The Role of Artificial Neural Networks in the Evaluation and Management of Acute Venous Thromboembolism

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Abstract:

Deep Vein Thrombosis and Pulmonary Embolism, collectively referred to as Venous Thromboembolism (VTE), are disease states associated with significant mortality and morbidity worldwide. While multiple diagnostic tools and structured algorithms exist for their management, these two states, particularly pulmonary embolism, still pose a major diagnostic challenge, particularly in the time-sensitive acute care setting. Artificial Neural Networks (ANN), computerized information processing structures, have been used extensively in medical fields, and have shown significant impact in the diagnosis and management of diseases ranging from myocardial infarction to breast cancer. While significant efforts in the past two decades have been made to turn the power of these systems towards acute VTE evaluation, concrete successes have been tenuous. This paper will attempt to highlight thus far promising directions for the application of ANN to VTE diagnosis and management, as well as briefly examine future avenues within the field.
Background:

Modeled on the interlaced array of neural synapses comprising the human brain, the artificial neural network is a paradigm for the analysis of complex datasets that demonstrates the ability of “machine learning,” that is, a means by which a computer system can improve subsequent analysis based on past experience. First proposed in the 1940s, these networks are capable of recognizing patterns within clinical datasets and refining that pattern recognition over multiple rounds of testing.

ANNs are comprised of at least three interconnected layers of nodes by which data is processed. These layers include an input layer, where given variables are entered, an output layer, usually some predefined outcome such as the presence of a disease state, and any number of hidden layers wherein the data is computed in such a way to give the output result [1]. During the process of data analysis, the ANN essentially defines a set of rules or relationships between input variables that allows for the desired output to be appropriately generated.

It is perhaps simpler and more appropriate to illustrate how these networks can be applied to disease diagnosis. An ANN can be issued an input layer comprised of patient symptoms, vitals, or lab results, and a defined outcome such as the positive diagnosis of a disease like myocardial infarction. Once given this information, the ANN is tasked with defining a system of rules and inter-variable associations leading to this positive disease diagnosis, a process referred to as “training” [1]. This training continues by presenting the ANN with new data sets corresponding to other patients. At each subsequent round of training, the neural network continually refines its system of rules for each new set of variable inputs and expected outputs. Once the network has defined a system that accurately generates the expected output for each set of test inputs, the ANN is considered refined to the extent that it can be used to predict the outcomes of an experimental population [1]. Thus, an ANN can “learn” the complex
associations between different patient findings and generate predictive rules on how those findings either confirm or reject the likelihood of disease.

ANNs have shown significant usage in various medical fields, with applications that include the diagnosis of appendicitis, myocardial infarction, sexually transmitted diseases, and skin disorders [1]. They have also prominently been featured in radiographic assessment of both breast and prostate cancers. In the early 1990s, these networks were first applied to evaluation of venous thromboembolism, a subset of diseases comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), respectively characterized by the formation of blood clots in deep leg veins, and the spread of said clots to the lung vasculature. In 1993, shortly after the landmark PIOPED trial which established guidelines for the use of ventilation/perfusion scanning in PE evaluation, Patil et al [2] used an artificial neural network to process both clinical and radiographic findings of the PIOPED test population. The group demonstrated that their artificial neural network could predict incidence of PE at nearly identical rates to the physicians making the original diagnoses. Despite failing to demonstrate superiority of ANN-based systems to conventional human diagnosis, the study was a promising initial step for the technology, generating optimistic outlook for future systems that could fully automate VTE evaluation.

**Imaging Analysis and Computer Assisted Diagnostics:**

Patil et al [2] in their 1993 work make note of the fact that the radiographic findings entered into their ANN were derived from official readings by radiologists; that is, no computer actually performed direct image analysis. This thus posed the question of how PE diagnosis might be improved with a computer reading the images and directly assessing the radiographic findings. In 1999, Holst et al [3] used an ANN to directly analyze ventilation-perfusion scintigrams of patients similar to those in the PIOPED trial, once again showing comparable PE detection rates with this revised neural network when compared to standard physician diagnosis. Lack of superiority notwithstanding, this study can be thought of as one of the
earliest forays into the field of computer-assisted diagnosis (CAD) in the context of VTE assessment.

Computer-assisted diagnosis can be thought of as a response to inherent limitations in human information processing. In contrast to machines, humans are susceptible to bias and fatigue, and may display wide variability in their drawn conclusions, depending on relative experience or subjectivity [4]. Moreover, these issues can be exacerbated in the current landscape of advanced medical imaging, where recent technological improvements have actually imposed larger labor and workflow demands on human readers. Multidetector CT scanning, for example, is a modality with excellent visualization of subsegmental pulmonary arteries, the tiniest branches of visible lung vessels, but routinely generates hundreds of images that need to be manually evaluated for detection of the most subtle emboli [5].

Both independently and in conjunction with other information processing systems, ANNs have shown effect in directly compensating for some of these limitations. Park et al [6], for example, used multiple computational algorithms in conjunction with ANN to parse CT scan data down exclusively to regions suspicious for emboli, thus generating a much more manageable data set. This filtered image data was ultimately processed by a back-propagation neural network model to make a final determination of true-positive or false positive PE [6].

A study in 2010 showed that an ANN-based model of CT scan evaluation significantly improved the PE detection rates of radiology residents when used as a supplementary tool. This effect was particularly pronounced in the detection of emboli located more peripherally in the lung fields, traditionally those that are hardest to be detected [4]. A prior study in 2009 showed similar results, applying a CAD model to CT scans performed exclusively in the on-call setting, where scans are often read by less experienced readers under more significant time constraints [7]. It is important to recognize that even when supplemented by CAD, the accuracy of inexperienced readers was still significantly lower than that of expert radiologists, demonstrating that present CAD systems are still limited in their generalizability. However, even
with very niche usage, these systems can provide meaningful reassurance and comprehensiveness to physicians-in-training or those still developing their image interpretation skills.

**Risk Stratification:**

While the field of imaging-based CAD offers numerous roles for artificial neural networks, it is widely acknowledged that advanced imaging modalities like CT angiography and ventilation/perfusion scanning carry significant time and cost limitations that challenge their role in VTE evaluation. At present, clinical prediction rules (such as the Wells Criteria) and pre-imaging testing like the D-Dimer assay, are used to risk-stratify patients into groups that can forgo further imaging, either due to low likelihood of disease, or conversely, high enough suspicion that treatment can directly be initiated. However, many cases remain unclear enough even after application of these tools that advanced imaging is necessary for a conclusive diagnosis. Thus a particularly important direction for ANN-based diagnostics is the development of systems that do not rely on imaging data for disease assessment.

Several groups have shown promising findings in alignment with this goal. In 2010, a pilot study out of China demonstrated high accuracy when using a combined logistic-regression and ANN-based model to assess patient cases suspicious for PE, only utilizing clinical symptoms and initial lab findings in lieu of diagnostic imaging [8]. An Iranian study in 2016 showed similar accuracy when using an ANN to stratify patients into low, medium, high, and highest risk groups based only on pre-imaging patient data; their risk stratification schema was further validated with subsequent ventilation-perfusion scanning, showing a particularly high predictive rate of PE in the highest risk subgroup [9]. Both studies were limited by relatively small sample sizes, and in the case of the Chinese study, a retrospective rather than prospective model. An Italian group, however, was able to improve upon both these works, applying a new advanced ANN model called “neural hypernetwork,” to the assessment of a significantly larger test population of 1427 patients. In the roughly half of these patients found
by subsequent CT angiography to indeed have pulmonary emboli, the neural hypernetwork was able to identify an unprecedented 93% of those positive for disease, prior to the acquisition of any imaging data [10]. Further validation is required before imaging studies can be supplanted as the gold standard of diagnosis. However, these studies demonstrate an exciting proof of concept, if not in a pure diagnostic setting, than certainly in the supplementary role of risk stratification.

**Genomic Analysis:**

According to the principle of epistasis, a gene’s final phenotypic manifestation is a sum result of multiple gene interactions, rather than independently coded effects [11]. As such, ANNs appear well positioned for a role in genetic profiling, utilizing their ability to process and weigh the importance of complex cross-variable associations. Indeed, neural networks have been extensively applied to the analysis of genomic and proteomic data, with a plethora of open-access programs available for DNA splice site prediction and protein modeling, and proven use in the study of gene expression profiles of cancer and other disease states [11]. Several groups have thus taken the power of these networks and applied them to the categorization of pathologic gene variants or gene mutations that may predict or correlate with VTE incidence. In a particularly illustrative case, Penco et al [11] used three different ANN models to analyze 62 gene variants in patients with known VTE; in doing so they identified nine specific gene variants marked by the ANN models as being most contributory to the VTE disease outcome. While three of these nine genes were already well known to be strongly associated with increased susceptibility to the disease state, the remaining six variables were presented as new potential targets for further investigation [11]. In another example, ANNs were used to refine genetic data analysis first performed by a statistical method called principle component analysis, in patients suffering VTE [12]. The addition of ANN-based interpretation significantly improved the accuracy of analysis, again demonstrating how well adapted this method is to the characterization of gene profiles associated with specific disease states. Other
studies in this field have shown concrete, albeit more modest, applications of the technology. One group employed an ANN-based DNA splice site predictor to better qualify the exact defect caused by a novel gene mutation in two patients with Protein S deficiency, a clinical state that significantly predisposes one towards the formation of venous clots [13]. Using the neural network, this group was able to show that the gene mutation knocked out a DNA splice site necessary for the production of a functioning Protein S molecule, an important anti-clotting factor for disease prevention in healthy patients.

**Future Endeavors:**

It is difficult to map the exact trajectory of ANN-based applications in the field of VTE management at present. Certainly while some literature has shown dramatic examples of success in ANN-driven diagnostics (ie [10]), the majority of publications in the field have shown more measured optimism for the technology. What is undeniable is that the technological landscape of even just the past few years has rapidly become one dedicated towards harnessing the potential of machine learning in the healthcare industry. A conservative estimate of new artificial intelligence startup companies in healthcare from April of 2016 to the present showed over 100 such companies applying machine learning to medical fields, with significant proportions dedicated towards diagnostics and medical imaging [14]. In addition, various companies have focused efforts on producing hardware specially designed to accommodate artificial neural networks; chip maker Nvidia, for example, released a powerful new chip in early 2016 stated by the company’s CEO to be capable of powering an ANN to learn from input data roughly 12 times faster than the previous standard [15].

As ANNs and computer-assisted diagnosis become more established in the commercial sector, it will be increasingly important for clinical investigators to keep pace with these innovations by better qualifying existing uses for the technology. While again, there is some current support for the view that ANNs can serve as truly automated diagnostic systems for VTE, perhaps the most appropriate initial step is to better validate the role of ANN models for
risk stratification. As previously stated, existing tools for risk stratification, such as the D-Dimer assay, are often limited in their ability to diminish the need for advanced imaging studies in the initial evaluation of patients with VTE. Thus, prospective trials that compare neural network systems against these tools, as well as studies showing improved clinical outcomes with ANN-based evaluation are necessary steps in bringing ANN into more widespread clinical use.

As diagnostic power of these systems improves, it is probable that truly automated models for VTE evaluation will one day become commonplace in emergency healthcare. Thus, the most ambitious and integrative direction for the technology will likely be the dissemination of diagnostic systems outside of the hospital setting. While far from a true proof of concept, a study by Lela et al [16] at least loosely proposed such a model, where mechanical sensors detecting patient vitals and symptom manifestations could be linked to an ANN, creating a sort of portable diagnostics device that might allow for VTE assessment in the field. In light of continued advances in the fields of wearable devices and cloud computing (a potential source of ANN training data) it is not impossible to think that such innovations may lie somewhere on the foreseeable horizon.

Conclusion:

In summary, artificial neural networks are powerful computing tools with great application to venous thromboembolism evaluation, particularly with regards to medical imaging, risk stratification, and genomics analysis. It is likely that these roles will continue to persist with the developing climate of innovative machine learning systems in healthcare.
Works Cited:


