SONIFYING 2D CELLULAR BEHAVIOR USING CELLULAR STETHOSCOPE

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ABSTRACT

This paper presents an approach to sonifying 2D cellular data. Its primary goal is attaining listener comprehension parity between original visual data and its sonified counterpart for the purpose of understanding cell behavior, including movement, mitosis (or division), and cell death. Here, we present the initial findings of the automated sonification prototype named "Cellular Stethoscope" that was assessed through a 19-subject pilot study to assess its ability to accurately reflect the cell behavior captured in the video footage. The resulting system is envisioned to serve as a foundation for a complementing and potentially more efficient approach to studying cell behavior when subjected to various pharmaceutical interventions.

1. INTRODUCTION

Heart disease is the leading cause of death for both men and women, accounting for one in three deaths in people over the age of 35 [1]. This warrants continued research towards improvement of the cardiac function and health. A major limitation to discovering new therapies that can improve heart cell function is the lengthy time for drug discovery, screening, and development.

One approach to studying cardiovascular disease involves studying cell forces. Nain et al. [2] has pioneered technology that allows for the observation of cell movement in a physiologically relevant environment. The observed cells reside on engineered scaffolds of nano fibers that can precisely measure forces exerted by and upon cells based on the deflections of the fibers, known as nanonet force microscopy (NFM).

The cells on the scaffold are exposed to conditions that mimic a heart attack and are then subjected to various forms of chemical treatment. This data is then collected by high-throughput imaging and can be analyzed through a visual interpretation of the microscopic images gathered. This approach, however, remains an extremely time-intensive method to determine efficacy of any treatments. It is extremely difficult to combine all of the visual cues from every cell in view and make rapid decisions on how the population of cells is responding to any treatment. This paper explores a new way of expanding our decision-making efficiency by interrogating our data using auditory patterns and creating a new sonic vocabulary based on the life, movement, and death of cells.

Sonification is traditionally defined as the mapping of non-speech sound to data in order to convey information to a listener [3]. In the context of this work we adopt an expanded definition of sonification to also include any sound (including those that occur naturally) that can be also seen as data points that convey information to a listener [4]. Under such a broad definition, observing ones heart health using a stethoscope, for instance, can be also seen as a form of information extraction through the sound generated by the heart, its valves, and the blood flow. This conscious choice serves as a motivation for this projects name, something that we will revisit further below.

Because humans are sensitive to small changes in the frequency of sounds over time, auditory displays may allow detection of fast-changing data that may be missed in visual displays [5]. In addition, because sound can be perceived even when a listener is not actively focused on a task, auditory perception can be suitable for monitoring applications or situations where visual attention is diverted. An example of this can be seen in the heart rate monitor used in hospitals, which "beeps" to reflect a heartbeat.

Sawe et al. [6] describes four key elements to consider when designing sonification mapping: data fidelity, level of complexity, aesthetics, and accessibility. Data fidelity is described as how closely the sonification represents the original data. This is a major challenge in sonification known as the mapping problem, where the parameters we choose to design a sonification determines how well the sonification is able to communicate information and be interpreted accurately [7]. In regards to complexity, we must consider the size and scale of the datasets, and whether or not we are able to simplify the data while still providing an accurate representation. Aesthetics provided by certain sounds or musical parameters such as pitch, loudness, and tempo can facilitate or detract from cognition of the data. Accessibility considerations include factors such as sighted versus blind listeners, as well as the hardware requirements needed for accurate listener perception.

2. RELATED WORK

2.1. Sonification in Biology

A similar project to sonify cells was done by Edwards et al. [8], which attempted to use sonification to complement a visual analysis of cervical cells for cancer screening. It aimed to provide support to a human cytologist by presenting additional information about the data rather than providing automatic classification of the data. Cell data was obtained through visual microscopic images of cervical cells, and the researchers used multiple approaches to attempt to sonify the data. Methods explored include: color map-

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ping via analyzing the chemical stains of the cells and using frequency modulation that result in darker or densely stained areas giving louder and higher frequencies; using granular synthesis to portray the distribution of chromatin inside a cells nucleus (aka the texture of the cell); rendering the cell distribution into a sound spatialization around the listener and representing abnormal cells with discordant or unpleasant sounds. This project demonstrated the importance of sound selection for certain cell behaviors or attributes and the spatialization of sounds.

Another project by Nattkemper et al. [9] studied cells in a blood sample for the presence of a molecule. It involved producing "artificial words" by mapping data to diphones in order to utilize the listeners presumed highly developed skills for perceiving linguistic sounds. This project observed no significant improvement in using sonification to support cellular analysis as opposed to visualization, outlining a potential for improvement in the method used to sonify cellular data.

Ballweg et al. [10] developed a plugin for an open-source molecular graphics platform, *UCSF Chimera*, to sonify the molecular dynamics of proteins. The sonification design involved parameter mapping of specific elements of the protein molecules that would be filtered when appropriate, to prevent overburdening the user. The design also involved spatialization to place sound sources from corresponding places in a protein into virtual space. The participant study demonstrated that this type of parameter mapping was intuitively understandable for most users to determine specific regions of a protein.

2.2. Spatial Sonification

Hermann et al. [11] evaluated a method of sonifying multichannel image data to allow simultaneous perception of frequency channels and dynamic patterns in the form of auditory scene generation. The project evaluated a different way of displaying a type of data that involves a stack of images, where each image contains different information about the subject. Because a visual analysis of this data would be limited in the amount of color channels, an auditory representation could allow for a larger number of frequency channels.

Zhao et al. [12] developed an interface that provided auditory feedback for users to determine the geographical data patterns of a given region. Users would use an input device such as a keyboard or a tablet to navigate through the regions of a map, where the system would provide auditory feedback to describe that region. However, there was difficulty in sonifying elevation using spatial sound and providing extra sound encoding to easily distinguish a region's elevation interfered with the perception of the sonification as a whole.

2.3. Assessing Human Pattern-Recognition Capabilities

One project conducted by Boschi et al. [13]involved assessing the capabilities for auditory analysis of seismogram data . In this project, participants listened to sonified seismograms and were instructed to group together sounds that were perceived to be similar. This project concluded that human auditory processing allows recognition of certain auditory clues with the ability to categorize these clues into relevant groups.

3. PROBLEM DEFINITION

The developments in observing cell movement using the aforesaid microscopic mesh have opened new opportunities for visually monitoring the cell health. For instance, cells that move slower tend to be less healthy, or, may be in the process of mitosis or splitting into two. As a result, the growing body of pharmaceutical research, particularly that pertaining to heart health, is bound to produce large amounts of visual data that will need to be analyzed and presented in an efficient manner to the researcher in order to identify potential candidates that show desired behavior, whether that be intentionally slowing the cells down, or ensuring their ongoing health. Given that under these circumstances the computer vision analysis alone may not be sufficient to disambiguate slow movement due to impending cell death or mitosis, analyzing such data in near-real-time appears to be inefficient. For this reason, the central question to this project is how can the resulting data be presented more efficiently to a researcher or a clinician without sacrificing necessary detail or accuracy? As a first step towards answering this question, this project presents the sonification of data with the goal of achieving accuracy parity when compared to the visual data. Note that this first step is not meant to address the efficiency, as the parity is seen as a precursor necessary for validating the proposed alternative approach. Once validated, given the high resolution potential of the human hearing, such a sonification may be compressed in time until it becomes a form of earcon. If successful, such navigation may prove instrumental in helping researchers efficiently navigate large amounts of generated data. Inspired by the use of the stethoscope to monitor heart and lung health, Bukvic, the designer of the ensuing sonification instrument named it the Cellular Stethoscope.

Cellular Stethoscope

Because of the ultimate goal of compressing the duration of the sonification, the Cellular Stethoscope was conceived to sonify data with minimal interpretation, and by doing so maximize the possibility of a listener intuitively uncovering patterns. This approach was complemented with one critical data interpretation–the cell death. Below we discuss its iterative implementation in greater detail and highlight notable developments.

The Cellular Stethoscope prototype is built using MaxMSP [14] and the CV.jit [15] library. 2D videos of cells with specially colored nuclei offered a high contrast footage (Figure 1) ideal for visual analysis using the computer vision blob tracking algorithm. Using the cv.jit librarys cv.jit.blobs.centroids object, the cell movement is converted into a series of data points, consisting of blob id, position, and the blob area.

The experimentation with the nucleus area and its calculated radius revealed that the blob area did not yield any new and useful information beyond that of positional data and was therefore left unused in the final implementation. cv.jit.label is used to ensure consistent numerical id assignment to each blob because the underlying sonification system leveraged the delta motion to identify important anticipated cell conditions and behaviors. The resulting data is fed to a poly˜-enabled synthesizer consisting of a marimba sample whose pitch is scaled based on the cells Y position (higher its location, higher the pitch).The panning of the sound reflects cells X position (e.g. the closer the cell to the left edge of the video, the more the sound is panned towards the left). Panning is the most

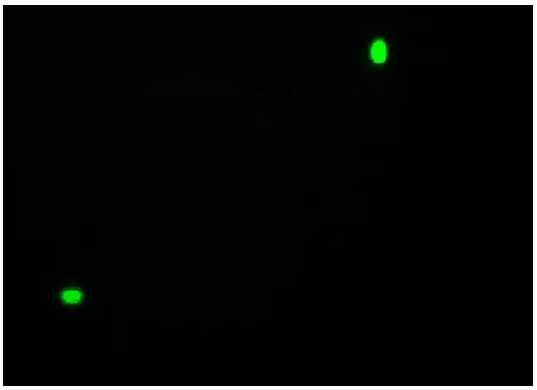


Figure 1: High contrast footage of two cells.

logical way to physically map a location horizontally. While the elevation could have been also rendered using elevation filtering using a binaural system, its subtlety would minimize the listeners ability to discern subtle spacing of cells close to each other, whereas the pitch enabled even sub-pixel differentiation among the cells vertical position. The pitch in this case could be also said to amplify the subtle pinna-induced signal filtering inherent to sound sources that emanate from higher elevation. It may be worth noting that"higher pitch is in part a cultural observation. Yet, it is also grounded in the science (higher pitches do have higher frequencies, or numbers of periods per second) and as such was seen as a reasonable mapping. Nonetheless, as is the case with most if not all abstract forms of sonification, a critical element to the sonifications successful conveyance of data is in good part rooted in the listener training.

The intentionally short duration of the marimba note was a conscious choice that allowed for a periodic repetition which would speed up and slow down based on the observed blobs movement delta. This allowed for multiple blobs to be heard and differentiated from each other, thus preventing potential fusion due to a synchronized onset. In addition, the delta observed through the repetition rate enabled listeners to observe both subtle and profound changes in the cell's movement. The choice of a marimba sound was based on the experimentation with a series of sounds, and was arrived at because of its natural and more pleasing nature that was seen as minimizing the potential listener fatigue. It further offers a naturally quick decay that enabled a broader perceivable range of rate repetition. The repetition was driven by a sawtooth wave to ensure appropriate rate scaling in between note onsets, something that non-signal Max objects, such as metro, are unable to accommodate. The end result offers a more natural and organic rate scaling and, more importantly, allows for capturing rapid changes in cell movement (e.g. a sudden spike due to mitosis), something that was easily lost using a metro-based approach. Lastly, in order to allow for capturing of the cell death, a singular and critical occurrence of interest, the system uses the sound of a cardiac monitor flatlining. In order to help pinpoint the cell in question, the flatline sound matches the pitch and panning of the associated marimba note. Initially, the cell mitosis (division) was ignored as a distinctive state with the assumption that the existing parameters would be able to provide enough information for listeners to be able to detect and interpret it.

Curiously, because of the similarity in the cell behavior pending its death and mitosis, the special treatment of the cell death also serendipitously offered a useful way to identify and differentiate both conditions. Whether a cell is about to die or divide into two (mitosis), in both cases it first stops moving. However, in the case of mitosis, the two resulting cells tend to rapidly distance from each other. As a result, the similar onset of a slowly fading-in flatline sound can serve as both a dramatic closure denoting a cell death, or as building of tension before the two resulting cells split and move apart, both resulting in a satisfying, almost musical gesture. Apart from the fading-in flatlining sounds arbitrary duration, the sonification engine was left by and large untouched, directly responding to the incoming data. When observing the ensuing system consisting of the raw data sonification and one special condition (cell death), the ability to also detect cell division as a distinct and easily identifiable event can be also viewed as an example of uncovering a new pattern through listening.

Although the prototype presented in the user study below offered accurate and aurally satisfying rendition of the visual data, its focus was limited to a dozen videos. As a result, its gestural utilization of the flatlining sound to reflect both mitosis and cell death, may benefit from further refinement, particularly to prevent misinterpretation of a prolonged cell mitosis as a death. We will discuss this and other observations in the discussion section below.

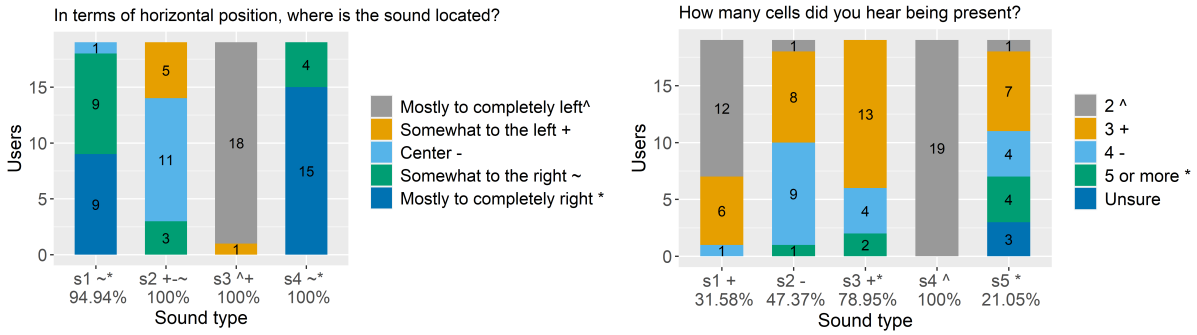
4. EXPERIMENTAL APPROACH

4.1. Study Hypothesis

Following the implementation of the Cellular Stethoscope, the research team sought to validate its implementation. The null hypothesis (H_0) that framed the initial study states that users observing cellular behavior using the Cellular Stethoscope will not be able to differentiate location, speed of motion, and two notable cell behaviors–death and mitosis. The alternative hypothesis (H_α) states that users observing cellular behavior using the Cellular Stethoscope will be able to differentiate location, speed of motion, and two notable cell behaviorsdeath and mitosis. If successful in conveying the said information, the Cellular Stethoscope will serve as a comparable surrogate to its visual counterpart and will be ready for the next stage of research exploring temporal compression.

4.2. Participant Demographics

Nineteen users, eight female, seven male, and four non-binary, participated in the study, with a mean age of 21 and a standard deviation of 2.32 years. Eleven of them had prior knowledge of music, and played an instrument. Five of them were music enthusiasts and had experienced musical performances before. Three of them sometimes listened to music. None of them had a physical disability that could affect their ability to identify the locus of a sound source. Only seven participants had consciously studied spatial sound before (for example, through an immersive VR experience where the spatial sound is particularly important, or through a spatial audio performance in a performance venue with multiple loudspeakers). Users were recommended to use earbuds or on-ear headphones and were explicitly told not to wear bone conduction headphones. The brand and model of headphones were recorded. All of the users were made aware that they could stop the test at any time if they felt uncomfortable for any reason, and the initial training provided listeners with the dynamic range of sounds utilized in the study.



(a) (b)

Figure 2: User responses based on the performance of the study tasks in (a): Hearing Test Horizontal Position, and (b): Number of Cells Present. The text overlaid on each color bar indicates the number of users who gave that particular response. The x-axis labels indicate the accurate answers and accuracy rates in percentages.

4.3. Study Design

In order to assess the aforesaid hypothesis, we have presented the following study design, approved by the Institutional Review Board (IRB). The entire experiment was transplanted onto an online survey format to maximize potential participation. This has proved particularly useful due to the unforeseen COVID-19 pandemic that affected the tail end of the study.

Before beginning the experiment, participants were asked to provide demographic information of age and gender. Next, they were asked to provide their prior experience with music; the options available were: "I have knowledge of music and play an instrument", "I am a music enthusiast and have experienced musical performances before", and "I sometimes listen to music". This information was used to determine if there would be any correlations between participants' music affinity/training and their comprehension of the sonified data. Participants were also asked whether or not they have consciously studied spatial sound before, with the option "yes" or "no", to determine any correlations between participants' experience studying spatial sound and their comprehension of the sonified data.

To qualify for the participation in the study, participants were asked to report whether or not they have a disability that could affect their ability to identify the locus of a sound source. They were also asked to use headphones and report the kind they used for the study. Participants were then asked to report how they were feeling (excellent, good, fair, or poor), to collect data on potential fatigue with using the system. They were also asked to confirm that they could stop the test at any point during the study if they felt uncomfortable for any reason.

Next participants observed a tutorial video demonstrating tone in the left and right speaker, respectively, to ensure that participants have their headphones placed over the correct ear. Participants were also given the opportunity to adjust the volume for comfort.

To fully ensure that study participants did not have any major impairments that would prevent them from participating in the study, the study started with a simple hearing test using a pre-rendered video of a frequency sweep coupled with a series of color changes that asked listeners to report at what color they lost their ability to hear the sound. It was followed by a series of stereo sounds that varied amplitude ratio between the two headphones to compare hearing parity between the two ears. Participants would report the horizontal position of four different sounds with the options of: 'mostly to completely left,' 'somewhat to the left,' 'center,' 'somewhat to the right,' or 'mostly to completely right. The collected user responses for the horizontal spatial sound test are shown in Figure 2 (a).

At this point we excluded any participant who had a severe vision, hearing, or physical impairment that may preclude them from experiencing video and spatial headphone-based audio and interacting with the computer keyboard and mouse to enter their responses under normal conditions. Participants were also disqualified from continuing if they failed to hear sound below a frequency threshold of 12kHz, indicated in the frequency sweep portion of the hearing test. In addition, if a participant's results were inaccurate during the horizontal sound test, for example, reporting a sound was located at the center rather than the left, they were disqualified due to imprecise hardware or other potential hearing impairments. This selective approach was critical given the study was administered remotely and asynchronously, with participants engaging at their own convenience.

Qualifying participants were then presented with a series of training videos demonstrating cell behavior with matching sonifications generated using the Cellular Stethoscope. The first was a moving cell reflecting the change in tempo corresponding to the increase in the cell's speed. Also, demonstrated were the horizontal positions of cells represented in the left and right speaker and the vertical position of the cell represented by pitch, a flatline sound corresponding with cell death, and the doubling of sound with cell division.

The next stage of the experiment involved a series of five different audio representations of cell behavior. For each scenario, participants were asked to answer a series of questions about the cell behavior regarding

- cell population size,
- relative horizontal position,
- relative vertical position,
- number of cell deaths, and
- number of cell divisions.

Each video (a.k.a. scenario) in the series contained a unique combination of cell behaviors and characteristics to best capture participants' comprehension of the data.

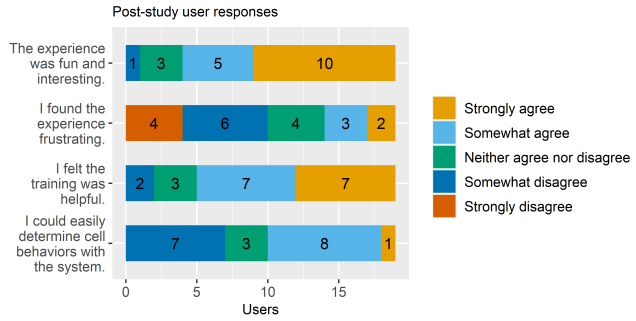


Figure 3: User responses based on the impressions of using the system. The text overlaid on each color bar indicates the number of users who gave that particular response.

- The first sound, *Sound 1*, served as an introduction to the video series, containing three cells that move without dividing or dying.
- *Sound 2* was the only sound containing a cell death.
- *Sound 3* was the only sound containing cell division.
- *Sound 4* only contained two cells, and
- *Sound 5* contained six cells.

The final stage of the experiment involved ten different audio representations of cell behavior where the subject was asked to match each sound to one of four different simultaneously displayed videos. The subject was also given the option to select "None of the above" if a sound did not correlate with any videos.

At the end of the experiment was a post-test questionnaire, where participants indicated whether or not they felt they were easily able to determine cell behaviors, if they found the training helpful, if the experience was satisfying, and how they were feeling in contrast to before they began the experiment. All questions were provided possible responses on a Likert scale from 1 to 5, from Strongly disagree to Strongly agree. The results from this questionnaire are shown in Figure 3. Lastly, participants were given an optional free-response entry where they could explain what portion(s) of the experiment was the most challenging for them, as well as provide any additional feedback.

5. RESULTS & DISCUSSION

Table 1 shows the average accuracy rate based on various factors such as number of cells present, horizontal localization, vertical localization, cell division and cell death. We discuss these results in detail and provide a discussion in following subsections.

5.1. Learning effect

The results from the audio-only portion of this study (Figure 4) suggest that accuracy in determining cell behavior improves with the system familiarity. The structure of the experiment encourages participants to proceed through each portion in a linear fashion, and, as a result, the observed average partcipant accuracy has showed steady linear increase. However, this trend is also interrupted in scenarios that involve cell division or a high cell count, both of which will be further discussed in section 5.3 below.

Table 1: Average accuracy per question.

Q.	Variable of Interest	Accuracy Rate
1	Number of cells present	55.79%
2	Horizontal location	69.47 %
3	Vertical location	27.37 %
4	Presence of cell death (yes/no/unsure)	93.68 %
5	Number of cell deaths	92.63 %
6	Presence of cell division (yes/no/unsure)	37.89 %
7	Number of cell divisions	35.79 %

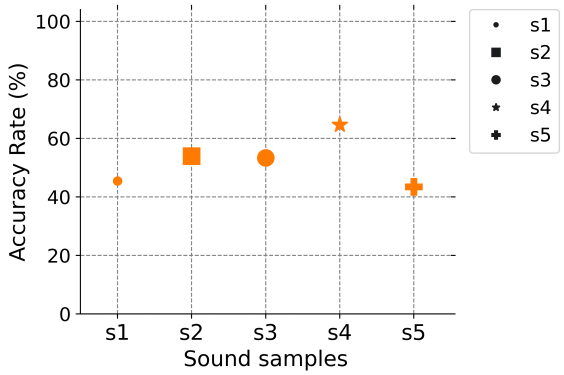


Figure 4: Average accuracy rates for "Recognition Based on Sound Alone".

Accuracy levels appear to increase with each sound in determining the horizontal position of the cells, as seen in Figure 4, which further suggests that familiarity with the system increases accuracy in determining cell behavior.

5.2. Vertical and horizontal localization

Determining the vertical position of the cells was the most difficult task for participants, with the lowest overall accuracy rate of all the questions. This is reflected in the Table 1 and Figure 5. It could be hypothesized that because the training video series did not clearly indicate the highest and lowest possible pitch for a cell's vertical position, each participant could have had a different perception of which pitches represented "top" and which represented "bottom" of any given sound sample. This difficulty of representing vertical position with spatial sound was also discussed by Zhao et al. [12], where using spatial sound is more effective at providing resolution for horizontal location than vertical location. Perhaps, this confusion could have been mitigated in the training portion by explicitly outlining the range of possible pitches when demonstrating the sonification of a cell's vertical position.

5.3. Cell division

Participants seemed to have the most difficulty determining by listening whether there was a cell division (Figure 10), especially for scenarios involving a high cell count. *Scenario 3* begins with three cells and ends with five cells and is the only scenario in the audio-only portion of the test that contains cell division. This scenario has the lowest accuracy for the questions: "Did any cells divide?" (Figure 6) and "How many cells divided?" (Figure 7). The low

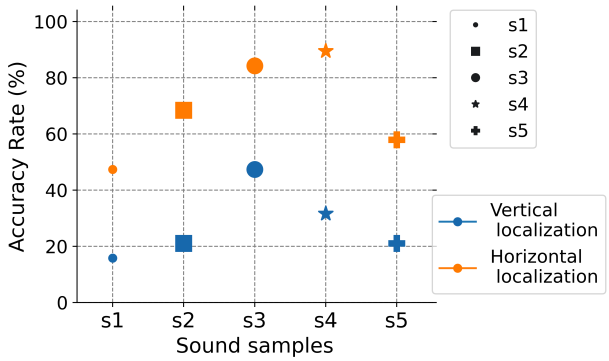


Figure 5: Comparison between the horizontal and vertical sound localization accuracy rates for five different sound samples used in the study.

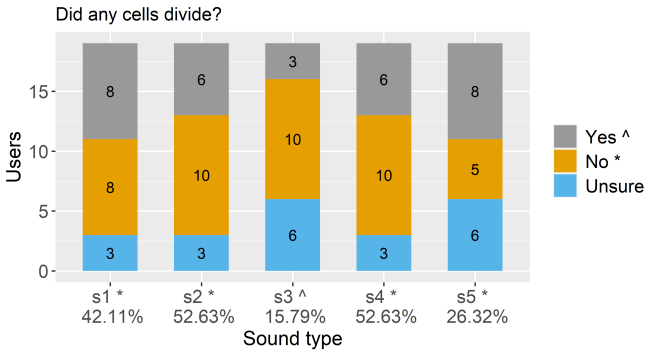


Figure 6: Accuracy rates of user responses for the question "Did any cells divide?". The x-axis label markers indicate the accurate answers and the accuracy rates are shown in percentages.

accuracy rate for determining cell division also correlates with the qualitative feedback received from the participants; nine participants stated that determining cell division was the most difficult task in this study. This may suggest that additional training may be necessary to master the subtleties of the sonification engine. *Scenario 5* contains a total of six cells and also has low accuracy for the cell division questions, suggesting that the overlapping sounds of an abundance of cells could be misinterpreted as cell division. It may also suggest that the lowest rate of the repetition may be to sparse and may lead to listener confusion, thus requiring some form of sustained sound to link otherwise sparse onsets of sound.

5.4. Cell death

Determining cell death seemed the easiest task for participants, as indicated by the two associated questions: "Did any cells die? (Figure 8)" and "How many cells died? (Figure 9)" containing the highest accuracy rate. This may be because the "flatline sound associated with a cells death is very prominent in contrast to the marimba sound of cell movement. However, three participants indicated in the feedback portion of the study that this sound was perhaps too loud and jarring, which could lead to fatigue with prolonged exposure. A future improvement may be to reduce the

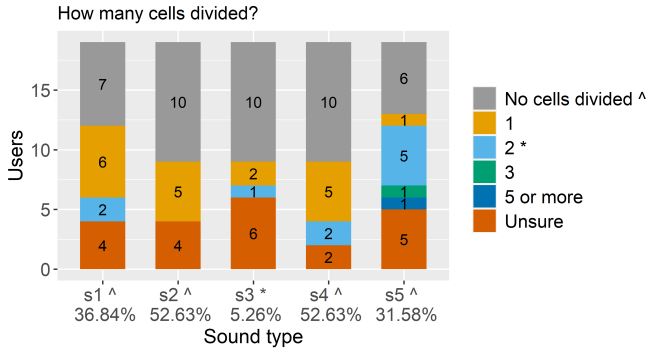


Figure 7: Accuracy rates of user responses for the question "How many cells divided?". The x-axis label markers indicate the accurate answers and the accuracy rates are shown in percentages.

loudness of this sound, so that it may blend better with the rest of the texture.

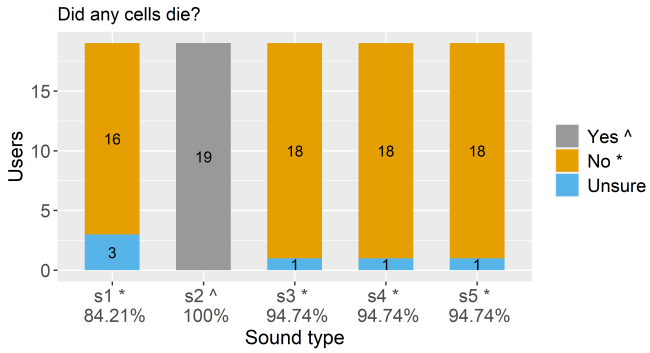


Figure 8: Accuracy rates of user responses for the question, "Did any cells die?". The x-axis label markers indicate the accurate answers and the accuracy rates are shown in percentages.

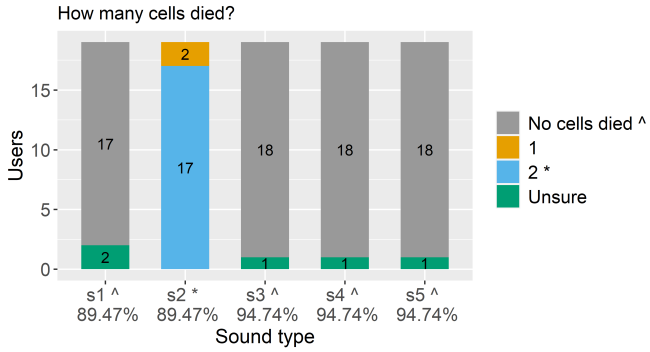


Figure 9: Accuracy rates of user responses for the question, "How many cells died?". The x-axis label markers indicate the accurate answers and the accuracy rates are shown in percentages.

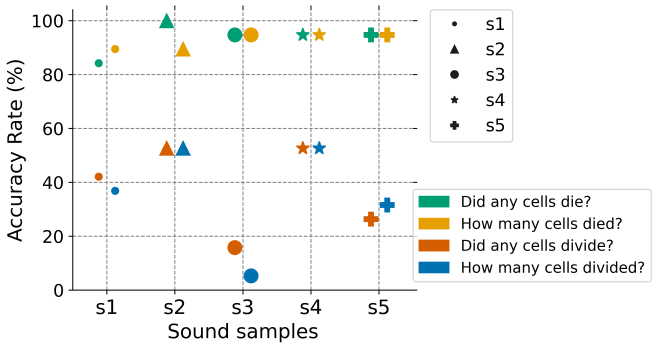


Figure 10: Accuracy rates of user responses based on cell division and cell death, for five different sound samples used in the study.

5.5. Musicality

Prior experience with music had no significant effects on the results, as shown in Figure 11. This may indicate that the system does not require musical skill or experience in order to determine cell behavior. This is promising, as this system is designed to be comprehensible for users regardless of their musical afinity or training.

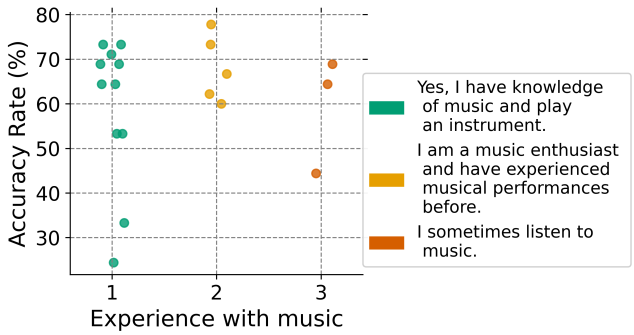


Figure 11: Effect of prior experience with music on accuracy rates.

Spatial sound experience had an effect on the results as shown in Figure 12. Those who indicated experience with consciously studying spatial sound had lower average accuracy than those who had not. Further research and a statistically higher pool of potential participants is needed to determine the reason for this effect.

6. CONCLUSION & FUTURE WORK

This study explored the usefulness of two-dimensional sonification using the Cellular Stethoscope as an alternative method to accurately and efficiently determine cell behavior by surveying participants with a varying range of experience in music and their ability to comprehend the system. The results show that participants are able to determine cell behavior, making this a potentially viable option given more enhancements to the system. However, comprehension of the system dropped with more complex sounds, such as those with a higher cell count or with cell division. A future goal

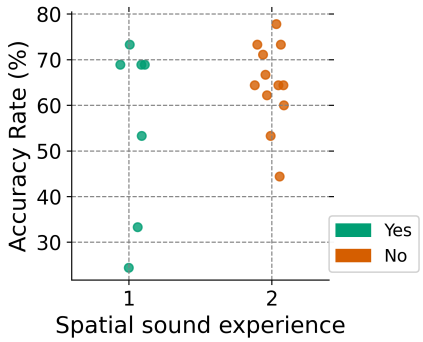


Figure 12: Effect of prior experience with consciously studying spatial sound on accuracy rates.

for improving the system will be to modify this sonification to enable better clarity of the data.

Once the aspirational parity is achieved, the immediate future goal of this research is to explore temporal compression of a large dataset of cell behavior into an earcon-like sub-second sound and once again reassess listener's ability to identify scenarios of interest that reflect a desired cell behavior. Such an implementation would then serve as a foundation for a system for medical researchers to quickly determine the effects of various treatments instead of the more labor-intensive visual analysis.

7. ACKNOWLEDGMENTS

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