ACOUSTICS AND VOCAL ENSEMBLE PERFORMANCE: INSIGHTS FROM SACRED CHANTS PERFORMED A CAPPELLA AT NOIRLAC ABBEY

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1 INTRODUCTION

The interpretation of the medieval monodic repertoire of sacred chants is rarely addressed in experimental acoustical research, despite its historical importance. This study focuses specifically on the performance of sacred chants, and in particular those composed by Hildegard von Bingen, in relation to the acoustics of an authentic architectural and musical venue. The recording of a chorus of seven singers was made in the Noirlac Abbey, as part of the historical reconstruction of songs from Hildegard von Bingen carried out by the Organum Ensemble within the framework of the HAPPNAE project (Hildegard Archeo Physiologico Psycho Neuro Acoustic Exploration) and a CD recording of "*Hildegarde de Bingen - Les Vêpres à Marie*". The research question posed here is how female singers vocally adapt to historically resonant spaces.

The influence of room acoustics on musical performance has been widely studied over the past three decades.This body of research encompasses both instrumental[1–4] and vocal performances,[5–7] in solo[2] and ensemble contexts[8,9] , and across a range of settings—from controlled laboratory environments[9] to live concert halls.[2] Within this broader research landscape, vocal performance has received particular attention.[5–7,10,11] Recent studies have shown that acoustic conditions influence various performance parameters, including vibrato characteristics,[5] pitch accuracy[5,8] and tempo.[7] Acoustics also shapes musicians' perceptual experience during performance.[12] Additionally, studies have examined how acoustics affect vocal production and gestural behaviour, revealing that room acoustics can impact loudness[7,8] and glottal behaviour,[6] which have been associated with vocal effort.[13] Interestingly, the acoustic parameters that shape vocal gestures may differ from those influencing broader musical interpretation.[6] While factors such as sound level have been studied in choral settings, no research to date has specifically investigated how room acoustics influences the glottal behaviour of individual choir singers. This represents a notable gap in our understanding of how vocal production adapts to acoustic environments in ensemble singing.

The extent to which acoustics influences performance varies significantly across musical contexts. Depending on the study, acoustic conditions explain between 11%[7] and 30%[6] of the observed variability in vocal performances. However, the literature reveals a wide variability in the parameters assessed and the methods used to calculate performance attributes, which often depend on the musical context and the available data. In vocal performance specifically, adaptations in vocal gestures are highly individual,[6,7] shaped by musical context and the stylistic conventions of performers,[14] as well as genre-specific aesthetic constraints. Despite this, most prior research has largely overlooked the role of musical context in acoustic adaptation. Recent developments in the field of archaeoacoustics[8,15] have emphasised the importance of musical context by examining specific historical genres and performance practices. These studies aim to better understand how past acoustic environments shaped musical experience.

A subset of this research has focused on medieval music, offering insights into the acoustic contexts in which this repertoire was originally performed. Investigating the influence of acoustics on vocal performance is particularly relevant for historically informed interpretations of medieval music. While early and late medieval polyphony has been studied in depth,[3,11,15] monodic traditions such as plain-chant have received little attention, despite their central place in medieval vocal practice. Studying the acoustic adaptation of singers in this repertoire provides a unique opportunity to explore the interplay between historically appropriate performance spaces and vocal production mechanisms. This is especially pertinent in a cappella contexts, where the voice alone must respond dynamically to reverberant environments.

This preliminary study contributes to ongoing research on the relationship between room acoustics and vocal performance. Specifically, it aims to deepen our understanding of how acoustics influence monodic a cappella vocal music performed by multiple singers, with the broader goal of informing historically informed performance (HIP) practices. By examining performances in acoustically relevant spaces—selected for their historical congruence with the repertoire—this study offers new insights into the interaction between acoustic environment and vocal production. Additionally, this work explores singers' physiological adaptation to acoustics by analysing changes in glottal behaviour, measured via contact quotient, across different acoustic conditions and laryngeal mechanisms. This case study is intended as a first step toward a systematic investigation. It assesses the influence of acoustics on key musical performance parameters identified in the literature—such as tempo and ensemble synchronisation—to ensure consistency with previous findings, and examines how vocal gestures and laryngeal mechanisms vary in response to room acoustics.

2 METHODS

2.1 Participants

A choir of seven female singers were recorded, six of them being members of the *Organum Ensemble* for at least a year. Ethical approval for the study was obtained from the Research Ethics Committee of CY Cergy Paris University (Approval Number: 202401 - 001, March 22, 2024). All participants were fully informed about the experimental procedures.

2.2 Musical pieces

Three monodic musical pieces were performed during the experiment. Two monodies were composed by Hildegard von Bingen (1098–1179) and selected by Marcel Peres, choir director of the Organum Ensemble, from *"Ad vesperas Sanctae Mariae Virginis" (Les vèpres à Marie)*: *O frondens virga* (***O***), a large ambitus antienne (D mode, with an ambitus of an eleventh) and *Hodie aperuit* (***H***) a more melismatic sequence (C mode, with an ambitus of a thirteenth). The source used was the Dendermonde Codex. The third monodic song was a syllabic Plainsong of the XII century with a reduced ambitus compared to Hildegard's songs, the *1st antienne des vêpres de Saint Jacques - Ad sepulchrum* (***C***) found in the Codex Clixtinius (D mode, with an ambitus of an octave).

A fourth song was also performed: an early polyphonic sequence (two voices), *Res est admirabilis* (***G***) from the Graduel d'Aliénor d'aquitaine. Due to the polyphonic nature of this piece, it was not taken into account in the analysis presented here.

2.3 Experimental design and data collection

The experiment took place in six different spaces within the Noirlac Abbey over the course of two evening sessions: in the ***Refectory***, in the cloister ***Walkway*** and ***Garden***, in the church ***Choir*** and

	BR	C_{80}	EDT_{10}	$ST1$	$ST2$	T_{30}
1 ***Refectory***	1.20	-1.82	3.42	-0.32	2.69	3.46
2 ***Walkway***	1.17	2.47	1.37	2.44	4.22	1.94
3 ***Garden***	1.26	8.62	0.98	-6.95	-5.52	1.83
4 ***Choir***	1.11	-0.97	4.41	1.10	3.43	7.22
5 ***Nave***	1.11	-3.29	6.87	-3.86	0.04	7.57
6 ***Outside***	NA	NA	NA	NA	NA	NA

Table 1: Average acoustic parameters

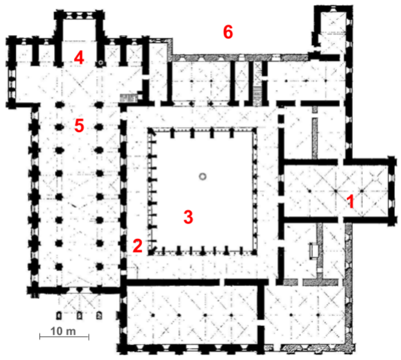


Figure 1: Plan of Noirlac Abbey and location of the measurements

Nave, and finally ***Outside*** of the monastery (see Fig. 1). All chants were performed without a conductor, contrary to the ensemble's usual performance practice, in order to better observe inter-musician interactions. The singers were arranged in a semi-circle and maintained the same spatial configuration and order for each performance. All performances were done using facsimiles of medieval manuscripts, rather than modern transcriptions. Recordings took place in the evening, following rehearsal sessions and interpretation work led by the ensemble's conductor. The four songs were performed in the same order.

All singers were equipped with head-worn microphones (DPA-4060). Four of them wore a respiratory inductance plethysmography vest (Etisense system). One singer was equipped with an the electrode collar of an electroglottograph (EGG EG2, Glottal Enterprises). Audio and EGG recordings were acquired using a Zoom F8n MultiTrack Field Recorder, with a sampling frequency of 48 kHz.

2.4 Rooms acoustics measurements and characterisation

Acoustical measurements were conducted in each location of performance in the Abbey except for the ***Outside*** condition. Acoustical measurements were conducted using a exponential sweep (20 s, 50 Hz-20 kHz), played on an omnidirectional source (Look Line S103), and recorded with two omnidirectional microphones (Bedrock audio omnidirectional BAMT1) and a dummy head (KU 100 - Neumann) on a Zoom F8n MultiTrack Field Recorder, with a sampling frequency of 48 kHz. Several source and receiver positions were measured in each location.

The room impulse responses (RIRs) were later extracted by deconvolution in MATLAB. RIRs were analysed using an in-house MATLAB IR analysis (IRA) toolkit in accordance with the ISO 3382 standard.[16] Acoustic parameters characterising reverberation (T_{30}, EDT_{10}), clarity (C_{80}), and stage support ($ST1$, $ST2$) were calculated in octave bands from *125* Hz to *4* kHz. The bass ratio (BR), defined as the ratio between the reverberation time in low-frequency bands ($TR_{125} + TR_{250}$) and the reverberation time in mid-frequency bands ($TR_{500} + TR_{1000}$) was also computed, using T_{30} for estimating the reverberation time.

The results were then averaged across each source - receiver position in each space measured. Note that the measurement setup did not respect the distance specification usually set for the measurements of $ST1$ and $ST2$. Therefore, the ST values are valid for comparison between configurations within this experiment, but not with published data from other venues.

Table 1 reports the values of the acoustic parameters computed for each measured acoustic environment and averaged over frequency bands.

2.5 Database annotation

The 8-channel signals (seven choristers' close-microphone audio signals and one EGG signal) were manually annotated using Praat.[17] The annotation included the timings of each sentence and syllable. The start and end times were annotated globally for the entire choir (i.e., not individually for each singer). The end of the segments corresponded to the onset of the next. This annotation did not account for silences or onset differences between singers.

A second annotation was then performed automatically to refine the onset annotation for each singer using a method adapted from Mullins (2024).[15] We employed the mironset function from the Mirtoolbox version 1.8.2,[18] using the "Emerge" detection method[19] in combination with the MM-BOP routine.[20] The search window for each onset was set to *1.5* s, with 1/4 of the window before and 3/4 after the manually annotated time. This approach allowed us to estimate the actual onset of each phrase for each singer.

Finally, the laryngeal mechanism used by the singer (either M1 or M2[21]) was manually annotated on the EGG signal with Praat, taking into account the EGG-signal envelope amplitude, cycle shape and contact quotient values (ratio of contact duration to the glottal cycle duration).[22,23] Laryngeal mechanisms M1 and M2, which are associated with the notion of vocal register, exhibit distinct features: CQ values are lower in M2 than in M1; M1 is generally used at lower frequencies, while M2 dominates higher ones. The EGG waveform is also more symmetrical in M2, reflecting differences in vocal fold contact dynamics.

2.6 Vocal performance analysis

Tempo-related attributes – Durations, alignments between recordings Based on the general annotations of starts and ends of songs and phrases for the choir, the duration of each segment (song and phrase) was extracted. The durations were then normalised relative to the total duration of each segment across each acoustic condition.

A second descriptor related to the tempo was computed : the alignment between performances. A mean performance was computed with the beginning time for each syllable being the mean value across performances. A Dynamic Time Warping (DTW function, Matlab) algorithm was applied to align each performance to the mean performance. The alignment score for each performance was calculated as the difference between the number of gaps added in the performance analysed and the number of gaps added in the mean reference performances to achieve optimal alignment. This score is closely related to overall duration and, therefore, the tempo of the performed musical passage. A positive alignment score indicates that more gaps were added in the performance than in the reference mean performance, suggesting a generally faster tempo compared to the mean performance, while a negative alignment score indicates a slower tempo compared to the mean performance.

Synchronisation Based on the individual onset for each singer, we computed the standard deviation between singers for each syllable. The Synchronisation was then defined as $1 - std(onsets)$. Synchronisation values at each syllable onset were then averaged across performances and normalised by the overall number of syllables.

Contact Quotient (QC) The contact quotient is defined as the ratio between the vocal fold contact time and the duration of one vibratory cycle.[22,23] Glottal contact quotient values were calculated using the "DEGG DECOM" method, which relies on the derivative of the electroglottographic (EGG) signal. The MATLAB code used for this analysis is described in Henrich(2004).[22]

	BR	C80	EDT10	ST1	ST2	T30
Phrase durations	-0.48	**-0.54**	0.36	0.48	0.53	0.50
Performances alignment	-0.45	-0.53	0.37	0.42	0.48	0.49
Synchronisation	0.38	0.26	-0.39	-0.00	-0.06	**-0.54**
QC(M1)	0.29	-0.18	-0.23	0.41	0.44	-0.31
QC(M2)	0.50	0.33	-0.54	0.29	0.19	**-0.59**

Table 2: Pearson correlation between acoustic parameters and performance parameters. Significant correlations (p-value < 0.05) are shown in bold.

2.7 Statistical Analysis

Statistical analyses were conducted using RStudio. A one-way analysis of variance (ANOVA) was performed to assess the effect of acoustic condition on musical performance parameters (phrase duration and synchronisation). When the main effect was significant, post-hoc comparisons were conducted using the emmeans function to identify pairwise differences between conditions.

Due to the bounded nature of the QC variable (ranging between 0 and 1), its relationship with acoustic condition and phonatory mechanism (M1 or M2) was examined using a beta regression model with random effects, implemented with the glmmTMB function from the glmmTMB package in R. The chant variable was included as a random effect. To evaluate the significance of the predictors, we performed likelihood ratio tests between nested models using the anova function. Multiple comparisons were conducted using the glht function from the multcomp package.[24]

All statistical tests were performed with a significance threshold set at $\alpha = 0.05$.

Pearson correlation analyses were also conducted, in MATLAB using the corr function, to explore the relationships between acoustic parameters of the performance spaces and performance-related measures. For this purpose, the acoustic descriptors were averaged across frequency bands for each condition (see Table 1), and these average values were then correlated with the corresponding performance metrics (e.g., tempo, synchronisation, glottal parameters).

Note that while the ***Outside*** acoustic configuration was included in the ANOVA, it was excluded from the correlation analysis because meaningful acoustic parameters could not be obtained in the free-field setting.

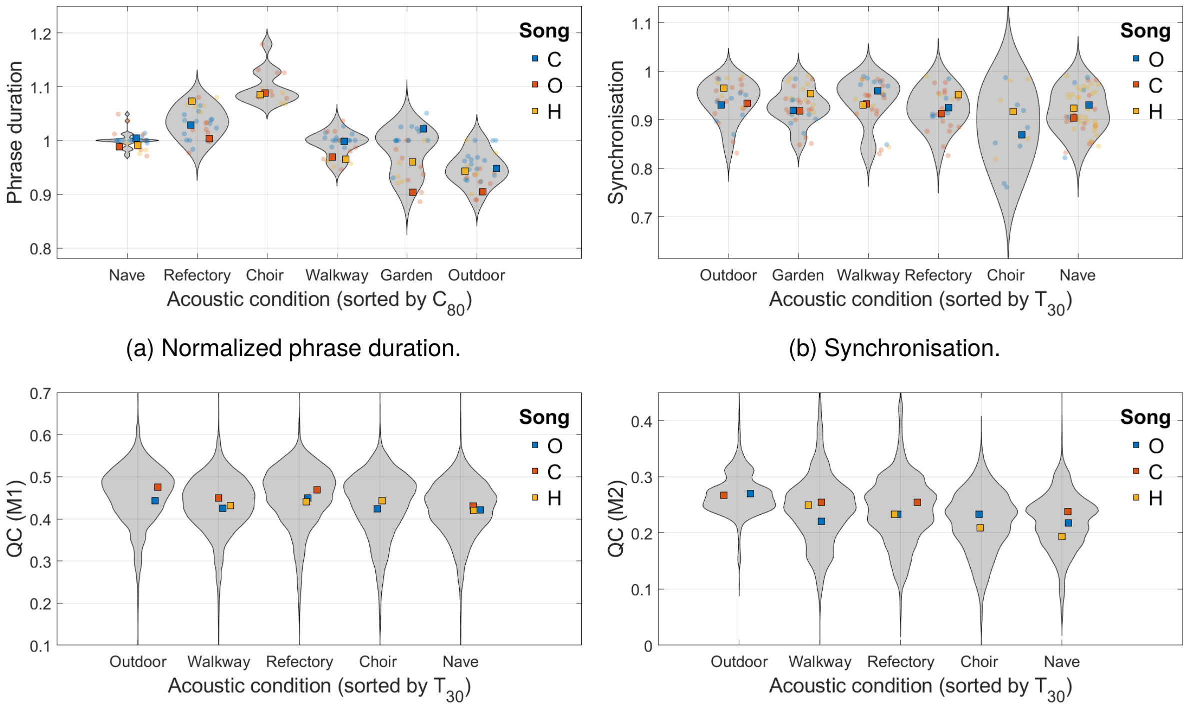
3 RESULTS

Tempo-related attributes Phrase duration and performance alignment were strongly correlated ($r = 0.98$, $p =$, $p < 0.0001$), indicating that both measures captured the same performance attribute. Therefore, only phrase duration was used in subsequent analyses.

A one-way ANOVA revealed a significant effect of acoustic condition on phrase duration ($F = 13.6$, $p < 0.001$). Post-hoc tests using estimated marginal means showed that phrase durations were significantly shorter in the ***Outside*** condition compared to both the ***Refectory*** ($p < 0.01$) and the ***Choir*** ($p < 0.001$), and shorter in the ***Walkway*** than in the ***Choir*** ($p < 0.01$).

As illustrated in Fig. 2a, negatively correlated with clarity (C_{80}, $r = -0.54$, $p = 0.045$), consistent with the correlations reported in Table 2.

Synchronisation To assess the influence of the acoustic environment on inter-singer synchronisation, a one-way ANOVA was conducted on synchronisation across acoustic conditions (Fig. 2b). The analysis revealed no significant effect of acoustics on synchronisation.



(a) Normalized phrase duration.

(b) Synchronisation.

(c) QC values (M1).

(d) QC values (M2).

Figure 2: (a) Duration distributions and scatter plots by chant and acoustic condition. Individual points represent duration for each phrase, while squares indicate the mean duration of phrases per chant and acoustic condition.(b) Onset deviation distributions across singers by chant and acoustic condition. Individual points represent onset deviations for each phrase, while squares indicate the mean deviation per chant and acoustic condition. (c) QC values distribution as a function of acoustic environment and laryngeal mechanisms. Squares indicate the mean QC values per chant and acoustic condition. Colors indicate different chants.

However, Pearson correlation analyses showed a significant negative association between synchronisation and reverberation time (T_{30}, r = -0.54, p = 0.048), suggesting that greater reverberation is associated with reduced temporal precision between singers.

Contact Quotient Due to missing EGG data, analysis was limited to the ***Refectory***, ***Walkway***, and ***Nave*** conditions. A beta regression model with random effects (chant as a random factor) was fitted using glmmTMB, with acoustic condition and laryngeal mechanism (M1 vs M2) as fixed effects.

Model comparisons revealed a significant interaction between acoustic condition and mechanism ($\chi^2(2) = 4256.9$, $p < 0.0001$). Post-hoc tests showed that, for both M1 and M2, QC values were significantly lower in the ***Nave*** compared to the ***Refectory*** and ***Walkway*** ($p < 0.0001$). In M1, QC values were also lower in the ***Walkway*** than in the ***Refectory*** ($p < 0.0001$), conversely, in M2 QC values were lower in the ***Refectory*** compared to the ***Walkway*** ($p < 0.001$).

Additionally, correlation analyses showed that QC in M2 was negatively associated with reverberation time (T_{30}, r = -0.59, p = 0.042), suggesting that more reverberant environments may reduce glottal contact in this mechanism. No significant correlation was observed for M1.

4 CONCLUSION

This preliminary case study aimed to explore how room acoustics influence the performance of 12th-century monodic sacred chant.

The results suggest that durations—reflecting tempo—were affected by the acoustic conditions, particularly by clarity. While some studies do report performance duration differences due to acoustics,[15] and some singers showed variations in tempo associated with different acoustic parameters,[7] this finding generally contrasts with prior studies which did not observe any effect of acoustics on tempo variations in singers.[1,8] These discrepancies could be attributed to several factors. The repertoire performed in this study contains no notated rhythmic values, potentially allowing for greater interpretative freedom compared to repertoires with precisely notated durations and tempi. Additionally, the methods used to calculate tempo-related parameters differ from those typically employed, due to the absence of explicitly defined note durations—possibly affecting how tempo variation is assessed.

Regarding the effect of acoustics on synchronisation, although no significant effect was found in the ANOVA (which aligns with previous work[15]), a correlation was observed between singer synchronisation and reverberation. This suggests that certain acoustic conditions may influence choir synchronisation. One possible explanation is acoustic masking caused by reverberation, which can obscure inaccuracies between singers.

Furthermore, contact quotient (QC) values were found to be lower in reverberant acoustic conditions for laryngeal mechanism M2. This result complements previous observations on vocal fold behaviour in varying acoustics,[6] which did not differentiate the analysis within laryngeal mechanisms. Reduced QC values together with loudness have also been associated with vocal effort.[13] In the context of this specific study on monodic sacred chant, this suggests that highly reverberant spaces, such as church transepts, where singing occurs during liturgical offices and for which the chants studied here were originally intended, may facilitate greater vocal comfort.

However, an important limitation of this study is that only one singer was equipped with an EGG device. As noted, adaptation strategies to acoustics appear to be highly individual,[6] which highlights the need for broader participant sampling in future work.

Still focusing on monodic repertoire, a future study will aim to verify whether the effects observed in this case study can be generalized to a full vocal ensemble, and will explore how contact quotient adaptation strategies to acoustic conditions vary across different ensembles.

REFERENCES

[1] K. Kato, K. Ueno, and K. Kawai, “Effect of room acoustics on musicians’ performance. Part II: Audio analysis of the variations in performed sound signals,” *Acta Acustica united with Acustica*, vol. 101, no. 4, pp. 743–759, 2015, doi:10.3813/AAA.918870.

[2] Z. Schärer Kalkandjiev and S. Weinzierl, “The influence of room acoustics on solo music performance: an empirical case study,” *Acta Acustica united with Acustica*, vol. 99, no. 3, pp. 433–441, 2013, doi:10.3813/AAA.918624.

[3] N. Eley, S. Mullins, P. Stitt, and B. F. G. Katz, “Virtual Notre-Dame: Preliminary results of real-time auralization with choir members,” in *Immersive and 3D Audio Conference*, pp. 1–6, 2021, doi:10.1109/I3DA48870.2021.9610851.

[4] S. Bolzinger, O. Warusfel, and E. Kahle, “A study of the influence of room acoustics on piano performance,” *Le Journal de Physique IV*, vol. 4, no. C5, pp. C5–617–C5–620, 1994, doi:10.1051/jp4:19945132.

[5] P. Bottalico, N. Łastowiecka, J. D. Glasner, and Y. G. Redman, "Singing in different performance spaces: The effect of room acoustics on vibrato and pitch inaccuracy," *The Journal of the Acoustical Society of America*, vol. 151, no. 6, p. 4131–4139, 2022, doi:10.1121/10.0011675.

[6] P. Luizard and N. Henrich Bernardoni, "Changes in the voice production of solo singers across concert halls," *The Journal of the Acoustical Society of America*, vol. 148, no. 1, p. EL33–EL39, 2020, doi:10.1121/10.0001524.

[7] P. Luizard, J. Steffens, and S. Weinzierl, "Singing in different rooms: Common or individual adaptation patterns to the acoustic conditions?," *The Journal of the Acoustical Society of America*, vol. 147, no. 2, p. EL132–EL137, 2020, doi:10.1121/10.0000715.

[8] J. De Muynke, N. Eley, J. Ferrando, and B. F. Katz, "Preliminary analysis of vocal ensemble performances in real-time historical auralizations of the palais des papes," in *The Acoustics of Ancient Theatres*, pp. 1–4, 2022, doi:10.58874/saat.2022.204.

[9] S. S. Mullins and B. F. G. Katz, "Immersive auralisation for choral ensembles," in *International Conference on Auditorum Acoustics*, vol. 45, pp. 1–8, 2023, doi:10.25144/16011.

[10] P. Bottalico, S. Graetzer, and E. J. Hunter, "Effect of training and level of external auditory feedback on the singing voice: pitch inaccuracy," *Journal of Voice*, vol. 31, no. 1, pp. 122–e9, 2017, doi:10.1016/j.jvoice.2016.01.012.

[11] J. Ferrando and J. D. Muynke, *Interpretation of a Medieval Vocal Repertoire in the Reconstructed Acoustics of the Great Chapel of the Palais des Papes*, ch. 7, pp. 151–175. Leiden: Brill, 2024, doi:10.30965/9783846769133_008.

[12] Y. G. Redman, J. D. Glasner, D. D'Orazio, and P. Bottalico, "Singing in different performance spaces: The effect of room acoustics on singers' perception," *The Journal of the Acoustical Society of America*, vol. 154, no. 4, pp. 2256–2264, 2023, doi:10.1121/10.0021331.

[13] D. Z. Huang, F. D. Minifie, H. Kasuya, and S. X. Lin, "Measures of vocal function during changes in vocal effort level," *Journal of Voice*, vol. 9, no. 4, pp. 429–438, 1995, doi:10.1016/s0892-1997(05)80206-1.

[14] D. M. Howard, H. Daffern, and J. Brereton, "Quantitative voice quality analyses of a soprano singing early music in three different performance styles," *Biomedical Signal Processing and Control*, vol. 7, no. 1, pp. 58–64, 2012, doi:10.1016/j.bspc.2011.05.013.

[15] S. Mullins, *Voices of the past: the historical acoustics of Notre-Dame de Paris and choral polyphony*. PhD thesis, Sorbonne Université, 2024.

[16] "ISO 3382-1: Acoustics – Measurement of room acoustic parameters – Part 1: Performance spaces," standard, International Organization for Standardization (ISO), Geneva, CH, 2009.

[17] P. Boersma and D. Weenink, "Praat: doing phonetics by computer." `https://www.praat.org`, 1992–2022. Computer program, Version 6.3, retrieved 23 January 2025.

[18] O. Lartillot, P. Toiviainen, and T. Eerola, "A Matlab toolbox for music information retrieval," in *Data Analysis, Machine Learning and Applications*, pp. 261–268, Springer, 2008, doi:10.1007/978-3-540-78246-9_31.

[19] O. Lartillot, D. Cereghetti, K. Eliard, W. J. Trost, M.-A. Rappaz, and D. Grandjean, "Estimating tempo and metrical features by tracking the whole metrical hierarchy," in *International Conference on Music & Emotion, Jyväskylä, Finland*, University of Jyväskylä, Department of Music, 2013.

[20] https://github.com/SpaceCadetAlba/MM-BOP.

[21] B. Roubeau, N. Henrich, and M. Castellengo, "Laryngeal vibratory mechanisms: the notion of vocal register revisited," *Journal of Voice*, vol. 23, no. 4, pp. 425–438, 2009, doi:10.1016/j.jvoice.2007.10.014.

[22] N. Henrich, C. d'Alessandro, B. Doval, and M. Castellengo, "On the use of the derivative of electroglottographic signals for characterization of nonpathological phonation," *The Journal of the Acoustical Society of America*, vol. 115, no. 3, pp. 1321–1332, 2004, doi:10.1121/1.1646401.

[23] N. Henrich, C. d'Alessandro, B. Doval, and M. Castellengo, "Glottal open quotient in singing: Measurements and correlation with laryngeal mechanisms, vocal intensity, and fundamental frequency," *The Journal of the Acoustical Society of America*, vol. 117, no. 3, pp. 1417–1430, 2005, doi:10.1121/1.1850031.

[24] T. Hothorn, F. Bertz, and P. Westfall, "Simultaneous inference in general parametric models," *Biometrical Journal*, vol. 50, no. 3, pp. 346–363, 2008, doi:10.1002/bimj.200810425.