Developing a Symbiotic Workflow between Pathologists and AI through Parameterization and Implicitization

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Abstract
Pathology is a fundamental element of modern medicine that determines the final diagnosis and portrays the prognosis in most medical conditions. Due to continuous improvements in AI capabilities (e.g., object recognition and image processing), intelligent systems are bound to play a key role in augmenting pathology research and clinical practices. Despite the pervasive deployment of computational approaches in similar fields such as radiology, there has been less success in integrating AI in clinical practices and histopathologic diagnosis. This partly has to do with the opacity of end-to-end AI systems, which raises issues of interoperability and accountability of medical practices. In this article, we draw on interactive machine learning to take advantage of AI in digital pathology in an attempt to open the Blackbox of AI and generate a more effective partnership between pathologists and AI systems based on the metaphors of parameterization and implicitization.

Keywords 1
Artificial intelligence, Medical diagnosis, Pathology, Histopathologic diagnosis, End-to-end AI, Interactive Machine Learning, Explainable AI, Interpretability, Accountability, Human-AI partnership

1. Introduction

The application of AI for medical diagnosis is expanding rapidly [15]. In recent years the use of machine learning, and specifically deep learning has made some great strides in computer-mediated pathologic diagnosis and offer promising standardized, reproducible, and reliable potentials for digital image analysis. Deep learning has provided unique affordances for “model-based assessment of routine diagnostic features in pathology, and the ability to extract and identify novel features that provide insights into a disease” [1].

Applications of AI in routine pathology; however, are constrained by some key challenges. These can include infrastructural deficiencies such as limited digitization practices, reliable computational infrastructures, or lack of reliable data storage. However, a closer examination into limited applications of computer-mediated tools in pathology, particularly AI systems, reveals deeper issues than failed technology and points to practice-level dynamics [13]. The blackbox nature of AI models and how AI algorithms arrive at a decision is one of the largest stumbling blocks [1]. Lack of interpretability is at odds with common standards of the medical community, which revolves around comprehending, justifying, and taking responsibility for the underlying reasons for medical decisions [15]. After all, to receive regulatory approval and much-needed buy-in from medical professionals, AI systems must provide a high level of transparency, currently lacking in most lab-based approaches towards AI.

The mysterious and versatile power of neural networks is exactly what makes them blackboxes to humans, but as AI is making inroads into various domains and providing unprecedented performance,

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it leaves medical domain experts with 'why' questions. The job of these experts is often founded on offering explanations and taking responsibility for decisions being made [14]. The accountability issues are even more pronounced in high-stake decisions in pathology as human experts (i.e., pathologists) are deemed irreplaceable and must actively participate in decision making. As others noted, historically "human-machine collaborations have performed better than either one alone" in these contexts [9], and such a partnership requires opening the Blackbox of AI.

An important fact to emphasize is that pathologic diagnoses rarely fall into Boolean answers (e.g., benign, or malignant). In real-life clinical practice, pathologists often build on a diverse and complex set of background information and foundations including their broad understanding of the clinical contexts, the patient's history, and years of tacit knowledge [10]. In how they report the results, pathologists may also use sophisticated languages and terminologies, reflective of the complicated and non-binary diagnosis process, to inform potential prognosis. The combination of these challenges could render pathologists, regulators, and other stakeholders skeptical of the bottom-line impacts of AI in clinical workflows [8]

In what follows we provide an overview of the common end-to-end approach towards the application of AI in medical diagnoses and juxtapose it with our approach, which centers on explainable AI.

2. End-to-end AI

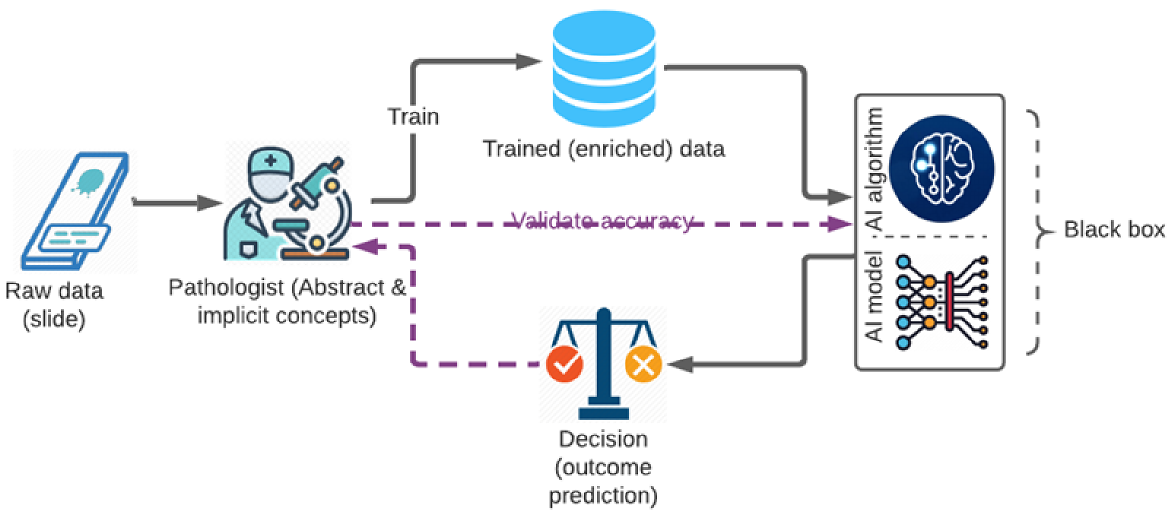

Figure 1: End-to-end AI work system

The typical uses of deep learning focus on training and optimizing a model based on training data, mostly medical images, that have been labeled by human experts, here clinicians/pathologists. The label can include information related to patient outcomes, clinical classifications, and image annotations. Some studies even go around the issue of pixel-wise manual annotations by pathologists, train AI models on large training data sets (e.g., whole slide images) and offer automatic extraction and identification of features [e.g., 5, 11].

In this typical work system, the role of the human expert is either eliminated or relegated to 1) trainer of the algorithmic system, and 2) validator of the system's recommendations and decisions (the loop marked in purple in Fig 1). It is important to note that beyond this stage in building and training end-to-end AI systems, the pathologist is not replaced in clinical practices but provided with automated binary decisions. Such routines of AI systems arguably increase the speed and efficiency since the pathologists receive a final diagnosis. However, as the AI-driven diagnoses are not evidence-based, the clinicians cannot interact with machines and their logic and therefore there are few opportunities for mutual learning. Due to the Blackbox nature of the AI system, there is not much room for learning on the part of the human expert. In essence, both AI and human experts retain tacit knowledge which is difficult to transfer to the other party.

3. Explainable AI: Expert-in-The Loop

Our approach is informed and inspired by current research on interactive machine learning (interactive ML), which is focused on training and optimizing algorithms through intuitive human computer interface; and integrating users' feedback into informing features. In interactive ML, human experts are not just labelers or annotators, but they serve as the primary driver, guide, and active explorer; she interacts with data and may directly contribute to feature extraction [2].

We contribute to interactive ML as this research stops short of presenting a more comprehensive work system, one that integrates nuanced organizational dynamics like developing a broader and embedded work system of collaboration between humans and AI. Current research on interactive ML typically stays at the level of user-interface interaction.

3.1. Meningioma diagnosis

We propose a framework for developing explainable AI workflows using a case study of grading of meningioma (see [6] for more details on the user study with pathologists). Meningioma is the most common primary brain tumor. Based on its histopathologic features, meningioma is classified into three grades. The prognosis, recurrence rate, and treatment management of different grades of meningioma vary. There are four routes to a grade 2 meningioma including brain invasion, more than 3 mitosis per 10 high power field (HPF), and 3 out of the following 5 morphological characteristics which are hypercellularity, sheeting architecture, prominent nucleoli, spontaneous necrosis, and small cell component. The presence of 3 out of the aforementioned architectural morphology upgrades a grade 1 meningioma to a grade 2 tumor. The last route to a grade 2 managerama is specific subtypes including clear-cell and chordoid meningioma. Our case study involves a redesigned workflow with key contributions from both pathologists and AI in faster and more reliable grading of meningioma.

We articulate the symbiotic interaction between pathologists and the AI system through the continuous process of parameterization and implicitization. These two concepts are used as metaphors to explain the reciprocal process through which the two partners work together and contribute to explainable AI workflows. Inspired by the mathematical process of parameterization and implicitization (mostly used in geometry), we describe how an effective partnership between humans and AI can help reduce uncertainty and complexity as key factors that riddle the efficacy of decision making in clinical settings and elsewhere. Humans have unique capacities in dealing with uncertainty whereas AI systems are more competent in handling the complexity of information [7].

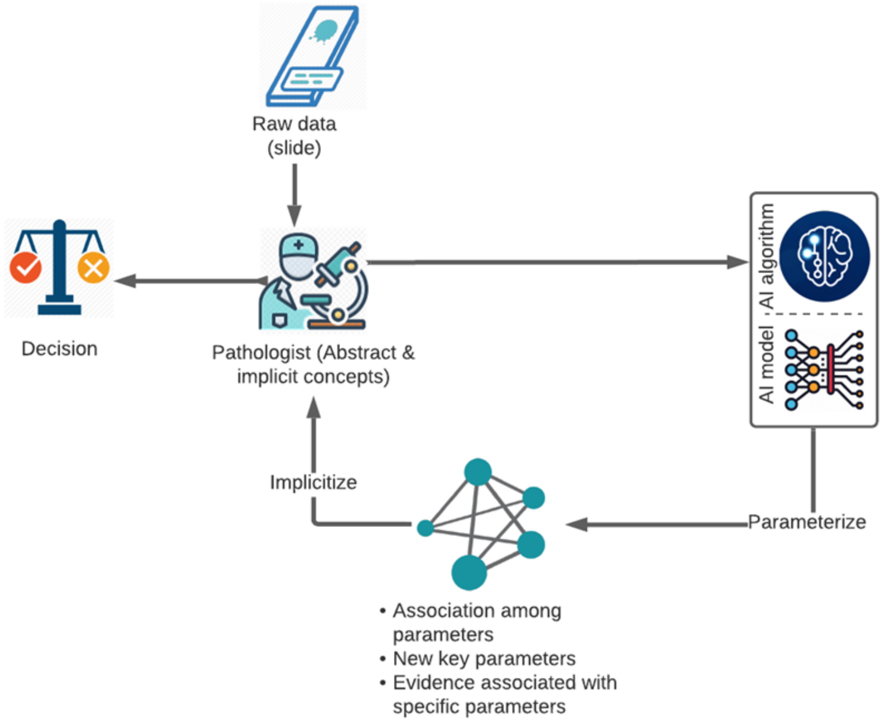

Figure 2: Explainable, expert in the loop AI work system

3.2. Parameterization

Parameterization is the process of identifying and expressing implicit equations using manifolds or a variety of parameters. Parameterization is instrumental in defining the state or quality of a system. Feynman parametrization, for example, helps express and evaluate loop integrals in so-called Feynman diagrams. Parameterization reduces complexity. Complexity refers to the abundance of variables and their associations. Parameterization 'divides and conquers' the problem area; that is, it breaks it down to sub-problems (parameters) so that these parameters and their associations become simple enough to be observed and understood directly.

Human experts' contributions are still irreplaceable in two ways: (1) Pathologists initiate the criteria for a specific diagnosis; choosing 'good' parameters (features) are always the first step in interactive ML and require domain and problem-specific knowledge [2]. (2) pathologists must stay "in the loop" to decide if parameters and relationships extracted by the machine are meaningful.

AI provides two contributions to the parameterization process. (1) It extracts features/parameters defined by pathologists (e.g., it showcases the structure of cells in the data with nuclei larger than certain diameters) (2) it could produce new knowledge (latent knowledge) by discovering new parameters and new relationships between parameters unnoticed or unknown by pathologists. Due to its analytical superiority in parsing and analyzing a large number of features and data points, AI can uncover parameters and associations that were not considered salient before. Humans decide if such new parameters/relationships discovered by AI are meaningful and valuable. The valuable new knowledge will be fed back to the algorithm for better diagnosis accuracy.

As noted, AI helps the discovery of associations between parameters decided by human experts as well as the association and parameters discovered by mass image processing and parametrization producing new knowledge. In cited work of grading meningioma, the algorithm looks for all the features that are compatible with a grade 2 meningioma and provides the histopathologic data such as brain invasion, specific subtypes, and all other features that qualify a grade 2 meningioma. The AI focuses on the criteria that are used by pathologists to grade the meningioma, not on a black-box process with which a pathologist has no way of interaction. The system receives feedback from pathologists based on their confirmation or rejection of an extracted feature; this leads to the improvement of the characteristic detection by the system.

In addition, AI can reduce complexity by adapting to evidence-based feature extraction and diagnosis. The advantage of the system is the speed of pattern recognition and characteristics that could take hours for a pathologist to go over. For instance, accurate detection of small foci of spontaneous necrosis is a challenging task that can take over an hour for a pathologist to check the entire set of slides. The system does the accurate detection task with high speed and provides the pathologist with all spontaneous necrosis candidates and the pathologist confirms or rejects the findings. And once again, such an interaction allows for the system to quickly get trained and apply newly discovered information with the help of the pathologist.

3.3. Implicitization

Implicitization is the inverse process of parameterization. Implicitization refers to converting back parameters and their association to a single implicit equation. Implicitization is key in keeping the holistic nature of a system in view (the system is bigger than the sums of its elements). In the decision-making context, humans enjoy a competitive edge in generating and maintaining a holistic and abstract view, which is central in overcoming uncertainty (defined as the lack of information about all alternatives or their consequences). The histological diagnosis, empowered by AI, offers a crucial but inexorably limited perspective. This piece of analysis must be complemented by a more comprehensive synthesis of the broader context to construct the final integrated diagnosis. The broader context consists of many factors (see Fig 3) and the synthesis that goes into the diagnosis report often include information such as sub-type/variant of cancer, grade, stage, as well as prognosis and recommendations relative to the further management/treatment decisions. AI algorithms in current forms lack this human-level general intelligence, and only perform efficiently and with high accuracy in narrow and specific (and often binary) tasks of histological diagnosis. This is what AI researchers refer to as "weak AI" [12]. Machines lack common sense [3]. Implicitization involves a crucial sensemaking component through which human experts put together all the parameters as well as contextual information and decide if a certain diagnosis or prognosis "makes sense."

This noted, AI can potentially contribute to the implicitization process by helping human experts in visualizing the associations between many parameters (i.e., patterns of associations) and understanding the ways interactions among those parameters/features or their unique combinations may give rise to the problem at hand.

In this workflow, the AI is utilized to recognize morphology and the final decision is made by the pathologists who make the final diagnosis and assemble the final report for the clinicians and patients. The pathologist decides on the accuracy of the results by going over all the findings detected and presented by the AI system. Such an approach is empowered by close and transparent interaction between the AI and pathologists.

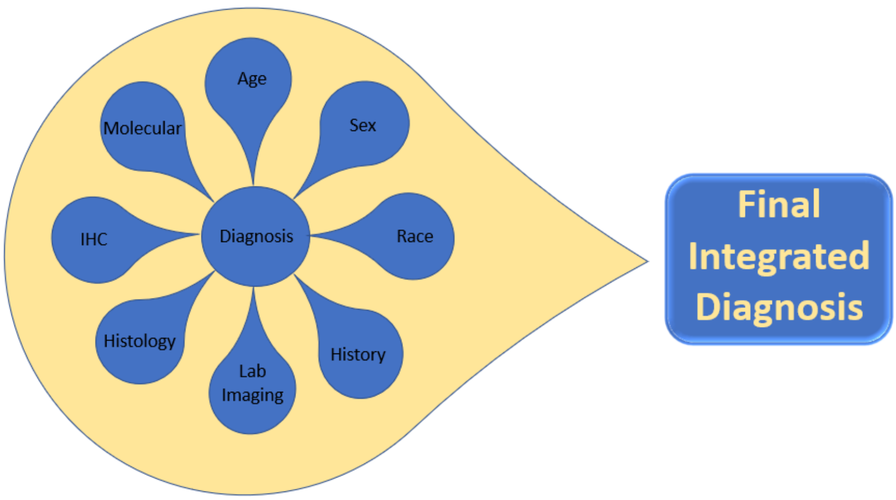

Figure 3: Entirety of contextual factors shaping a final integrated diagnosis.

The holistic view possessed by medical experts is often of an implicit/tacit nature and derives from an intuitive decision-making style [4]. Considering human-AI interaction, humans can 1) specify the key parameters and feed them into the AI system, and 2) put the AI-enabled analysis and parameterization into perspective and produce a final recommendation or decision. A crucial component of the activity (2) here has to do with the pathologists' unique ability to "contextualize." While AI systems may reveal more contextual features, it is the human expert that can bring all together (e.g., patients' prior history) in the form of a final decision/diagnosis and report.

Parameterization and Implicitization help to open the Blackbox of AI-empowered systems and fulfill the vision of human-AI partnership. This approach reinforces the mutual learning between human experts and AI: The inner circle in figure 2 facilitates mutual learning through continuous parameterization and implicitization. Finally, the interpretability achieved here enables higher levels of trust and accountability as the human expert retakes the helm in understanding how the whole work system arrives at a decision. In this new work system, each partner brings unique capabilities and comparative advantage to the table (see Table 1).

Table 1

Constitution of human experts and AI system

Actors	Parameterization	Implicitization
Human experts (pathologists)	• Initiate the criteria for a specific diagnosis. • Decide if discovered parameters and associations (by machine) are meaningful.	• Bring different parameters together towards a holistic diagnosis. • Place decisions into the broader diagnostic context.
AI systems	• Extract parameters defined by pathologists. • Discover new parameters impacting the case in question.	• Help identify the relationships among parameters and their interactions.

3.4. Elevating pathologists

In contrast to the end-to-end approach, our approach places humans at the center of "the learning loop". Rather than consumers of the AI-generated diagnosis or trainers of the AI system; they occupy a more critical role (beyond feeding the ML model) and learn alongside the machine as the process of human-AI interaction is parameterized and unpacked. Such collaboration enables pathologists to discover new parameters and relationships identified by machines while they are enabled to feedback their verdict into the system.

4. Conclusions

Contribution of our approach to computer-mediated pathology is twofold. First, it provides a more effective approach towards human-AI interaction, one that reinforces and elevates the role of pathologists as human experts. Second, we offer a middle ground between (1) end-to-end AI and (2) manually engineered feature extraction by human experts. In our approach, we draw on the strength of both methods while overcoming their inherent limitations.

In this approach, AI closely collaborates with humans and contributes to parameterization and differential diagnosis by 1) capturing the complexity of multiple factors lying outside the cognitive processing of humans, 2) discovering new parameters, and finding connections between multiple parameters and evidence, and 3) learning alongside pathologists by using their inputs. In addition, AI can facilitate knowledge transfer among pathologists. Parameterization and finding criteria (as well as corresponding evidence) help experienced pathologists in the process of knowledge transfer to novices and students. Over the years these experts tend to internalize knowledge in a way that transcends explicitly connecting evidence and parameters; so, in their diagnostic approach, some of these experienced experts are less attentive to individual parameters and instead rely on holistic, implicit and automatic evaluations that do not easily lend themselves to explicit knowledge transfer and explanation. Through AI-enabled parameterization, interactions between experts and learners are facilitated.

Lack of interpretability and transparency stands in the way of clinical adoptions of these systems. This symbiotic relationship presented here could clarify the unique contributions of both humans and machines and raise trust in the application of AI in pathology. Our approach takes up the challenge of interpretability and accountability, as common end-to-end approaches based on artificial neural networks "do not provide a verifiable path to understanding the rationale behind its decisions" [13].

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