

A Proposed Machine Learning Based Collective Disease Model to Enable Predictive Diagnostics in Necrotising Enterocolitis

Jacqueline van Druten
*School of Architecture, Computing and Engineering,
College of Arts, Technology and Innovation, UEL.
University Way, Dockland Campus
London, E16 2RD, UK.
u1639256@uel.ac.uk*

Minesh Khashu
*Neonatal unit, Poole Hospital NHS Foundation Trust
BH15 2JB, UK
Perinatal Health, Bournemouth University, UK.*

Mhd Saeed Sharif
*School of Architecture, Computing and Engineering,
College of Arts, Technology and Innovation, UEL.
University Way, Dockland Campus
London, E16 2RD, UK.
s.sharif@uel.ac.uk*

Hassan Abdalla
*School of Architecture, Computing and Engineering,
College of Arts, Technology and Innovation, UEL.
University Way, Dockland Campus
London, E16 2RD, UK.*

Abstract— Despite 60 years of research into necrotising enterocolitis (NEC), our understanding of the disease has not improved enough to achieve better outcomes. Even though NEC has remained the leading cause of death and poor outcomes in preterm infants, there remain vital questions on how to define, differentiate and detect the condition. Numerous international groups have recently highlighted NEC as a research priority and called for broader engagement of the scientific community to move the field forward. The three foremost barriers at present are lack of suitable definition(s), lack of clean datasets and consequently a lack of scope to gain sufficient insights from data. This research paper proposes a new direction of travel to advance neonatal gastro-intestinal monitoring and strengthen our efforts to gain better insights from global databases. An integrated machine learning based model is recommended to produce a comprehensive disease model to manage the complexity of this multi-variate disease. This intelligent disease model would be used in the daily neonatal settings to help aggregate data to support clinical decision making, better capture the complexity of each patient to enrich global datasets to create bigger and better data. This paper reviews current machine learning and CAD technologies in neonatology and suggests an innovative approach for an NEC disease model.

Keywords— *Machine Learning, Necrotising Enterocolitis, NEC, Big Data, AI Based Diagnosis, Predictive Modelling, Multi-Variate Analysis, Deep Learning, Ensemble Modelling, Computer Assisted Detection, Disease Model.*

I. INTRODUCTION: THE CHALLENGE OF NEC

Necrotizing enterocolitis (NEC) is considered the most devastating gastrointestinal emergency in the neonatal unit. It has remained a significant cause of neonatal death and poor developmental outcomes with a mortality of up to 60% [1]. Extensive research has been performed to understand NEC better, but despite these efforts, it remains an elusive disease to diagnose and differentiate from other Acquired Neonatal Intestinal Diseases (ANID) [2].

Acquired Neonatal Intestinal Diseases (ANID) is a group of conditions that are complex multi-variate conditions that are difficult to delineate, detect and diagnose. Of concern, is the disease course of ANID conditions such as SIP and NEC

as they can be unpredictable and can rapidly progress to peritonitis and shock. Highlighting the urgent need for non-invasive, readily available and dynamic computer-aided detection support in clinical practice. ANID research also lacks a structure to uniformly capture the complexities of a patient's presentation in its entirety to recreate rich data sets that can globally be aggregated to create big data for research.

Timely diagnosis and monitoring is an important focus area for current NEC research as it can improve outcomes [2]. In current practice, the diagnosis of SIP and NEC is made based on clinical findings, laboratory investigations and medical imaging. The diagnosis strongly relies on imaging, as it provides an objective measurement to move beyond suspected NEC (suggestive clinical findings) to medically confirm NEC. However, imaging interpretation can also be challenging showing great inter-expert variability, as nonspecific results do not preclude NEC entirely [3]. There is currently no computer-aided detection software (CAD) for abdominal radiographs (AR) or abdominal ultrasound (AUS) in neonates. Newer imaging modalities such as AUS has excellent potential to outperform AR but unfortunately is underutilised. The use of AUS has been mainly limited to when AR findings are inconclusive. This is despite AUS showing several advantages over AR and outperforming AR in diagnosing NEC [4].

It is unlikely that traditional clinical research methods will progress NEC research as rapidly as machine learning (ML) and CAD enabled technology can. Although a randomised control trial is still considered the golden standard for univariate research to determine causality, observational trials as a research methodology have received renewed interest due to advanced analytic technologies being powerful enough for multivariable processing and management of confounders. Using real-world evidence (RWE), neonatology can overcome uncertainties about benefits, risk, real-life utilisation and performance of biomarkers or new therapies [5]. Obstetrics and Neonatology have limited ethical scope in trials approval, further advocating for insights from databases. ML can enable richer extraction of data, overcome bias (as it offers more objective

processing) and lead to the extraction of better insights [6]. Furthermore, it is also able to cleanse existing databases of non-NEC entities, therefore improving the quality of current databases.

II. GAINING INSIGHTS THROUGH PREDICTIVE MODELING OF CLINICAL PRESENTATION

A. Differentiating NEC from other ANID's clinical features

The most common three forms of the Acquired neonatal intestinal disease (ANID) is: spontaneous intestinal perforations (SIP), classic necrotising enterocolitis (Preterm NEC) and Term-NEC (primarily seen in term infants) [7]. See Table I for their differential features.

TABLE I. DIFFERENTIAL FEATURES FOR THREE COMMON FORMS OF ANID [7].

Spontaneous Intestinal Perforation	Preterm NEC	Term NEC
<p>Onset of symptoms: Birth weight < 1250g: onset within first seven days. Birth weight > 1250g: onset within two weeks.</p>	<p>Onset of symptoms: Onset usually after two weeks. In cases that are ischemia-driven, onset is within first month of life.</p>	<p>Onset of symptoms: Onset within the first month of life, often within 11-25 days.</p>
<p>Gestational age: Most cases of SIP involve infants < 30 weeks gestation and <1500g. Older infants often have IUGR</p>	<p>Gestational age: <36 weeks gestation</p>	<p>Gestational age: ≥36 weeks gestation</p>
<p>Clinical Features: Insidious onset of symptoms. In most cases affects low birth weight (<1500g) with <30 weeks gestation. Abdominal distention Blue-grey discoloration of the abdominal wall. No enteral feeding association.</p>	<p>Clinical Features: Abdominal distention, ileus and/or blood in stools. Persistent platelet consumption Meets "Two out of Three" rule* Requires three preconditions: A. Naive bowel, food in the bowel. B. Trigger event. C. Fits Sartwell's model of disease onset.</p>	<p>Clinical Features: Abdominal distention, ileus and/or bloody stools. Birth weight greater than 2500g. Associated maternal illicit drug use, intestinal anomalies and congenital heart disease.</p>
<p>Imaging Features: AUS or AR visualisation of Pneumoperitoneum without pneumatosis.</p>	<p>Imaging Features: AUS or AR visualisation of Portal Venous Gas (PVG) or Pneumatosis Intestinalis (PI).</p>	<p>Imaging Features: AUS or AR visualisation of Portal Venous Gas (PVG) or Pneumatosis Intestinalis (PI).</p>

B. The rationale for CAD insights to improve clinical decision making.

Clinicians are faced with ever-increasing demands on their time and expected to evaluate information across systems to extract insights to provide recommendations continually and quickly throughout the day. This requires the ongoing data collection and aggregation to assess the infant. Various cognitive shortcuts can develop, unknowingly. These paradigms are timesaving strategies, to enable the clinician to meet an ever-increasing workload.

Unfortunately, as various cognitive biases develop, this can result in clinicians making assumptions that are often only seen in retrospect.

By enabling CAD, it can work as the clinicians assistant in aggregating data and summarise findings. This can save a significant amount of time, free cognitive processing capacity to make more thorough enquiry of the summarised data and utilise more energy on patient care planning. Furthermore, as CAD does not rely on biased experience and didactics, more productive and more uniform data is created that can readily be aggregated to international databases.

C. Predictive modelling trials relevant to NEC

Predictive modelling of NEC's clinical features would utilise data from, but is not limited to, clinical findings, assessment scores, lab results and clinical outcomes (see Figure 1). It needs to be appreciated that some data varies from static (binary) to dynamic values (example respiratory status). The current guidance case definitions and differential features (as provided in Table I) should form the foundation to formulate the supervised machine learning model. Collaboration with systems researchers, clinicians and radiologists would be needed ongoing insight and final approval of results. Techniques in building a supervised model are very diverse in the literature and would require ongoing comparative assessments against standardised techniques versus an ensemble model to accomplish the highest area under the curve (AUC).

FIGURE 1: OVERVIEW OF SUITABLE NEC DATA SOURCES AND VARIOUS MACHINE LEARNING TECHNIQUES SUITABLE TO BUILD A PREDICTION MODEL.

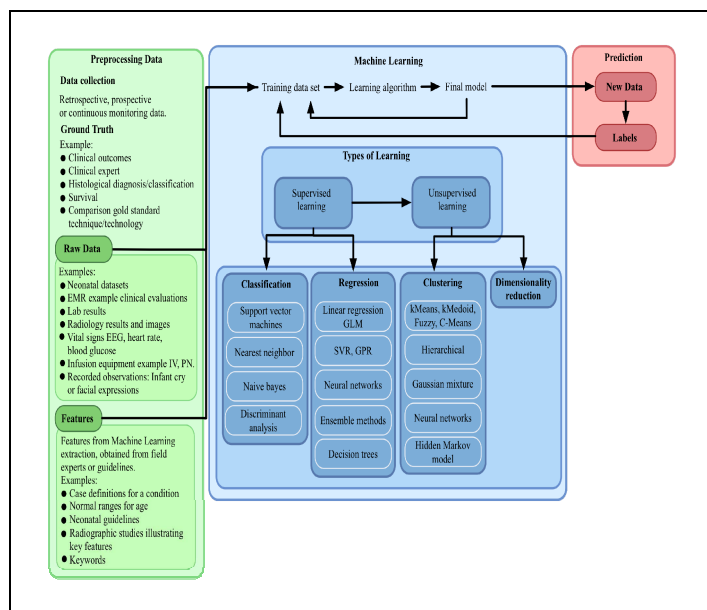


Figure 1 shows several such examples of how modelling could be approached. Of note these trials do deploy various techniques simultaneously of supervised and unsupervised models, again showing the heterogeneous nature of modelling. These are, but are not limited to, Support Vector Regressor (SVR), Support Vector Machines (SVM); - Gaussian Processes Regression (GPR); Generalized linear model GLM and Fuzzy c-means (FCM). In the next section focus will be to elaborate on ML and Deep Learning trials in

NEC or those that show promise in building a collective disease model (Figure 2).

Information can be extracted from neonatal electronic medical records (EMR) using classification models such as Support Vector machines and Naïves Bayes. A recent systematic review looking into ML classification techniques [8], recommended extensive tuning of classification parameters. Recommending further refining of the impact of kernel type, adding or removing Gaussian mutation, gamma value, epsilon value, participant numbers, and C in SMV. In the case of Naïve Bayes classification, the smoothing values and baseline class weighing needed careful consideration to refine. Cohen et al. 2016, in his HER extraction only optimised only kernel type, C, and gamma to improve accuracy [9]. His study also highlighted that careful consideration should be given to training database size, feature selection, classification technique, class balance, and reference baseline as they all significantly affected classification performance. In his trial, SMV outperformed Naïves Bayes by AUC of 0.82 versus 0.71.

Investigations into biomarkers in NEC have found that pairing clinical features with biomarkers can significantly improve predictive value. Classifying each case on clinical findings and validated biomarkers using Linear Discriminant Analysis (LDA) in an ensemble model, Sylvester et al. 2014, estimated the predictive value of three urine peptide biomarkers. He found modelling biomarker panel alone yielded an AUC of 0.858. Clinical parameters alone had an AUC of 0.817 and left 40.1% of all patients in an ‘indeterminate’ risk group. Once three UPD parameters (fibrinogen peptides: FGA1883, FGA1826 and FGA2659) were added to the clinical model the AUC increased as high as 0.856. Illustrating a popular approach in biomarker research, to improve accuracy by incorporating a combination of various biomarkers and clinical findings. Reisinger et al, also studying biomarkers in NEC, found improved diagnostic accuracy of combining serum amyloid A and faecal calprotectin with intestinal fatty acid-binding protein. Accuracy improved when both faecal calprotectin and I-FABP were combined (sensitivity 94%, specificity 79%). As various biomarkers [10] are being investigated for various outcomes in NEC it would be advisable to create more sophisticated ensemble models to combine clinical and biomarker data to ease the interpretation for clinical practice.

Ensemble modelling can also test if prognostic variables are associated with a condition. This is especially useful in NEC as new biomarker combination, and imaging modalities (aka features) are being explored. Habibi et al. 2016 compared the use of Artificial Neural Networks (ANN MLP) versus Linear regression (LR) in ensemble models, in extracting prognostic factors and diagnose shunt infections using clinical information. ANN outperformed LR models in predicting shunt infection with an accuracy of 83.1 % (AUC; 91.98%, 95% CI and $p < 0.001$) and 55.7% (AUC; 76.5, 95% CI). ANN showed five prognostic features including gestational age, weight, first shunt actual age, shunt revision, and myelomeningocele was significantly associated with shunt infection [11].

The predictive modelling needs for the clinical parameters of NEC would need a more dynamic and intuitive model. There are currently various assessment tools that have been developed to aid in the diagnosis of NEC [2], [12], [13] but these need to be comparatively tested in various settings

to give a fair assessment of their performance. This would be useful to integrate into an ensemble model. An excellent example of such a model is the intelligent Jaundice diagnosis tool [21]. Hao et al. 2017, created an ensemble ‘Jaundice’ model using dynamic uncertain causality graph “chaining” inference algorithm and weighted logic operational flow for diagnostic reasoning. His model was able to integrate a diverse set of clinical features and their cut-off points. ‘Jaundice’ model achieved an accuracy of 99.01% and 84.73%. The results had a better pattern of logic and were easier to interpret than conventional methods such as Bayesian Networks, providing more objectivity. This illustrates the potential use of a more sophisticated system suitable for NEC diagnosis.

Another sophisticated model is the three-dimensional mathematical and computational model of necrotising enterocolitis by Barber et al. 2013 [15]. This model shows great promise in advancing insights into pathophysiology. Unlike other ensemble models based on ordinary differential equations, their mathematic model considered both transient and spatial effects. Using cell-focussed fixed characteristics and a definitive Euler method, a structure of nonlinear transitional sectional differential equations can be solved mathematically. The system monitors the evolution of an initial event (trauma) spatially in the intestinal wall. This model can provide an alternative or adjunct to animal trials to better explain the pathophysiological cascade of events. This will be particularly important when testing therapies and delineating various types of ANID.

III. GAINING INSIGHTS THROUGH STANDARDISED CAD IMAGING AND PREDICTIVE MODELING OF FEATURES

The timely diagnosis and monitoring is an important focus area for current research as it can improve outcomes in NEC [2]. In current practice, the diagnostic differentiation of SIP and NEC is based on clinical presentation, laboratory tests and imaging. The diagnosis of NEC strongly relies on imaging, as it provides an objective measurement to move beyond suspected NEC (suggestive clinical findings) to medically confirmed NEC, imaging of Portal Venous Gas (PVG) or Pneumatosis Intestinalis (PI).

Abdominal radiographs were the standard gold imaging for visualising pathognomonic signs of NEC. Recently, two new non-invasive imaging modalities have shown promise in NEC, Abdominal ultra-sound (AUS) and broadband optical spectroscopy (BOS). The challenge in neonatology is great inter-expert variability in interpreting findings. This is mainly in AUS as it is a newer modality without guidelines in NEC. CAD can be a crucial enabler to overcome these challenges in adapting newer non-invasive imaging modalities. Since 1960's CAD has contributed significantly in AUS diagnostics. The first AUS CAD system was applied in the diagnosis of breast tumours [16]. CAD demonstrated improved the accuracy of diagnosis, reduced the time consumption, and decreases workload doctors [17]. Not surprisingly as the system enables guided assessment, rapid data processing, predictive analytic insights and enabled peer consensus from the clinician and radiologists [18].

A. Challenges and opportunities for AUS

The challenge in using AUS in ML is acquiring a standard plane (for feature extraction and classification), to then in turn define the diagnostic plane (for evaluation of

changes and detection of pathognomonic findings). With radiology fellows, sonographers and clinicians this technique needs an experienced examiner. This very time-consuming even for experienced examiners and challenging for training fellows to master. Because the use of AUS in ANID (NEC) is new; finding experienced examiners is challenging, and with no standard guidelines we can expect the quality of insights to vary. Hence CAD has a critical role in integrating AUS in clinical practice, which in turn generates real-world data for validation of AUS in diagnostic criteria for various ANID's [19].

The benefits of deep learning (DL) is it can detect both a ultrasound standard plane and sonographic diagnostic plane automatically. The sonographic diagnostic plane can enable the detection of epithelial changes (thickening, thinning or perforation) and detect anomalies. Yaqub et al. 2017, showed that CNN can automatically detect a foetal neuro-sonographic diagnostic plane [20]. If the traditional method of feature input is used, then NEC AUS features as described by Faingold et al.2005 [21], Epelman et al. 2007 [22], Muchantef et al. 2013 [23], Bohnhorst et al. 2013 [24], Cuna et al. 2018 [25], [41], [42] should be considered to define the full breadth of textural and morphologic features.

Techniques for feature input or extraction of AUS differ between organ systems needing examination by their respective conditions. This also shows considerable variability in accuracy between organ systems rather than traditional versus DL techniques. This suggests that in developing an NEC AUS CAD, both traditional and DL systems need to be comparatively analysed to find the best accuracy. Textural features are the most commonly used for traditional feature input and are often combined with morphologic features. The classifying techniques often combined with supervised models are: SVM, ANN, FCN, decision trees and AdaBoost.

Recently, Ni et al. 2014, successfully developed an ML technique to acquire a standard plane in AUS in infants. In his study, he used a hierarchical, supervised learning framework to determine the standard plane from successive two-dimensional ultrasound images. The stomach bubble, umbilical vein and spine formed the critical anatomical coordinates for the standard plane in the ultrasound video. A radial component-based model was used to describe the spatial limits of these anatomical coordinates and novel discriminatory search approach too advantage of the vessel probability algorithm to estimate the likelihood of the vicinity of the spine and umbilical vein. Results from 223 new-born abdominal videos show it significantly outperformed total abdomen and other anatomy tracking software without spatial restrictions; the overall detection accuracy was 85.6% [28].

These results are at the lower range in comparison to other AUS CAD traditional techniques and DL. Hence it would be worth doing comparative trials using DL techniques such as GoogLeNet [29], [30], Boltzmann machine [31], Convolutional layers (CNN) [32], [33], Sparse encoder [34] and stacked denoising autoencoder (SDAE) [35] using his AUS standard plane from three key anatomical structures. To optimise accuracy other DL methods can be comparatively tested, for example looking at results from thyroid ultrasound models, accuracy was as high as 98.86-99.13% for GoogLeNet [29] and CNN [32] respectively. Whilst using traditional textural feature input with

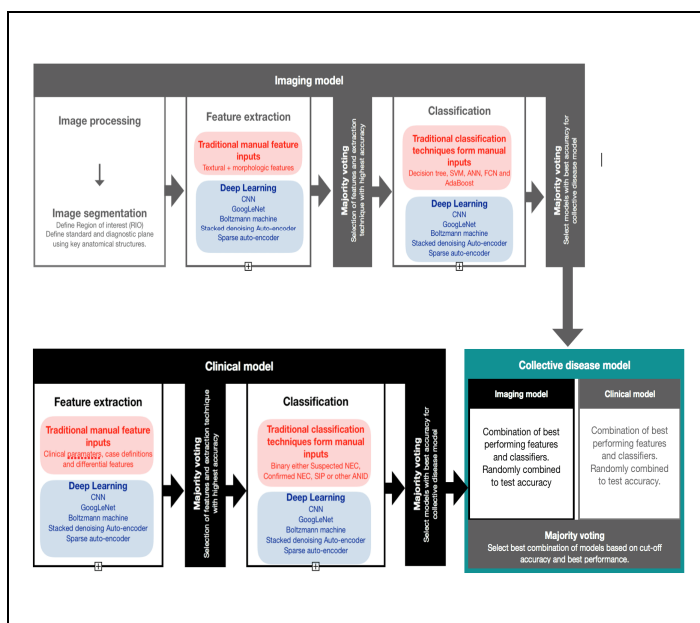
classification techniques using either SVM [36], FCN [37], decision tree's [38], ANN [39], or AdaBoost [40], we may see accuracy improve to 88.8 - 93,3 - 94,3- 98, and 100% respectively.

IV. CLINICAL AND IMAGING PREDICTIVE MODEL FOR NEC

A. Combined clinical and predictive imaging model

Figure 2 shows combined traditional CAD and deep learning models for feature extraction and classification. Majority voting is used to choose the highest accuracy from the best combination of features and ML techniques. Once the best model for each of the sections, clinical and, is determined this will form the collective disease model by combination to try and further improve the accuracy of the case definition and find differential features to build each entity of ANIDS.

FIGURE 2: PROPOSED COLLECTIVE DISEASE MODEL FOR NEC.



V. FUTURE RECOMMENDATIONS AND CONCLUSION

Clinical research as a whole, have a significant challenge ahead. The current set-up costs of once-off trials are causing a trajectory of costs that are unsustainable. Also, as our understanding improves we realise that the complexity of conditions is making it less likely to obtain answers through these traditional trials. A breakthrough in insight into the pathogenesis of some NEC subtypes or NEC mimickers may transform the NEC landscape. However, currently, we do not know if and when that moment will be. Integrating the capabilities of advanced data analytic technologies such as machine learning and CAD yields ongoing insights that can significantly improve clinical practice. The administration, integration, analysis and big data demands of such an understanding will be demanding, but it is an investment that will yield ongoing returns, not only in early diagnosis but continuous evaluation of newer modalities of treatment

The current pace of change and the surmounting challenge to advance not only NEC research but to build case definition of every ANID entity will require a faster pace of adaptation to accommodate personalised medicine. Bedside

practice in neonatal units needs to be adaptable to embrace new technology to improve productivity, accuracy, and data collection. Predictive modelling holds great promise to advance NEC research and diagnostics. CAD can be the critical enabler to not only save time, resources and cost of research but can also help capture uniform, more productive and dynamic data to improve databases. The big data potential of this is substantial, but careful consideration must be made by neonatal networks to place an international data strategy in place to reap future rewards.

Thorough planning should ensure that the integration of guidelines and regulations in clinical trials design are met. As predictive models are receiving more attention from regulators, failing to meet the requirements will jeopardise efforts. Currently, in Europe, the Standards for Reporting Diagnostic Accuracy Studies (STARD 2015) guidelines define these needs. For multivariate modelling TRIPOD guidelines stipulate standard measures of accuracy as well as transparent reporting for diagnostic model trials. There should be careful consideration of terminology, as defined by FDA BEST, when reporting on the model and their outcomes. As this is a rapidly evolving field, new publications from these regulatory bodies should be carefully monitored for updates.

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