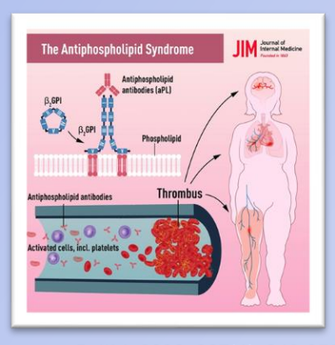
Research Question

Introduction

Antiphospholipid antibody syndrome (APS) is an autoimmune disorder where the immune system attacks phospholipids in the blood, leading to the formation of blood clot. This is a major cause of pregnancy complications and miscarriages. The prevalence of the disease is 50/100,000 population. Diagnosing APS requires identifying a lupus anticoagulant.



Svenungsson E, JIM, 2020, 287(4): 349-372

Laboratory Identification of Lupus Anticoagulant requires:

- Prolongation of a phospholipid-dependent screening test, usually a LAC-responsive dilute Russell's viper venom time (DRVVT) or activated partial thromboplastin time (APTT)
- Inhibition on mixing with pooled normal plasma depending on the guideline
- Confirmation of phospholipid-dependent inhibition by repeating the prolonged test with excess phospholipid.

Challenges

- Due to many factors such as the heterogeneity of antiphospholipid antibodies, the marked variations in reagents, inconsistencies in post-analytic processes, and interferences that may mimic a LAC, diagnosis of an LAC is both challenging and subjective.
- In addition, anticoagulant drugs, such as heparin, warfarin and direct-acting oral anticoagulants may cause false-negative and false-positive results during LAC testing.
- Exclusion of anticoagulant drug effects is therefore a critical step when evaluating lupus anticoagulant test results.

Research objectives

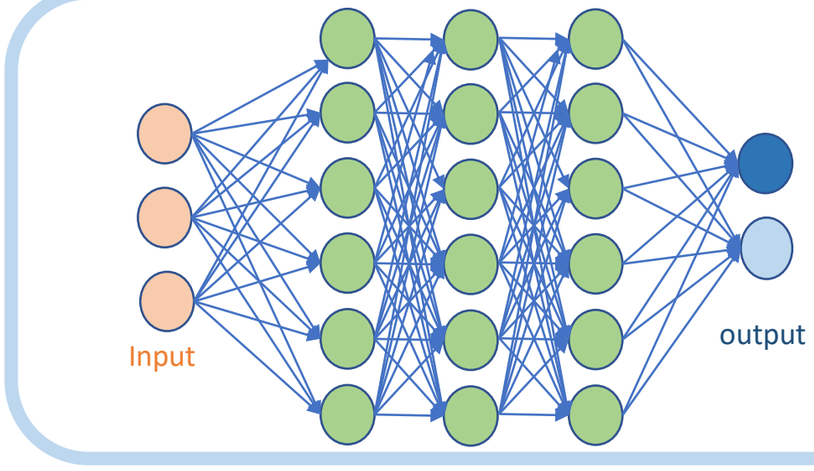
- Develop a deep neural network model for classification of a LAC by the DRVVT and APTT methodologies and the presence of anticoagulant drugs Heparin and Warfarin.
- Train a DNN to achieve high diagnostic accuracy
- Evaluate the performance of the DNN model in the testing cohorts by comparing diagnostic accuracy between the model and a expert rater

Methodology/Project Design

All patient data for training, validation, and testing were obtained from the Mayo Clinic Anticoagulant Laboratory.

Training Cohort
N=4608

Training



Multi-output DNN Model

Validation

Validation Cohort
N=1153

- Diagnostic Accuracy
- Area Under the Curve (AUC)
- Precision recall curve (PRC)

Testing

Testing Cohort
N=1441

- Sensitivity
- Specificity
- Accuracy
- F1 Score
- Index of balanced accuracy

Data Analysis & Results

Labels	Accuracy	AUC	PRC
LAC-DRVVT	96.36%	0.997	0.964
LAC-APTT	96.95%	0.994	0.847
HEP	96.24%	0.976	0.929
WAR	100%	0.994	0.965

Table 1: Validation of diagnostic accuracy of the multi-output DNN model in the validation cohort. AUC: area under the receiver operating characteristic curve; PRC: area under the precision-recall curve.

Labels	TP	TN	FP	FN	Accuracy	Sensitivity	Specificity	PPV	NPV	F1	IBA
DRVVT	180	1235	13	13	0.982	0.933	0.990	0.933	0.990	0.933	0.961
APTT	112	1314	6	9	0.990	0.926	0.995	0.949	0.993	0.937	0.961
HEP	122	1293	11	15	0.982	0.891	0.992	0.917	0.989	0.904	0.941
WAR	177	1252	7	5	0.992	0.973	0.994	0.962	0.996	0.967	0.983

Table 2: Performance metrics of Multi-output DNN model. TP: true positive. TN: true negative. FP: false positive. FN: false negative. PPV: positive predictive value. NPV: negative predictive value. IBA: index of balanced accuracy.

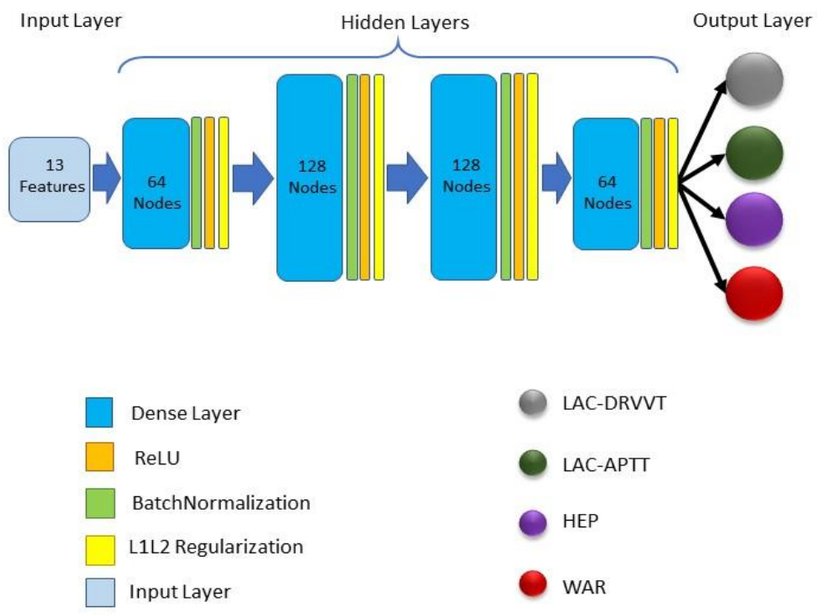


Figure 1: Schematic of multi-output DNN architecture, consisting of an input layer with 13 features, four hidden layers (64, 128, 128, and 64 nodes), and four different output modes for each label (LAC-DRVVT, LAC-APTT, HEP, and WAR).

Conclusions

- In conclusion, the DNN model can accurately classify LACs and common anticoagulation effects without the need to manually extract features.
- Automated AI/ ML-based approach has the added benefit of standardizing classification of LAC profiles across different human raters.
- Model predictions can be potentially be used in downstream processing to append textual comments to cases for review by laboratory specialists prior to releasing results.
- The main limitation of this study was that only one expert-rater was used to determine the ground-truth. Since LAC is a rare disease that has subjective diagnosis, having multiple raters would significantly strengthen the accuracy of the model.