PROJECT

Supervisor: Prof. Anna Palmisano

Title: Automating Methodological Audits in Digital Oncology: A Neuro-Symbolic Multi-Agent Approach for Compliance Verification with PROBAST+AI and TRIPOD+AI Standards

Curriculum: Clinical and Experimental Medicine

Link to the personal page of the University or relevant hospital site website: _____Palmisano Anna Università Vita-Salute San Raffaele_____

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Artificial Intelligence (AI) in oncology faces a severe "reproducibility crisis." Despite its promise in personalizing treatments, many predictive models fail to meet the rigorous methodological criteria required for clinical adoption, creating a dangerous gap between algorithmic performance (often overfitting) and clinical utility. International consortia have released "Gold Standards" like PROBAST+AI (assessing Risk of Bias) [ref. 1] and TRIPOD+AI (validation standards) [ref. 2] to address this. However, manual application of these guidelines is unfeasible due to literature volume and model complexity. Current automated tools rely on stochastic Natural Language Processing (NLP), which suffers from "hallucinations" and lacks the formal logical reasoning required to detect subtle methodological flaws like data leakage or look-ahead bias [ref. 3, 4].

Rationale and hypothesis

This project hypothesizes that a Neuro-Symbolic (Ne-Sy) Multi-Agent System can overcome the limitations of pure Generative AI in automating compliance verification [ref. 5]. Ne-Sy architectures merge the semantic understanding of neural models (System 1) with the logical robustness of formal reasoning systems (System 2). By hybridizing neural perception with symbolic logic, the system will effectively automate methodological audits of highly complex clinical AI models. This approach will shift Medical AI from an opaque "Black Box" to a transparent "Glass Box" paradigm, providing rigorous validation for critical oncology workflows.

Objectives and specific aims

The project will be carried out at the San-Raffaele AI Center (S-RACE) of UniSR, and will leverage on the AI platform [ref. 6-8] developed in partnership with Microsoft, and in collaboration with the company Relatech, SpA, sponsor of the fellowship.

The primary aim is to develop a Ne-Sy Multi-Agent System to automate methodological audits. Specific objectives are:

1 - Logical Formalization: Translating the discursive domains of PROBAST+AI and TRIPOD+AI into computable logical constraints and formal rules.
2 - Controlled Neural Perception: Exploiting LLM/VLM modules to extract multimodal "facts" from scientific papers (text, tables, survival curves) preserving information.
3 - Hybrid Inference Engine: Implementing a symbolic reasoning engine that uses extracted facts to verify formal rules and detect methodological contradictions (e.g., statistical inconsistencies).
4 - Clinical Application: Validating the framework on specific predictive models for Metastatic Colo-Rectal Cancer (MCRC)(RECOLMET study) and Non-Small Cell Lung Cancer (NSCLC)(AI-HOPE study) [ref. 9].
5 - Explainability (XAI): Ensuring every automated "Risk of Bias" judgment is justified by an explicit logical trace.

Expected outcomes

The project will deliver an Auditable Validation System capable of automatically assigning PROBAST+AI and TRIPOD+AI compliance scores to digital oncology clinical papers. It will produce a comparative study offering empirical evidence that Ne-Sy architectures outperform standard Generative AI in detecting methodological flaws guarantying traceability. Ultimately, applying this automated audit loop will enhance internal clinical knowledge and procedural validity for MCRC and NSCLC studies, increasing their likelihood of successful clinical translation.

Skills that the student should acquire (max. 600 characters including spaces):

1. Knowledge Engineering: Translating clinical guidelines into computable logical constraints.
2. Agentic AI Architecture & Development: Coding Multi-Agent Systems by integrating neural perception modules (fine-tuning LLMs/VLMs) with deterministic symbolic logic solvers.
3. Validation & Benchmarking: Designing robust experimental frameworks to evaluate automated AI audits against human expert reviews.
4. Explainable AI (XAI): Advancing Trustworthy AI by generating explicit logical traces for automated decisions.

References (max. 15)

1. Moons KGM, Damen JAA, Kaul T, Hooft L, Andaur Navarro C, Dhiman P, Beam AL, Van Calster B, Celi LA, Denaxas S, Denniston AK, Ghassemi M, Heinze G, Kengne AP, Maier-Hein L, Liu X, Logullo P, McCradden MD, Liu N, Oakden-Rayner L, Singh K, Ting DS, Wynants L, Yang B, Reitsma JB, Riley RD, Collins GS, van Smeden M. PROBAST+AI: an updated quality, risk of bias, and applicability assessment tool for prediction models using regression or artificial intelligence methods. **BMJ.** 2025 Mar 24;388:e082505. doi: 10.1136/bmj-2024-082505. PMID: 40127903; PMCID: PMC11931409.
2. Collins GS, Moons KGM, Dhiman P, Riley RD, Beam AL, Van Calster B, Ghassemi M, Liu X, Reitsma JB, van Smeden M, Boulesteix AL, Camaradou JC, Celi LA, Denaxas S, Denniston AK, Glocker B, Golub RM, Harvey H, Heinze G, Hoffman MM, Kengne AP, Lam E, Lee N, Loder EW, Maier-Hein L, Mateen BA, McCradden MD, Oakden-Rayner L, Ordish J, Parnell R, Rose S, Singh K, Wynants L, Logullo P. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ. 2024 Apr 16;385:e078378. doi:

10.1136/bmj-2023-078378. Erratum in: **BMJ**. 2024 Apr 18;385:q902. doi: 10.1136/bmj.q902. PMID: 38626948; PMCID: PMC11019967.

3. Jardim, P.S.J., Rose, C.J., Ames, H.M. et al. Automating risk of bias assessment in systematic reviews: a real-time mixed methods comparison of human researchers to a machine learning system. **BMC Med Res Methodol** 22, 167 (2022). doi:10.1186/s12874-022-01649-y
4. Schmidt W, Rincon-Yanez D, Kharlamov E, Paschke A. Scaling Scientific Knowledge Discovery with Neuro-Symbolic AI and Large Language Models. Joint Proceedings of Posters, Demos, Workshops, and Tutorials of the 20th International Conference on Semantic Systems (SEMANTiCS 2024)
5. Pascal Hitzler, Aaron Eberhart, Monireh Ebrahimi, Md Kamruzzaman Sarker, Lu Zhou, Neuro-symbolic approaches in artificial intelligence, **National Science Review**, Volume 9, Issue 6, June 2022, nwac035, doi:10.1093/nsr/nwac035
6. Traverso A, Tiano D, Corvaglia A, Dimonte A, Draetta EL, Fabiani B, Scuri P, Barbieri S, Agazzi M, Arslan M, Celada D, Chiabrando F, Cibrario L, Cielo G, Colombo A, Contini S, Liberotti M, Montagna M, Ogliari FR, Palmisano A, Pisu F, Serra D, Varani D, Vignale D, Vitali AL, Zambello A, Chiapponi C, Denti M, Esposito A, Tacchetti C. Powering responsible artificial intelligence with high-quality real-world data: the S-RACE platform for scalable, multi-specialty clinical research. **NPJ Digit Med**. 2026 Jan 3;9(1):6. doi: 10.1038/s41746-025-02132-w. PMID: 41484225; PMCID: PMC12770359.
7. van Genderen ME, Kant IMJ, Tacchetti C, Jovinge S. Moving Toward Implementation of Responsible Artificial Intelligence in Health Care: The European TRAIN Initiative. **JAMA**. 2025 May 6;333(17):1483-1484. doi: 10.1001/jama.2025.1335. PMID: 39928513.
8. Palmisano A, Vignale D, Boccia E, Nonis A, Gnasso C, Leone R, Montagna M, Nicoletti V, Bianchi AG, Brusamolino S, Dorizza A, Moraschini M, Veettil R, Cereda A, Toselli M, Giannini F, Loffi M, Patelli G, Monello A, Iannopollo G, Ippolito D, Mancini EM, Pontone G, Vignali L, Scarnecchia E, Iannacone M, Baffoni L, Sperandio M, de Carlini CC, Sironi S, Rapezzi C, Antiga L, Jagher V, Di Serio C, Furlanello C, Tacchetti C, Esposito A. AI-SCoRE (artificial intelligence-SARS CoV2 risk evaluation): a fast, objective and fully automated platform to predict the outcome in COVID-19 patients. **Radiol Med**. 2022 Sep;127(9):960-972. doi: 10.1007/s11547-022-01518-0. Epub 2022 Aug 29. PMID: 36038790; PMCID: PMC9423702.
9. Ogliari FR, Traverso A, Barbieri S, Montagna M, Chiabrando F, Versino E, Bosco A, Lin A, Ferrara R, Oresti S, Damiano G, Viganò MG, Ferrara M, Riva ST, Nuccio A, Venanzi FM, Vignale D, Cicala G, Palmisano A, Cascinu S, Gregorc V, Bulotta A, Esposito A, Tacchetti C, Reni M. Exploring machine learning tools in a retrospective case-study of patients with metastatic non-small cell lung cancer treated with first-line immunotherapy: A feasibility single-centre experience. **Lung Cancer**. 2025 Jan;199:108075. doi: 10.1016/j.lungcan.2024.108075. Epub 2024 Dec 31. PMID: 39752796.