INTERACTIVE SONIFICATION FOR STRUCTURAL BIOLOGY AND STRUCTURE-BASED DRUG DESIGN

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ABSTRACT

The visualisation of structural biology data can be quite challenging as the datasets are complex, in particular the intrinsic dynamics/flexibility. Therefore some researchers have looked into the use of sonification for the display of proteins. Combining sonification and visualisation appears to be well fitted to this problem, but at the time of writing there are no plugins available for any of the major molecular visualisation applications.

Therefore we set out to develop a sonification plugin for one of those applications, released as open-source software, in order to facilitate scrutiny and evaluation from as many parties as possible.

This paper presents our open source sonification plugin for UCSF Chimera, which we have developed in collaboration with medicinal chemists and structural biologists. We determined two tasks that we deemed were not well represented visually and developed sonifications for them. Furthermore, we extended a general-purpose Chimera tool to map attributes of protein residues to pitch.

We evaluated one of the tasks with eight participants and present the results of this evaluation.

1. INTRODUCTION

Molecular graphics and visualisation has a long tradition in analysing and interpreting computational chemistry and structural biology data. High demand for a powerful software, rendering the structural and dynamic attribute of macromolecular datasets in accurate yet visually elegant and intuitive ways, has resulted in the development of several molecular graphics packages and platforms, open-source (VMD, UCSF Chimera, PyMol) as well as commercial (MOE, Schrodinger).

UCSF Chimera is one of the leading software packages for interactive visualisation and analysis of macromolecular complexes (protein-protein, protein-ligand, DNA), their structure and dynamics [1]. It is open-source licensed for academic use, has a long history, a considerable user base, and is constantly in active development. As it provides a Python API it is easily extendable and has a strong user base developing plug-ins.

Recent advances of visualisation platforms suitable for macromolecular settings exposed the limitations of visualisation as a technique; namely, its difficulty to deal with intrinsic dynamics of molecular targets, and limitations in the number of molecular attributes visualised simultaneously. Most molecules are not static in time, and different parts of the structures might be more or less flexible. To account for flexibility is very important in certain aspects of structural biology and rational drug design, and representing the flexibility in an accessible and intuitive way is of a crucial importance for medicinal chemists, in particular for users without extensive background in computational chemistry. Another limitation is the number of attributes that can be visualised simultaneously. Only a certain number of attributes can be shown at any time by varying colours or shapes, but being able to assign several molecular attributes to a molecular fragment (such as group of atoms, residue, protein domain) and access these in a straightforward way could be pivotal for the drug design community. Both functionalities would also be highly useful in research outreach contexts and for crossing boundaries between disciplines (e.g. science-inspired art projects).

In these respects, enhancing molecular graphics software packages with sonification plugins could make dramatic differences in the accessibility of macromolecular data.

To assess its applicability and feasibility, we have chosen the macromolecular system, in which intrinsic dynamics plays a pivotal role in its biological function - the human nF-kappaB inducible kinase (NIK). It is a central component of so-called non-canonical nF-kB pathway, which is upregulated in many inflammatory conditions and cancers, such as T-cells lymphoma (TCL). This is what makes NIK an attractive target for cancer research - finding an inhibitor could open new possibilities for treatment of TCL, which has a very poor prognosis in general. The area around the Adenosine triphosphate (ATP) binding site, which can be druggable by inhibitors, is surrounded by highly flexible loops, including the activation loop, which directly controls the biological activity of the enzyme (Figure 1). The dynamics of the so-called hinge region is also involved in regulation of the ligand/drug binding to the protein. Despite their biological importance, these features may be challenging to spot in conventional visualisation strategies, i.e. when a single structure of the protein is visualised.

2. RELATED WORK

Sonification of proteins and DNA has a long history, dating back to Hayashi and Munakata's mapping of DNA sequences for analysis [2]. Following that, are many more examples of artistic and scientific auditory display mapping the building blocks of proteins, especially of DNA, to pitches or other attributes of sound. Dunn and Clark provide a very musical example of this, in an artistic collaborative project to sonify protein chains [3]. Garcia-Ruiz and

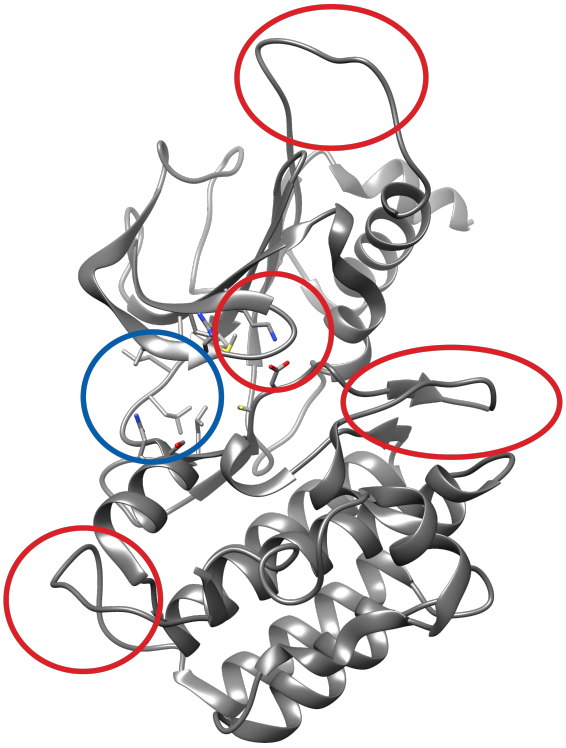

Figure 1: *Ribbon diagram of the kinase domain of human NIK (PDB code 4IDT). The secondary structure is represented as grey elements (helices, sheets, and loops). The flexible loops are marked in red circles. The hinge regions is marked in blue circle. The residues involved in the ligand binding are displayed and coloured by atom.*

Gutierrez-Pulido provide an extensive overview of auditory display of molecular structures [4].

The CoRSAIRe project [5, 6] developed a multimodal environment for protein docking analysis. In the project, a researcher works in a virtual environment interacting with proteins. Sonification is used to augment the display and the interaction of proteins in 3d space.

Multiple sonification plug-ins have been developed for molecular visualisation software: Grond and Dall'Antonio's [7] SUMO framework is a sonification plugin for the molecular visualisation application PyMOL. In their framework, they implemented two example sonifications: an amino acid sonification and a B-factor sonification.

Rau *et al.* [8] use sonification to augment events extracted from molecular dynamics simulations in MegaMol, a visualisation middleware for visualising point-based molecular datasets. They used OpenAL to provide spatial audio and auditory icons to highlight events happening in the simulation. This aimed to prevent the user from missing them due to occlusion, e.g., H-Bonds forming and breaking in the simulation. Presenting the plugin to collaborators in the field of structural biology, they received positive feedback, though they did not see any immediate advantage for their day-to-day work.

As a side note, the FoldSynth environment for protein folding synthesis [9] provides an (as of yet) undocumented sonification plugin.

3. DESIGN

3.1. Spatialisation

As other immersive approaches were successfully using spatialisation as part of the sonification technique, we decided to test this approach in our experiments [8, 6]. As we were binding the sound to the visualisation it also seemed the most intuitive choice to bind sound sources corresponding to parts of the protein to virtual spatialised sound sources.

We intended the plugin to easily integrate into the current workflow and technical setup of the intended users. Therefore we used headphones as preferred delivery method. This also gave us the possibility to use HRTFs to render a 3D soundfield on standard stereo headphones.

3.2. Interaction

As macromolecules such as proteins, nucleic acids, and their complexes can be very large and flexible and we wanted to avoid overloading the user with information, we chose to use interactive sonification in the user experience. The user can click on elements of the molecules to get sonic feedback and a temporary colour change of the component which is sonified. This visual feedback provides a point of reference to the user, especially as spatial distribution in the sound is not easy to discern when the zoom level is small.

In most tasks where molecular visualisation is used, not only the current element but also its surroundings are important. Therefore we decided to implement a travelling wave paradigm, i.e., an interaction based on the idea of a wave circularly spreading outwards in all directions from a point in space. In our case, a wave front spreads outward from the point the user interacted with, similar to the Data Sonogram method of Model-based Sonification introduced in [10]. The wave loses energy as it travels, rendering later elements of the sonification less pronounced. The visual feedback is coupled with the wave front, i.e., the moment an element is "hit", the temporary colour change occurs with the colour intensity relative to the energy of the wave.

We plan to use three different wave propagation methods in the final version of the framework (currently only (1) is implemented):

1. propagation to the directly connected neighbours of the origin element;
2. propagation as in 1, but also to elements connected with H-bonds;
3. propagation in 3d space according to the radius of the wave's reach.

This will provide the user the choice to concentrate on the immediate vicinity of the element (1), the logical vicinity (2) or the spatial vicinity (3). We found that in some applications it is beneficial to stagger the wave front in mode (1) to prevent simultaneous events. This means that instead of playing the element the user clicked on and then the adjacent elements, the adjacent elements are staggered, so if the user clicks on element 3 in a chain of 5 elements, the elements are played in the order 3, 2, 4, 1, 5 instead of 3, 2+4, 1+5.

We provide controls to change the propagation rate and radius of the wave, as well as enable or disable the staggering of the wave.

3.3. Backgrounding of sound objects

We found that with mapping parameters to pitch, high-pitched permanently sounding objects in the soundscape can overburden the user, especially in our stereo version. Our sonification design demanded some elements of the molecules we deemed important to be sonified permanently though. Therefore we implemented an interactive property to enable us to keep sounds in the mix, in a volume corresponding to their location in space, but still not dominate the soundscape.

The permanently sounding objects are therefore low-pass filtered to 300 Hz (subject to further evaluation) after their creation. We hope that this puts them in the perceptual background of the scene by removing their dominance in the soundscape. The filter is lifted for a short amount of time only when a "wave" hits these elements or the user clicks on them, restoring the backgrounded sound objects to their former spectral glory.

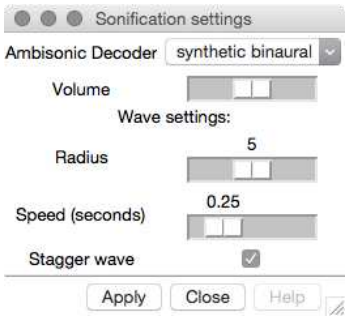

Figure 2: *Sonification settings GUI. Allows the user to change the Ambisonic decoder used and the volume of the sonification. The "Wave settings" part relates to the Data Sonogram-like travelling wave interaction. The radius determines how many elements the wave reaches and the speed determines the wait time between elements. "Staggering" refers to not simultaneously playing parts of the wave that would be played simultaneous otherwise.*

4. IMPLEMENTATION

4.1. Framework

We chose UCSF Chimera as the target platform as it is widely used, open source, free for academic use, and relatively straightforward to extend. It provides support for all data formats (PDB and mol2) and applications (visualisation of molecules and docking tasks) we targeted.

The plugin is written in the Python programming language. Chimera takes care of translating the source files in PDB or other formats into hierarchical data structures representing models, made up of residues, atoms, and bonds, etc. It provides triggers for changes in these data structures which we use to detect loading and deleting of molecules, updating the sonification accordingly.

All other data processing is done in Python with the help of the open-source scientific computing library Numpy [11].

SuperCollider is used as the synthesis engine, as it has good support for all major operating systems, supports 3D sound with Ambisonics, and has good sound synthesis plugins [12].

The plugin communicates with SuperCollider over UDP using the Open Sound Control (OSC) protocol. As all data processing is done in Python, other sound rendering options are possible as well, e.g., using Pure Data or Cycling74's Max, as the OSC commands used are relatively language-agnostic (see Table 1).

In Python, the individual parts of the sonification are represented by "sound objects", data structures that correspond to synthesis processes in the sound rendering software. In our current implementation they correspond to *Synths* in SuperCollider. Each "sound object" has a unique id shared between sound rendering software and plugin, and can be modified by setting arbitrary strings to numerical values, corresponding to arguments to those synthesis processes.

SuperCollider's *sclang* is used to implement handling of sound generation and synthesis processes. Sound is spatialised with the help of the Ambisonic Toolkit (ATK) [13]. Sounds are placed according to the position of the represented part of the molecule (atom, residue, bond) in relation to the camera position of the user's viewer. Chimera provides a trigger for changes in viewpoint, which is used in our plugin to recalculate all sound objects' spatial positions.

As the listener's coordinates are taken from the camera position, the user is not able to manipulate the listening position separately from the viewing position. Possible future work could include placing a separate "listener" in the scene, or positioning the listening position in front of the viewing position.

The plugins GUI enables switching between different Ambisonic decoders. Several decoders for headphone output based on head-related transfer functions (HRTFs), are provided, with a choice between KEMAR and synthetic HRTFs, enabling 3D sound experience over stereo headphones. A UHJ stereo decoder is also provided to enable output over Stereo speakers. The plugin is free software under the terms of the GNU General Public License and work-in-progress source code can be found online[1].

4.2. Sonification for molecular docking

The first task we looked at is the docking of small molecular drug compounds to their cognate protein receptors, in order to design tight-binding (potent) and selective inhibitors (a process called iterative lead optimisation). The same task is routinely performed by medicinal chemists in order to select the best binder from a list of small molecular compounds, a process known as structure-based virtual screening. In this application, the chemists need to understand the structure and intrinsic dynamics of the binding site of the protein to draw conclusions about factors governing the binding potency, specificity, and selectivity.

This information allows for the rational design of drug-candidates with the optimal pharmacological profile in order to minimise the number of adverse effects. As some parts of the binding sites can be very tightly embedded in the structure they can be challenging to visualise in a way that is required for the task. Also, the dynamics of the binding site, which are notoriously difficult to inspect visually, may sometimes play a pivotal role in governing the ligand-protein associations (e.g., HIV-1 protease inhibitors, hERG potassium channel and cytochrome P450 binders).

We designed an auditory display to illustrate the electrostatic and van der Waals' interactions influencing the enthalpic contribution to the free energy of protein-ligand association, and the atomic positional fluctuations (APFs), which are the measure of the conformational flexibility of the protein target and ligand molecules

[1] See `https://github.com/mortuosplango/chison`.

Table 1: *Simple sound object OSC protocol. Sound objects correspond to synthesis processes on the synthesis engine and data structures on the client.*

OSC command	Explanation
`/obj/new id sound_type [attr_name attr_value]*`	Add new object with id and sound type
`/obj/modify id [attr_name attr_value]*`	Modify existing object by id
`/obj/delete id`	Delete object by id
`/reset`	Reset everything (delete all sound objects and samples)
`/sample/new id path`	Load sample at path to this id
`/decoder/set name`	Switch Ambisonic decoder
`/volume/set volume`	Set global volume between 0 and 1.0

(entropic contribution to the free binding energy), in order to navigate the user in the processes of virtual screening and iterative optimisation of the lead molecule.

We used auditory icons and interactive parameter mapping sonification (PMSon) to give interactive feedback.

Auditory icons represent the H-bonds present between the ligand and the protein.

PMSon is used for the display of the ligand atoms. The constant sound of the ligand is represented using phase modulation synthesis. It is mapped linearly to the modulation frequency, whereas the grid van der Waals' score is mapped exponentially to the carrier frequency. Therefore each sound object in a ligand has the same carrier frequency, while the modulation frequency depends on the individual atoms' charge. This provides a unique overview sound for each ligand depending on the van der Waals' score while providing feedback on the charge of the object on click. Through the addition of vibrato we livened up the sound by adding a bit of randomness to the pitch and wanted to improve source separation according to the principle of common fate [14].

Inspired by science fiction film soundscapes we chose to go with a space ship docking metaphor, with the H-bonds closing represented with a sound modelled after a magnetic seal docking on an air conduit.

The protein's residues are sonified only on interaction, where the B-factors (also known as DebyeWaller factors, a measure of the intrinsic flexibility of parts of a protein) are mapped to the pitch of the sound objects. We used interactive PMSon to show which components are more flexible than others. We mapped the B-factor values exponentially to the pitch of a slightly distorted sine wave (see Figure 3) produced by $f(x) = tanh(sin(x) * 2.8)$. This provides a relatively small spectral and CPU-footprint while still having some timbral qualities of a square wave, making it easier to localise than a pure sine tone.

By clicking on a residue or atom, the user can play the corresponding pitch of that region and of the neighbouring residues or atoms according to the wave settings.

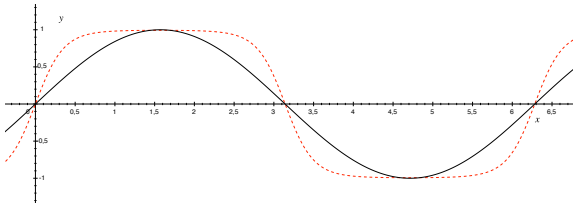

Figure 3: *Sine wave (black) vs. distorted sine wave produced by* $f(x) = tanh(sin(x) * 2.8)$ *(red, striped).*

4.3. B-factor sonification

The second task is the sonification of DebyeWaller factors, also known as B-factors, and/or atomic positional fluctuations (APFs) of atoms or amino acid residues, related to their intrinsic flexibility. Combined with a simple animation of the sonified parts this will help the researchers understand the dynamic behaviour of the protein of interest better.

We used the same interactive PMSon for displaying the B-factors as in the previous paragraph. Additionally, we continuously displayed the 20% of residues with the highest values. They are displayed as sequence of sound events with a percussive envelope. The wait time between events is inversely proportional to the B-factor value. We added vibrato as in the other task. Additionally, the vibrato gets more pronounced in higher pitch ranges (if the MIDI note number is bigger than 80) to create a threshold as used in [15].

By clicking on a residue, the user can play the corresponding pitch of that region and of the neighbouring residues according to the wave settings.

4.4. General-purpose sonification GUI

In addition to these tasks, the plugin comes with a GUI that enables the user to specify which data they want to sonify. We extended a widely used Chimera tool that enables the mapping of attributes to rendering parameters (e.g., colour or radius) to also give an option to render in pitch. This general-purpose sonification option will hopefully in future versions of Chimera be integrated into the current user experience.

The current version can be seen in Figure 4. After choosing a structural element level (atom, residue, or molecule) and an attribute, users can define markers in the histogram view and which MIDI pitch they represent. Values in between these markers are mapped with linear interpolation to the chosen pitches. They can specify a sound, as well as if a pitch and which pitch is played in case there is no value associated with the element. The user then can interact with the molecule by clicking certain parts of it and configure the resulting wave front in the sonification settings (see Figure 2).

5. EVALUATION

In an informal evaluation, we asked 8 participants to evaluate our prototype for displaying molecular dynamics. 7 out of 8 participants are working in the field of structural biology or computational chemistry at least on a PhD candidate level. One participant is an electroacoustic composer. Each was shown a MD-Movie, a

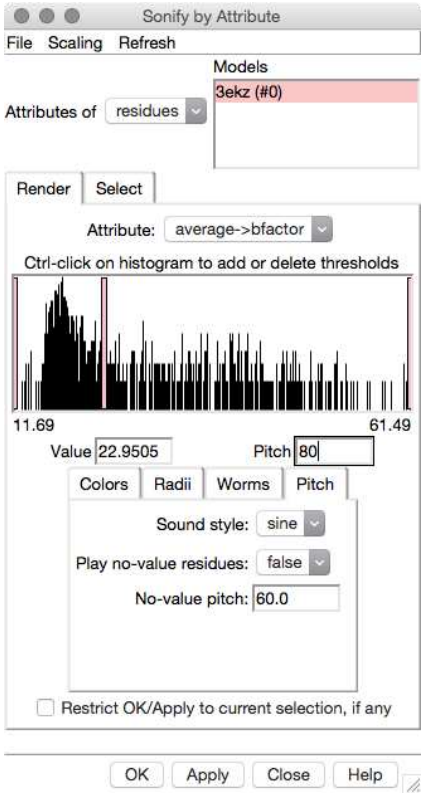

Figure 4: *Sonify by attribute GUI. In this case, mapping the average B-factor of the residues to pitch. There are 3 markers defined in the histogram, each setting a pitch. The pitch values in between markers are linearly interpolated.*

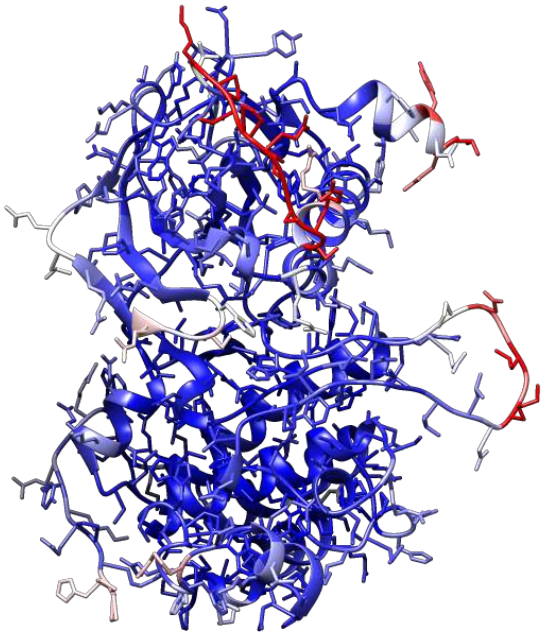

Figure 5: *Coloured representation of B-factors in human NIK protein. Red parts represent high, white middle, blue low B-factors.*

coloured representation of B-factors and our sonification displaying the same protein (see Figure 5). The participants were asked to identify the most flexible region of the protein in each representation. By monitoring the response and asking the participants to fill out questionnaires before and after the study, we aimed to determine: how the system could be integrated into their workflow; if the software system with sonification could have a positive influence on drug design tasks; and how the system could be improved. We gave minimal instruction on how to use the sonification, just explaining the mapping and the interaction possibilities.

Before using the software, we asked the participants to fill in a short questionnaire about their listening habits, their working habits and their work place. We also asked them what they imagined proteins would sound like.

7 out of 8 participants filled out our questionnaires. 4 reported working in a quiet environment. 5 use Chimera daily. 5 participants had some level of musical training. None of the participants reported associating any sound with proteins. Besides the composer, nobody reported using sonification or sound in their work. 6 participants listen to music while working at least once a day.

Participants were audio- and video-recorded while using the system. After using the sonification, the participants were asked to fill in a questionnaire about their experience using the software.

Our questionnaires and informal chats with the participants showed a wide range of responses. One experienced researcher entirely dismissed the whole idea of sonification and our setup. Comparing it to the visual modality, this researcher was quick to point out that it was much easier to see than to probe the protein for sonic information, and that this endeavour therefore is a waste of time. The less senior participants were more open to our work in general and its possibilities. 3 participants remarked that although the visual modality was quicker to present the information, the different interaction type and the relatively lower speed of interaction lead to a more contemplative exploration.

In general, no participant had problems using the sonification to fulfil the task. 7 out of 8 found the most flexible region using the sonification.

Rating their experience on a 5 point Lickert scale, 5 out of 7 participants agreed with or strongly agreed with the sonification being “beneficial”, 4 being “musical”, 0 being “annoying”, 5 being “helpful”, 0 being “fatiguing”, 1 being “transparent”.

On the other hand, 3 participants agreed with or strongly agreed with the mapping between data and sound being “transparent”.

5 participants reported they were interested in using this sonification in their work, 4 participants were interested in using it in research, 4 in teaching, and 2 in an art context. One participant remarked that it “would be good to use if teaching students or individuals who do not have a lot of experience in using chimera or other applications”. 4 reported they would be interested to use sonification in general in their work.

In conclusion, there seems to be at least some general interest in sonification in the field. The general work environment noise level appears to be sufficiently quiet to use sonification. As most participants listen to music at work, the hardware for sound reproduction is already there. The interaction in our mapping turned out to be intuitively understandable even for participants which

do not regularly use Chimera. The difference between participants perceiving the mapping as transparent and the sonification as transparent points to a problem in sound design of the overall sonification, showing an imbalance between the volume levels of permanent and interaction-triggered sounds.

6. DISCUSSION

We presented our work-in-progress sonification plugin for the molecular visualisation application UCSF Chimera. We developed two initial sonifications for important tasks in computational chemistry and a general-purpose sonification GUI.

In presenting our work to potential users we received valuable, mostly positive feedback. Using a travelling-wave paradigm related to Data Sonogram scheme for interaction with the molecular structures proved intuitive for novel users. The backgrounding via low-pass filtering for permanent sounds seemed to be valuable, but the filtering needs to be adjusted to account for the feedback.

Although no direct improvement on task performance could be measured, participants were interested in using sonification in their research and teaching, and our current approach to interaction was intuitively comprehensible.

7. VIDEO EXAMPLE

We illustrated the described tasks and the general purpose sonification GUI with a video example[2]. It shows first the docking task, then the B-factor sonification, and last the general purpose GUI.

8. FUTURE WORK

We plan to conduct an extensive user study on master's students in chemistry soon. We are currently working on improving the sonifications described here and on the design of the study, constructing a concrete task related to molecular docking that is manageable for beginners and provides quantifiable data.

Additionally, we want to evaluate our general sonification plugin with experienced Chimera users to come up with some mapping presets as well as other useful features, e.g., mapping to rhythm or other sound attributes.

We released the source code online already but plan to package it in a form that is easier to install. If the concept of sound objects and spatial sonification proves valuable in other sonification tasks, we will decouple general components from the Chimera plugin to provide another Python sonification framework or integrate it into Sonipy [16].

9. MOLECULAR DYNAMICS (MD) SIMULATION PROTOCOL

Molecular dynamics simulations of NIK kinase domain, which were used for assessing the developed sonification strategy, were carried out using GROMACS 5.1.2 [17], with Amber99SB-ILDN [18] force field for the protein and the TIP3P water model.

The protein (PDB code 4IDT) was rendered to its apo (unliganded) form by removing the co-crystallised ligand, and immersed in a cubic TIP3P water box containing 50,000 atoms. Simulation unit was maintained neutral by adding sodium and chloride counterions (0.1M concentration). Prior to MD simulations, the systems undergone 25000 steps of molecular mechanical energy minimisation. This was followed by 100 ps MD simulations, during which positional constraints were used on all duplex atoms. After the following unrestrained equilibration phase (10 ns) the production runs were carried for 100 ns, with an integration time step of 2 fs. The cutoff for non-bonded interactions was 0.1 nm. The coordinates were saved every 10 ps.

The temperature was kept constant at T= 298 K by using velocity rescaling with a coupling time of 0.1 ps. The pressure was kept constant at 1bar using an isotropic coupling to Parrinello-Rahman barostat with a coupling time of 0.1ps [19]. A cutoff of 1nm was used for all nonbonded interactions. Long-range electrostatic interactions were treated with the particle-mesh Ewald [20] method using a grid spacing of 0.1nm with cubic interpolation. All bonds between hydrogens and heavy atoms were constrained using the LINCS algorithm [21].

The intrinsic flexibility of the protein chain, hydrogen-bond network, and conformational changes were computed and analysed using tools implemented in the Gromacs package [17]. The intrinsic flexibility was quantified by root-mean-square fluctuations (RMSF) of atomic positions and calculated B-factors. For the visual inspection of the results prior to the choice of the sonification strategy we used xmgrace and UCSF Chimera [22, 23] packages.

[2]Available at `https://uiae.de/ison-2016`.

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