# Predict Drug-induced Nausea with Deep Learning using a new Gastro-Intestinal Pacemaker Activity Drug Database (GIPADD)

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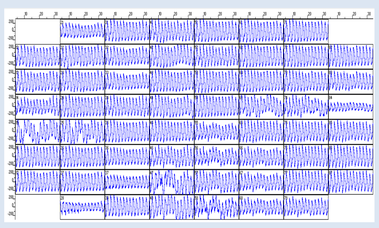
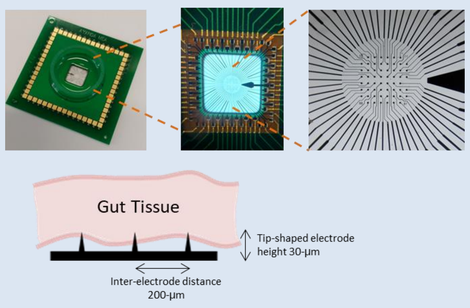
## INTRODUCTION

Bio-electrical data is a new type of big-data for training artificial intelligence (AI) in drug discovery. We make use of a microelectrode array platform for efficient drug screening of drug-induced acute effects on gut pacemaker activity [1], creating a novel drug database named "Gastro-Intestinal Pacemaker Activity Drug Database" (GIPADD). As a proof of concept, we had previously trained a few machine learning classification models based on a smaller database in 2021 (89 drugs, 4,867 datasets) [2]. In this study, we use our updated GIPADD (>170 drugs, >10,000 datasets) to predict a selected drug adverse effect (ADR), nausea, by deep learning models.

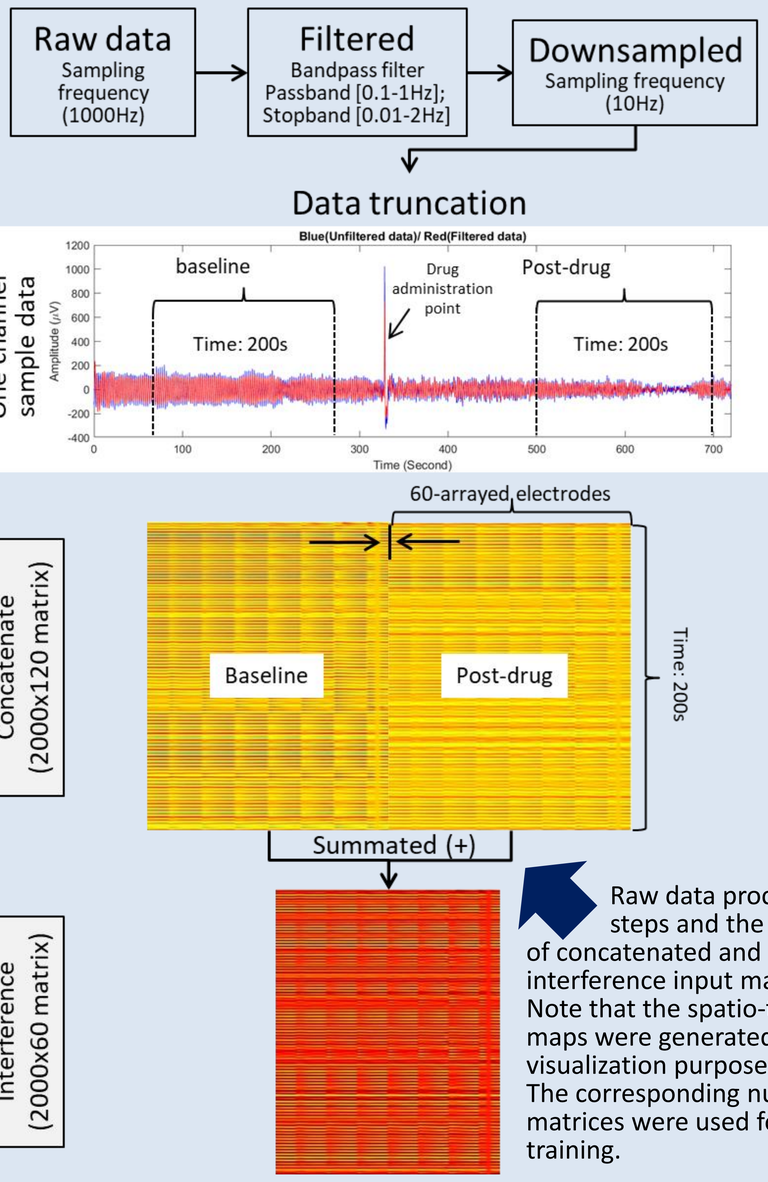
## METHODOLOGY



Raw data recorded from 60-channels simultaneously




The Microelectrode Array technique



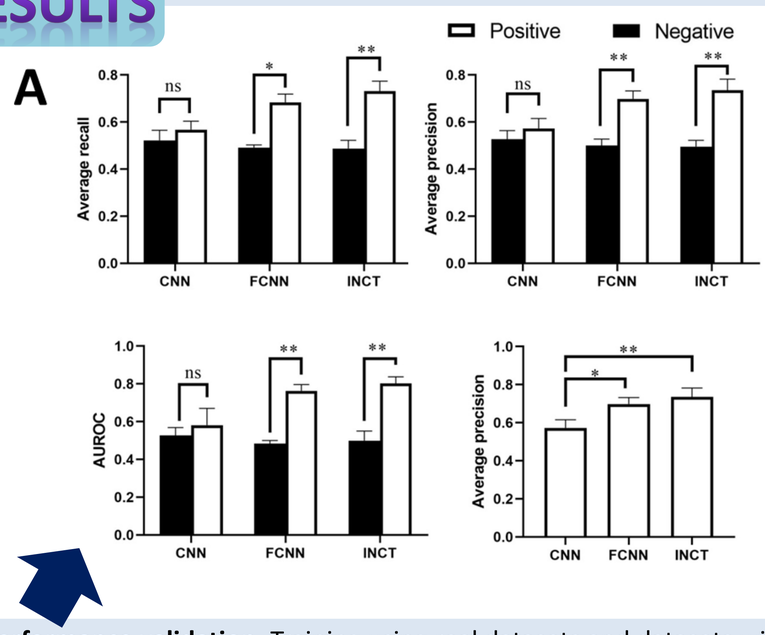

Raw data processing steps and the creation of concatenated and interference input matrix. Note that the spatio-temporal maps were generated for visualization purposes only. The corresponding numerical matrices were used for training.

| | Old publication [2] | This abstract |
|---|---|---|
| Size of GIPADD database | 89 drugs; 4,867 datasets | >170 drugs; >10,000 datasets |
| Cutoff time | Feb 2022 | Aug 2023 |
| Model used | Machine learning classifiers: Naïve Bayes, discriminant analysis, classification tree, k-nearest neighbors, support vector machine and an ensemble model | Deep learning classifiers: simple CNN classifier (CNN), a fully connected neural network (FCNN) and an inception time classifier (INCT) |
| Nausea-prediction model | Accuracy <70% | Internal validation accuracy 73% (INCT) |
| External validation | Not performed | A few non-SIDER-listed drugs |
| Parameters (per datasets) | 24 | >8.3k (CNN), >320k (FCNN), >500k (INCT) |

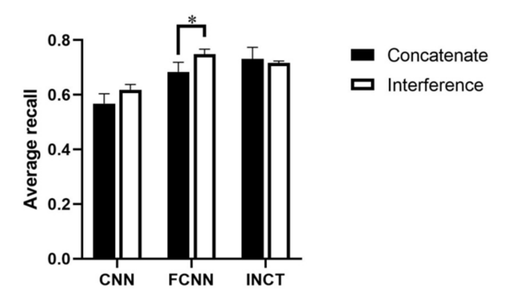
## WORKFLOW

1. Drugs tested were matched with **SIDER-ID** in Side Effect Resource
2. Two-hundred seconds of baseline and post-drug filtered data were extracted and combined to create a joined 2,000x120 ("concatenate") or summated 2,000x60 ("interference") **input matrix** for training deep learning models
3. A **balanced** (positive-to-negative) dataset (1352:1352) was created
4. Further divided into training and validation datasets with a ratio of **8:2**
5. **Negative controls** were tested by shuffling the annotations in training datasets
6. **Deep learning training** Three AEON-Tensorflow models were tested: simple CNN classifier (CNN), a fully connected neural network (FCNN) and an inception time classifier (INCT)
7. **Model performance** was evaluated for precision, recall and AUROC
8. External validations were tested on a few drugs known to induce nausea, but not listed in SIDER database

## RESULTS




| B | | |
|---|---|---|
| **Model** | **Training time** | **Accuracy** |
| CNN | + | -/+ |
| FCNN | ++ | +++ |
| INCT | +++ | ++++ |




**Performance validation.** Training using real datasets and datasets with shuffled labels (negative control) were performed three times separately. Different balanced subsets of positive and negative datasets were extracted from GIPADD for each training attempt. Models were trained using a concatenated input matrix. FCNN (Zhao et al., 2017) and INCT (Fawaz, 2020) have significantly higher average recall, average precision and AUROC when using real datasets compared to negative controls (*p<0.05, **p < 0.01, n = 3, paired t-test), but CNN model (p>0.05, n = 3, paired t-test) does not. (B) Comparison between 3 deep learning models. Both INCT and FCNN have a significantly better performance than CNN. (C) The difference in performance of a concatenated versus interference input matrix is insignificant for all models except FCNN (p<0.05, unpaired t-test), with interference matrices eliciting better recall for FCNN. Training time is shorter using interference because a smaller input matrix (2,000x60) was used compared to the concatenated counterpart (2,000x120) .

| Drug Name (Known relations to ADR: nausea) | Predicted Nausea-index |
|---|---|
| **Internal Validation** (With SIDER ID) Used in training model | |
| Cisplatin (Nausea-inducing) | 0.913 |
| Apomorphine (Nausea-inducing) | 0.710 |
| Domperidone (Nausea indication) | 0.389 |
| Ondansetron (Nausea indication) | 0.079 |
| **External Validation** (Without SIDER ID) Not used in training model | |
| Cisapride | 0.317 |
| Rolipram (Nausea-inducing) | 0.840 |
| Exendin-4 (Nausea-inducing) | 0.811 |
| GLP-1 (Nausea-inducing) | 0.596 |
| Semaglutide (Nausea-inducing) | 0.671 |
| Sulpiride | 0.382 |

Table showing the prediction results (predicted nausea index) of a few drugs used in training models (i.e. with listed SIDER-ID) for internal validation and a few drugs without SIDER-ID for external validation (data not used in training models). The external validation drugs have known associations with nausea in literature: nausea-inducing drugs include exendin-4 (Fineman et al., 2004), GLP-1 (Sikirica et al., 2017), semaglutide (Loomba et al., 2023) and rolipram (Gobejishvili et al., 2022); and drugs reducing nausea include sulpiride (Bianconcini et al., 1988) and cisapride (Russel, 1996).

## REFERENCE

[1]
[2]

## CONCLUSION

- A nausea prediction model was successfully trained using GIPADD as the input database
- Apply for novel drug safety assessments
- More models are now being trained for other ADRs to optimize GIPADD potential.

Follow updates of our "bio-electrical" drug database GIPADD (to be launched Jan 2024)

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