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Sensitivity and Generalization of a Neural Network for Estimating Left Atrial Fibrotic Volume Fractions from the 12-lead ECG

Abstract: Features extracted from P waves of the 12-lead electrocardiogram (ECG) have proven valuable for non-invasively estimating the left atrial fibrotic volume fraction associated with the arrhythmogenesis of atrial fibrillation. However, feature extraction in the clinical context is prone to errors and oftentimes yields unreliable results in the presence of noise. This leads to inaccurate input values provided to machine learning algorithms tailored at estimating the amount of atrial fibrosis with clinical ECGs. Another important aspect for clinical translation is the network's generalization ability regarding new ECGs. To quantify a network's sensitivity to inaccurately extracted P wave features, we added Gaussian noise to the features extracted from 540,000 simulated ECGs consisting of P wave duration, dispersion, terminal force in lead V1, peak-to-peak amplitudes, and additionally thoracic and atrial volumes. For assessing generalization, we evaluated the network performance for train-validation-test splits divided such that ECGs simulated with the same atria or torso geometry only belonged to either the training and validation or the test set. The root mean squared error (RMSE) of the network increased the most in case of noisy torso volumes and P wave durations. Large generalization errors with a RMSE difference between training and test set of more than 2% fibrotic volume fraction only occurred if very high or low atria and torso volumes were left out during training. Our results suggest that P wave duration and thoracic volume are features that have to be measured accurately if employed for estimating atrial fibrosis with a neural network. Furthermore, our method is capable of generalizing well to ECGs simulated with anatomical models excluded during training and thus meets an important requirement for clinical translation.

Keywords: atrial fibrosis, neural networks, regression, sensitivity, generalization, P waves, ECG simulations

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1 Introduction

Atrial fibrillation (AF) is the most common supraventricular tachycardia and is associated with a progressive structural remodeling process affecting the atrial tissue. The formation of fibrotic tissue in the atria is one of the hallmarks of this process. Fibrosis contributes to the AF arrhythmogenesis as fibrotic tissue exhibits slower conduction properties and thus facilitates functional reentry of the depolarization wave. [1]

Therefore, estimating the amount of atrial fibrosis could contribute to stratify the risk of new-onset AF. Furthermore, it could help to select the right strategy during catheter ablation as standalone pulmonary vein isolation has shown to entail considerable AF recurrence rates especially in patients with large arrhythmogenic substrate areas. Late gadolinium enhancement magnetic resonance imaging or uni- and bipolar voltage maps recorded during electrophysiological studies are commonly relied on in clinical practice to quantify the amount of atrial fibrosis. As an alternative to these start-of-the-art approaches, we have shown the general potential of features extracted from the P wave of the 12-lead electrocardiogram (ECG) as non-invasive surrogate measures of atrial fibrosis. We demonstrated that a combination of P wave duration, dispersion, terminal force in lead V1, peak-to-peak amplitudes in all 12 leads and measures for the atrial and thoracic volume could estimate the left atrial fibrotic volume fraction with an absolute RMSE of 6.3% in a computational study [2].

For a successful clinical translation, two aspects not covered by our in silico study so far are to be investigated. On the one side, our regression model relies on features extracted from P waves of the 12-lead ECG. Those features are easily and robustly extractable from noise-free simulated signals, but their values are subject to several disturbances in the clinical use case. We therefore aim to quantify how sensitive the network is with respect to inaccurately determined feature

values and to what extent the network's estimation of the fibrotic volume fraction is still reliable if the feature values are corrupted by noise. On the other hand, the network should be able to estimate the amount of atrial fibrosis also for previously unseen ECGs if applied in practice. For this reason, we evaluate how well the network can generalize to simulated ECGs coming from atrial and thoracic geometries not included during training of the network.

2 Methods

2.1 ECG Simulations

In order to generate a large-scale database of simulated P waves, we relied on statistical shape models of the atria [3] and the torso [4] to realize 80 atrial and 25 thoracic geometries. For each atrial geometry, we defined a fraction of 0%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% and 45% of the total LA tissue volume as fibrotic [5]. The amount of right atrial fibrosis was subsequently defined according to the findings in [6]. To account for the diffuse and patchy nature of fibrotic tissue in the atria, we chose several disconnected patches accumulating to the total degree of fibrosis in which the density of fibrotic cells was reduced to ~80%. In these fibrotic cells, maximum ionic conductances were rescaled and tissue conduction velocity (CV) was either reduced by 80% and 50% in transversal and longitudinal fiber direction, respectively, or set to 0mm/s [2]. We subsequently received the transmembrane voltage distribution in the healthy control cases (0% fibrosis) and diseased cases (5%-45% fibrosis) by solving the Eikonal equation and applying an atrial action potential template.

Each atrial geometry was rotated by -20°, 0° and +20° around the x-, y- and z-axis resulting in 27 rotation permutations per atrial geometry. By placing them in each of the 25 thoracic geometries we obtained a cohort of 54,000 model combinations covering a wide range of anatomical variability in our virtual population [2]. Subsequently, we obtained a total of 540,000 P waves (80 atrial geometries × 27 rotation angles × 25 torso geometries × 10 fibrotic volume fractions) by extracting the extracellular potentials at the standardized ECG electrode positions from the body surface potential distributions.

2.2 Feature Extraction

For each of these 540,000 P waves, the following 15 features were extracted as described in [2]:

- P wave duration PW_{dur} as the time difference between the earliest detectable P wave beginning and the latest detectable P wave ending across all 12 leads detected with a fixed voltage threshold.
- P wave dispersion PW_{disp} as the time difference between the earliest and latest detectable P wave ending across all 12 leads.
- P wave terminal force in V1 (PTF V1) as the product of the amplitude and the duration of the negative deflection of the P wave in lead V1.
- Peak-to-peak amplitudes in each lead (I_a, II_a, …, $V6_a$) as the voltage difference between the minimum and maximum amplitude in each lead.

Furthermore, we also included the following anatomical measures of the atria and the torso as input features for the neural network:

- left and right atrial volume (LA_{vol}, RA_{vol})
- torso volume (T_{vol})
- torso diameters along the anterior-posterior axis in the abdominal (T_{da}) and the chest region (T_{dc})

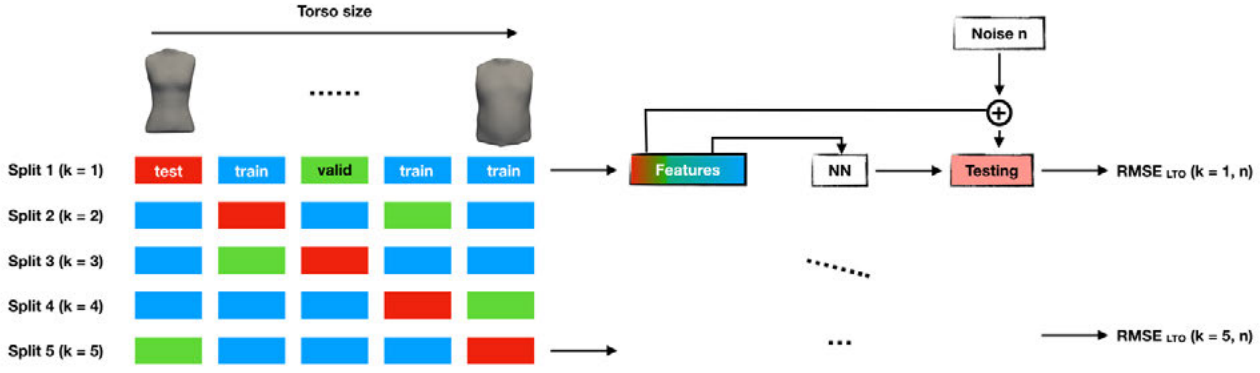

Figure 1: Setup for evaluating generalization and sensitivity of the neural network for the leave-torsos-out (LTO) splits. Red, green and blue samples are used for testing, validation and training, respectively.

2.3 Noise Model

To recreate the clinical case of inaccurately extracted features, we superimposed the feature values extracted from our simulations with noise. For each feature, we realized 11 noise vectors consisting of Gaussian noise with zero mean and a standard deviation (σ_N) set to different fractions n ∈ [0, 0.05, 0.1, ..., 0.5] of the standard deviation of the respective feature distribution (σ_S). By choosing Gaussian noise, we were able to account for different levels of imprecise extracted feature values occurring when applying automated feature extraction software.

2.4 Neural Network Setup

We used the 15 extracted P wave features as well as the 5 anatomical measures listed in section 2.2 as input and trained a regression model to estimate the left atrial fibrotic volume fraction as an output. The network architecture counted 1 hidden layer comprising 10 neurons and was set up as explained in [2]. To evaluate the network's generalization ability, we used 5-fold cross-validation to evaluate the performance of the regression model in the case of noise-free input data. For that purpose, we considered two scenarios: To evaluate how well the network can generalize to unseen torso geometries, we split the dataset into 5 subsets, each comprising 108,000 ECGs simulated with 5 different torso geometries of ascending volumes (leave-torsos-out split (LTO)). For each cross-validation run, one of these five sets were used for

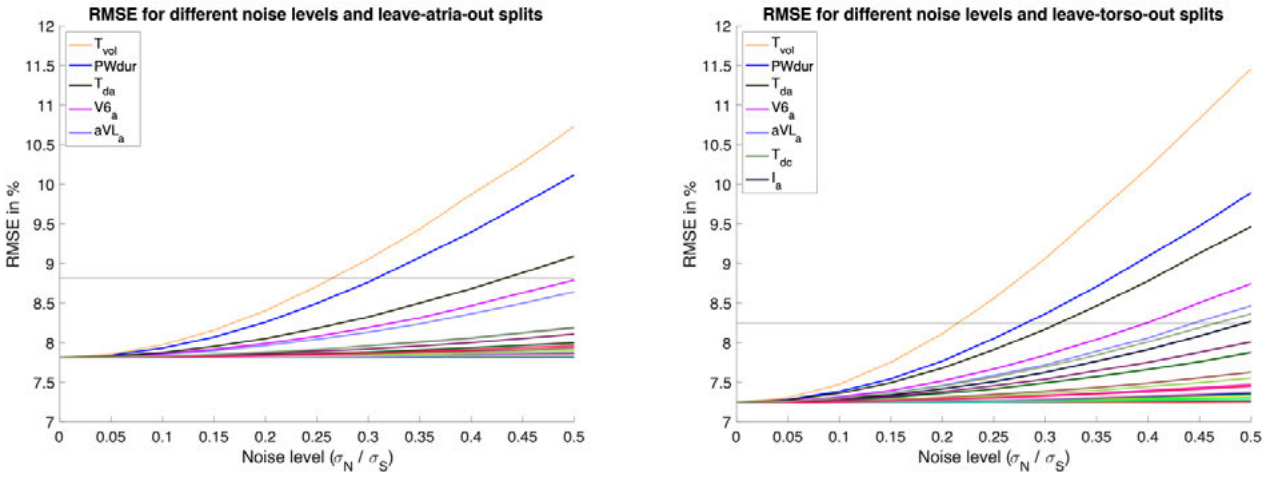

Figure 2: Sensitivity results for LAO splits (left) and LTO splits (right). The RMSE output by the network is shown for different noise levels applied to the input features. The vertical lines indicate an increase of the RMSE by 1% compared to the noise-free case. The legend entries show the features that cause a RMSE increase by more than 0.8%.

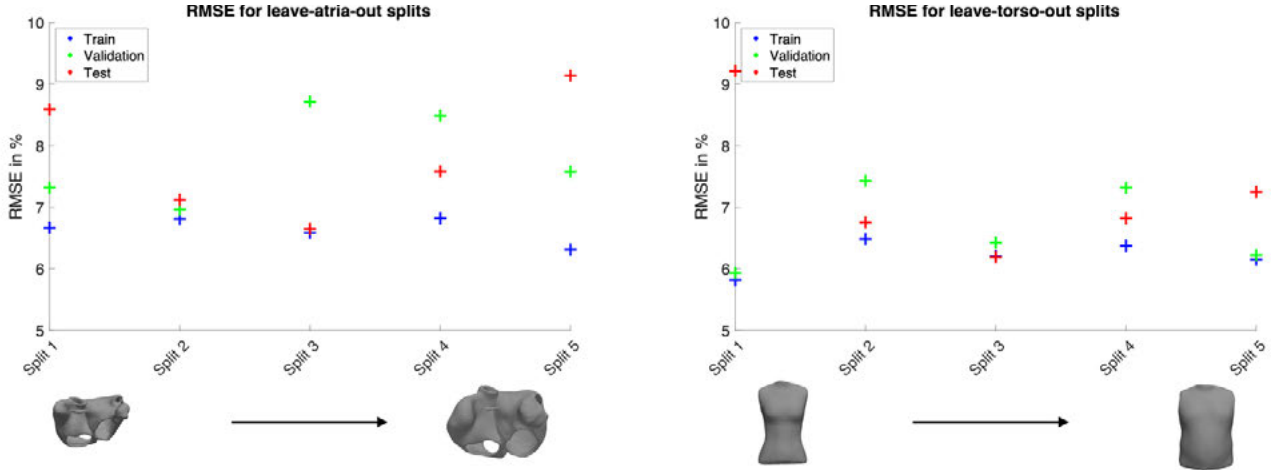

Figure 3: Generalization results for LAO splits (left) and LTO splits (right). The RMSE for training, validation and test sets are marked in blue, green and red, respectively for each split.

testing, the remaining four for training and validation, resulting in a train-validation-test distribution of 60% - 20% - 20%. This procedure is illustrated in Figure 1. A similar division was realized to assess the network's generalization ability in the case of previously unseen atrial geometries. The five-fold split resulted in 108,000 ECGs per subset simulated with 16 different atrial geometries of ascending volumes (leave-atria-out split (LAO)).

3 Results

3.1 Sensitivity

Figure 2 shows the RMSE of the network output averaged over all 5 LTO and LAO test results depending on the applied noise level n. For the LTO scenario, the absolute RMSE increased by 1% compared to the noise-free baseline case for a noise level of $\sigma_N/\sigma_S = 0.2$ for the torso volume (corresponding to an absolute noise standard deviation of σ_N=0.0028m^2) and a noise level of $\sigma_N/\sigma_S = 0.3$ for the P wave duration (σ_N = 4.3ms). For the LAO scenario, an absolute RMSE increased by 1% compared to the noise-free case occurred for a noise level of $\sigma_N/\sigma_S = 0.25$ for the torso volume ($\sigma_N = 0.0036$m^2) and a noise level of $\sigma_N/\sigma_S = 0.3$ for the P wave duration.

3.2 Generalization

The generalization results for the different train-validation-test splits are shown in Figure 3. The RMSE of the test sets increased if very small and large atrial geometries were left out during training in the LAO scenarios. For the LTO splits, the test accuracy was decreased the most for split 1 in which small torso volumes were excluded during training.

4 Discussion

We found that the RMSE increased the most if noisy feature values for the torso volume and P wave duration were provided to the network independent on how the data were split for training, testing and validation. The presence of fibrotic tissue reflects in a change of the P wave amplitudes that are also affected by the torso volume. Furthermore, the reduced CV in the fibrotic regions cause P wave durations to increase. For these reasons, those two features are most important to separate the changes in P wave features resulting from fibrotic infiltration of atrial tissue from those caused by healthy anatomical variations and thus must be accurately measured. The network was able to generalize well to ECGs simulated with unseen atrial and torso geometries if ECGs generated with different geometries, but similar atrial and thoracic volumes were included during training. In our simulation study, we only assessed the network's sensitivity in case of noise being added to a single input feature. However, in clinical practice, usually even a combination of different features is determined with uncertainty. Therefore, clinical ECG recordings as input for the network require robust signal processing methods for extracting key features accurately.

Conclusion

We have shown that an accurate assessment of the torso volume and the P wave duration is necessary for reliably estimating the amount of atrial fibrosis with our proposed method. Furthermore, we demonstrated the capability of the network to generalize well to unseen ECGs during training paving the way for clinical translation of a machine learning tool for risk stratification and therapeutic decision support.

Author Statement

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