**Editorial**

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# Machine learning and coagulation testing: the next big thing in hemostasis investigations?

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"*The Only Constant in Life Is Change*." – **Heraclitus**

Change has been a continuum in the field of hemostasis since the field began. The elder of us has personal recollections of starting in the field performing manual coagulation tests. He thought the workload was high, performing up to 40 prothrombin times (PTs) and activated partial thromboplastin times (APTTs) in a day. Specialist testing was also introduced, and again, many tests such as factor assays and lupus anticoagulant (LA) were also performed using manual testing – namely the manual tilt tube method (in duplicate of course) using a water bath and stop watches. To cope with the high workload, we introduced various cutting-edge innovations, such as a metal clip to hold up to eight test-tubes at a time for water bath immersion, and withdrawal. He thought he had hit the jackpot with his first automated analyzer, the Coag-A-Mate, which used a large plastic carousel with wells for the reaction and clot detection, and peristatic pumps and tubing that could do perhaps accomplish 20 coagulation tests an hour. The instrument required some time and trial and error to alter the set-up for specialised tests, so this was rarely done. The Coag-A-Mate was eventually replaced with an ACL-300R, followed by ever larger and higher throughput analyzers to cope with the growth in test number and variety, including an MDA-180 and more recently Stago Star Evolutions. Fast forwarding to 2021, and the large networks of laboratories, where Westmead is leading the introduction of 75 ACL-TOP analyzers into 60 laboratories of NSW Health [1], the Network now performs over one million PTs and one million APTTs a year. Indeed, the Westmead laboratory alone now performs around 400 PTs and 400 APTTs a day. In another setting, halfway across the world, the Verona Hospital laboratory also performs around 750 PTs and 600 APTTs per day.

Such high throughput and the increasing breadth and complexity of hemostasis tests certainly needs better strategies than use of 'metal clips'. Indeed, the automation and high throughput means that extra care needs to be placed on ensuring sample integrity. Thus, it is not good enough to get a fast PT or APTT (for example), we need to ensure that these test results are accurate and reflect the patient's status, and not just the sample status. Modern instruments are generally very reliable; nonetheless, errors in test results can occur. Importantly, pre-analytical issues account for the majority of test errors in modern times [2]. Such pre-analytical issues often arise due to poor blood collection, and the arising sample activation and clotting prior to receipt by the laboratory. The major outcome is the development of hemolysis and also partial or complete clots. Neither is easily identified by visual inspection of the whole blood, unless the clot is large enough to prevent blood mixing; however, both can certainly compromise sample quality. Typically, samples arrive in the laboratory, patient details and ordered tests are entered into the laboratory information system (LIS), and the collection tubes quickly centrifuged. The primary sample, with the plasma supernatant resting on top of the centrifuged cells is typically placed on the analyzer and the tests performed, usually after automatic query of the test(s) required through interrogation of the LIS, and then test results are outputted from the analyzer to await verification. This process may be manual, or automated through a series of rules [3]. In general, normal test results can usually be verified automatically, but the 'abnormal' test results require a higher level of scrutiny. For any individual patient, the 'abnormal' test result may actually be expected (e.g., on anticoagulant therapy), or else unexpected. In the latter case, the question arises: is the test result truly

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reflective of the patient status, or is the result an artefact of a pre-analytical issue?

Modern instruments now come with several checks for pre-analytical problems, including the so called HIL (hemolysis, icterus, lipemia) triad [4]. In such case, the instrument can usually overcome the spectral effects and get an accurate test result reflective of the test sample; however, the instrument cannot account for any biological effects of HIL and a recollection may still be recommended. In the case of potential sample clotting causing a spurious coagulation test result, the usual check requires closer visual inspection of the sample, potentially using wooden sticks to physically check the sample for visual clots. This is a time-consuming process, and even if well performed may miss small clots which could still compromise sample quality. It is therefore of some interest that the current issue of the journal contains a publication by Fang et al. [5] on Machine Learning (ML) to identify clotted specimens in coagulation testing.

The concept of ML is not in itself new. Indeed, a PubMed search using 'machine learning' yields over 55,000 hits, dating back to at least 1967. Adding the terms 'coagulation or hemostasis or haemostasis', however, cuts the yield down to 105 papers, with over 80 of these published in the last five years; hence the concept is certainly 'new' for our field. Many of the prior papers applied ML techniques to predict diseases or their severity (e.g., sepsis-induced coagulopathy in critically ill patients, coagulopathy in spontaneous intracerebral hemorrhage emergency patients, and even detection of COVID-19 [6]). To our knowledge, no prior paper has ever explored ML to identify clotted specimens in coagulation testing.

ML is considered as an extension of traditional statistics; usually, in the supervised approach, a computer program is trained from already classified (training) data to make predictions or decisions on unclassified (test) data. To assess its performance, a subset of data is used as training set, and the remaining part (whose classification is hidden to the algorithm) is used to perform a simulation. Many models can be exploited to accomplish this task; each of them has theoretically defined advantages, but a practical comparison between algorithms is necessary in many cases [7]. Fang et al. [5] in their publication decided to use backpropagation neural networks (BPNNs), which is a widely used approach in neural networks classifiers. Fang et al. [5] retrospectively retrieved from their LIS the results of coagulation testing, with 192 clotted and 2889 no-clot-detected (NCD) samples, to form datasets for training and testing. Standard and momentum BPNNs were trained and validated using the training dataset with 5-fold cross-validation, and then the predictive performances of the models were assessed on a testing dataset. The standard and momentum BPNNs could identify the sample status (clotted and NCD) with areas under the receiver operating characteristic (ROC) curves (AUCs) of 0.966 (95% CI, 0.958–0.974) and 0.971 (95% CI, 0.9641–0.9784), respectively. These represent extraordinarily high AUC values and indicate both high sensitivity and specificity for identification of clotted vs unclotted samples.

So, does this mean we now have a method for identification or exclusion of clotted samples, and no longer need to visually inspect samples? Well, not just yet. As a caveat to the application of this process, the dataset from Fang et al. [5], comprised samples with five tests performed, being PT, APTT, thrombin time (TT), fibrinogen, and D-dimer. In other words, the model requires results from all five tests to enable the prediction to occur. In most laboratories, PT and APTT are the most often performed tests, and TT, fibrinogen, and D-dimer are performed far less frequently, and generally in <10% of patients who have coagulation studies performed. Nonetheless, TT, fibrinogen, and D-dimer are often those tests that expert rules will reflex to in the case of unexplained prolongation of PT and/or APTT, and also with reference to patient information suggesting their potential utility [3].

Thus, the work of Fang et al. [5], as reported in this journal, should be seen as an important first step in the path towards an automated identification (or exclusion) of clots as the cause of unexpected abnormal coagulation test times. We look forward to further work in this area over coming years.

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