UNFOLDING | CLUSTERS: A MUSIC AND VISUAL MEDIA MODEL OF ALS PATHOPHYSIOLOGY

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ABSTRACT

Unfolding | Clusters is a music and visual media installation modeled from published scientific data related to the pathophysiology of amyotrophic lateral sclerosis (ALS). The work aims to create an engaging multimodal experience useful for raising awareness in the greater public about the disease and its scientific process. This paper describes the motivation behind the adoption of a *musification* approach and the musical criteria applied to the data mapping process. Details regarding the mapping structure are illustrated in relation to the different phases of the progress of the disease. The results are then discussed, noting that adopting a musification approach not only helped in obtaining a more engaging audience experience but also in providing expressive solutions that would be useful for modeling other complex biomedical data and processes.

1. INTRODUCTION AND BACKGROUND

This project explores the use of combined sonification and visualization in a multi-modal installation for the purpose of illustrating the condition and progress of degenerative amyotrophic lateral sclerosis (ALS). The use of sonification (or auditory display) in biomedical applications is a growing and progressive field, with many such applications in existence.
"Sonification conveys information by using non-speech sounds. To listen to data as sound and noise can be a surprising new experience with diverse applications ranging from novel interfaces for visually impaired people to data analysis problems in many scientific fields." [1].
We consider the sonification in this project a *musification*, on the grounds that the data is not just auralized but various constraints are created and applied in order to create a musical performance of the data (see section 4 for full details of this process). For this project, the advantage of using a musification to display this data is threefold. Firstly, the data involved in the unfolding process is extremely complex, and some of the mutation processes involve minute changes that would be difficult to illustrate meaningfully using either a visual modality or a direct sonification (see section 4. Method).
Secondly, one of the aims of this project was to generate and raise further awareness of the condition, in line with existing MND/ALS charity core aims. Thus, a musical installation which could engage the audience both visually and in an aurally engaging manner was a useful prospect. Thirdly, the kind of numerical data which represents the amino acid structures and the process of cluster formation as ALS progresses is not easily represented in a manner which can be readily analysed by the casual viewer – musifying this data by first sonifying it, and then applying a set of musical constraints to the sonified data offers the possibility of engaging the listener with this complex data by allowing them to engage and analyse the music, a process which listeners do automatically and intuitively as part of their everyday listening process in the real world. These reasons are common to many auditory display projects making use of multimodal techniques in the biomedical arena. "*The idea behind sonification is that synthetic non-verbal sounds can represent numerical data and provide support for information processing activities of many different kinds."* [2].
Combining the musification with a visual representation of the datastream further targets one of these functions; that of increased audience engagement through a multimodal experience. Multimodality is a complimentary human perceptual process which has also been exploited by the bio-medical world, e.g., [3]–[5]. *"The human auditory system is very good at detecting minute changes in audio signals and can also monitor several parallel audio streams at one time. This means hearing offers an exciting opportunity for parallel information interpretation tasks to complement existing visual representational techniques."* [6].
Thus, the criteria for this project include creating the maximum engagement for audience members whilst accurately representing, to a high level of detail, the changes involved in the data in a combined musification and visualization.

2. ABOUT ALS

ALS is generally fatal within 5 years of onset and "has a prevalence of 2–3 per 100.000 people" [7]. It is classified as familiar (FALS), if associated to inherited mutations, or sporadic (SALS) if not. SALS represents the majority (about 80%) of cases [8]. The disease is characterized by progressive degeneration of the upper and lower motor neurons of the spinal cord. This causes muscle weakness and atrophy throughout the body, leading gradually to paralysis and death by respiratory failure. Several factors contribute to neuronal death including Ribonucleic Acid (RNA) and protein dysfunctions and immunity [9]. Due to its high complexity, the

pathophysiology of the disease is yet to be completely clarified, however a shared theory is that the involvement of protein aggregation and deposit in neurons is a factor linked to the neuronal toxicity of the disease. Superoxide Dismutase-1 (SOD1) is a ubiquitous enzyme involved in the anti-oxidant processes of the cell. Numerous studies indicate that loss of function of SOD1 is not linked to ALS onset and progression, but rather to the toxic property acquired with its structural changings. SOD1 as a normal form (wild-type) is a homodimer of two identical aminoacidic sequences linked by a disulfide bond formed by cysteine 57 and 146 of the sequence. Zn^{++} ions allow for stability of the proteic structure, together with the Cu^{++} ions of the catalytic site – these portions are referred to as *metal binding sites* (MBS). About 140 different genetic mutations of SOD1 sequence were detected during the last twenty years of study, some of which were associated with a more aggressive form of the pathology. In this study we considered the most common pathology, that is, the substitution of Alanine with Valine in position 4 of the aminoacidic sequence (A4V). Both genetic mutations and biochemical reactions (oxidation) are associated with loss of ions and the consequent dimer loosening (i.e. apoprotein). This structure is more reactive than the wild-type to the association process of different dimers (oligomerisation) in chain-like structures. Note that a more aggressive ALS form is associated to wild-type and apoprotein aggregates [10]. A recent study by Banci and colleagues showed the specific sites indicated as single amino acids of the new-formed bonds in mutated forms SOD1 and the geometrical characteristics of the oligomerisation [11]. Finally, the chain-like structures form clusters associated with neurotoxicity, although a proof of concept of this mechanicistic event has yet to be verified [7].

Today, gene therapy seems to be the most promising strategy for intervention of FALS, and recent findings, depicting a deep heterogeneity of the disease, are paving the way for a multi-targeted therapeutic strategy [12].

3. *UNFOLDING | CLUSTERS*: THE MODEL

Unfolding | Clusters is an installation that maps scientific data from ALS pathophysiology to sonic timbres and melodic patterns in a video-synchronous spatial speaker array that represents the nervous system. The accompanying video presents cues showing neural pathways as they are activated, whilst the associated neuromuscular junction is sounded on corresponding speakers in the array. Over time, the timbre, rhythm, and spatialization of these sonic patterns gradually changes to reflect the progress of the protein unfolding and aggregation. Melodic sequences change according to the mutation of the amino-acidic sequence. As the amino acids aggregate into clusters, timbres become noisier to create additional spectral harmonics and, ultimately, introduce inharmonic distortion and dissonance. Video synchronicity gradually degrades as the nervous system loses control over the muscles and sclerosis hardens the affected nerves of the spinal cord. The spatialization in the 3D speaker array, initially a fully immersive sound world, eventually shrinks completely, reflecting the patients' loss of movement and motor function.

The work aims to create an engaging experience that can appeal to the greater public and raise awareness about the complex scientific findings regarding ALS. Therefore, the criteria adopted for the musification of the data are designed to go beyond direct sonification and include elements of tonality and the use of modal scales to create musical auralizations. The resulting musical structures take advantage of higher-level musical features such as polyphony and tonal modulation in order to engage the audience and at the same time find alternative ways to model the complex processes which occur during the progress of the disease.

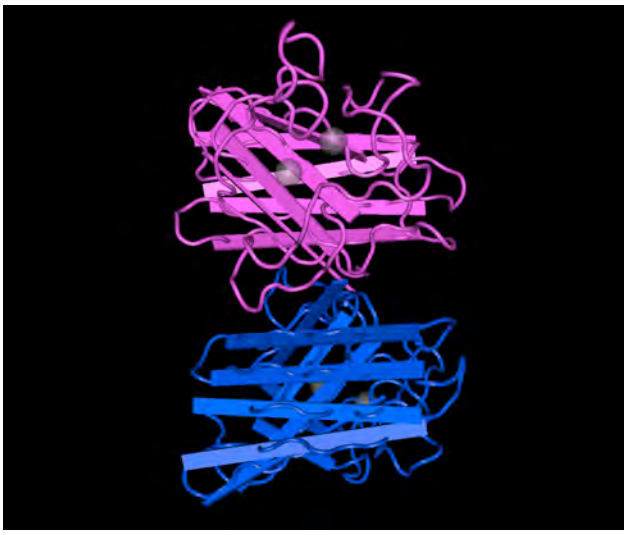

Figure 1: 3D structure of SOD1 protein.

4. METHOD

The installation presented in this research utilizes published data obtained from Nuclear Magnetic Resonance (NMR) studies of SOD1 protein [13]. In NMR spectroscopy the chemical shift is the resonant frequency of a nucleus compared to a standard [14]. This analysis was chosen among the other qualitative protein assays on the basis of the nature of the phenomenon observed during the NMR analysis as close to that of an audio signal. Chemical shifts of amino acid structures change slightly depending on the whole protein molecular structure in which they are arranged. Since the chemical shifts of each single amino acid (AA) composing SOD1 protein sequence are not published, these were obtained from the Biological Magnetic Resonance Data Bank (BMRBD) [13]. These data represent averages of 6486124 chemical shifts of the same AAs in different molecular contexts published to date and are expressed in parts per million (ppm)[1] and approximated to the second decimal figure.

4.1. Mapping layer 1: basic melodic features

Data mapping to musical features is organized in a layered framework (see Table 4). In the first layer, data resulting from NMR analysis [13] is used to assign basic musical features – such as pitch, duration and velocity – to each of the 20 classic amino acids. The main melodic material is defined by the

[1] ppm = (sample value in Hz - standard in Hz) / spectrometer frequency in MHz.

amino acidic sequence of the wild-type SOD1 protein, which comprises 154 instances of the classic amino acids. The molecular structure of an amino acid consists of amine (-NH_2), carboxylic acid (-COOH) and a side-chain (R) specific to each amino acid (Fig. 2).

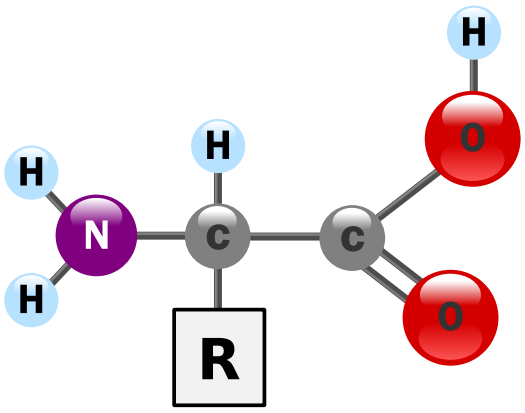

Figure 2: generic structure of an amino acid consisting of amine (-NH2), carboxylic acid (-COOH) and the R group, which is a side-chain that varies for each type of amino acid [15].

The pitch value of each amino acid was defined by mapping the average chemical shift of the respective R group to a note of the chromatic scale. By doing so, the 20 classic amino acids are indexed by increasing R group chemical shift and each one is associated to a note of an ascending chromatic scale, therefore covering a total note range of an octave and a fifth.

AA (short)	R group av. shift	Pitch index	Note
G	0,19	1	C1
P	3,99	2	C#1
M	4,44	3	D1
V	5,80	4	D#1
L	6,07	5	E1
I	7,55	6	F1
A	10,21	7	F#1
C	10,33	8	G1
R	12,03	9	G#1
K	12,72	10	A1
T	14,20	11	A#1
F	14,72	12	B1
W	15,20	13	C2
Q	15,53	14	C#2
S	16,08	15	D2
E	31,08	16	D#2
Y	38,40	17	E2
H	42,36	18	F2
D	43,89	19	F#2
N	48,94	20	G2

Table 1: pitch mapping for each amino acid.

To determine the duration of each note, the average chemical shift of the hydrogen atoms in the molecular structure of the amino acid is used. A set of five discreet durations was defined in order to obtain more consistent rhythmic patterns. The values for each amino acid are calculated and then mapped to the five durations in milliseconds, which correspond to the following note values at 120 beats per minute: sixteenth note, eighth note, quarter note, half note and whole note, as shown in Table 2.

AA (short)	H group Av. shift	Duration (msec)	Note value @ 120 bpm
L	2,66	125	1/16
P	2,78	125	1/16
K	3,18	125	1/16
V	3,21	125	1/16
M	3,30	125	1/16
I	3,33	125	1/16
E	4,04	250	1/8
C	4,29	250	1/8
Q	4,43	250	1/8
A	4,60	500	1/4
R	4,63	500	1/4
T	4,66	500	1/4
D	4,72	500	1/4
S	5,20	500	1/4
G	5,40	500	1/4
N	5,51	1000	1/2
F	6,00	1000	1/2
Y	6,11	1000	1/2
W	6,48	1000	1/2
H	7,02	2000	1

Table 2: duration mapping for each amino acid.

The note velocity is determined from NMR data of the nucleotide nitrogen atoms. The four main nucleobases are ordered according to the increasing value of the respective nitrogen group chemical shift and are then associated with four MIDI velocity values (1, 43, 85, 127). The velocity corresponding to each amino acid is determined by taking the value of the first nucleotide of the respective nucleotide triplet.

Nucleotide	N group av. shift	MIDI velocity
Guanine (G)	138,08	1
Cytosine (C)	139,70	43
Uracil (U)	152,54	85
Adenine (A)	178,18	127

Table 3: velocity mapping for each nucleotide.

A custom Max[1] patch was designed to translate the numeric data taken from spreadsheets into MIDI values, which then can be used to control electronic musical instruments and music production software. Each one of the 154 amino acids in the sequence is played as a note and the resulting melody

[1] http://cycling74.com/products/max/

	1. Initial State: Wild-type	2. Binding sites	3. Mutation	4. Bindings breaking
Layer 1: basic melodic features	Wild-type SOD1 melodic sequence.	Notes extracted from the binding sites in the sequence.	Mutation/Change of key A–>V = F#–>D#	The melody continues in the new key.
Layer 2: polyphony and arrangement	Dimer: two symmetrical melodic lines.	New parts extracted from the metal binding sites and disulfide bonds are played by new voices.	MBS lose ions, change in timbre.	The monomers separate = the melody and its inverse are respectively transposed down and up the scale.
Layer 3: spatialization and visuals	Correspondance between speakers and visuals.	New voices correspond to new instances of the visuals.	Correspondance between speakers and visuals.	Correspondance between speakers and visuals.

	5. Oligomerization	6. Fibrillization	7. Clusters	8. End
Layer 1: basic melodic features	Both the original and the "mutated" melodies are present.	The melodies are trasposed to different registers.	The melodies are trasposed to many registers of the whole audio spectrum.	The melodies are trasposed to many registers of the whole audio spectrum.
Layer 2: polyphony and arrangement	The original melody is stacked with the mutated inverse and vice-versa.	Voices playing the melody in different registers are layered.	Phasing, increasing dissonance and saturation of the audio spectrum, more and more layered voices.	Gradually less saturation.
Layer 3: spatialization and visuals	Increased speed, multiple voices moving.	Increased noise in the visuals and asynchronicity between visuals and sound.	Gaps and sudden movements in the sound spatialization, saturation towards white in the visuals.	Some speakers/neurons stop working. The soundscape converges to one speaker and one instance of the visuals.

Table 4: table displaying the phases of the development of the piece across the three mapping layers.

represents a musical translation of the wild-type superoxide dismutase amino acidic sequence. The melody is then fed through a 'tonalizer' algorithm, which maps the incoming notes to various modal scales. During the mutation, the fourth amino acid of the sequence changes from A to V [10]. To render this event musically, the note corresponding to the mutating amino acid is considered the root of the scale in which the whole melody is played. The mutation therefore causes the melody to change key, modulating from F# to D#, which correspond to the amino acids A and V respectively. As the mutation affects the protein as a whole, a tonal modulation has an impact on the entire melody and is thus clearly delineated to the audience.

To model the process of fibrillization, the SOD1 melodies are transposed to different registers in order to express the formation of different layers of fibrils which occur after the protein unfolding. This eventually leads to the formation of clusters, conveyed through an increasing saturation of the soundscape due to the high number of dissonant voices playing at the same time.

4.2. Mapping layer 2: polyphony and arrangement

The second layer of the mapping framework contains higher concept level mappings related to the development of the musical piece, such as polyphony and arrangement. All the different steps that lead to SOD1 structural changes involve specific amino acids of the sequence. Other voices and parts of the piece are in fact determined by structural features of the SOD1 protein and processes occurring along the development of ALS. To represent the structure of the SOD1 protein – a dimer consisting of two identical amino acidic sequences displaced in symmetrical fashion (see Fig. 1) – the original melody extracted from the amino acidic sequence was inverted and added as a second voice. The symmetrical structure of the resulting 2-voice counterpoint deliberately reflects the shape of the SOD1 dimer. Other timbres and parts are introduced along the piece to denote various further processes. The first step leading to protein unfolding involves the breakage of the disulfide bonds and the loss of metal ions [16]. To represent this musically, the disulfide bonds are located in the protein sequence and the corresponding notes are then used to define a new melodic line played by a synthesized bass. In addition to the disulfide bonds, another important step that leads to the unfolding of the protein structure is the detachment of the Zn^{++} ions associated to specific portions of the protein sequence, also known as metal binding sites [17]. Once again, the corresponding notes in the sequence are employed to determine the part played by a new voice in the composition. The same approach is used to model the new bonds between protein monomers which form during the oligomerization process [11].

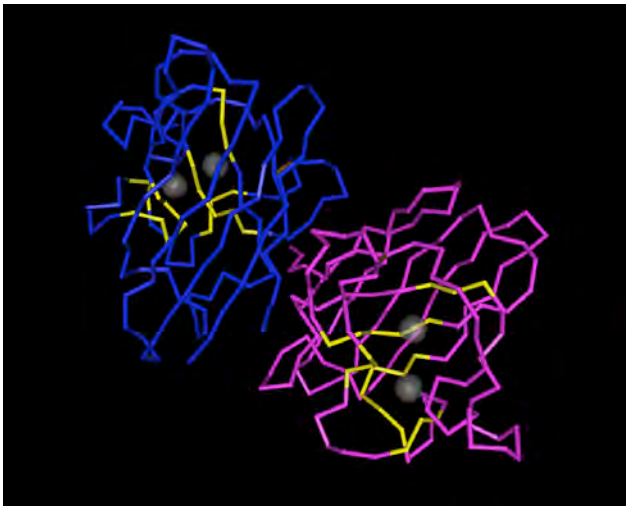

Figure 3: 3D structure of the SOD1 protein. The grey spheres represent the metal ions while the segments in yellow the metal binding sites.

4.3. Mapping layer 3: spatialization and visuals

The third mapping layer consists of high-level features in the installation, such as sound spatialization and visualization. The speaker array is arranged around a cylindrical projection screen on which the visuals are projected (see Fig. 4). This is a representation of a neural structure, where the central cylinder, acting as the central neural system, sends impulses (the visual cues) to cells of the peripheral nervous system, represented by the speakers (Fig. 5). There is an instance of the visuals projected in front of each speaker in the array. As long as the system is "healthy", the speakers respond with sound to the impulses sent by the central system. As the disease advances, communication between central and peripheral systems becomes increasingly asynchronous to reflect the death of motor neurons. The visuals are designed to avoid gratuitous decorative effects, which would violate the criteria laid out for the design of the model. There is a projected vector line that corresponds to each speaker which vibrates according to the frequency emitted by the latter. Increasing noise and distortion are reflected in the visuals – the vibrating line becomes more jagged and as the soundscape becomes more saturated the luminosity of the visuals increases towards white. As some speakers (and the neurons they represent) stop working, the corresponding line ceases to vibrate and the multimedia environment converges to one speaker and one instance of the visual.

4.4. Apparatus

The installation is designed to adapt to different room sizes, from approximately 25 m^2 to 50 m^2 and over. The speaker array consists of 6 or 8 speakers (depending on room size) connected to a multi-channel audio interface. The cylindrical projection screen is made of highly reflective, opaque fabric mounted on a fiberglass ring. To cover the whole projection surface, two or three (depending on room size) projectors are arranged around the cylinder and operated simultaneously via a video expansion module. The audio interface and the video module are both stored inside the cylinder and controlled by a laptop, which streams the multi-channel audio and video data (Fig. 5).

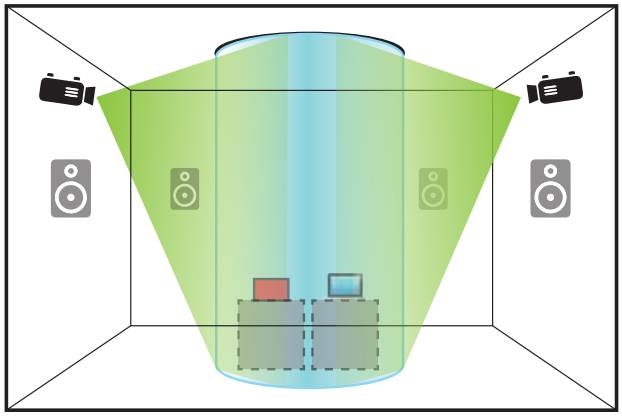

Figure 4: installation layout, front view.

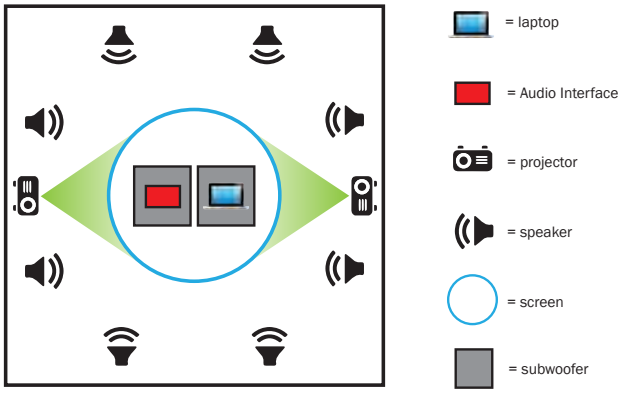

Figure 5: installation layout, floor plan.

Figure 6: *Unfolding* | *Clusters* installed in the UCLA Art|Sci Gallery, Los Angeles, California, United States.

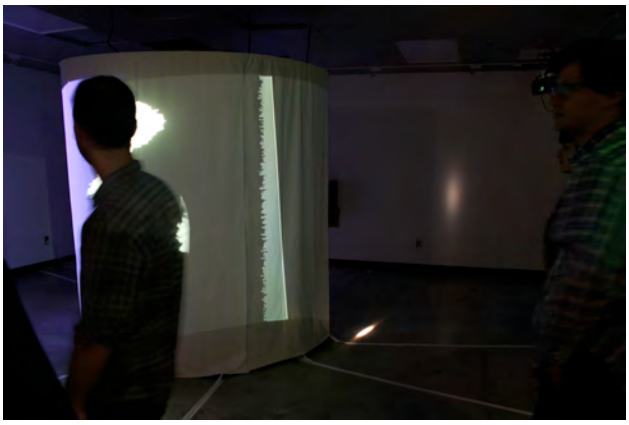

Figure 7: *Unfolding* | *Clusters* in progress, installed in the UCLA Art|Sci Gallery, Los Angeles, California, United States, June 2014.

5. CONCLUSION AND FUTURE WORK

This paper described the design and development of a multimedia installation which models ALS pathophysiology using music and visuals. The work was aimed at the greater public in order to rise awareness about the disease and its workings, therefore the criteria and constraints for the mapping of the NMR data were adopted in order to control the

'musicality' of the final result and make the piece accessible to a wider audience while, at the same time, remain faithful to the source data without trivializing the seriousness of the condition. The resulting musification employed modal scales, discreet durations and a rhythmic grid to create a surprisingly musical mapping that still retained the complexity of the source data. The sequences of the piece would be relatively difficult to perform for a human musician, even though they sound 'easy' and listenable to a non-musical audience.

Adopting a musification approach not only allowed for a more accessible musical result but also provided expressive solutions for modeling complex events critical for the development of the disease, such as the protein mutation which was represented by a tonal modulation.

Overall, the approach proved to satisfy the initial aim of designing an immersive installation to raise awareness about scientific facts related to ALS and engaging a casual audience. Future work could usefully be directed towards enriching the timbral variety of the installation, possibly by gathering new data for mapping sound synthesis parameters or timbre morphing.

Additional data mapping could also be useful to further develop the visualisation, which was purposely kept minimalistic in order to avoid unjustifiable decorative effects. A sensible use of colours, for example, might be helpful to further aid the communication of the underlying complex events in a multimodal fashion.

Also, it has been observed that ALS may have many different causes and SOD1 may not be the only protein involved in the progress of the disease [12]. Therefore, it would be interesting to model other possible forms of ALS and develop a stochastic system that determines different progressions of the piece based on the probability of different forms of ALS to occur.

6. ACKNOWLEDGMENTS

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7. REFERENCES

[1] T. Hermann, A. Hunt, and J. G. Neuhoff, *The sonification handbook*. Logos Verlag, 2011.

[2] S. Barrass and G. Kramer, "Using sonification," *Multimed. Syst.*, vol. 7, no. 1, pp. 23–31, 1999.

[3] P. Toharia, J. Morales, O. Juan, I. Fernaud, A. Rodríguez, and J. DeFelipe, "Musical Representation of Dendritic Spine Distribution: A New Exploratory Tool," *Neuroinformatics*, pp. 1–13, Jan. 2014.

[4] G. I. Mihalas, S. Paralescu, N. Mirica, D. Muntean, M. Hancu, A. TUDOR, and M. ANDOR, "Sonic Representation of Information: Application for Heart Rate Analysis," in *Proceedings MIE*, 2012.

[5] E. Jovanov, D. Starcevic, A. Marsh, Z. Obrenovic, V. Radivojevic, and A. Samardzic, "Multi modal viewer for telemedical applications," in *Engineering in Medicine and Biology Society, 1998. Proceedings of the 20th Annual International Conference of the IEEE*, 1998, vol. 3, pp. 1254–1257.

[6] P. Vickers, "Sonification for process monitoring," 2011.

[7] D. W. Cleveland and J. D. Rothstein, "From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS," *Nat. Rev. Neurosci.*, vol. 2, no. 11, pp. 806–819, Nov. 2001.

[8] J. M. Ravits and A. R. La Spada, "ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration," *Neurology*, vol. 73, no. 10, pp. 805–811, Sep. 2009.

[9] G. Liu, M. Fiala, M. T. Mizwicki, J. Sayre, L. Magpantay, A. Siani, M. Mahanian, M. Chattopadhyay, A. L. Cava, and M. Wiedau-Pazos, "Neuronal phagocytosis by inflammatory macrophages in ALS spinal cord: inhibition of inflammation by resolvin D1," *Am. J. Neurodegener. Dis.*, vol. 1, no. 1, pp. 60–74, Mar. 2012.

[10] R. L. Redler and N. V. Dokholyan, "The Complex Molecular Biology of Amyotrophic Lateral Sclerosis (ALS)," *Prog. Mol. Biol. Transl. Sci.*, vol. 107, pp. 215–262, 2012.

[11] L. Banci, I. Bertini, M. Boca, V. Calderone, F. Cantini, S. Girotto, and M. Vieru, "Structural and dynamic aspects related to oligomerization of apo SOD1 and its mutants," *Proc. Natl. Acad. Sci.*, vol. 106, no. 17, pp. 6980–6985, Apr. 2009.

[12] W. Robberecht and T. Philips, "The changing scene of amyotrophic lateral sclerosis," *Nat. Rev. Neurosci.*, vol. 14, no. 4, pp. 248–264, Apr. 2013.

[13] E. L. Ulrich, H. Akutsu, J. F. Doreleijers, Y. Harano, Y. E. Ioannidis, J. Lin, M. Livny, S. Mading, D. Maziuk, Z. Miller, E. Nakatani, C. F. Schulte, D. E. Tolmie, R. K. Wenger, H. Yao, and J. L. Markley, "BioMagResBank," *Nucleic Acids Res.*, vol. 36, no. suppl 1, pp. D402–D408, Jan. 2008.

[14] A. Kowalsky and M. Cohn, "Application of Nuclear Magnetic Resonance in Biochemistry," *Annu. Rev. Biochem.*, vol. 33, no. 1, pp. 481–518, 1964.

[15] Y. Mrabet, *Structure générale d'un acide aminé*. 2007.

[16] K. Teilum, M. H. Smith, E. Schulz, L. C. Christensen, G. Solomentsev, M. Oliveberg, and M. Akke, "Transient structural distortion of metal-free Cu/Zn superoxide dismutase triggers aberrant oligomerization," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 106, no. 43, pp. 18273–18278, Oct. 2009.

[17] F. Ding and N. V. Dokholyan, "Dynamical roles of metal ions and the disulfide bond in Cu, Zn superoxide dismutase folding and aggregation," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 105, no. 50, pp. 19696–19701, Dec. 2008.