2024 Sonification Awards — Analysis Category

Sonification Project:

Hydrogen bonding heterogeneity correlates with protein folding transition state passage time as revealed by data sonification

Supporting documentation:

Supporting Information

Please see below for a detailed discussion of how this work addresses each of the criteria outlined on sonificationawards.org

Part 1: An outstanding sonification in the analysis category must meet ALL of the following six criteria.

1. It must convey useful information to its intended user.

In the context of sonifications that are intended to increase knowledge about specific data in a specific, applied context, where listeners (the end users of the sonification) need to understand the data to perform specific tasks, the information conveyed by the sonification must prioritise the needs of the intended users and provide appropriate insights on the data it represents.

Our multidisciplinary research group included individuals trained in biophysics, biochemistry, software engineering, digital signal processing, sound design, music composition, music performance, quantitative biology, and chemistry: (Carla Scaletti , Premila P. Samuel Russell , Kurt J. Hebel , Meredith M. Rickard, Mayank Boob , Franz Danksagmüller , Stephen A. Taylor , Taras V. Pogorelov , Martin Gruebele)

The intention for this sonification work was *scientific discovery*: we wanted to increase our knowledge about the impact of hydrogen bond dynamics on various protein-folding pathways. The sonification was designed to prioritize the needs of the intended users (biophysicists, chemists, and molecular biologists) and to provide them with insights into their (multiple) data sets.

We used data sonification to listen to and analyze time series obtained from long, all-atom simulations in which a small protein folds and unfolds many times to examine, in atomistic detail, the role played by hydrogen bonds to water and within the protein during the "transition state passage" — the moment when a protein switches between folded and unfolded states.

The sonification tools conveyed information that allowed us to identify three transition categories: Highway (faster), Meander (slower), and Ambiguous (intermediate) and enabled us to analyze hydrogen bond dynamics before, during, and after these transition events. Data sonification provided the researchers with insights into the characteristic hydrogen bonding patterns that distinguish “Highway” versus “Meander” versus “Ambiguous” transitions and served as the basis for algorithms that could identify these same folding pathways and critical protein–water interactions directly from the data.

2. It is easy to understand by its intended audience.

An excellent sonification for data analysis will provide a solution that does not add cognitive load for the intended users: for instance, it minimises the need for specialised sound or music related training or it optimises existing data representation tools already familiar to the intended users.

Irrespective of their diverse backgrounds and training (represented by our multidisciplinary co-authors who ranged from quantitative biologists with no music background to professional musicians without science backgrounds), our intended users quickly learned to use the sonification tools, which require no specialized or music-related training.

Extracting meaning from any data sonification requires concentration and focused analytical listening, and our group members, all of whom were immediately able to identify patterns in the sound mappings, became increasingly adept at this kind of listening over the course of the project. As a result of our weekly meetings (which always included listening to a new sound-mapping), everyone in the group became increasingly interested in sound design, sound perception, and “aural skills”, as *well* as biophysics.

Once the paper had been submitted for consideration by PNAS, the intended audience expanded to include the editorial board and scientific peer reviewers whose comments included:

> “The idea of using sounds to code properties found in the highly complex MD trajectories of folding and [to] exploit our innate ability to Fourier-transform extremely complex sound waves to identify speech patterns is highly innovative, as well as intriguing.”

The published paper has been read by over 1600 people (as of December 2024), suggesting that the multidisciplinary audience of PNAS readers finds the sonification easy to understand, especially when it is presented in the context of the full text, figures, tables, supplemental information, and visualizations. The attention score for the article is, according to Altmetric, in the top 97th percentile compared to other papers of the same age.

3. Its data-to-sound mapping strategy is grounded in relevant scientific research.

In an excellent sonification for analysis project, the authors must be able to make the explicit criteria they used to design the data-to-sound mapping strategy. Such criteria should be grounded in relevant scientific research for instance (but are not limited to) cognition & attention studies, psychoacoustics, ergonomics & affect studies, auditory perception studies, context-analysis studies.

Hydrogen bonding dynamics during protein folding is a time-dependent and massively parallel process, making it a suitable candidate for sound mapping.

Our challenge was this: Design a mapping that enables the listener to monitor time-dependent changes and cooperative patterns among multiple hydrogen bonds identified both by their position along the small protein and the type of bond (e.g., Backbone Nitrogen to Protein sidechain, and so on). Our data sets tracked 16 residues (amino acids) positioned along the protein and 21 bond types for each of those positions (for a total of 336 event types).

To assist in auditory stream segregation (enabling a listener to identify onset times and to distinguish among bond positions and bond types), we made use of several capabilities of the human auditory system:

- The tonotopic organization (maintained along the full length of the auditory pathway, from position on the basilar membrane in the cochlea, to the brainstem to the auditory cortex) and spectral-analysis capabilities of the human auditory system

- Pitch (log frequency) discrimination: Each of the residues was associated with a unique pitch and the pitches were separated by at least one half-step (about ten times larger than the just noticeable difference JND in pitch which is roughly 0.05 to 0.1 half-steps)

- Binaural localization based on Interaural Intensity Differences (IIDs) using equal-power pan functions: The stereo position of each sound source is proportional to the position of its corresponding residue along the chain

- Temporal integration over short time spans (for “density” tracking over time)

By basing the variable-to-sound-parameter mappings on innate capabilities of the auditory system, our intention was to make them easily learned and quickly understood by any listener, irrespective of musical training or cultural background.

4. It follows an explicit design methodology.

Authors of excellent sonifications for analysis are expected to explicitly describe the methodology they followed for the design of the sonification, regardless of the chosen approach. For instance (but not limited to), they might have followed a design-driven approach that relies on design thinking methodologies, or a scientific approach that applies scientific methods borrowed from hard sciences, or methods used in HCI studies.

In the Supporting Information, we describe the design, data analysis and methodology for this research, including a detailed description of the sound-mappings.

Here, we provide additional details on the design-driven approach applied specifically to the sonification. Design-thinking methodologies have been described in numerous papers and can be summarized as: Empathize, Define, Ideate, Prototype, and Test.

We assembled a *multidisciplinary* team (the stakeholders), representing artistic, scientific, and engineering backgrounds, to benefit from their multiple perspectives and complementary knowledge. We met regularly, once a week over the course of 4 years, to brainstorm about the problem(s) and to listen, interpret, discuss, and refine a new sonification and visualization approach each week.

Early in the process, while the team members were familiarizing themselves with each other's "culture" and coming up to speed on the problem domain, various members presented seminars on their areas of specialization; this was also a period of exposure to new software tools and domain-specific approaches to data. For example, the culture of collaboration is more extensively practiced in scientific communities than in artistic fields (which tend to idealize the "sole auteur" or "lone genius" mythology), so the musicians learned more from the scientists than mere facts or techniques surrounding protein folding; they also learned to participate in a culture where collaboration is expected, essential and respected. The scientists, in turn, were often pleasantly surprised by the insights provided by the unexpected juxtapositions and creative imagination of the musicians.

During the early stages of our collaboration, we prototyped, tested and refined several sonifications that proved useful to our stakeholders as tools for explaining protein-folding pathways to their undergraduate students in biophysics at the University of Illinois. (We published a summary of this work in the ACS Journal for Chemical Education as *Sonification-enhanced Lattice Model Animations for Teaching the Protein folding Reaction*). The development, testing, brainstorming, and iterative refinement of a new data sonification approach, as well the process of collaboratively writing and submitting a paper to a peer-reviewed journal served as a rehearsal for the scientific collaboration that followed.

We then turned our full attention to the research problem — a target that evolved, based on our discussions to focus on the role of hydrogen bonding and its impact on the speed of state transitions. We generated multiple datasets, each week testing new sound mappings and visualizations, listening to them during group meetings and iteratively refining both the datasets *and* the mappings. In other words, the number of sonifications that we have *not* presented here (but which contributed to the discussion, refinement, and design process) far exceeds the number that are presented in the paper. At all times the primary design criterion was that the sonification tool should serve the stakeholders (in this case, biophysics researchers) by revealing patterns in the data generated by their molecular dynamics simulations.

The final stage of testing and subsequent translation to an automatic algorithm is described in the Supporting Information (page 40). The final stage of the design process was to verify, through introspection, by translating the human summary process to an algorithm that produced repeatable results consistent with our listening tests. The sonification design had successfully pointed to a pattern in the data that had not been detected when we looked at the visualization. It then served as a model or a template for how to automate the process (a task we never would have undertaken if we had not first had our attention drawn to its utility by the sonification).

5. It is successful (i.e., efficient and effective) in supporting the intended users in achieving their goals.

Evidence that the sonification supports users in achieving their intended goal (e.g., solving a specific problem, completing a specific task, improving specific conditions, and so on) must be provided. There are no limitations to the methods used to measure the success of the sonification solution (i.e., using qualitative or quantitative evaluation methods) provided that the evaluation was conducted following scientific standards.

The sonification successfully led the researchers to discover several new results: the researchers identified three pathways to protein folding based on hearing the temporal patterns of hydrogen bond formation; a report on these results successfully passed peer review; and they succeeded in getting it published in the *Proceedings of the National Academy of Sciences* (a journal whose overall acceptance rate is only 17%).

In the judgement of the anonymous peer reviewers:

"Gruebele and coworkers investigate an important question in protein folding dynamics, i.e., the role of water-protein hydrogen-bonding (H-bonding) interactions in the transition through a kinetic bottleneck (or transition state) of folding. Their results revealed that such H-bonds can play different roles, manifesting a heterogenous scenario. Overall, this is an important piece of work with significant findings."

"In summary, the approach is innovative, the analysis is intriguing, and the results are interesting as they help connect the dots from prior work"

"This manuscript by Scaletti et al. analyzes hydrogen bond dynamics in molecular dynamics simulations of protein folding-unfolding with the aim of identifying the possible roles of hydrogen bond formation-dissolution in defining the transition paths for folding and unfolding and hence the mechanisms … One could in fact argue that it is impossible to understand the molecular mechanisms behind the large conformational transitions that lead to (un)folding without having a clear description of what is going on at the level of backbone (de)solvation and hydrogen bond formation. Therefore, the aim of this work is a very important one, and one that remains unresolved and virtually untapped."

6. It must pay attention to the quality and appropriateness of the sonic experience.

An excellent sonification for analysis has to take into account 1) the quality of the sonic experience of its intended users: the sounds used in the sonification must be of the highest standard in terms of how they were produced (recorded, or synthesised) and must not, at the very minimum, be unpleasant to listen to (unless this is an intended characteristic of the sonic experience) and 2) that the authors must be able to explain how the sound design choices were done i.e., why the chosen sound material is appropriate to the context of usage. For instance, it does not increase cognitive load, it does not collide with existing sound events, and so on.

This sonification's unique soundscape does not collide with naturally occurring ambient sounds. It is not unpleasant. It *does* require the full attention of the listener.

Sounds were generated at 48 kHz sampling rate, using 32 and 64-bit internal calculations and synthesis algorithms carefully structured to avoid undesirable characteristics such as clipping, aliasing, and other sources of distortion.

The Kyma sound design environment that was used for this work is also the choice of professional sound designers who use the system to craft sound effects for major motion pictures (e.g. WALL-E).

Part 2: An outstanding sonification in the analysis category must meet at least ONE of the following criteria.

- It is reproducible by other researchers.

By following the steps outlined in the Supporting Information, other researchers can reproduce the results. On pages 38-40, under the heading **Sonification of hydrogen bond dynamics** and (sub-headings *Polyphonic Geiger Counter* and *Piano Roll*), readers can find a detailed outline of the mapping from hydrogen bond characteristic to sound parameter (including stereo position, fundamental in pitch space, and harmonic of that fundamental). Here is a compressed file containing the code and datasets used for the Polyphonic Geiger Counter and Piano Roll.

- The work achieves something that could only be achieved in sound, and could not be achieved in other sensory media (i.e., through visuals alone).

While it is not *impossible* to perceive the massively parallel, time-dependent patterns of hydrogen bond formation visually, these dynamic patterns are easily perceivable and immediately obvious when the data are presented as sound. The contrast between silent visualization of the hydrogen bonding versus the data-sonification of that same data is evident in Movie S1 of the paper (https://www.youtube.com/watch?v=Yyk5ULs1S24) where the red spheres in the center of the panel represent the positions of hydrogen bonds as they form and break while the protein is folding or unfolding.

Our conclusion was that data sonification is a tool for pattern discovery that should be part of any researcher's tool set — not as a *replacement* for visualization and standard data analysis, but as an enhancement to existing tools.

In this case, listening to patterns resulting from solvation and H-bonding with many water molecules was easier than looking at animations with so many H-bonding partners. We heard something that we hadn't seen when we used conventional visualization (most notably the changing H-bond soundscape). Once we heard that changing soundscape, we pursued that avenue, using more conventional analysis and visualization to confirm what we had heard.

In other words, one should use any and all means available for exploring, explaining, and discovering patterns in experimental or simulation data — the more ways of studying the phenomenon, the better.

- In data analysis and exploration, the needs of the users might change over time. An excellent sonification for analysis is designed as an interactive solution so that users can autonomously explore data through sound according to their specific needs.

Our sonification tools were designed to provide each researcher with the agency to explore the data interactively and with multiple data filters that can be adjusted in real time while listening. We provide a demonstration of how one might interact with the panel in Movie S2 (https://www.youtube.com/watch?v=ozspnQB0SVc) of the paper.

During our weekly research meetings, we were able to explore with even greater flexibility, applying the power of the Smalltalk programming language and the data analysis and matrix manipulation tools in Kyma.

- It is accessible to users regardless of their cultural background i.e., it does not require knowledge that is related to specific auditory or musical cultures, for instance Western or Oriental music, modal or serial music, and so on.

This sonification can be characterized as a “soundscape” or a “sound texture” and it is accessible to any listener; it does not rely on formal musical training and is not specific to a particular musical culture.

- It is accessible to blind or visually impaired users.

While extracting information from the sonification itself is accessible to BVI listeners, interacting with the graphic user interface is likely to require the assistance of a sighted research partner.

Resumés of the corresponding authors:

- A resume of the author(s) which include name, affiliation (if applicable), and academic background / relevant experience.

Carla Scaletti collaborates with scientific partners to interpret, analyze, reason about, and communicate aspects of their data by mapping those data to sound. Co-founder of Symbolic Sound Corporation, she is the creator of the Kyma sound design language, widely used in films, games, music, and scientific data sonification. In addition to her software development work, Scaletti also composes and performs experimental electronic music for live performance, contemporary dance, and virtual reality.

She has a doctorate in Music Composition (with a minor in Psychoacoustics) as well as a Master of Computer Science degree from the University of Illinois at Urbana-Champaign, where her CS adviser Ralph Johnson was one of the "Gang of Four" who revolutionized software development with his book on design patterns for object-oriented programming. She also holds a Master of Music composition from Texas Tech University (where she received a Distinguished Alumna Award for contributions to the field of music) and a Bachelor of Music composition (magna cum laude) from the University of New Mexico.

Scaletti's collaboration with Alan Craig at the National Center for Supercomputing Applications (NCSA) resulted in the 1991 publication, Using Sound to Extract Meaning from Complex Data whose accompanying video of scientific visualizations with data-driven sound tracks was awarded the 1991 NICOGRAPH Multimedia prize and led to an invitation to participate in the inaugural International Conference on Auditory Displays (ICAD) at the Santa Fe Institute. She is the author of numerous tutorials, talks, book chapters, articles, and papers on data sonification and has served in an advisory role on data sonification for the United Nations, NSF grants, as a peer reviewer, and as an external reader on doctoral dissertations. In 2017, she was invited to present the keynote address at ICAD.

To read more about her sonification work: (https://carlascaletti.com/sounds/data-sonification/).

Martin Gruebele was born in Stuttgart, Germany in 1964. He obtained his BS in 1984 and his PhD in 1988 at UC Berkeley with Richard Saykally, did a postdoc with Nobel laureate Ahmed Zewail at Caltech, and then joined the faculty at the University of Illinois in 1992. There, he is currently the James R. Eiszner Chair in Chemistry, Professor of Physics, of Biophysics and Quantitative Biology, in the Center for Advanced Studies, and in the Carle-Illinois College of Medicine.

His research interests include sonification in education and biophysics research; biomolecule dynamics in live cells; vibrational energy flow in molecules; quantum scrambling and control; nanoscale imaging of excited states; glassy dynamics; and locomotion behavior.

He is a Fellow of the American Physical, Chemical, and Biophysical Societies, and a member of the American Academy of Arts and Sciences, the National Academy of Sciences, and the German National Academy of Sciences. He has edited for the Journal of Physical Chemistry, the Journal of the American Chemical Society, and the Proceedings of the National Academy of Sciences. His group's work is published in over 325 papers and reviews.

Martin Gruebele is married to Nancy Makri, and they have two children: Alexander and Valerie. In his free time, he competes in ultra-endurance sports (swimming biking, running), plays pipe organ, and builds miniatures.