CHAPTER 3   53

Sonicules - Designing drugs with sound: approaches to sound design for film, audiovisual performance and interactive sonification

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Introduction

The key to effective design of new anti-cancer drugs is the ability to target specific biomolecules by carefully engineering the 3D shape of the drug molecule to allow for optimal docking between a drug and target enzyme. 'Sonicules' is an interdisciplinary project involving a variety of multi-modal media for public engagement. This includes an audiovisual computer game with interactive spatial sonification, an audiovisual performance and a documentary film. Each of these is designed to engage the public with the challenges inherent in drug design processes.

In this chapter, we will discuss how sound is used as the subject of the video, game and performance to engage audiences in an effective way. Furthermore, we will discuss the use of sound and its potential impact in health sciences research.

The game involves a number of staged interactive sonification tasks that incorporate complex non-linear multi-parameter mapping. Numerical data from over 100 gameplays was collated at several public engagement events and analysed in order to investigate whether the interactive sonification provided improved player accuracy and/or efficiency in completing the drug-docking task. The audiovisual performance takes the sound design system and soundworld used in the project (modular synthesis), using it in a creative way for live performance outside of the bounds/constrictions of scientific parameter mapping, adding additional rhythmic elements. Visual aspects of the performance are based on the biomolecules used in the game (i.e anti-cancer drug Tamoxifen). The abstract performance engages the public in a musical and artistic way, creating an immersive experience using spatial sound where the audience is presented with molecular docking from a first-person perspective. The performance showcases four scenarios that envision future drug design processes using immersive auditory and visual display. The video documentary tells the story of the project and its development. Its focus is on spatial sound and its use in the drug design process. It includes interviews with members of the research team. The video was designed to engage with the wider public via social media to allow engagement in a variety of places and times, unlike the game and the performance that were time and place specific. The sound design used in the film is, by its nature, linear and therefore distinct from the other parts of the project. Spatial sound is driving the narrative of the story, through its dynamics and density, and its connection to the spoken word that brings focus to specific aspects of the project.

The Use of Sound

The process of designing anti-cancer drugs is so complex that achieving an effective solution through computational "brute force" alone has been found to be, as yet, still slower than reaching the solution through human manipulation of visual representations of molecular structures. Furthermore, even with the aid of state-of-the-art visualisation software such as PyMol (Schrödinger, 2017), the lengthy process is imperfect, slow, and often misses some of the principal electronic interactions between the atoms of each molecule, which form the basis of drug-enzyme docking. Recently, researchers have started to investigate whether displaying such complex molecular interactions through sound can aid comprehension of the structures involved, and support chemistry researchers to design more effective drug molecules. Garcia-Ruiz & Gutierrez-Pulido (2006, pp. 853 – 868) showed that the auditory display of molecular structures and bonding aided better understanding of complex biomolecular relationships, which chemistry researchers and students found difficult to grasp solely through visualisation. Férey, N. et al (2009) have also investigated continuous provision of multi-modal (visual, aural and haptic) feedback during protein docking manipulations. Initial work at the University of York on a spatialised sonification system to display drug enzyme interactions (McIlraith, Walton, Brereton, 2015) demonstrated the potential of sonifying molecular interactions using binaural beats to represent molecule positional information. The Sonicules project built on this work to develop an audiovisual interactive molecule docking computer game, complemented by a live audiovisual performance and a documentary film in order to engage with the wide public on the challenges inherent in drug design processes.

This chapter describes the interactive sonification used in the Sonicules audiovisual computer game, the soundworld created for the audiovisual live performance and its adaptation for use in the documentary film. It investigates briefly whether the use of a staged interactive sonification improves accuracy and efficiency of task completion, and reflects on naive user engagement with non-linear, musically informed complex auditory display. Furthermore, it discusses how the soundworld is used as a subject in the different media reinforcing the impact and engagement with the audience in an effective way.

Sonicules: Game

The Sonicules game presents a number of increasingly difficult molecule docking tasks, based on anti-cancer drug molecules and their target enzymes. Representations of the

molecular structures are presented on screen, and the player is able to manipulate the position (translation) and rotation of the drug molecule in order to fit it within the active site of the enzyme. After an initial tutorial level to allow the player to become familiar with a 3D mouse controller (SpaceMouse) and numerical keypad, the game includes a number of staged levels in which the user has to find a known target position (known solution). A complex set of auditory mappings are introduced to the user in stages, so that during the tutorial levels of the game he/she may become gradually more aware of the target 'sound' signifying the correct solution.

Levels

Level 1 is a simple translation and rotation task with the correct solution displayed in gold (left side of screen in Figure 1).
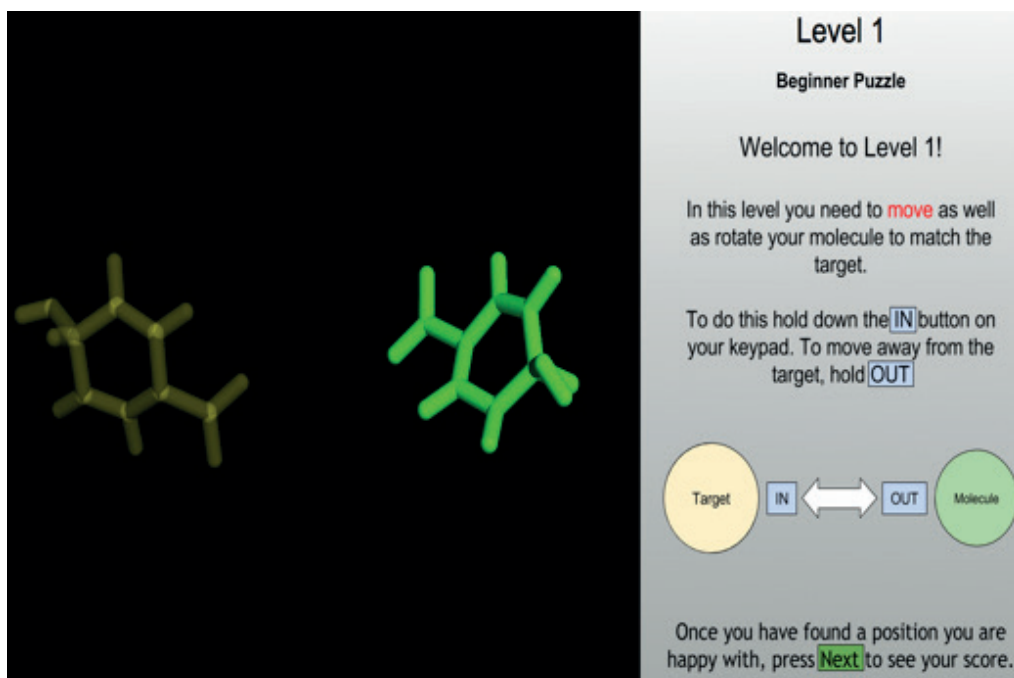

Figure 1: Screenshot of Level 1 gameplay - the drug molecule manipulated by the player is pictured on the right-hand side, and the target position pictured in gold on the left-hand side of the screen. Reproduced with permission of the Sonicules Project Team.

In Level 2 the player must rotate and translate the drug molecule (green) that is initially placed at the right-hand side of the screen (Figure 2 below). The correct solution is displayed in gold (within red circle in Figure 2) and is nestled within the target biomolecule structure (pictured in blue). Level 3 of the game is similar to Level 2 but the correct solution is not displayed in gold, and the player must find the correct solution using visual and aural means alone.

In the final, and most complex, level, a visual representation of a real anti-cancer drug (Tamoxifen) is presented, but the outline of the correct solution is not shown. When the correct position is reached the green drug molecule is visually partly obscured by the structure of the target biomolecule (the large blue molecule as pictured in Figure 3).

Sonification

[Audio files to illustrate the auditory display accompany this submission rendered as stereo files.]

The game incorporates interactive spatial sonification, presented binaurally over headphones, which aids the player in probing the 'physical' and 'electronic' space of the interaction between an anticancer drug and the active site of its target biomolecule. Sonification is also referred to as 'auditory display' and is the process of translating quantitative data into sound to enable investigation and understanding through auditory, rather than visual, means.

Ambient Harmonic Chord

In effect, two main phases of auditory display are heard. When the drug molecule is outside of the nominated 'target-zone' (see Section 4) an 'ambient harmonic chord' (Audio File 1) is heard which does not change even when the drug-molecule is rotated on the screen by the player.

Once the 'target zone' is reached the auditory display alters according to the overall accuracy score that incorporates measures of rotational accuracy on the X, Y and Z planes together with translational accuracy. As the position of the drug molecule becomes more accurate the ambient harmonic chord becomes increasingly 'present' in the mix by increased volume, reduced reverberation and opening of low pass filter that brings high frequencies and harmonics to the mix.

As the positional accuracy of the drug molecule 'homes in' further on the correct solution, beats are heard which gradually reduce in frequency as the accuracy improves.
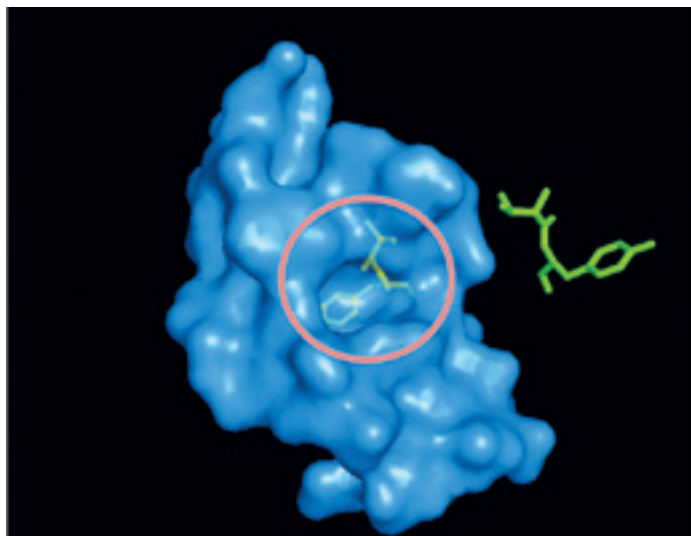
Figure 2: Screenshot of Level 2 gameplay - the drug molecule manipulated by the player is pictured on the right-hand side (green), and the correct target position (gold) within the target biomolecule (blue) on the left-hand side of the screen. The 'target zone' is indicated by the central orange circle. Reproduced with permission of the Sonicules Project Team.
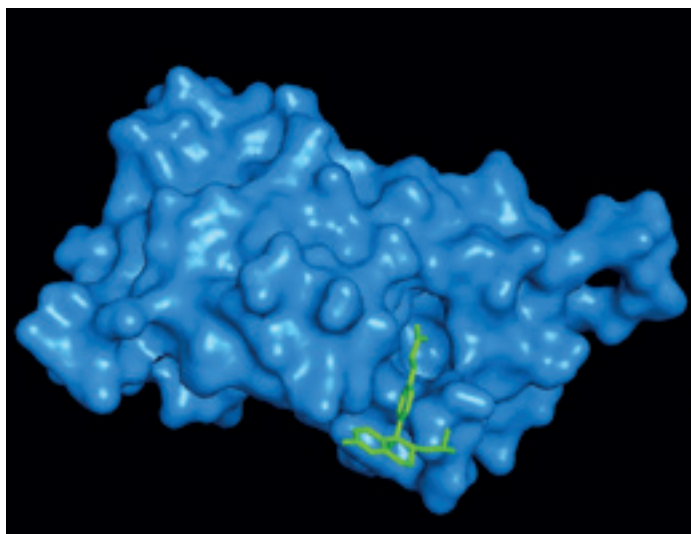

Figure 3: Screenshot of Level 4: the drug molecule (green) is pictured off-centre right in the lower part of the screen; the player must translate and rotate the drug molecule to fit inside the larger target molecule. Reproduced with permission of the Sonicules Project Team.

In addition, the width of the stereo field narrows as positional accuracy increases, meaning that the whole of the auditory sound field narrows and focuses to a central point as the player's accuracy relative to the position of the ligand, the molecular structure which creates a bond to the target enzyme

Collisions

Collisions, where the drug molecule's structure overlaps with the target enzyme molecule, are represented visually by red dots, and are sonified via repeated samples of 'crunchy' sounds, spatialized in the auditory environment according to the centre of gravity of each group of collisions.

Sound Design

The aesthetics of the soundworld for each element of the project were designed on a Eurorack and Serge modular synthesizer (James, 2013).

The aesthetics are reminiscent of the work of Post-Digital composers (Cascone, 2001) such as Sasu Ripatti's *Anima* or Autechre's algorithmic sound design work (Muggs, 2016), incorporating irregular rhythms, dense textures and ambient soundscapes using sound synthesis. Similar generative strategies in composition are used through signal processing and sampling using hardware devices, as well as algorithms for sound synthesis and signal processing. The difference here is the use of data, spatial sound, audiovisual material and interaction with a visual artist as well as scientific concepts.

Three layers of sounds were created and taken into account.
1.   Ambient harmonic chord
2.   Glitches / irregular rhythmic material
3.   Collisions

Ambient harmonic chord sounds were designed using a wavetable oscillator (Intellijel Shapeshifter) in chord mode that uses eight parallel oscillators to form a chord (Intellijel, 2017). This was processed through a Cwejman DMF-2 low pass filter. This particular combination gives a smooth and easy-to- listen-to sound, ideal for creating a pleasant sound to indicate successful task completion in the game. It was also used to create the low background hum with the DMF-2 filter closed, as well as to create movement in sound at the start of the game, performance and film.

The sound was modulated by LFOs and random voltage generators (SSF Ultra Random Analog) to achieve a sense of movement and frantic instability. This was achieved by

changing filter parameters such as modulating the cut off of the filter and animating waves in the table. Both methods allowed for timbral manipulation of the sound.

'Glitchy' sounds were produced using the Harvestman/Industrial Music Electronics Piston Honda MK2, a wavetable oscillator where waveforms are organised into 16x16x16 cube giving a total of 4096 choices (Industrial Music Electronics, 2017). In addition, each axis can be modulated by control voltage (CV). The oscillator uses 8bit waveforms creating raw and 'edgy' sounds. The oscillator was processed with Modcan Dual Delay with modulated delay time and feedback to produce an irregular and almost granular sound of delayed particles. These sounds were recorded before and during the live performance, in real time to an Elektron Octatrack sampler containing multiple audio tracks of different lengths. This created polyrhythms and evolving patterns during the performance, portraying the complexity of the molecular data.

Collisions were designed on a Serge Modular System using an STS X-fader VCA for 'punchy' and dynamic sounds clicks. These sounds were achieved by sending gate signals and waveforms from a VC Timegen Oscillator, modulated by Dual Universal Slope Generators, creating irregular patterns of clicks that were used to present collisions between molecules. To make this sound we used 'punchy' and with high dynamic range Serge Modular Synthesiser Voltage Controlled Amplifiers that with modulated amplitude created distinct 'crispy' and clear click sounds.

The sound design utilised a trial-and-error process to find aesthetically interesting combinations of various modules within the system in order to create the desired sounds which provided perceived ecological validity for molecule docking tasks in the game. All three layers of sounds are mixed in the performance and the film. They fade in and out and morph through control voltage modulations. The combination of hardware and software systems during the live performance was utilised for flexibility in sound design and sound spatialisation. The series of sound design ideas associated with each sound were provided for the programmer to utilise in the game. Each sound was sampled and resynthesized in NI Reaktor and then used in a Max/MSP-based game system. This made it easier for the users to understand and interact with the system, as the interaction/gestures had a more obvious effect on the sound and therefore made the interactive data sonification system more intuitive.

Sonicules: Audiovisual Performance

The Sonicules audiovisual performance is inspired and informed by the game. It takes the game's sound design, as well as visual aspects of the data visualisation into an

artistic and aesthetically challenging environment. It showcases, in an abstract way, how sound and visual display of information can work together, aiding one another. It is performed by a duo comprising a visual artist (Jakub Hader) and a sound artist (Radek Rudnicki). The visual artist uses the vvvv programming environment (vvvv group, 2017) for generative visualisations and the sound artist uses a modular synthesiser system, sampler and send effects. Mixing, sequential switching and modulations management create complex shapes and irregular sound patterns.

The performance is based on four molecules that are represented as separate 'movements' of the piece. The visual artist performs molecule docking while the music follows his actions in real time and vice versa, so that the visual performer also follows the sound changing position of the ligand while docking. The interplay between the two artists represents the interaction between machines, software and chemists using the system to dock the molecule. It also places the audience in the position of a spectator as well as mimicking the viewpoint of user-interactive molecule docking software. Furthermore, the audience experiences the molecule in a first-person perspective, since any movement of the ligand is represented on a seven-loudspeaker array with two subwoofers. The immersive soundfield needed for this effect was achieved via custom-made software using an Max/MSP IRCAM Spat package. It was used to pan three stereo mix buses.

1. Dry modular synthesiser signal.
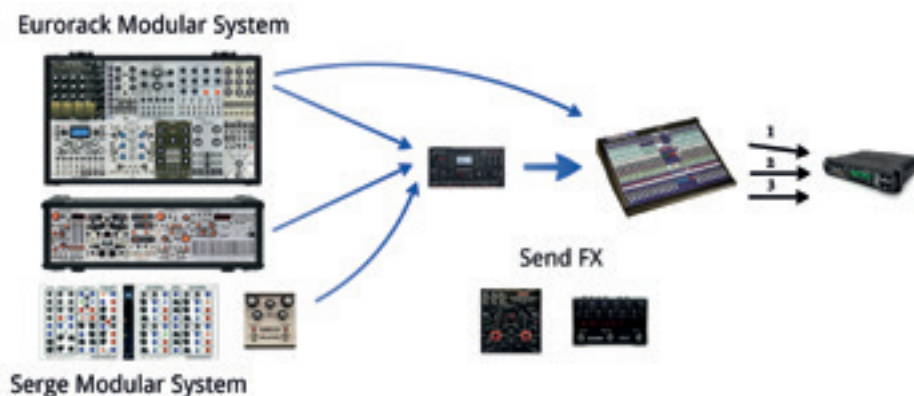2. Sampled and processed modular synthesiser signal.
3. Send effects.

Figure 4: Graph showing the live performance audio setup and signal flow. Reproduced with permission of the Sonicules Project Team.

The molecular visualisation was controlled by the visual artist using a SpaceMouse controller, as used in the game system. What is more, one audio channel, with a stereo effects mix (delay and reverb effects), was linked to the molecule interaction performed by the visual artist. Whenever the image zoomed in visually this effect was enhanced by sending the sound towards the rear speakers in order to give the audience a sense of movement in space. Additionally, visual aspects of the live performance were audio reactive through amplitude and spectral analysis of the master stereo mix which affected the shapes, shaders and graphic textures in the visual content. This audiovisual reactive approach allowed interplay, not only between the performers, but also between the audio and visual systems used and resulted in unified aesthetics for sound and image.

Sonicules: Video Documentary

The video documentary focuses on the sound itself and its use in health sciences and the development of anti-cancer drugs. As a narrative, each member of the research team is interviewed describing their role. They present their views on the impact of using sound in public engagement, health science research, and work in multidisciplinary projects. The film shows this as an example of successful collaboration and combination of arts and science research. It features the views of scientists and artists working together collaboratively and exchanging their knowledge and expertise.

The sound design and music used in the film were generated during rehearsals and preparation for the live performance, as well as in the sound design process for the game. Since the author both filmed and edited the video, as well as designing the sound composition, the creation of the documentary was unified and holistic. There is a synergy between the video and audio material as both were generated from the very start of the project. The sound design uses non-linear generative patches that had been made on the Eurorack synthesizer. These were too complex for use in the game where simplicity and accuracy of aural detail was crucial. In the video these recorded modular patches are edited bringing a focus to specific parts, for example the ambient parts at the beginning and end of the task and the beat-based material used between the spoken parts in the video. There are parts where the video determined what sound material is used; for example when Radek Rudnicki is talking about the collisions, they appear in the background (04:21) and the collision sounds are heard. Similarly, at the film's ending (08:25) the ambient chord sounds are used again to provide a calm resolution to the film. The same source material was used at the end of the game once the docking task

has been successfully completed. On the other hand, at 03:07 the video is paced to the sound in order to make a bigger impact, once louder and more intense sound material is present. This happens right after Andrew Chadwick is talking about the challenge of designing the software and computational effort required in that task.

Figure 5: Sonicules performance at Stockholm Tech Fest 2017 Reproduced with permission of the Sonicules Project Team.

The role of the video was to engage the public online via social media and also to document the project development process. It was successful in that sense as it contributed to the overall promotion of the project resulting in additional live performances outside of the UK e.g. at the Stockholm Tech Fest 2017 in Sweden and in the Copernicus Science Centre, Warsaw, Poland.

Analysis / discussion

The Sonicules project engages audiences of all ages not only with health science and biochemistry research, but also with auditory display, spatial sound and data sonification. It raises awareness of the scientific, engineering and artistic aspects

involved in the project and allows users to interact (via the game), experience (via the performance) and to find out more about drug design (via the film). In that sense, the film plays an educational role. The importance of sound and its impact for public understanding and engagement is showcased in every aspect of the project. Sound is the main subject of the project and is treated differently in each part, bringing the audience a different angle, point of view and method of engagement.

The video is the only linear part of the project containing non-linear material that was used in rehearsals and the sound design process of the game. The performance was semi-structured and improvised, while the game was based on interactive sound design giving the player a hands-on, tactile feel. This multi-modal and diverse way of addressing the audience is an effective means of engagement, especially when used in combination, because it allows the project to target multiple senses and, by multiple media use, can engage with a wider audience. Furthermore, the game and the sonification system (mapping and interaction) as well as live performance (aesthetics) work as proof of concept. These parts of the project show how, in the future, sound can be used in scientific research and be part of actual antidrug design process.

Future Work

The audiovisual performance is still evolving by the nature of the medium. For example, the artists experimented with the size of the physical setup, venue, duration of the piece, different scenarios, the number of loudspeakers and the type of sound system used. Future work will include more extreme dynamics and density of sound material. The simplicity, duration and ease of transportation are crucial factors in the performance's life cycle. Keeping the hardware setup as an entirely modular system makes it easier to transport and will be worth exploring further, not only to experience the logistic, but also the artistic implications. Furthermore, linking the visual artist (who controls the visual parameters) with the sound parameters simultaneously could be explored further in order to bring an element of gameplay to the performance.

Finally, incorporating augmented reality, virtual reality and 3D environments within the project seems to be a natural development and a perfect fit to enhance the immersive surround sound and visual experience in the future.

Since all gameplays were undertaken during public engagement events, conditions of the playing environment were not controlled and varied considerably during the day, so that at some points background noise levels would have been reasonably

high, and as such may have affected a player's ability to attend fully to the interactive auditory display. It will be interesting to assess the learning curve in relation to the Sonicules game performance: further analysis of gameplay data across the staged levels, leading from Level 2 (solution given on simplified molecular structure) to Level 4 (real molecule, no solution given) is planned. Furthermore, systematic testing under controlled experimental conditions will be undertaken in order to better assess the validity of providing spatial sonification in comparison with completing the task with visual display alone.

Conclusion

The sound design used in the project is primarily non-linear, complex and musically informed. Created for three parts of the project including game, performance and video, it engages with audiences of all ages and addresses audiences with different media and environments. Using such diverse methods and engagement outputs, is effective, as it widens the audience and targets diverse interests.

The video not only allows documentation of the project, but also helps with its promotion. It is a key aspect of future development, funding acquisition and generation of additional outputs. It is an effective way of telling the story and showing what the project is about. Furthermore, it allows engagement with the wider public online and via social media, therefore helping to boost the impact of the project.

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