

THE SPATIALISED SONIFICATION OF DRUG-ENZYME INTERACTIONS

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ABSTRACT

This paper presents the preliminary work into the creation of an interactive spatial sonification system used to model the interactions between drug molecules and their target biomolecules within the human body. With the aid of sonification and a 3D soundscape, the user is able to optimize these interactions to a much greater precision than the sole use of the current visual model. This system gives a promising means to aid the rapid design of new drug molecules that can interact more strongly with the enzyme's active site, therefore creating more effective drugs for the treatment of cancer and other diseases. This paper gives a full account of the relevant theory, the techniques used and details of preliminary user testing.

1. INTRODUCTION

During the chemical design process of drug molecules, the researcher needs complete knowledge of the readily changing energetic interactions between the drug's molecular structure, and that of the site of the target enzyme. The optimum energy potential between the drug and enzyme atoms is determined by the distance between them, which varies from atom to atom within the molecules. The optimal distance is given by the Lennard-Jones potential graph (Figure 1). Currently, chemists and biochemists aim to 'tune' interactions using visual software that docks the drug molecule with an enzyme biomolecule. However, when researchers look at the interactions between molecules their complex nature is very difficult to perceive visually, not only causing the process to be slow, but also some of the principal electronic interactions that form between drug and biomolecule can be overlooked. Through sonification, multiple data parameters can potentially be perceived instantaneously with the aid of sonic parameters such as timbre, pitch and amplitude. The sonification technique that associates information with auditory parameters, for the purpose of data display is known as *Parameter Mapping Sonification* (PMS) [1].

One of the key limitations to standard sonification systems is the limit on the number of sounds heard at a given time without causing confusion. A 3D spatial soundscape might allow a further level of information to be provided for the user. By using a spatial component, the sounds are discrete in the immediately surrounding area, giving the user a feeling of space and distance. This results in less confusion when multiple sounds are heard at once

and also allows the user to focus on a particular sound with greater ease.

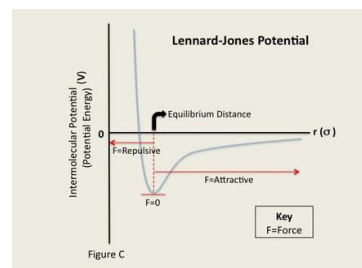


Figure 1: The Lennard-Jones Potential graph, showing the optimal point of interaction between two atoms [2].

2. SYSTEM OVERVIEW

A prototype spatial sonification system has been developed by the authors to investigate its potential to aid the molecular design of drug molecules; it uses a highly simplified model of the interactions between the atoms of the drug molecule and the active site of the enzyme, both comprising three atoms. For simplicity the current system only takes into account the interactions between the atoms of each molecule which are in closest proximity, giving three instances of the Lennard-Jones potential graph. The energy potential of each interaction is summed; hence, there are three levels of optimal energy potential, with more atoms at the optimal distance corresponding to a deeper trough on the combined graph.

The system incorporates a spherical loudspeaker array consisting of 16 loudspeakers, with sounds rendered using Vector Base Amplitude Panning (VBAP) [3]. The system includes a fixed molecule (red as illustrated in Figure 2) and a control molecule (green) which can also be rotated around its central atom.

The relative distances between atoms of each molecule are calculated as the sum of the distances along each axis and passed through the Lennard-Jones potential graph, relating a change in relative distance between atoms to a change in energy potential. Using *Parameter Mapping Sonification*, the change in energy potential between the two molecules is mapped to the change in pitch of a synthesized tone, positioned in the spatial location of the control molecule, moving in space with the control molecule. The synthesized control molecule tone is paired with a reference tone, a second tone which also appears in the same spatial location as the control molecule, but has a constant pitch.

When one control molecule atom is placed at the optimal distance with a reference molecule atom an interval



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of a 5th is heard between the reference tone and the changing (control molecule) tone. When two atoms are at their optimal distance a major 3rd is heard, and unison is heard when all three atoms are at their optimal distances. These are clear auditory markers, as they sound 'correct'. To avoid confusion between the desired major 3rd, and a non-desired perfect 4th, amplitude modulation in the form of pulsing was added to the changing tone, with the rate of pulsing corresponding to instantaneous proximity of the molecules to an optimal distance trough. Consequently, as the atoms move closer to an optimal trough, the rate of this pulsing increases until eventually a pure tone (sine wave) is heard. Once a pure tone is sounding, frequency beating can be heard between the control and reference tones, allowing for greater precision of positioning. The fixed molecule is also assigned a low frequency amplitude modulating tone, enabling the user to hear the position of the fixed molecule.

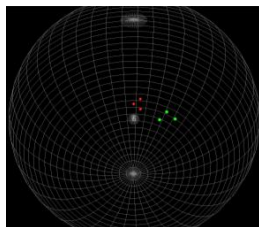


Figure 2: A screen shot of the visual display of the system.

For a better aural perception of the 3D soundscape, subtle sound alterations are incorporated. The control molecule tone's amplitude level decreases as it moves from the centre of the sphere to the outer edges, giving an aural sense of distance. Furthermore, localisation tests revealed difficulties locating sounds in the vertical plane. Therefore, by utilising the perceptual effect of higher frequencies being higher in space, and lower frequencies as lower in space, the control molecule tone's pitch is set to increase as the molecule moves upwards and vice versa, in order to aid localisation.

The user sits in the central point of the 3D loudspeaker array and is given a visual representation of the molecules, displayed on a projection screen (see Figure 2). Two 3D computer mice control both the position and orientation of the control molecule, and the viewpoint of the visual display.

3. PRELIMINARY USER TESTS

A preliminary user test was carried out to investigate two aspects of the system design: 1) to identify the optimum spatial scaling of the Lennard-Jones potential graph, and 2) to determine the intuitiveness of the system. During these tests the visual representation is excluded, in order to determine the effectiveness of the spatial sonification system using audio alone. The test consists of five tasks with each task completed once. Each task varies the spatial scaling of the Lennard-Jones graph between Distance 1 (approximately 1/3 of the furthest possible distance between the control molecule and the fixed molecule) to Distance 5 (the furthest distance). During each test the user is asked to click the relevant button on an iPad display if they believe they have found the correct position, indicated by the sound that they hear. The user also has the option to play example tones for each of the optimal positions (musical third, fifth and unison) at any time.

3.1. Results

The results show that the optimum distance is Distance 3 with the largest number of correct points, and the greatest combined accuracy. The numerous errors could be caused by confusion between the transition from amplitude modulating pulses to a pure tone, with the user then needing to find the precise optimal point by listening to frequency beats between the changing tone and the reference tone. This transition to a pure tone is clearly heard, and could be misinterpreted as the correct point without any further change. Furthermore, frequency beats can often be difficult to perceive when listening to intervals as opposed to unisons.

Distance	Optimal Point	Correct	Error	Wrong Button	Percentage Correct	Percentage Error	Average Error (V)
1	A	4	5	5	44.4	55.6	0.0010
	B	1	7	2	12.5	87.5	0.0010
	C	0	1	3	0.0	100.0	0.0017
2	A	6	9	2	40.0	60.0	0.0010
	B	2	14	1	12.5	87.5	0.0010
	C	0	4	1	0.0	100.0	0.0013
3	A	8	8	3	50.0	50.0	0.0011
	B	7	12	4	36.8	63.2	0.0010
	C	2	6	2	25.0	75.0	0.0011
4	A	9	7	0	56.3	43.8	0.0013
	B	4	10	1	28.6	71.4	0.0012
	C	0	7	2	0.0	100.0	0.0015
5	A	5	3	2	62.5	37.5	0.0008
	B	0	10	1	0.0	100.0	0.0014
	C	2	10	2	16.7	83.3	0.0011
TOTAL		50	113	31	Key A: -0.019V, B: -0.038V, C: -0.057V		

Table 1: Results of the test, carried out by 6 users.

The significant number of wrong buttons pressed indicates a difficulty identifying the correct interval. Further research and tests are necessary to find a more appropriate method to indicate the optimal points of energy potential.

With increasing distance, the space that each optimal point holds increases. However, these optimal points are then located further apart in space. It was estimated that fewer points would be found at larger distances, but with greater accuracy.

4. FUTURE DEVELOPMENT

A more intuitive means to represent the optimal points of the combined Lennard-Jones potential graph, including real world values for the energy potentials between atoms, and an increased number of atoms will be developed in the short-term. In the long term, the user should be able to control the spatial positioning of the drug molecule in relation to multiple molecules in order to find the optimal point in a larger area.

5. ACKNOWLEDGMENT

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6. REFERENCES

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