Comparing Inductive and Deductive Inference Approaches in Understanding Autoantibody–Proteomic Interactions in Systemic Lupus Erythmatosus (SLE)

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Abstract

Systemic Lupus Erythematosus (SLE) is a highly heterogeneous autoimmune disease where clinical assessment, such as the SLEDAI score, often fails to capture underlying molecular states of disease. This project introduces a novel diagnostic framework that integrates proteomic co-expression modules, anti-cytokine autoantibody (ACA) titers, and clinical scores. We compare the predictive performance and interpretability of two distinct approaches: a probabilistic, inductive Random Forest classifier, and a deterministic, deductive Expert System. The deductive system's Knowledge Base is constructed using robust statistical associations (T-tests and Spearman correlations) derived from the training data. We demonstrate that the deductive expert system achieves a competitive F1-score (0.60 vs. 0.64 for the inductive baseline), with the interpretable advantage of providing a rules-based chain-of-thought justification for every classification (forward chaining). This approach offers a significant step towards creating diagnostic tools that can integrate biological mechanisms with clinical manifestations of disease.

Background

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by periods of flare and remission, driven by dysregulated immune responses against a wide array of self-antigens. Because its clinical manifestations span various organs such as the blood vessels, brain, lungs, skin, kidneys and joints, quantifying disease activity can be challenging due to the heterogeneity in patients' symptoms (Dai, Fan, and Zhao 2025). Combined with the variability in clinical observations, there is a need for integrative frameworks that combine clinical observations with high-resolution molecular measurements to better describe a patient's disease state.

Accurate monitoring of disease activity SLE is an important aspect of effective patient management. For lupus, the current standard relies on the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), a composite score composed of 24 clinical descriptors (SLE). While widely adopted, SLEDAI scoring can be subjective and does not

represent underlying molecular pathology. This project integrates three distinct data modalities—proteomic module eigengenes (derived from WGCNA (Langfelder and Horvath 2008)), anti-cytokine autoantibody (ACA) titres (derived from a Luminex xMAP assay (Lum)), and clinical SLEDAI scores—to develop a mechanistically informed disease activity prediction tool. The combination of proteomic modules, which represent functional protein pathways, and ACAs, which are direct agents of immune dysregulation, is designed to capture a more complete picture of the disease state.

Recently, Machine learning (ML) and computational approaches have emerged to address the clinical practice gap where objective, consistent measures of disease activity are needed. A notable machine learning model was developed to estimate SLEDAI score categories (no activity, mild activity, moderate activity, or high/very high activity) using unstructured clinical notes, achieving an area under the curve (AUC) of 0.93 for the development cohort and 0.91 for the validation cohort (Alves et al. 2021). This model demonstrated strong correlation with actual clinical outcomes, including steroid and analgesic prescriptions and healthcare resource utilization (Sebastiani et al. 2022). The automated estimation of SLEDAI scores provides significant clinical value by dramatically increasing the number of available endpoints for tracking patient outcomes when clinician-recorded scores are unavailable (Alves et al. 2021).

Other specialized algorithms have been developed to predict High Disease Activity Status (HDAS) without requiring knowledge of the actual SLEDAI score. One algorithm utilizing seven pathology measures and three demographic variables achieved 88.6% accuracy with an 11.4% misclassification rate, demonstrating superior performance compared to a Naive Bayes Classifier (AUC = 0.829 vs. 0.663) (Lilli et al. 2025) (Hoi et al. 2021). This approach enables the rapid identification of patients suitable for treatment escalation or clinical trial enrollment using routinely available clinical measurements.

While these inductive machine learning tools assist in tracking disease progression and generating insights into intervention effectiveness, they fundamentally function in a black-box manner: they excel at correlation and prediction but offer limited insight into the specific molecular interactions driving a patient's active state.
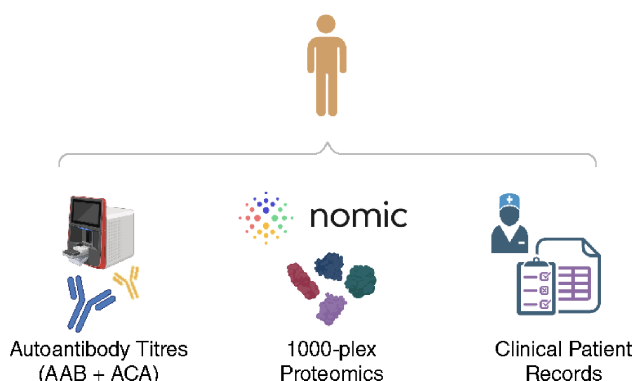
Figure 1: Modalities for each patient

We propose the use of a deductive expert system to encode the interactions of these factors into deterministic rules. Unlike traditional inductive machine learning approaches, such as Random Forests, which provide probabilistic estimates, a deductive system uses explicit knowledge representations to reach definite, traceable conclusions, thereby enhancing interpretability. The inductive phase of the project establishes the strength and robustness of molecular associations, which are then hardened into the logical rules governing the deductive system. This dual approach ensures that the resulting diagnostic logic is both data-driven and structurally rigorous, combining empirical evidence with transparent reasoning pathways.

Materials and Methods

Data Set Description and Cohort Characteristics

Our dataset consists of $N = 180$ patients diagnosed with Systemic Lupus Erythematosus (SLE). The cohort is 86% female and 14% male. The mean age was 45.8 ± 15.3 years. The cohort included a spectrum of disease activity, with adequate representation of active (SLEDAI ≥ 4) and inactive states. Each patient had paired measurements across three data modalities, as described in Figure 1.

Data Modalities Each patient sample yielded the following data modalities:

1. **Protein Co-expression Module Scores (WGCNA):**
   - **Origin:** These scores are derived from large-scale plasma proteomics data performed on a larger cohort of autoimmune patients and healthy controls. Plasma proteomic data was generated through NOMIC Bio's nELISA platform (Dagher et al. 2023). Weighted Gene Co-expression Network Analysis (**WGCNA**) (Langfelder and Horvath 2008) was applied to the full autoimmune cohort. WGCNA is a method employed to move from roughly a thousand of individual protein measurements to a few robust pathway activity scores, achieved by constructing a network where proteins are nodes and their co-expression levels are weighted edges. The process begins by calculating the pairwise correlation (s_{ij}) between all proteins across the patient cohort (the Similarity Matrix S), which is then transformed into an adjacency matrix A using a soft-thresholding power β: $a_{ij} = |s_{ij}|^{\beta}$. This emphasizes strong correlations and filters noise by forcing the network toward a scale-free topology. Next, the matrix is converted into the Topological Overlap Measure (TOM) matrix, which measures not just direct co-expression but also the extent to which two proteins share common neighbors, ensuring a more biologically relevant clustering. Hierarchical clustering is applied to the TOM distance ($1 - \text{TOM}$), and a dynamic tree cut algorithm identifies dense clusters, termed co-expression modules (e.g., ME1, ME2). Finally, the activity of each module is summarized by the Eigenprotein value, which is the first principal component of the expression data for all proteins within that module.
   - **Feature Definition:** The module activity is summarized by the Eigenprotein value, a continuous numerical score representing the weighted average expression of all proteins within that module. This score acts as a quantitative proxy for the pathway's overall activity in a given patient. By using these Eigenproteins, we significantly reduce the dimensionality of the original proteomic dataset.

2. **Anticytokine Autoantibody (ACA) Titers:**
   - **Origin:** Titers for a panel of $K = 39$ specific ACAs were quantified using Luminex xMAP, an immunoassay. These ACAs include immune mediators such as $\text{ACA}_{\text{IFN}\alpha}$, $\text{ACA}_{\text{IL-1}\beta}$, $\text{ACA}_{\text{TNF}\alpha}$, and others.
   - **Feature Definition:** The measurements are continuous titer values that were transformed using the arcsinh transformation, $\text{arcsinh}(x) = \ln(x + \sqrt{x^2 + 1})$, to mitigate the effects of outliers and create a distribution closer to normal, which lends the measurements better for statistical tests. The transformed values represent the relative abundance of that patient's autoantibody levels.

3. **SLEDAI Scores (Clinical Target):**
   - **Origin:** The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) score was recorded by a certified clinician based on available information extracted from the electronic health record.
   - **Range:** While the score can range from 0 (no activity) to as high as 105 (severe activity), we define active disease (a flare) as having a SLEDAI ≥ 4, and inactive disease (remission) as having a SLEDAI < 4.

Data Preprocessing for Deductive Logic

Moving from high-dimensional, continuous biological data to a symbolic, rule-based expert system requires rigorous discretization of features of interest.

Feature Discretization: Defining Symbolic Premises The M module scores and K ACA titers were transformed into symbolic premises using fixed quantile cutoffs.

- **Procedure:** The entire training dataset was used to calculate the 33rd and 67th percentiles for each continuous feature (Module_i or ACA_j). The use of the 33rd and 67th percentiles was specifically chosen to partition the data into three roughly equal-sized bins (LOW, MED, HIGH), ensuring a balanced representation of the different symbolic states while also providing statistical robustness against data skewness.

- **Discretization Formula:** For any continuous feature X:

$$X_{\text{disc}} = \begin{cases} \text{LOW (0)} & \text{if } X < \text{Q}_{0.33} \\ \text{MED (1)} & \text{if } \text{Q}_{0.33} \leq X \leq \text{Q}_{0.67} \\ \text{HIGH (2)} & \text{if } X > \text{Q}_{0.67} \end{cases}$$

This converts the continuous values into discrete symbolic facts (LOW, MED, HIGH), which form the **IF** clauses of the deductive rules.

Target Discretization: Defining the Conclusion The SLEDAI score was binarized to define the expert system's conclusion ($\text{SLEDAI}_{\text{active}}$):

- **Cutoff Selection:** A clinical threshold of $\text{SLEDAI} \geq 4$ was chosen to define active disease.

- **Binary Conclusion:** The target variable is $\text{SLEDAI}_{\text{active}} \in \{0, 1\}$, where 1 denotes active disease and 0 represents inactive disease.

Data Partitioning The complete dataset was split into a training and testing set using an $80\% : 20\%$ split, with a random state of $seed = 42$ for reproducibility.

- The training dataset was used exclusively to (a) calculate the quantile cutoffs, (b) inductively derive the strong associations that form the knowledge base, and (c) train the inductive and deductive classification algorithms.

- The testing dataset ($N = 36$ patients) was used exclusively for evaluation, serving as unseen data to assess the generalizability of the different approaches.

Design

The study employs a two-pronged approach, first establishing an inductive baseline for performance comparison, and then constructing a deductive expert system which utilizes a knowledge base and an inference engine.

Inductive Strategy: Baseline Performance

To contextualize the performance of the final deductive model, two baseline inductive **Random Forest Classifiers** were trained:

1. **Random Forest Classifier (ACA-Only):** This model was trained using only the continuous Anticytokine Autoantibody (ACA) titers as features. This established a baseline for how well the serological data alone can predict disease activity.

2. **Random Forest Classifier (All Features):** This model was trained using the complete set of features: continuous ACA titers, continuous Protein Module Scores (WGCNA), and patient age as an additional covariate.

This model, achieving an F1-score of **0.64** and an AU-ROC of **0.71** on the test set, represents the maximal predictive capability achievable with an inductive approach and the available features.

Knowledge Base Construction and Rule Definition

The knowledge base is a collection of the domain's knowledge, expressed as a set of logical formulas. Unlike an original inductive model which provides a probability of observing a target variable, these rules are treated as established truths within the system's logic.

Derivation of Deductive Rules Associations between ACAs, proteomic modules, and clinical variables remain understudied in SLE; as such, there are no rules that could be confidently derived from existing domain knowledge. Instead, we establish rules based on a statistical analysis using our training dataset.

High Inductive Confidence: Statistical Derivation The core task of the inductive phase was to identify robust, statistically significant associations in the continuous training data and harden them into deterministic rules. This was achieved through two primary statistical approaches targeting different relationships:

- **Feature-to-Target (Final Rules) Analysis using T-tests and Conditional Probability:** To identify features that strongly predicted active disease ($\text{SLEDAI}_{\text{active}} = 1$), the continuous values for all ACA titers and Protein Module Scores were compared between the active and inactive patient groups using unpaired t-tests. This statistical test determined if the mean expression of a feature was significantly different in the active disease group ($\text{SLEDAI} \geq 4$) compared to the inactive disease group ($\text{SLEDAI} < 4$). Features with a statistically significant p-value ($p < 0.05$) were considered strong inductive signals for disease activity.

- **Feature-to-Feature (Intermediate Rules) Analysis using Spearman Correlation:** To build the causal linkages connecting a serological ACA titer to a proteomic module activity, **Spearman Rank Correlation** analysis was performed on the training data. This non-parametric correlation measured the strength and direction of the monotonic relationships within ACAs and between ACAs and proteomic modules. Only relationships that were significant ($p < 0.05$) were selected to form the premises for the intermediate rules.

Formal Rule Structure The Knowledge Base comprises rules of the following general structure:

IF(Premise) THEN (Conclusion)

In some cases, premises can compounded using logical conjunction ($\wedge$, AND) or disjunction ($\vee$, OR). For simplicity sake, we did not include any boolean connectives in the facts in our knowledge base.

ACA	Module	Correlation	P Value
ACA.IFNALPHA	ME1	-0.209625	0.011680
ACA.IFNALPHA	ME4	0.202685	0.014836
ACA.IL15	ME4	0.175135	0.035768
ACA.IL31	ME1	-0.185789	0.025782
ACA.IL31	ME4	0.226557	0.006322
ACA.LIF	ME4	0.231573	0.005227
ACA.GMCSF	ME4	0.164030	0.049468
ACA.IL22	ME1	-0.221875	0.007524
ACA.IL22	ME4	0.210956	0.011148
ACA.CT	ME4	0.216329	0.009208
ACA.IL6	ME1	-0.187947	0.024080
ACA.IL6	ME7	-0.186492	0.025216
ACA.IL17A	ME1	-0.186673	0.025072
ACA.IL17A	ME4	0.220557	0.007898
ACA.IL7	ME1	-0.170292	0.041288
ACA.IL17F	ME4	0.166884	0.045587
ACA.OSM	ME1	-0.222514	0.007349
ACA.PDGFBB	ME1	-0.213596	0.010154
ACA.VEGFB	ME4	0.165686	0.047184
ACA.IL10	ME1	-0.175460	0.035420
ACA.IFNGAMMA	ME1	-0.201149	0.015627
ACA.CCL11	ME1	-0.192589	0.020744
ACA.CCL11	ME7	-0.169548	0.042196
ACA.CNTF	ME1	-0.195065	0.019133
ACA.ACE2	ME1	-0.166964	0.045482
ACA.IFNOMEGA	ME1	-0.173137	0.037964
ACA.IFNOMEGA	ME4	0.164235	0.049180

Table 1: Caption

Module 1	Module 2	Correlation	P Value
ME1	ME2	0.725352	0.000000
ME1	ME4	-0.355554	0.000012
ME1	ME5	-0.433916	0.000000
ME1	ME6	0.583972	0.000000
ME1	ME7	0.528326	0.000000
ME1	ME8	0.244791	0.003106
ME2	ME3	0.208315	0.012226
ME2	ME5	-0.337839	0.000035
ME2	ME6	0.597737	0.000000
ME2	ME7	0.508367	0.000000
ME2	ME8	0.511108	0.000000
ME3	ME5	-0.379125	0.000003
ME3	ME8	0.363214	0.000008
ME4	ME5	0.608275	0.000000
ME5	ME6	-0.224472	0.006835
ME5	ME7	-0.235926	0.004417
ME5	ME8	-0.396612	0.000001
ME6	ME7	0.662704	0.000000
ME6	ME8	0.339615	0.000031
ME7	ME8	0.338132	0.000034

Table 2: Caption

Module	SLEDAI	T-statistic	P Value
ME7	SLEDAI Active	-2.351991	0.020596

Table 3: Caption

- HIGH ME2 $\implies$ HIGH ME1
- LOW ME1 $\implies$ HIGH ME4
- HIGH ME1 $\implies$ LOW ACA.IL22
- LOW ACA.IL22 $\implies$ LOW ME4
- HIGH ME7 $\implies$ LOW SLEDAI (SLEDAI$_{active}$ = 0)

These examples illustrate both intermediate deductions (linking two proteomic modules, or an ACA to a module) and final deductions (linking a module to the SLEDAI status).

Inference Engine and Deductive Strategy

The Inference Engine is the control structure that applies the KB rules to patient facts.

Forward Chaining Strategy We employ a Forward Chaining (or data-driven) approach. This strategy is chosen because the system starts with a set of known facts (the patient's $M + K$ symbolic facts, or initial data) and seeks to draw all possible intermediate and final conclusions (the SLEDAI$_{active}$ status).

The process for a single patient in the test set is:

1. **Input Facts:** The engine receives the patient's observed symbolic data.

2. **Rule Evaluation:** The engine iterates through every rule in the knowledge base. For each rule, it checks if the patient's known facts (both initial and newly deduced) precisely match all the rule's premises (IF clause).

3. **Deduction/Assertion:** If a rule fires, the rule's conclusion is asserted as a new known fact.

4. **Iteration:** The process repeats until no new facts can be deduced, at which point all possible inferences have been made, and the final conclusion is determined.

Deductive Conclusion Policy Due to the system's reliance on deduction, we define a policy for handling conflicting or multiple conclusions:

- **Active Conclusion:** If any rule concluding SLEDAI$_{active}$ = 1 fires, the prediction is SLEDAI$_{active}$ = 1. This prioritizes the detection of active disease, reflecting a bias towards sensitivity.

- **Inactive Conclusion:** The prediction is SLEDAI$_{active}$ = 0 only if no SLEDAI$_{active}$ = 1 rules fire or if an overriding inactive disease rule (e.g., HIGH ME7 $\implies$ LOW SLEDAI) fires.

The final output is a definitive binary assignment (0 or 1), coupled with the chain of specific rules that logically arrived at that conclusion.

Example Deductive Rules Encoded in the KB

Demonstration

The inductive classifier (Random Forest All Features) was applied to the testing set ($N = 36$ patients) and had an F1 score of 0.64 and an AUROC of 0.71 (Figure 2). Feature im-
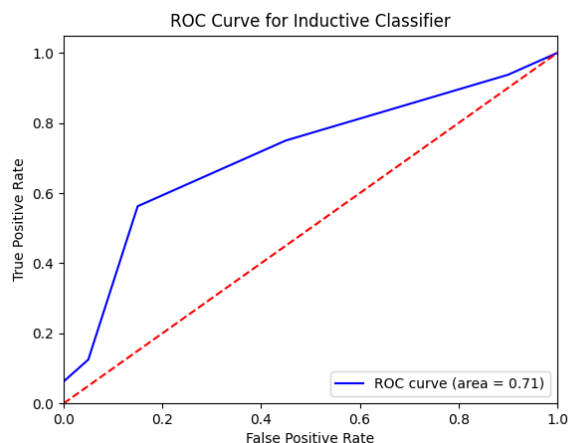

Figure 2: Receiver operating characteristic (ROC) curve of random forest classifier trained on all features. Area under curve = 0.71.

portance scores were extracted from the inductive classifier, with age, proteomic module 2 (ME2), and anti-CCL11 ACA being the most important features (Figure 3). Next, the deductive classifier (expert system) was applied to the testing set to evaluate its deductive power against the ground truth $SLEDAI_{active}$ status.

Effect of Number of Initial Facts on Deductive Capacity

We first investigated how the number of available initial facts impacts the system's ability to reach a conclusion, particularly in preventing 'UNKNOWN' predictions. This was evaluated by changing how many ACA features were used as initial facts for the patients in the testing set. The system achieved its most robust performance (highest F1-score with zero unknown predictions) when at least 20 of the ACA facts was provided to the inference engine (Figure 4). The result suggests that supplying approximately 51% of the total available ACA features is sufficient for the expert system to maximize its predictive performance. We also show that supplying a minimum of 15 initial facts is necessary to avoid unknown predictions (failure of the expert system to reach a final rule).

Comparison of Inductive vs. Deductive Approaches

After training both the inductive and deductive approaches, we compared the two approaches' performance on the testing set. We show that the deductive approach using the expert system significantly outperforms the inductive classifier trained on only the ACA features, and approaches the performance of the inductive classifier trained on all the continuous features (Figure 5). The F1-score of the deductive

system was $\mathbf{0.68}$, surpassing the all-feature inductive baseline of $\mathbf{0.64}$.

Discussion

The deductive expert system has the potential to translate complex molecular and serological patterns into clear disease activity conclusions. The high degree of clinical and biological interpretability is the primary advantage; unlike black-box machine learning models, this system provides a clear, traceable justification for every prediction (e.g., "The patient is active *because* the elevated $ACA_{IFN\alpha}$ titer triggered the $Module_{IFN}$ pathway, according to the chain of Rule $\mathbf{R}_3 \rightarrow$ Rule $\mathbf{R}_A$"). Furthermore, the performance of the deductive system (F1 $= 0.60$) is comparable to the baseline inductive model (F1 $= 0.64$). This suggests that the process of biologically-informed rule construction and the forced adherence to logical, discrete associations did not significantly compromise predictive power. In fact, the regularization effect of abstracting continuous data into robust, statistically derived symbolic rules appears to improve generalizability on unseen data.

Limitation of Statistically Generated Rules

The major limitation is the system's reliance on statistically generated rules derived purely from data analysis (t-tests and correlation) rather than being validated or augmented by domain knowledge. While the statistical method ensures the rules are empirically grounded in the cohort, the relationships may be specific to the idiosyncrasies of this dataset.

Limitation of Fixed Discretization Thresholds

The second major limitation stems from the categorized binning of features using fixed thresholds. The inductive process of creating the rules necessarily involved fixed quantile cutoffs (the $Q_{0.33}$, $Q_{0.67}$ cutoff) to define the LOW/MED/HIGH symbolic facts. This approach forces a patient measurement that is only marginally above the $Q_{0.67}$ threshold to be treated identically to an extreme outlier (the highest observed value). Conversely, a measurement just below the threshold is treated as "MED" when it is functionally much closer to "HIGH." This binary nature fails to capture the inherent biological uncertainty, risk, and magnitude of a measurement, treating the entire upper third of the data as a deterministic fact. A patient on the borderline of a threshold is classified deterministically, which is inappropriate for complex clinical decision-making where the continuous probability of a flare could better inform the diagnosis.

Future Work

A major direction for future work is incorporation of uncertainty into the deductive framework. The current system assumes that each rule fires with absolute certainty, which is advantageous for interpretability but limits flexibility when patient measurements are noisy or missing. Incorporating confidence scores for rules—derived from effect sizes, sample sizes, or through a Bayesian framework would allow the
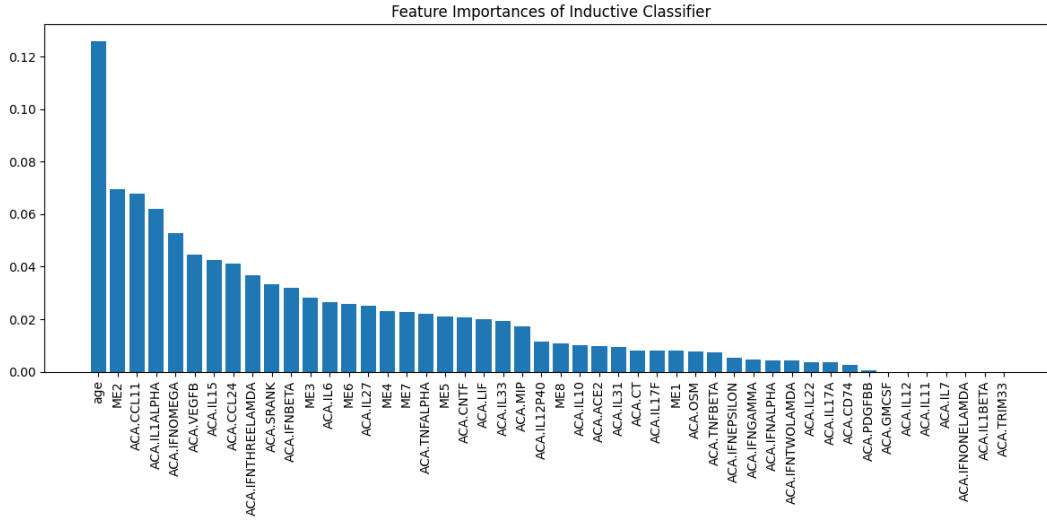
Figure 3: Feature importance scores for the random forest classifier trained on all features
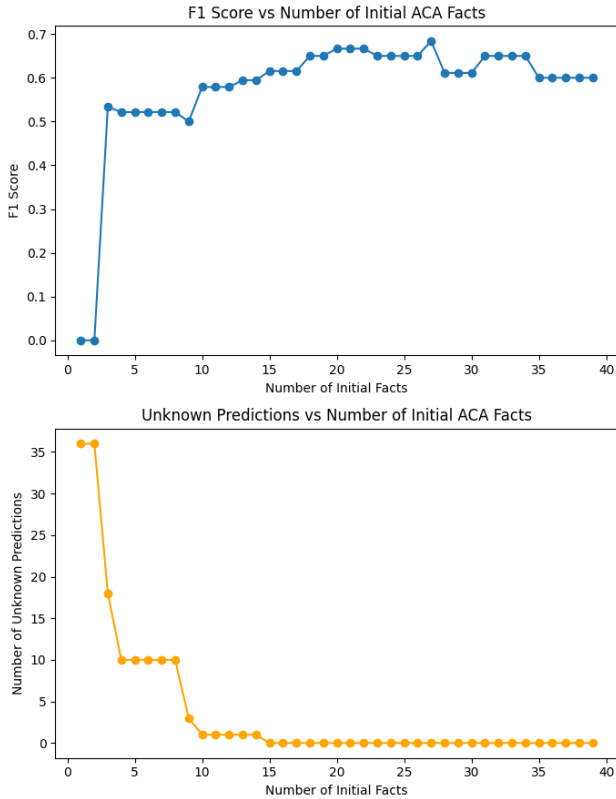

Figure 4: Effect of number of initial facts supplied to the expert system on F1 score of testing set and unknown predictions.
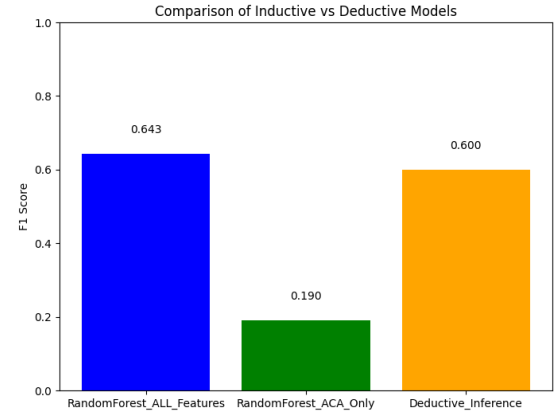

Figure 5: Comparison of F1 scores across the three classification models on the testing set, from left to right: inductive classifier trained on all features, inductive classifier trained on only ACA features, and deductive inference forward chaining on the knowledge base.

inference engine to propagate graded beliefs rather than discrete truth values. This could potentially help handle conflicts between rules, enable more robust inference in clinically ambiguous cases.

Another area of future work involves expanding the knowledge base facts beyond ACAs and modular transcriptomic signals. SLE disease activity is influenced by a rich set of clinical variables including complement levels (C3, C4), dsDNA titers, eGFR, etc (Goteti et al. 2022). Integrating other routinely collected lab measurements would make the rule system more reflective of how clinicians synthesize evidence in practice. Additionally, incorporating other autoantibodies used in SLE — such as anti-dsDNA, anti-Sm, anti-RNP antibodies - could improve the model and potentially detect specific disease subtypes and flare

phenotypes (Gómez-Bañuelos, Fava, and Andrade 2023). Together, these extensions would bring the expert system closer to real-world applicability.

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