can alter the equilibrium states but more smoothly than genetic changes. In general, it was exposed that both factors can play a crucial role in the determination of cell fate. **Discussion.** The results demonstrated how these basic alterations can radically change the attractors of this system and accordingly alter the differentiation, development, and phenotypic characteristics. This scheme can be generalized for the in-silico study of the complicated behavior of various pathways in the presence of subcellular variations.

Keywords: Genetic Toggle Switches, Genetic and Epigenetic Alterations, Cell Fate, Nonlinear Systems, Attractor, Stochastic Differential Equations.

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Modeling the Epithelial-Mesenchymal Transition Involved in Tumor Invasiveness and Metastasis

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Abstract

The genetic factors that enable primary tumor cells to invade and metastasize are to a great extant unknown. It has been proposed that carcinoma cells may complete invasive and metastatic steps by the activation of the so-called epithelial-mesenchymal transition (EMT). Although more pre-clinical and clinical studies are required to elucidate the process of EMT and the molecular pathways involved in carcinoma cells, the development of mathematical models grounded on available experimental data can contribute to the generation of rational hypotheses that can be validated through future experimental work. Hence, the known molecules involved in the EMT and their interactions were scrutinized and a complicated network of receptors, signal transducers and transcription factors was drawn. Three key regulatory proteins involved in this process (E-cadherin, beta-catenin, and Snail-like transcription factors) were chosen and a simple mathematical model was proposed. The model was based on ordinary differential equations and contained constant rates of synthesis and degradation of molecules and the effect they had on the transcription rates of each other. We utilized MATLAB codes and referred to an empirical study in order to validate our model. The model was consistent with the available experimental data and can be extended from subcellular state to the cellular and tissue levels and may also be used to predict possible treatment strategies.

Keywords: mathematical modeling, epithelial-mesenchymal transition, invasiveness, E-cadherin, beta-catenin, Snail-like transcription factors

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Human dead end protein RRM1 and RRM2 interactions: for which purpose?

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Abstract

Introduction: In primordial germ cells, dead end protein (Dnd) binds to the 3'-UTRs of some mRNAs such as P27 transcript and blocks the inhibitory function of microRNAs (miRNAs) from these mRNAs [1]. Human Dnd has two RNA recognition motifs (RRM1 and RRM2) and P27 has two Dnd interacting sequences (p27-1 and p27-2) and this study focuses on their interactions. **Methods:** To build RRM models, we used YASARA homology modeling [2]. p27 interacting sequences models were constructed using RNAComposer modeling server [3, 4]. The best models were chosen after quality evaluation. A total of 105 ns molecular dynamics simulations (MDS) were performed on each of [RRM1+p27-1], [RRM1+p27-2], [RRM2+p27-1] and [RRM2+p27-2] complexes using YASARA.19.1.27 [5].
Results and discussion: The interactions between RRMs and P27 were studied and compared in snapshots sampled at 0, 0.1, 15 and 35 ns. Between all studied complexes, [RRM1+p27-1] complex had the highest Van Der Waals (VDW), hydrophobic, and pi-pi forces average values after 35 ns simulation. The highest number of H-bond and cation-Pi interactions were observed in [RRM1+p27-2]. There was no pi-pi and cation-pi interaction in [RRM2+p27-2]. Further 1800 ns MDS were performed on [RRM1+p27-1] and [RRM1+p27-2] again in order to verify those findings. Except for cation-pi interactions, all results were similar in this time span. At 600 ns, [RRM1+p27-1] had higher cation-pi interaction strength than [RRM1+p27-2]. In conclusion, it is suggested that RRM1 is the key motif in the interaction with p27 and it seems that RRM2 helps achieving higher affinity to this transcript.

Keywords: RNA binding protein; dead end protein; RRM; miRNA; germ cells

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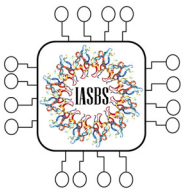

Probabilistic Modeling of Alzheimer's Disease

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Abstract

One of the important problems in medicine is using statistical models to describe the trajectories of chronic diseases such as Alzheimer's, Parkinson's and different kinds of cancers. Chronic diseases start from mild symptoms which slowly get to the severe stages during a long time. Medicines are interested in early detection of symptoms, because the therapies could be more effective in the first stages. What machine learning can do to help them is to employ different algorithmic models to discover the disease progression using time-series data from patients with varying severity. Furthermore, we have to figure out strategies for challenges of medical data, like missing values, different subtypes of disease and limited supervision. Previous researchers had a major focus on using well-known limited features employing algorithms such as Random Forests and SVMs, to distinguish the controls and patients with mild or sever impairments. In this project with a great focus on Alzheimer's disease progression, we used TADPOLE challenge dataset which is derived from the ADNI website. It contains 1906 features from different kinds like demographics properties, cognitive scores, genetic biomarkers, MRI, and PET scans. Due to the vast amount of features and lack of knowledge about their effects on the disease progression, we were very curious about finding more features which could be as much informative as the known ones. Therefore, in this work we used Variational Inference algorithm and sparse priors as an automatic feature selection method in Bayesian models.
As a result we compared our model with some other probabilistic ones such as the same model with normal prior, Expectation Propagation algorithm and Linear Mixed-Effects regression. The interesting tasks for follow-up work are, expanding our investigations on Parkinson's and cancer datasets and generating synthetic patients in order to test the robustness of the proposed algorithm.

Keywords: Chronic disease progression; Bayesian model; Variational inference; Probabilistic programming; Sparse prior; Bayesian feature selection

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Sequence-Based Prediction of Protein- Protein Interactions Using Cellular Automata

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Abstract

Introduction

Investigation and analysis the interaction between two proteins is among the important issues of interest in biological sciences. Experimental investigation of protein-protein interactions (PPIs) are mostly intensive and costly. In this way, defining a mathematical model for prediction of PPIs using only the sequence information is of great significance. Shen et al. [1] proposed a pridiction method based on SVM which uses a 686-dimensional feature vector obtained by reduced alphabets and word based method. Xia et al. [2] used a local protein sequence descriptor with reduced amino acid alphabets to extract numerical features to design a k-nearest neighbor (KNN) classifier. In [3], a binary coding approach along with cellular automata were used to extract rich sequence related features to predict structural class of the protein.

Methods

In this study, the hydrophobic index used to reduce the amino acid alphabets and represent them using a two bits code. The binary string of the protein sequence is then used as the initial state of a cellular automata (CA). Evolution of the CA results a binary matrix which can be used as a monochrome image. According to the texture and patterns of the images, related features are extracted from the CA image of each protein. Concatenated features of protein pairs are used to predict the interacting and non-interacting pairs by the K-nearest neighbor (KNN) classifier.

Results

The Human dataset were used to evaluate the performance of the proposed method and the accuracy, sensitivity and MCC were 97.85%, 96.07% and 95.73% respectively.

Discussion

A computational method is proposed to predict the interaction between two proteins. The obtained features from CA have been used to represent proteins and build a KNN classifier. The classification performance shows the potential of the proposed approach to predict the interaction of proteins using only the sequence information.

Keywords: protein sequence, amino acid contact, feature extraction, Protein-protein interaction, Cellular automata images, KNNs.

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Bioinformatic Studies and Comparative Modeling of Bacillus haloduranse DnaK

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Abstract
DnaK (the homolog of Hsp70 in prokaryote cells) is believed to play a prominent role in the maintenance of protein hemostasis and protein folding. This protein composed of two domains. The N-terminal domain is conserved and has ATPase activity while the C-terminal domain is required for polypeptide binding. The gene encoding DnaK has been recently isolated from Bacillus haloduranse and there is no structural information about it. In this regard, we simultaneously investigate experimentally and theoretically its structural features. In this study, following comparative searches through the national center for biotechnology information (NCBI) server, the multiple sequence alignment and phylogenetic tree were made with the Clustal omega and MEGA-X programs, respectively. Finally, the 3D model of B. haloduranse DnaK was constructed using the MODELLER program Ver. 9v23. Geobacillus kaustophilus DnaK (PDB code: 2V7Y) was selected as the main template due to the high homology between the two sequences (83%) and E. coli DnaK (PDB code:2KHO) was used to model the end part of C-terminal domain. Two classes of verification methods were used to determine the validation of quality. In the environment-oriented methods, Verify3D gave a scoring value that was nearly equal to the patterns, and the protein structure quality score (PSQS) gave equal values for all structures. In the geometry-oriented methods ERRAT and ProCheck, the scoring differences between the model and the main template were small. The results of the Ramachandran plot revealed that many of residues are in most favored regions. These data suggest high quality for the constructed 3D structure. Based on comparison with the amino acid sequences of model and templates, we also suggested that there is a high identity in the nucleotide-binding motif between model and templates.

Keywords: Molecular chaperone - DnaK – Comparative modeling - Bacillus haloduranse

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Bioinformatic Studies of Bacillus persicus DnaK Modeled by Homology Modeling

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Abstract
DnaK (the homolog of Hsp70 in prokaryote cells) is believed to play a crucial role in the maintenance of protein hemostasis and protein folding. This protein composed of major functional domains. The N-terminal domain is conserved and has ATPase activity while the C-terminal domain is required for polypeptide binding. The gene encoding DnaK has been recently isolated from Bacillus persicus and there is no information about its construction. In this regard, we simultaneously investigate its structural features experimentally and theoretically. In this study, following homology searches through the NCBI server, the multiple sequence alignment was made with the T-coffee program. Finally, the structural model of B. persicus DnaK was created by the MODELLER program Ver. 9v23. DnaK from Geobacillus kaustophilus (PDB code: 2V7Y) was selected as the main template in the modeling process due to the homology between the two sequences (84.12%) and DnaK from E. coli (PDB code:2KHO) was used to model the end part of C-terminal domain. To determine quality validation, two classes of methods were used. In the environment-oriented methods, Verify3D gave a scoring value for the model that was approximately equal to the templates, and the protein structure quality score (PSQS) gave equal values for the model and templates. In the geometry-oriented methods ERRAT and ProCheck, the scoring differences between the model and the main template were small. The data suggests high quality for the constructed model. The deduced amino acid sequence of the DnaK from B. persicus shows a high sequence identity and similarity between the model and templates. Calculation of salt bridges, hydrogen bonds, and disulfide bonds was made using What If web server.

Keywords: Molecular chaperone - DnaK - Homology modeling - Bacillus persicus

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Mathematical modeling to understand the response of M. extorquens to formaldehyde toxicity

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Abstract
In this research we use modeling approach to explore possible scenarios in response to an internal stressor in a bacteria. Metabolism of this bacteria involves generation of formaldehyde. Using the model we were able to test two different hypotheses: In the first scenario, we speculated consumption as a way to decrease toxin's concentration, in a same manner which B-lactamase in E. coli decreases cefotaxime [1]. Model system of ODE's suggested a threshold of toxin's concentration where the fate of cell could be determined; only below a certain concentration cells survive. Experimental data of formaldehyde consumption rejected this scenario as the mechanism of response to the stressor. In the other scenario we explored heterogeneity in tolerance level as a strategy to overcome stress. Example of such a heterogeneity in response to a stressor have been observed in cancer cells when exposed to vincristine [2]. Our experimental data and PDE model confirmed such a heterogeneity in the population [3].

Keywords: Mathematical Modeling, Differential Equations, Bacterial Physiology

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Kinetic and simulation studies between methionine with bovine liver catalase.

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Abstract

The catalase enzyme is a highly active homoprotein which converts hydrogen peroxide to water and oxygen without producing free radicals [1]. Methionine is an basic amino acid in mammals that are not combine in the body and should be given by diet, because normal mammalian growth is necessary [2,3]. The effect of methionine on catalase function and structure was investigated in this study using various techniques such as kinetic experiments, fluorescence spectroscopy, UV−Vis absorption, molecular dynamics simulations, and molecular docking. The findings of the kinetic studies show that methionine stimulates catalase activity. The result of UV−Vis absorption demonstrated that bovine liver catalase has 2 important absorption bands: (1) an significant band at around 280 nm, which arises from the aromatic amino acids including tryptophan, tyrosine, and phenylalanine and (2) a Soret absorption band at 405 nm for the heme group. Therefore, UV results display that the addition of methionine to catalase increased the uptake. In addition, according to the fluorescence results, it was observed that catalase tryptophan's changed during binding, indicating a change in the environment and the catalase composition in the attendance of methionine. According to the results of molecular docking, ΔG° is negative and the reaction is spontaneous. The RMSD diagram was stable during the simulation indicating that catalase had reached a conformational steady state. Also, with the change of ASA values, it can be seen that the activity of BLC increased in the presence of methionine.

Keywords:
Bovine Liver Catalase (BLC), Fluorescence spectroscopy, UV−Vis absorption, Molecular dynamics simulations, Molecular docking and Kinetic study.

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Metabolomics dataset analysis workflow from data acquisition to interpretation

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Abstract

Metabolomics or Metabonomics includes measurement and qualification of metabolites in a biological sample [1]. In the system biology information level, metabolomics are located after transcriptomics and proteomics layers, which indicated metabolomics as a last product of biological process, connecting genotype and phenotype [2]. The major instrumentations for high-throughput metabolomics analysis are including GC/MS (Gas chromatography/ Mass Spectrometry) and NMR (Nuclear Magnetic Resonance). In this presentation, general pipeline of metabolomics experiment will be explained consisting Biological question, Experimental design, Sample collection, Data acquisition, Data pre-processing and metabolite identification, Statistical analysis and finally Interpretation [2]. Various software packages and also web resources have been developed to analyze the metabolomics datasets [3]. Subsequent to comprehensive literature review, common software packages and online resources of Data pre-processing and metabolite identification will be listed in this review which are including OpenMS, XCMS, MetaScape, Metabolite Detector, MetAlign, AMDIS, MAVEN, CytoScape, MetDat, MZedDB, LipidMaps, KEGG, MetaboAnalyst and MetExplore. Among the mentioned packages and online resources, main focus is on MetaboAnalystR [4]. Finally relevant univariate and multivariate approaches are explained to interpret the data processing outputs.

Keywords: Metabolomics; Data analysis; Dataset; Statistical analysis; Pre-processing

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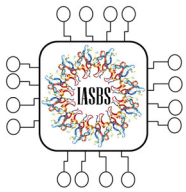

Efficient MCMC based inference of Gene Regulatory Networks

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Abstract

There are several computational methods for reconstruction of gene regulatory network (GRN) model from gene expression data. For learning the structure of these networks, one possible approach is to search over all structures and find the structure considering which the dataset is more likely. Since searching the space of all possible structures is computationally impossible (NP-complete), heuristic methods are hired to perform this search. In the previous studies, evolutionary search algorithms are suggested for inferring the most probable structure. Also, many methods ignore searching the dataset and just infer weights over all possible edges of gene network. This weight is computed using methods such as mutual information or by Bayesian model averaging. However, in current studies, Monte Carlo Markov chain algorithms based on random sampling, have been used for searching the best structure of all possible structures with the posterior probability distribution in the GRN. Sampling methods guarantee convergence to the most probable structure, if the algorithm is run long enough. The goal of this work is to discover the more effective approach by comparing the above algorithms on the real-world datasets. One of the metrics we used for comparing the results in this work is observations of false positive edges. A false positive edge, is an edge which is present in the inferred network structure and not in the true structure. According to the obtained result, we found out that the MCMC approaches is better than the other methods and other methods have much higher proportion false positive edges between related genes in the inferred network. The drawback of sampling-based methods is their efficiency.

Keywords: Gene regulatory networks; Monte Carlo Markov Chain (MCMC) methods; false positive edge; reference network

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Compressing the genomic signals by wavelet transform and their phylogenetic tree analysis

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Abstract

Nowadays, the cost of gene sequencing has decreased harshly. As a result of this decline, as well as advances in sequencing technology, considerable genomic data are continually being produced. None the less, the cost for saving, transmission and processing of such data is increasing. At present, handling this enormous volume of information is done by the base character methods, the deficiencies of which are the invisibility to the human eye and the great time required for their process. Bunching of organisms is a fundamental anxiety of biology which is investigated in this study through characterization of DNA molecules that carry inheritance properties. It is almost impossible to bunch multi-millionth sequences, and only small portions of the chromosome can be processed. On the other hand the signal outlook to the genome, signal processing of the genome and compression of the genome are regarded as very hot issues nowadays. Compression profits from the reduction of cost, memory space, bandwidth for exchange, and the time needed for analysis.

In this work, firstly the genes of the organisms were characterized in a signal format and we chose cumulated phase signal representation, so that the capabilities in the digital signal processing (DSP) field would be available. Consequently, these genomic signals were compressed through wavelet transform. Dynamic Time Warping (dtw) algorithm were used to calculate distance between each Pair of signals. Finally, the organisms were bunched according to base character and base signal methods to drawing phylogenetic tree. In terms of time, the signal method was more efficient. From the point of view of performance, resembling procedural efficiency was detected; the signals were compressed at the rate of 50-95%.

Keywords: Gene sequence, Genomic Signal, compression, wavelet transform, phylogenetic tree digital signal processing (DSP).

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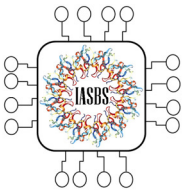

Urea-induced unfolding of a bacterial albumin-binding domain

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Abstract

High temperature, protein mutation, or solvents (other than water) can cause protein unfolding (1). Here, molecular dynamics (MD) simulations have been used to study the protein unfolding by exerting two of the deleterious conditions. Urea was used as the solvent and increasing the temperature was a factor to speed up the unfolding reaction rate (2). We studied a three helical bacterial albumin-binding domain with the PDB ID: 2j5y. After preparing the protein, energy minimization was performed. Then MD simulations were performed at 310K and 500K in the presence of 6M urea solution in periodic box using YASARA program 17.3.30 and AMBER14 force field (3, 4). We ran three individual simulations in each temperature at the same conditions with a total time of 180 ns and analyses reports were based on average values. Average radius of gyration after 30 ns shows the value obtained at the higher temperature to be 1.4 greater than at 310K. RMSD changes occurring at 500K is remarkably more than 310K. Average percentages of secondary structure content after 30 ns in 310K were 81.94, 1.02, 16.91 for alpha helix, turn, and coil respectively while being 22.50, 25.43, and 46.59 respectively at 500K. In addition, comparison of energy values and solvent accessible surface area shows that their trends match foresaid changes. In conclusion, using urea and increasing temperature can reduce the computation time to reach the denatured state. This method can be used to find the important spots in the unfolding process.

Keywords: Molecular dynamics simulation; High temperature; Urea; Unfolding; Albumin-binding domain

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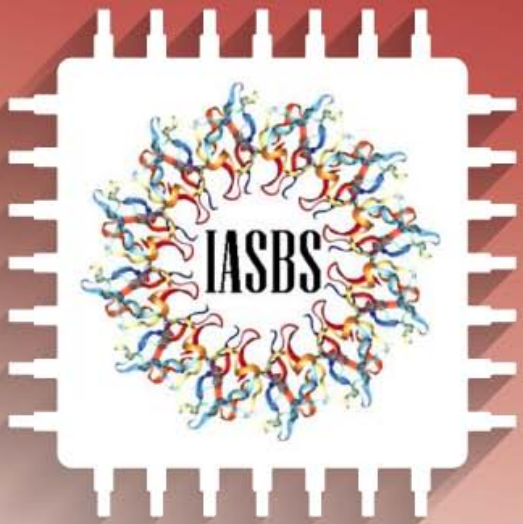

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