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Activity

Interactive Docking Workshop: Docking the Anticancer Drug Belinostat to Its Cellular Histone Deacetylase (HDAC) Target

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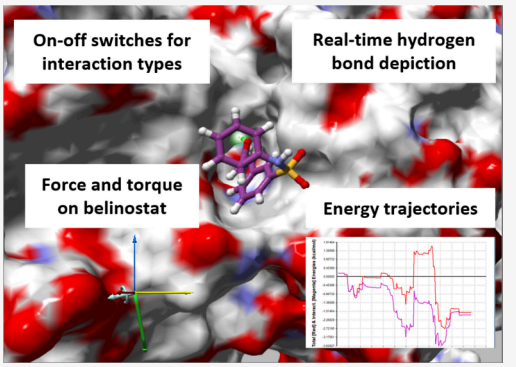
ABSTRACT: DockIT is an interactive molecular docking tool suitable for teaching students about concepts related to drug−receptor interaction. Its most unique feature is the ability to model both local and global conformational change in the receptor based on information derived from the trajectory of a molecular dynamics (MD) simulation. The workshop presented here uses DockIT to bind the anticancer drug belinostat to its target protein, histone deacetylase 6 (HDAC6). To model the conformational response of HDAC6 to the binding of belinostat, a 200 ns explicit-solvent MD simulation was performed on HDAC6. The workshop challenges students to predict the experimentally determined binding pose of belinostat by finding a minimum of the binding energy. The task is "semi-blind" in the sense that the binding pocket location on HDAC6 is indicated, but not belinostat's orientation. The workshop contrasts with previous docking workshops that use automated docking tools in that the docking process itself is under the control of the student, enabling them to experiment and test ideas. Results of a pre- and postworkshop multiple choice questionnaire showed an improvement in the students' understanding of key features of molecular binding.



KEYWORDS: *Second-Year Undergraduate, Computer-Based Learning, Proteins, Biochemistry, Conformational Analysis, Molecular Modeling, Molecular Recognition*

INTRODUCTION

In silico computational methods play an increasingly important role in the drug discovery process. A common approach, used when the structure of the protein target is known, computationally docks candidate drug molecules into the protein active site by variation of their relative position and orientation in order to optimize the binding energy. These docking methods can be divided into two types: automated and interactive. In automated docking, where prominent examples among a multitude of tools are AutoDock[1] and ZDock,[2] the user is presented with a predicted binding pose, whereas in interactive docking the user controls the docking process. Automated docking is suited to those cases where the binding site is unknown, and if sufficiently fast, it is a high-throughput method that can screen a large library of drug candidates. In interactive docking, the binding process is under the control of the user. Interactivity leads to exploration, the ability to test ideas, and collaboration, making it suitable for educating students about biomolecular binding. Interactive tools should also be suitable for structure-based drug design (SBDD) where the binding site is known and there are a small number of lead compounds to consider. Interactive docking tools include, DockIT,[3,4] DockPro,[5] IMD,[6] and UDock2.[7]

Student laboratory molecular docking exercises reported in the literature[8−12] exclusively involve the use of automated docking tools, and the task is to analyze the final predicted binding pose. Here we use the interactive docking tool, DockIT, where students are in control of the docking process itself. DockIT is unique in being able to model in real-time a smooth conformational response in the receptor protein to the binding of the ligand, at both the global and local level. It does this by using a precalculated trajectory from a molecular dynamics (MD) simulation, which simulates protein motion. An advantage of the DockIT approach is that the computationally expensive simulation is carried out independently of the interactive session.

As demonstrated in a recent study, students respond very well to being taught chemistry concepts aided by interactive computer simulations.[13] Here, we use DockIT to enhance students' understanding of molecular interactions and molecular flexibility. Students were tasked to dock the drug belinostat to enzyme histone deacetylase 6 (HDAC6). The workshop could be used as an introduction to docking

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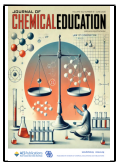

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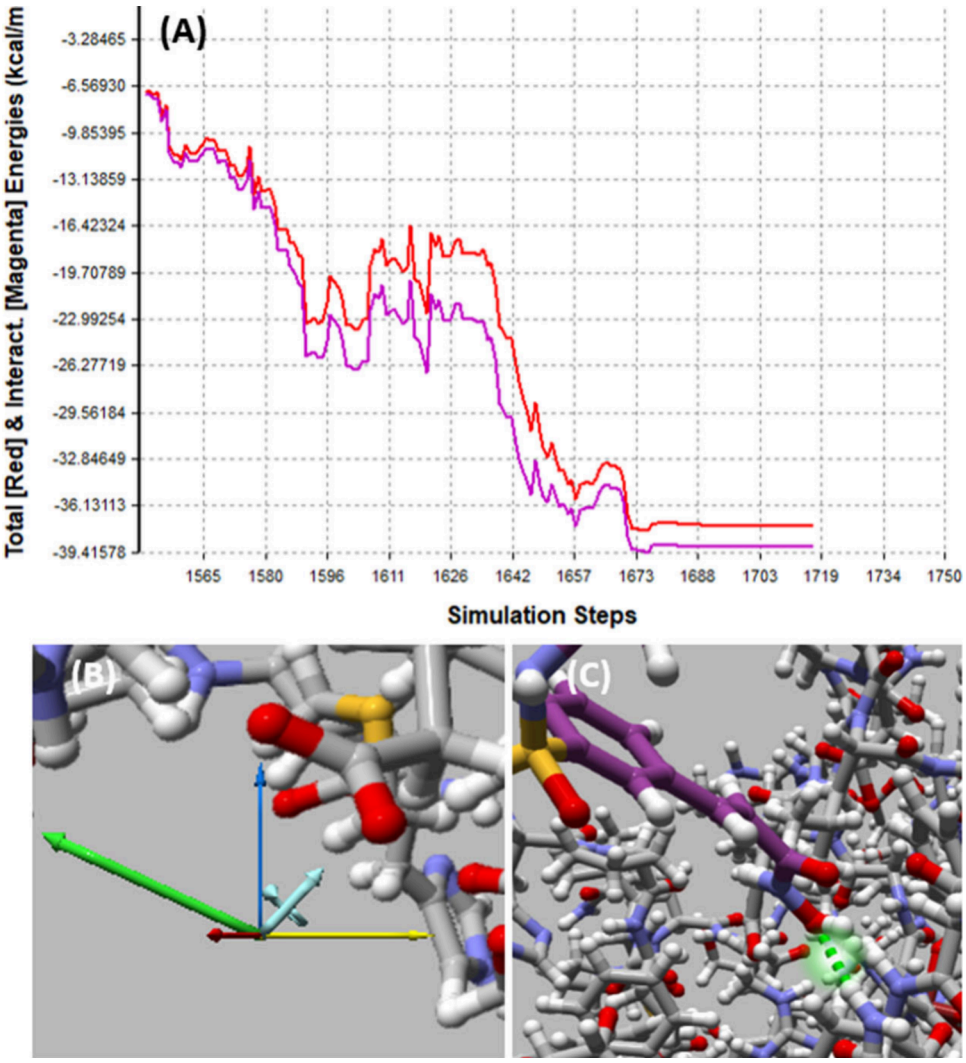

Figure 1. (A) Plot of the interaction energy (magenta) and total energy (red) for a docking trajectory. The total energy is the sum of the interaction energy (between the ligand and the receptor) and the strain energy. The strain energy is the energy required to deform the receptor. (B) Force and torque arrows indicating the total force and torque acting on the ligand (not visible). (C) A hydrogen bond between the ligand and receptor indicated by the green dashed line.

principles ahead of workshops that use automated docking tools with a library of compounds.

DockIT

DockIT can be used with a standard keyboard and mouse or with a VR headset and hand-held controllers. It enables the user to control the position of the ligand relative to the receptor, controlling the binding process. Supporting Information 1 gives details on the MD simulation of HDAC6 (Protein Data Bank (PDB): 5EEM;[14] 200 ns; explicit solvent) and the linear response method used to model the conformational response of the receptor. Supporting Information 2 gives information on the computational requirements for running the workshop and further information on the following features used in this workshop: the display of interaction and total (interaction plus strain) energy trajectories (see Figure 1(A)); the display of the total force and torque on the ligand (see Figure 1(B)); the display of hydrogen bonds in real time (see Figure 1(C)); the ability to switch on and off specific interactions; flexible molecular surface depiction (showing shape changes in the binding pocket due to the presence of the ligand); the ability to record and replay a docking trajectory; the ability to save the workspace; the ability to load and see a noninteracting ligand, called a "ghost" ligand, that can be used to compare the docked ligand position with an experimentally determined position of the ligand; and the ability to measure interatomic distances.

Student Background

For this workshop, the students were final-year undergraduates studying for a Master of Pharmacy (M.Pharm.) at the University of East Anglia (UEA) in the United Kingdom, assigned a medicinal-chemistry-based individual research project. Key learning objectives of the overall research project are to experience firsthand the boundaries of pharmaceutical knowledge and to work in collaboration with an academic supervisor to build expertise and in-depth subject-specific knowledge. The workshop was used as an introduction to docking principles at the start of the research project. It may also be suitable for second-year undergraduates in biochemistry or related subjects.

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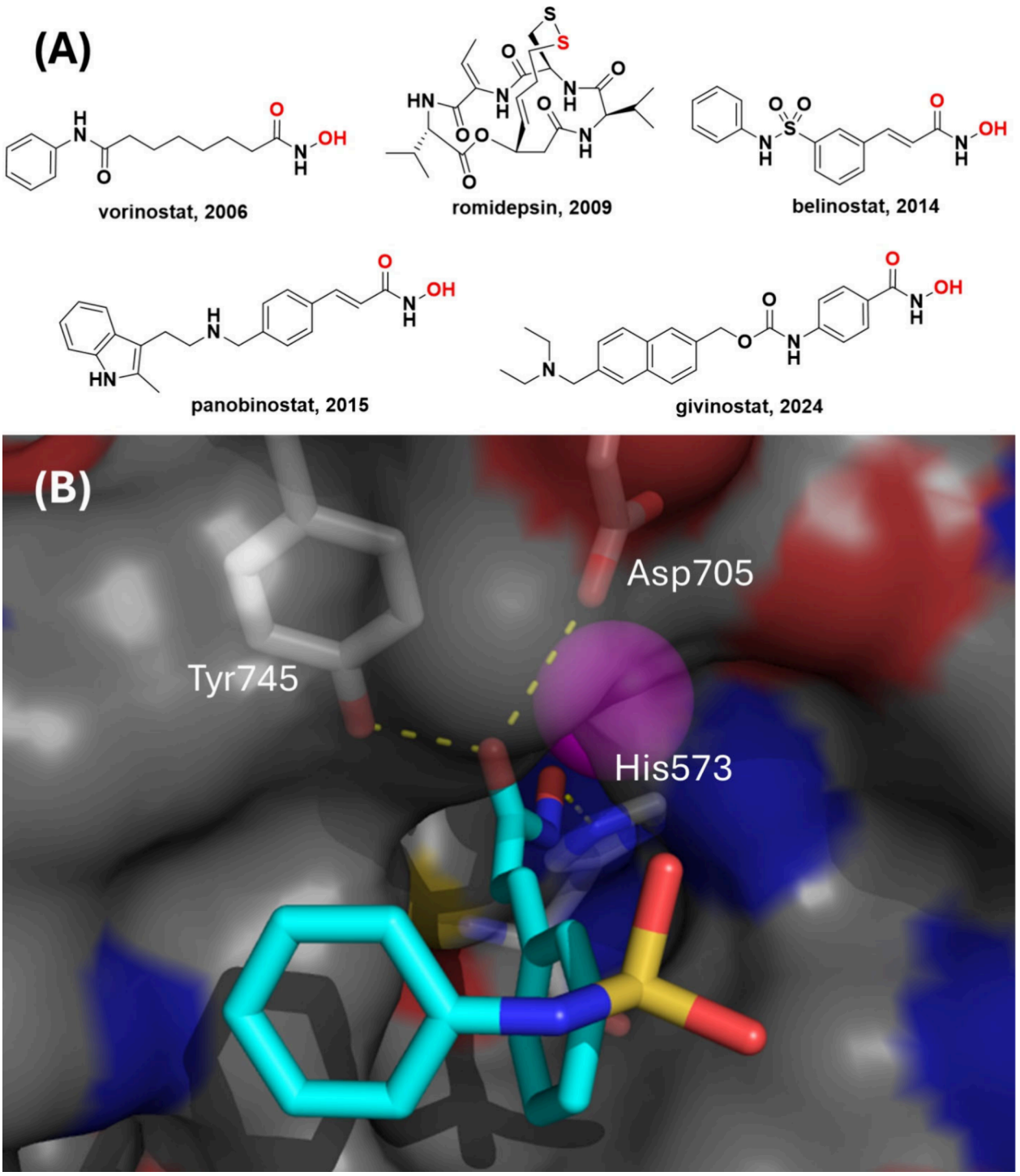

Figure 2. (A) The five FDA-approved HDAC inhibitors, with the year of approval indicated. The sulfur atom in romidepsin and the oxygens in the others that are involved in zinc binding are highlighted in red. (B) Belinostat (in cyan stick) in the binding pocket of HDAC6 from the crystallographic structure (PDB: 5EEN), showing key hydrogen bonds as yellow dashed lines. The zinc ion is a magenta sphere.

■ PROTEIN TARGET AND DRUG MOLECULES

HDACs are conserved proteins present in all eukaryotic life forms that catalyze the hydrolysis of specific amide bonds to their corresponding carboxylic acid and amine fragments. These metalloenzymes contain a zinc cation in the active site that coordinates to the amide substrate and a water molecule, thereby activating both toward nucleophilic attack by the water on the carbonyl group. Important substrates for the HDACs are the histone proteins in nucleosomes, where the action of HDACs results in the compaction of chromatin and transcriptional repression.[15] HDAC6, on the other hand, performs a similar catalytic function on proteins in the cytoplasm, such as tubulin and cortactin.

HDACs are activated or overexpressed in various diseases, particularly cancer, where their role in replication and DNA repair means that their inhibition is a popular approach for drug discovery.[16] Multiple small molecules that occupy the enzyme active site and coordinate to the zinc cation with high

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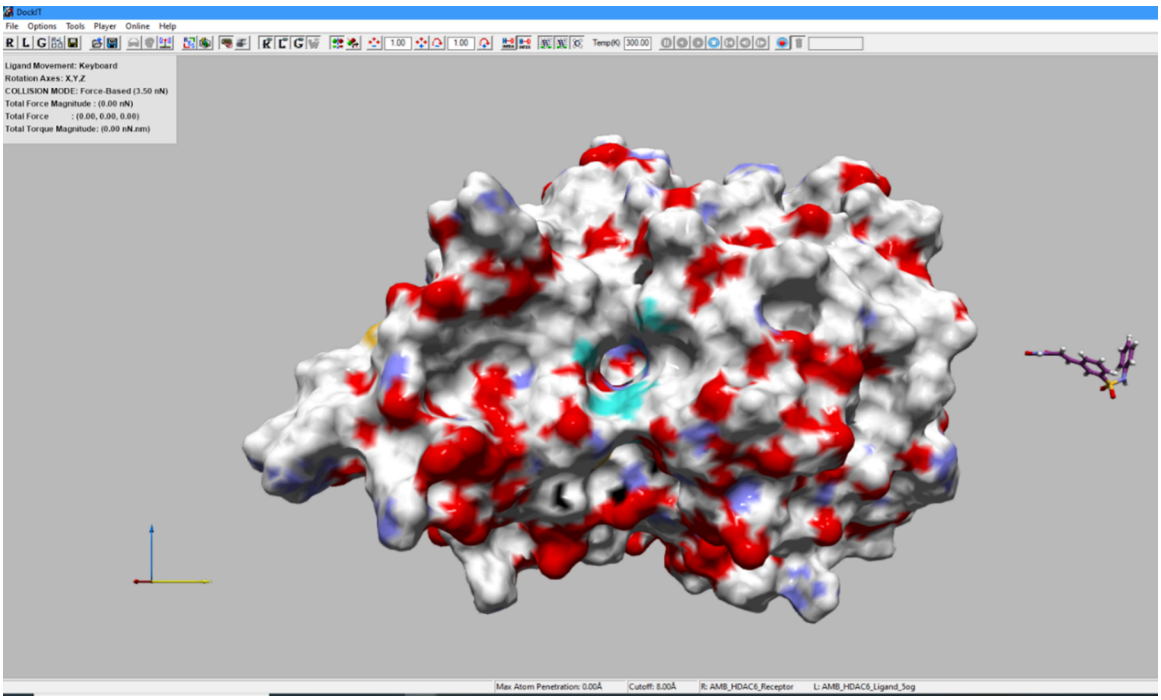

Figure 3. DockIT starts the configuration immediately after loading the workspace file. It shows HDAC6 in the molecular surface model and belinostat on the right in the ball and stick model. The aperture of the binding site is highlighted in cyan.

affinity have been identified. Five of these have received FDA approval (Figure 2): the natural product romidepsin and the synthetic compounds vorinostat, belinostat, panobinostat, and givinostat. The synthetic compounds share the common feature of a hydroxamic acid that is the zinc binding "warhead", as confirmed by X-ray cocrystal structures of enzyme−inhibitor complexes.[17]

DESCRIPTION OF THE TASK

The task is described in the worksheet available in Supporting Information 3, which can be freely adapted. Along with the worksheet, a workspace file is supplied (available with the DockIT installation: C:\Program Files\HaptiMOL\DockIT\Worksheets\Ligand_belinostat_Receptor_HDAC6.wsp), which upon loading into DockIT presents the view shown in Figure 3. This is a semiblind task in that the aperture to the binding site is indicated. Although HDAC6 is treated flexibly, belinostat is treated as rigid for computational efficiency. This approximation should be explained to students, noting that a more realistic approach would require consideration of ligand flexibility. We recommend playing the video of the HDAC6 MD trajectory (Supporting Information 4) at the start of the workshop, as it shows the fluctuations used for modeling the conformational response of the receptor to interaction forces imposed by the ligand.

The task is divided into two parts, the first to find the binding pose with the lowest energy and the second to evaluate their result by comparing it to the crystallographic binding pose as seen in Figure 2(B). The students should be told that translating the ligand according to the force arrow and rotating according to the torque arrow lowers the interaction energy and that they should attempt to find the binding pose with the minimum total energy (interaction energy plus strain energy) by observing the energy trajectory plot window. The torque arrow comes with a curved arrow to indicate the direction of rotation of the ligand. Although following the force and torque arrows lowers the interaction energy, one should allow for the possibility that there may be an energy barrier to overcome to reach the lowest energy binding pose, which would mean one has to move against the direction indicated by the force or torque arrow. The students are asked to practice first in finding a binding pose with the lowest total energy before evaluating their predicted binding pose.

In the second part, the students evaluate their results by loading the "ghost" molecule (Supporting Information 6), which represents belinostat in its crystallographic binding pose (from the HDAC6-belinostat complex structure, PDB: 5EEN[14]). By determining distances between key atoms as per the worksheet (Supporting Information 3), they calculated the root mean-square deviation (RMSD) to quantify how close their predicted binding pose is to the crystallographic binding pose.

Key Objectives and Learning Outcomes

The desired learning outcomes from participation in the HDAC6-belinostat DockIT workshop are for students to be able to:

- Recognize the types of interactions involved in molecular binding.
- Identify hydrogen bonds and appreciate the nature of the hydrogen bond interaction.
- Recognize the impact of molecular flexibility and its role in binding, e.g., induced fit (know that binding can cause a change in conformation that leads to enhancement or inhibition of activity).
- Identify potential complementary molecular surfaces on the ligand and receptor.
- Demonstrate an understanding of the interaction and the strain energy.

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- Demonstrate an understanding of the common approximations made in computational simulation of molecular binding.
- Calculate the RMSD to quantify the proximity (closeness) of two bound poses.

To evaluate learning of concepts in the workshop, we developed a multiple-choice questionnaire (MCQ) comprising five questions based on the learning objectives to be completed pre- and postworkshop (see Table 1 and Supporting Information 5). As for the worksheet, the MCQ can be freely adapted.

Table 1. MCQ and Improvement

Question/Statement	Preworkshop (number of correct answers)	Postworkshop (number of correct answers)	Improvement
(1) Identification of the types of molecular interaction	26	28	+2
(2) Understanding of different types of interactions between protein and drug molecule	27	28	+1
(3) Understanding of movements on a molecular scale	14	21	+7
(4) Value of binding affinity	26	28	+2
(5) Binding energy trajectory	19	26	+7

RESULTS

In all, 28 participated in the workshop, with several working in pairs. The study fell under UEA's general protocol for laboratory activities, and in the course of the laboratory no unexpected or unusually high safety hazards were encountered.

None of the students were familiar with the crystallographic structure of the belinostat−HDAC6 complex. At the start, the students were told to view the two molecules in different depictions and to consider the most suitable for the docking task.

After getting used to the controls and trialing various paths to a minimum total energy binding pose, the students saved their results in a workspace file (which can be used later by the teacher for checking results). They then loaded the ghost molecule representing belinostat in the crystallographic binding pose to evaluate their result by calculating the RMSD. This was done using the distance-measuring feature in DockIT to determine distances between corresponding atoms in the predicted pose and the experimental pose. Figure 4 shows the total energy of each student's/student pair's predicted pose of belinostat plotted against its RMSD with the experimental pose. It shows that generally, the lower the total energy, the lower the RMSD. Those students that inserted the hydroxamic acid group into the binding pocket had the lowest energies. Those who inserted belinostat into the binding pocket in the wrong orientation had higher energies, indicating a bad binding pose.

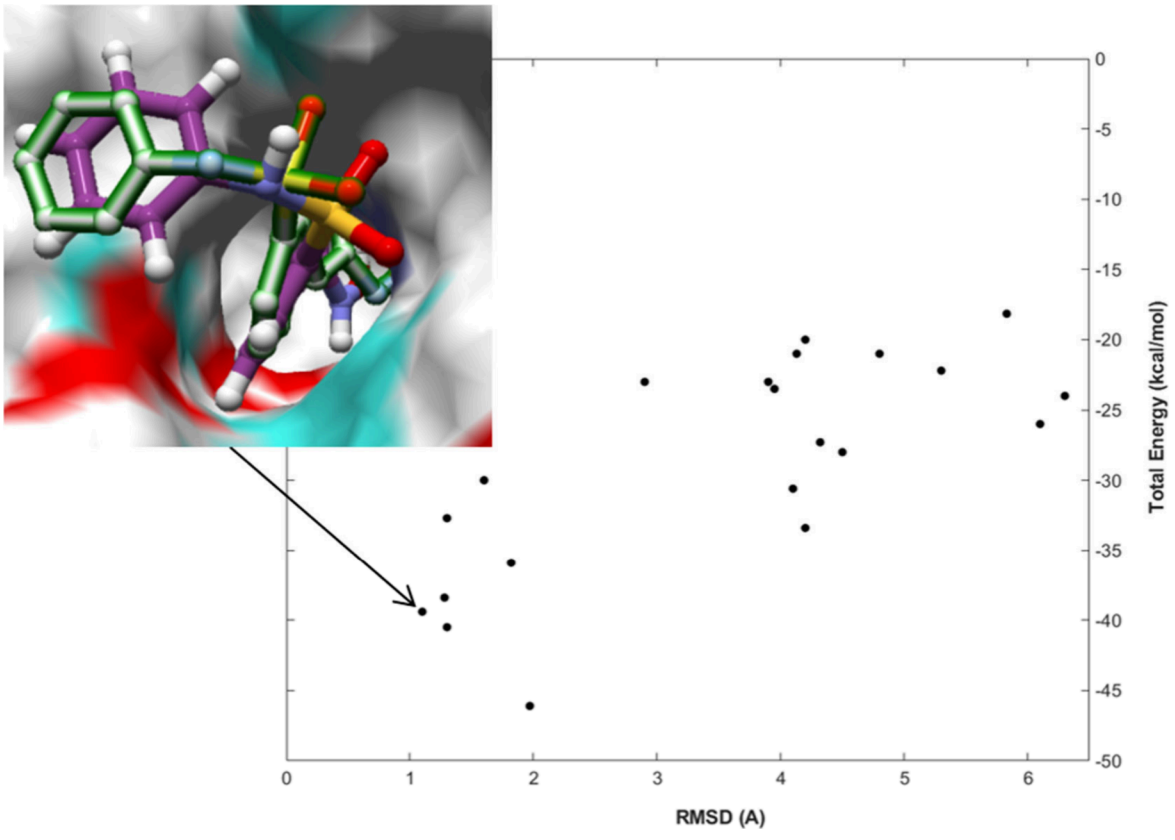

Figure 4. Total energy of the predicted pose plotted against the RMSD for each of the 21 students/student pairs. It shows that, in general, the lower the total energy, the lower the RMSD. Inset: view of one of the low-energy, low-RMSD docking poses with the predicted pose of belinostat as a purple stick and the experimentally determined binding pose (ghost) in a green-tinged stick. HDAC6 is in the molecular surface model.

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Evaluation of Learning Objectives

We evaluated the answers to the MCQ taken pre- and postworkshop. Table 1 gives the results, showing an improvement (using a standard paired t test, $p = 0.045$), with a particular improvement in their understanding of conformational change and how the binding energy changes during the binding process. The students also learned about RMSD as a measure of structural proximity by actively calculating distances between corresponding atoms in predicted and experimental poses.

DISCUSSION

We presented a molecular docking workshop that puts the docking process itself under the control of the students. It may be instructive for the teacher to explain the difference between interactive docking and automated docking, pointing out that automated docking tools can be used to screen a library of compounds, whereas interactive docking tools can be used to learn about the binding process itself and may also be used in SBDD where only a small number of lead molecules are considered.

As one can see from Figure 4 a significant proportion of students did not find a binding pose close to the experimentally determined pose. However, they still achieved most of the learning outcomes, as they did experience the formation of hydrogen bonds and conformational change that occurs upon molecular binding. They may not, however, have seen complementary surfaces between the belinostat and HDAC6 form. Our experience in running the workshop suggests that despite the binding pocket being indicated, the search space is still too large. It might be better, therefore, to adapt the workshop by informing the students that it is the hydroxamic acid group of the belinostat that enters the binding pocket.

Below we discuss the impressions we obtained from our workshop and make suggestions for the achievement of the individual learning objectives.

Recognizing the Types of Interactions Involved in Molecular Binding

During the docking of belinostat, one can demonstrate the contribution of the different interaction types to the total interaction energy by switching them on and off while viewing the energy trajectory plot. The students came to appreciate the repulsive interaction between atoms by switching it off as two atoms came into collision (best demonstrated using a space-filling depiction), resulting in a significant decrease in the interaction energy. The attractive dispersion interaction between atoms can also be appreciated by switching this component off as two atoms come close, resulting in a sudden increase in the interaction energy. From comments made by the students, it was clear that experiencing the effects of interactions by switching them on and off in an interactive environment helped to enhance their understanding.

Understanding of the Common Approximations Made in Computational Simulation of Molecular Binding

In our workshop, it was pointed out to the students that the effect of the solvent is only partially included. The MD simulation was performed using an explicit solvent model, and so some effect of the solvent will have been included in modeling the fluctuations for the linear response. It is stating the obvious that one cannot include an explicit solvent model within DockIT, as water molecules would block the ligand from docking to the protein. One effect of the solvent water is to reduce the strength of the electrostatic interactions between atoms. This is modeled in DockIT implicitly by reducing the strength of these interactions by using a distance-dependent relative permittivity (dielectric constant).[18] However, it is important to tell the students that an additional solvent-induced interaction is not currently modeled. The hydrophobic interaction is an entropically driven, short-range interaction by which nonpolar atoms tend to attract to reduce their exposure to the solvent water. It is not known to what extent this interaction will influence the results for this docking exercise. Those students that achieved the low-energy pose close to the experimentally determined pose (as shown by the position of the ghost) could see (using a transparent surface depiction on the receptor) that the molecular surface for a large portion of the binding pocket is complementary to the belinostat molecular surface.

It was also pointed out that there is normally a reduction in the binding free energy due to the decrease in entropy caused by a decrease in conformational freedom upon binding and that this is also not included.

Identification of Hydrogen Bonds and Appreciation of the Nature of the Hydrogen Bond Interaction

Hydrogen bonds that might be seen to form during docking were (atom names as given in PDB: 5EEN): between the side chain NH of Asn530 and the O4 oxygen on the hydroxamate group of belinostat; between the side chain NH of Asn645 and the O1 oxygen of the sulfuryl group of belinostat; between the mainchain NH of Phe643 and the O1 oxygen of the sulfuryl group of belinostat; and, when belinostat is near the lowest-energy pose, between the side chain hydroxyl group of Tyr745 and the O3 atom on the hydroxamate group of belinostat.

The electrostatic nature of the hydrogen bond can be demonstrated by switching off the electrostatic interaction, which weakens hydrogen bonds between the receptor and the ligand, causing the interaction energy to change abruptly and the receptor to relax to a new stable state. A more dramatic demonstration of the electrostatic interaction is provided by the salt-bridge tutorial that comes with the DockIT installation (see the PDF file: "Tutorial_Dynamic_salt_bridge_formation_and_the_electrostatic_interaction").

Impact of Molecular Flexibility and Its Role in Binding

Proteins are inherently flexible molecules, and this flexibility is engaged for function as demonstrated by the many examples, e.g., in F_0F_1-ATP synthase for the synthesis of ATP from ADP, where a dramatic and complex motor-like motion occurs. For HDAC6 there is very little conformational change between the belinostat-bound and ligand-free HDAC6 crystallographic structures. However, by maneuvering belinostat into the binding pocket, the students were able to observe global conformational changes in HDAC6 as well as local changes in regions close to the ligand. A more dramatic example of global conformational change can be demonstrated with the tutorial for docking maltose to maltose binding protein (MBP) (see the PDF file: "Tutorial_Maltose_to_MBP" with the DockIT installation). Comparison of the crystallographic structures of ligand-free and maltose-bound MBP shows that a clear domain movement occurs when maltose moves into its binding site in the interdomain crevice. In the tutorial, the students are instructed to move maltose into its binding site. Doing this reveals a clear domain movement that is remarkably similar in character to the experimentally determined domain move-

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ment.[4] Note that the linear response method does not directly restrict bond length, bond angles, and other constrained internal degrees of freedom. If the strain energy is large, then unphysical distortions of the bonded structure occur. Of course, it should be pointed out that the rigid-ligand model is a severe approximation that has been made for computational expediency and will be addressed in the future.

Understanding of the Interaction and the Strain Energy

The strain energy is the amount of energy required to deform the receptor from its relaxed state loaded at the start of the session. Following the path indicated by the force and torque arrows means that the interaction energy decreases. It is, however, the sum of the interaction energy and the strain energy that is to be minimized, and it is not possible to know how movements that decrease the interaction energy will affect the strain energy and consequently the total energy.

DockIT in Virtual Reality

Although VR was not employed for the workshop at UEA, small groups of students in laboratories of colleagues in Japan attempted the task using DockIT in VR mode. These more informal sessions demonstrated that performing the task in VR is much more engaging compared with using a keyboard and mouse due to its immersive nature. In the development of DockIT for VR, we did a small survey that confirmed an earlier study using a related tool,[6] which found navigation in VR to be easier than navigation with a keyboard and mouse. However, these informal sessions also showed us that performing the task in VR is more tiring, as it requires a finer degree of control and longer continuous periods of concentration.

CONCLUSION

We have presented a workshop for interactively docking the anticancer drug belinostat to its target protein HDAC6 using the interactive docking tool, DockIT. In contrast to automatic docking tools, with DockIT students are in full control of the docking process and free to experiment and test ideas, for example, whether a particular interaction is dominated by electrostatics. The results show a clear correlation between lower binding energies and lower RMSDs. A comparison of the results from the pre- and postworkshop MCQ showed that there was an improvement in the students' understanding of key features of molecular binding.

ASSOCIATED CONTENT

Supporting Information

DockIT is free for academic use and can be downloaded from https://dockit.uk/. The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.4c01347.

Teacher's notes: computational underpinnings (PDF, DOCX)

Teacher's notes: computational requirements and DockIT features (PDF, DOCX)

Worksheet (PDF, DOCX)

Video of the MD trajectory of HDAC6 (MP4)

Teacher's notes: introduction for students and MCQ (PDF, DOCX)

PDB-formatted file of ghost belinostat in the crystallographic pose (from PDB: 5EEN) (PDB)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Forli, S.; Huey, R.; Pique, M. E.; Sanner, M. F.; Goodsell, D. S.; Olson, A. J. Computational protein-ligand docking and virtual drug screening with the AutoDock suite. *Nat. Protoc.* **2016**, *11* (5), 905−919.

(2) Chen, R.; Li, L.; Weng, Z. P. ZDOCK: An initial-stage protein-docking algorithm. *Proteins-Structure Function and Genetics* **2003**, *52* (1), 80−87.

(3) Iakovou, G.; Alhazzazi, M.; Hayward, S.; Laycock, S. DockIT: A Tool for Interactive Molecular Docking and Molecular Complex Construction. *Bioinformatics* **2021**, *36* (24), 5698−5700.

(4) Iakovou, G.; Laycock, S. D.; Hayward, S. Interactive Flexible-Receptor Molecular Docking in Virtual Reality Using DockIT. *J. Chem. Inf. Model.* **2022**, *62* (23), 5855−5861.

(5) Cakici, S.; Sumengen, S.; Sezerman, U.; Balcisoy, S. DockPro: A VR-Based Tool for Protein-Protein Docking Problem. *International Journal of Virtual Reality* **2019**, *8* (2), 19−23.

(6) O'Connor, M. B.; Bennie, S. J.; Deeks, H. M.; Jamieson-Binnie, A.; Jones, A. J.; Shannon, R. J.; Walters, R.; Mitchell, T. J.; Mulholland, A. J.; Glowacki, D. R. Interactive molecular dynamics in virtual reality from quantum chemistry to drug binding: An open-source multi-person framework. *J. Chem. Phys.* **2019**, *150* (22), 220901.

(7) Plateau-Holleville, C.; Guionnière, S.; Boyer, B.; Jiménez-Garcia, B.; Levieux, G.; Mérillou, S.; Maria, M.; Montes, M. UDock2: interactive real-time multi-body protein-protein docking software. *Bioinformatics* **2023**, *39* (10), btad609.
(8) Acuna, V. V.; Hopper, R. M.; Yoder, R. J. Computer-Aided Drug Design for the Organic Chemistry Laboratory Using Accessible Molecular Modeling Tools. *J. Chem. Educ.* **2020**, *97* (3), 760−763.
(9) Frank, L. E.; Koehler, B. R.; Yoder, R. J.; Bouley, R. A. Testing the Ability of Protein-Protein Docking Programs to Model Known Complexes: A Project for the Biochemistry Classroom. *J. Chem. Educ.* **2023**, *100* (10), 3968−3973.
(10) Kholod, Y.; Hoag, E.; Muratore, K.; Kosenkov, D. Computer-Aided Drug Discovery: Molecular Docking of Diminazene Ligands to DNA Minor Groove. *J. Chem. Educ.* **2018**, *95* (5), 882−887.
(11) McDougal, O. M.; Cornia, N.; Sambasivarao, S. V.; Remm, A.; Mallory, C.; Oxford, J. T.; Maupin, C. M.; Andersen, T. Homology modeling and molecular docking for the science curriculum. *Biochem Mol. Biol. Educ* **2014**, *42* (2), 179−182.
(12) Sharma, N.; Badhani, B.; Vaijayanthi, B.; Aggarwal, P.; Gupta, A. Conceptualizing the Essence of Protein-Ligand Interaction at Undergraduate Level: Reinforcing Computational Skills. *J. Chem. Educ.* **2023**, *100* (7), 2746−2754.
(13) Batamuliza, J.; Habinshuti, G.; Nkurunziza, J. B. Students' perceptions towards the use of computer simulations in teaching and learning of chemistry in lower secondary schools. *Chemistry Teacher International* **2024**, *6*, 281.
(14) Hai, Y.; Christianson, D. W. Histone deacetylase 6 structure and molecular basis of catalysis and inhibition. *Nat. Chem. Biol.* **2016**, *12* (9), 741.
(15) Shvedunova, M.; Akhtar, A. Modulation of cellular processes by histone and non-histone protein acetylation. *Nat. Rev. Mol. Cell Biol.* **2022**, *23* (5), 329−349.
(16) Ho, T. C. S.; Chan, A. H. Y.; Ganesan, A. Thirty Years of HDAC Inhibitors: 2020 Insight and Hindsight. *J. Med. Chem.* **2020**, *63* (21), 12460−12484.
(17) Han, H.; Feng, X.; He, T.; Wu, Y.; He, T.; Yue, Z.; Zhou, W. Discussion on structure classification and regulation function of histone deacetylase and their inhibitor. *Chemical Biology & Drug Design* **2024**, *103* (1), No. e14366.
(18) Mehler, E. L.; Solmajer, T. Electrostatic effects in proteins: comparison of dielectric and charge models. *Protein Eng.* **1991**, *4* (8), 903−910.

https://doi.org/10.1021/acs.jchemed.4c01347
J. Chem. Educ. 2025, 102, 2514−2521