Artificial Intelligence for the artificial kidney: pointers to the future of a personalized hemodialysis therapy

Running Head. Artificial Intelligence and Machine Learning for dialysis

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Abstract

Background: Current dialysis devices are not able to react when unexpected changes occur during dialysis treatment, or to learn about experience for therapy personalization. Furthermore, great efforts are dedicated to develop miniaturized artificial kidneys to achieve a continuous and personalized dialysis therapy, in order to improve patient's quality of life. These innovative dialysis devices will require a real-time monitoring of equipment alarms, dialysis parameters and patient-related data to ensure patient safety and to allow instantaneous changes of the dialysis prescription for assessment of their adequacy. The analysis and evaluation of the resulting large-scale data sets enters the realm of Big Data and will require real-time predictive models. These may come from the fields of Machine Learning and Computational Intelligence, both included in Artificial Intelligence, a branch of engineering involved with the creation of devices that simulate intelligent behavior. The incorporation of Artificial Intelligence should provide a fully new approach to data analysis, enabling future advances in personalized dialysis therapies. With the purpose to learn about the present and potential future impact on medicine from experts in Artificial Intelligence and Machine Learning, a scientific meeting was organized in the Hospital of Bellvitge (Barcelona, Spain). As an outcome of that meeting, the aim of this review is to investigate Artificial Intelligence experiences on dialysis, with a focus on potential barriers, challenges and prospects for future applications of these technologies.

Summary and Key Messages:

Artificial Intelligence research on dialysis is still in an early stage and the main challenge relies on interpretability and/or comprehensibly of data models when applied to decision making.

Artificial Neural Networks (ANN) and Medical Decision Support Systems (MDSS) have been used to make predictions about anemia, total body water or intradialysis hypotension and are promising approaches for prescription and monitoring of hemodialysis therapy.

Current dialysis machines are continuously improving due to innovative technological developments, but patient safety is still a key challenge.

Real-time monitoring systems, coupled with automatic instantaneous bio-feedback, will allow changing dialysis prescriptions continuously.

The integration of vital signs monitoring with dialysis parameters will produce large data sets that will require the use of data analysis techniques, possibly from the area of Machine Learning, in order to make better decisions and increase the safety of patients.

KEY WORDS: Artificial Intelligence, Machine Learning, Hemodialysis.

LIST OF ABBREVIATIONS:

ACM: Anemia Control Model

AI: Artificial Intelligence

ANN: Artificial Neural Networks

DL: Deep Learning

EHR: Electronic Health Records

ESA: Erythropoiesis Stimulating Agents

ESRD: End Stages Renal Diseases

FS: Feature Selection

HD: Hemodialysis

IDH: IntraDialytic Hypotension

GDPR: General Data Protection Regulation

GPU: Graphical Processing Units

MDSS: Medical Decision Support Systems

ML: Machine Learning

RBV: Relative Blood Volume

SVM: Support Vector Machines

UF: Ultrafiltration

WAK: Wearable Artificial Kidney

BODY (4000 words)

Background

Renal transplantation is the best option for End Stages Renal Diseases (ESRD) in terms of patient's life expectancy and quality of life, but the shortage of organ donors and clinical contraindications make dialysis the only real option for many patients 1 (Saran R, 2017). Complications in dialysis occur during the treatment, but current dialysis software is not able to make real-time changes when unexpected events happen, or to learn from experience to improve therapy and personalize treatments. Great efforts have been made to pre-set ultrafiltration (UF) and dialysate sodium profiles to counterbalance the negative effects of uncontrolled water or solute removal 2 (Fisheux, 2017). However, this approach has failed, since predetermined ultrafiltration and sodium profiles do not allow adaptations during treatment if the designed profile was inadequate 3 (Ronco C, 1999). Thus, we need real-time data monitoring using multiple biosensors to detect the most important chemical/physical signals from patients and achieve an automatic, immediate and adequate change of dialysis parameters to reduce patients morbidity 4(Locatelli F, 2005).

Data analytics, delivered by Artificial Intelligence (AI) and Machine Learning (ML) is likely to play an important role in patient monitoring of dialysis efficacy and safety. AI is already having an impact on healthcare in areas such as medical image analysis, smart robotics in surgery and voice-enabled assistants 5-6 (Senders JT, 2017; Feng R, 2017). Can this success be exported to dialysis? Is it possible to design and develop smart dialysis devices? A first scientific meeting to discuss the present and future of AI in dialysis was organized at the Hospital of Bellvitge (Barcelona, Spain) with the aim to answer these questions and discuss the state-of-the-art in the field. As a result from that meeting, this study reviews AI experiences in dialysis and discusses barriers, challenges and future applications in the field.

Present of Artificial Intelligence in medicine: Challenges for the application of machine learning in this area and the importance of model interpretability.

Current research in the life sciences relies heavily on data acquisition and analysis 7 [*Leonelli, 2016*]. The drive towards data-based science is especially strong in the –omics fields, where fast technological advances in data acquisition have shifted part of the research challenges to the computer science domain. These challenges maybe only relatively less pressing in healthcare or biomedicine, but, even here, the complexity and heterogeneity of medical information means that "it is not yet possible to create a comprehensive model capable of considering all the aspects of health care systems" 8 [*SM Reza, 2016*].

The widespread adoption of computers and networked digital systems is creating a fast-evolving medical information ecosystem. This situation of data abundance, only bound to increase, may be seen as the perfect opportunity for data analytics, be it in the form of statistics, ML, or combinations of both under the umbrella of AI. Data analytics is at the heart of medical decision support systems (MDSS), which are often based on AI methods such as ML. MDSS, although still

far from the mainstream of medical practice, have made substantial advances in specific domains 9-11 [*Safdar, S., 2017// Pombo, N. 2014// Vellido, A., in press*].

This opportunity seems like a win-win scenario but, in fact, the implementation of AI methods in healthcare and biomedicine is riddled with non-trivial challenges. We argue here that, unless those challenges are appropriately addressed, this type of methods is unlikely to be adopted in practice beyond a limited number of niche applications. Some of these pressing challenges have their origin in societal issues. Let us illustrate this with two examples. One of the currently most fruitful applications of ML in medicine is Electronic Health Records (EHR) text mining. It has been argued, though, that this application might lead to a reduction of skills among medical experts. This negative consequence of the use of ML methods in medicine has been described as ML methods' undue "focus on text and the demise of context" 12 [*Cabitza, F., 2017*]. The second example involves the implementation of a European Union directive for General Data Protection Regulation (GDPR) that will be enforced in 2018 and mandates a *right to explanation* of all decisions made by automated or AI algorithmic systems 13 [*Goodman, B. 2017*]. Note that this regulation should be a warning for any AI-based MDSS for which the required explanation is unfeasible.

Let us now turn to a challenge that is directly derived from the characteristics of many AI methods: the potential lack of interpretability and/or comprehensibility of the data models they generate. Interpretability has become a central issue in ML research over the last years 14 [*Vellido, A., 2012*]. Such surge of interest is at least partly caused by the resurgence of connectionist ML in the form of Deep Learning (DL), a family of successful methods that have also found their way into biomedicine and healthcare 15 [*Jackups, R. 2017*].

Three main challenges for the application of ML in medicine have been recently listed 12 [*Cabitza, F., 2017*] and one of them is precisely interpretability, expressed as "the need to open the machine learning black box". Not that this is a new challenge for ML, because the *black box syndrome* was already on the table decades ago 16 [*Tu, J V.1996*]. The problem can also be expressed as the impossibility to describe in clear terms the relationship between the observed data and the resulting outcomes due to its complexity. This has obvious implications in the medical context: if an MDSS churns out decisions that cannot easily be described in comprehensible terms, a potentially insurmountable barrier is raised between the MDSS and the human users. For instance, the medical expert could not trust to implement a decision that cannot be explained, while the patient might not trust an expert that bases her or his judgement on unexplainable algorithmic outcomes. Also, and on the basis of legal safeguards such as the GDPR, a healthcare system might not be willing to implement an opaque MDSS in clinical practice.

It has been argued that the role of ML in healthcare should be acting "as a tool to aid and refine specific tasks performed by human professionals" 17 [*MJ Reid, 2017*]. Note that this means that interpretability cannot be dissociated from the human interpreter. Some formal framework for machine-human interaction in the pursuit of interpretability is required. One such framework is outlined in Figure 1.

A similar augmented framework was recently proposed for ML interpretability through visualization 18 [*Sacha, Dominik, 2017*], emphasizing interactivity between human and algorithm.

Visualization can be seen as a powerful tool for exploratory data analysis and it has also been mentioned to play a central role in interpretability for medicine in recent research 19 [*Bhanot, G., 2017*].

This is the context in which we need to appraise the present of the application of AI and ML in Nephrology and, specifically, dialysis. Research in this area is still somehow disconnected and tentative. For instance, AI and ML have addressed problems concerning anemia and other issues in HD patients 20 [*Brier, M. E., 2016*], 21 [*Fernández, E.A., 2013*] . Artificial Neural Networks (ANN) were used for predicting total body water in HD patients 22 [*Chiu, J. S., 2005*], and the target range of plasma intact parathyroid hormone concentration 23 [*Wang, Y.F., 2006*]. Support Vector Machines (SVM) and Reinforcement Learning have been proposed for erythropoietin dosage prediction and personalization 24 [*J.D. Martin-Guerrero, 2009*]. Full ML-based MDSS have also been proposed, like a tool for anemia management in renal disease patients undergoing dialysis 25 [*Barbieri, C., 2016.*].

In continuous ambulatory peritoneal dialysis for monitoring patients with severe kidney failure, ML has been used as the basis for an MDSS for blood tests analysis to ascertain their stroke risk levels 26 [*Rodrigues, M., 2017*]. A completely different use of ML is the application of Classification Trees and Naïve Bayes to the prediction of the quality of life in HD patients 27 [*Saadat, 2017*]. Data feature selection can help the interpretation of a given problem by providing guidance about the relative impact of input features on the outcome. An example of such approach is the analysis of the relative relevance of genetic and phenotypic data features associated with the inflammatory status of patients on dialysis 28 [*Bobrowski L, 2014*].

As with the application of AI and ML techniques to medicine in general, a word of caution about the existence of non-trivial challenges must be included here also for the case of dialysis. Ricci and colleagues 29[*Ricci, Z., 2017*] have recently described an scenario where "often the dialysis/Continuous Renal Replacement machine is seen as a black box where nothing can be modified from the scheduled functionality and the machine is automatically selecting the best operational mode to achieve therapeutic targets". Authors warn that this scenario might lead to the progressive deskilling of clinicians. It is also a context in which lack of model transparency can only be overcome by achieving a synergy between machine and human experts in which both tap into each other's expertise to increase their own.

Clinical experiences of AI and ML techniques to HD: Anemia Therapy control and Hemocontrol ™.

Anemia Therapy control, or how algorithms make systems smart.

Although dialysis partially restores kidney blood filtration function, it is unable to replace its role in regulating metabolism and in endocrine function, producing common dialysis complications such as anemia 30 [Lankhorst, 2010.]. The availability of exogenous Erythropoiesis Stimulating Agents (ESA) have improved the treatment of anemia but a high intra- and inter-individual response variability has been detected 31 [Foley,2011]. Thus, with the aim to support the nephrologist in ESA and iron dosing, an AI tool has been developed. The Anemia Control Model (ACM) consists of two components: (1) an ANN model that uses updated patients' clinical data to predict future hemoglobin concentration; (2) an algorithm that suggests the optimal ESA and

iron dosage to achieve the hemoglobin target. It is important to stress that ACM only provides therapy recommendations and that has to be validated.

The neural network was trained to predict the change in hemoglobin value occurring over a month, based on the current patient condition (lab tests, baseline characteristics, and dialysis treatment parameters) and the administered ESA and iron doses. This predictive model is used to assess how hemoglobin is expected to change as a function of different ESA dosages, and is used in the next dose selection step 32,33 [Martínez-Martínez JM, 2014; Barbieri C 2015]. In summary, based on model simulation, the algorithm looks for the drug dosage that would move hemoglobin to the target interval, while avoiding excessive hemoglobin drops or jumps 34 [Escandell-Montero P, 2014]. Patients' updated clinical information is fed to the ACM by means of an automatic interface module with the clinical system, which ensures continuous recording of clinical and laboratory data.

The clinical introduction of ACM has allowed an increase of number of patients in target (70.6% to 83.2%), a decrease in hemoglobin variability (from 0.95 g/dL to 0.83 g/dL), a significant reduction of hemoglobin> 12g/dL (18.06% to 7.5%) and a reduction of ESA and iron consumption 25 [Barbieri C, 2016].

Hemocontrol ™ and Machine Learning Systems

Intradialytic hypotension (IDH) occurs in 20% of patients and increases cardiovascular mortality and morbidity 35 (Stefansson. 2014;). IDH are caused by an imbalance between the prescribed weight loss, the plasma refilling capacity, and the cardiovascular system compensatory mechanism. To prevent IDH, an innovative, multi-input multi-output controller named Hemocontrol™ has been developed 36 (Santoro, 1994). Hemocontrol™ assesses three variables (blood volume, total weight loss and average dialysate sodium level) and controls two dialysis parameters: UF and dialysate sodium level. Relative blood volume (RBV) changes are monitored by an optical absorption biosensor (Hemoscan™) that estimates haemoglobin concentration using spectrophotometry. The estimated RBV used on the hemocontrol prescription is based on the patient's ratio of total UF and final BV changes (BV/UF volume). Hemocontrol ™ modifies sodium concentration of dialysate and regulates the UF rate through a biofeedback mechanism to adjust it to the predetermined RBV trajectory. The changes in UF rate and in sodium concentration are carried out within a defined limit to avoid sodium overload and to achieve the prescribed weight loss. Biofeedback systems that only adjust UF without changing dialysate sodium concentration will not reduce the rate of IDH compared to conventional therapy 37 (Leung, 2017). The dialysis team will be able to follow up the patient's response adjusting the UF goal and change on RBV as required by the patient's clinical condition. Biofeedback systems like Hemocontrol ™ have shown to significantly reduce the incidence of IDH by a 39% 38 (Nesrallah, 2013) and myocardial stunning 39(Selby,2006), while achieving higher UF volumes per treatment 40 (Roland E. 2011) compared to conventional HD. Hemocontrol ™ initial rise in the dialysate sodium concentration has shown to increase the plasma levels of vasopressin that might contribute to a decrease in the number IDH episodes at the end of the treatment 41 (Ettema, 2012). It has also shown to reduce the number of antihypertensive medications in the long term, improving the patients haemodialysis experience by decreasing post-haemodialysis fatigue, increasing the number of event-free sessions

and reducing the number of dialysis sessions that require nursing interventions 42 (Doria, 2014).

The future in medical devices that will revolutionize the treatment of dialysis patients.

Miniaturization, portability, flexibility, "water use" efficiency, and wearable technology are goals subject to intense research that will contribute to the metamorphosis of current dialysis machines. Achieving these goals will require innovative technological developments in the field of membranes (smart biocompatible nanotechnology-produced membranes or composite membranes containing specific sorbents) 43 (Tijink MS, 2013); dialysis fluids regeneration with cation-exchange sorbent systems and enzyme technology 44 (Agar 2010); highly efficient pumping system both for blood and dialysis fluids; anticoagulation and non-thrombogenic surfaces for clotting avoidance; and a safe vascular access for a therapy that should operate continuously 45 (Armignacco P, 2015). Developments in bioelectronics and semiconductor technologies have made possible to design circuits that can be integrated into a single chip and consume less power. Smaller but powerful batteries with longer backup time will further allow miniaturization, enhancing portability. This technology has allowed the development of Wearable Artificial Kidney (WAK) based on dialysate-regenerating sorbent technology 46 (Gura V, 2016). Another development in miniature dialysis devices, still in the preclinical studies stage, is the implantable bioartificial kidney based on silicon nanotechnology to create membranes mimicking glomerular filtration in combination with renal tubular cells 47 (Roy S, 2011).

Wireless technology will also enhance clinical workflow for EHR or remote monitoring. However, electrical leakage in wearable devices is a matter of concern given that patient safety is a key challenge for the development of future dialysis devices, where stringent regulatory and compliance requirements catalyze innovation. To improve patients' security, a system of alarms is required for air detection, blood leaks, transmembrane pressure, and proper blood pump functioning. In addition, miniaturized sensor technology in dialysate affluent and effluent are also important for adequate monitoring of electrolytes and acid-base disturbances. On-line monitoring systems with automatic instantaneous bio-feedback based on real-time and repeated measurement of chemical and physical signals from the patient, such as blood-volume changes, dialysate conductivity, urea kinetics and thermal energy balance, followed by the analysis and evaluation of the data, will allow more personalized treatments 4 (Locatelli F2005). Treatment parameters will change continuously through a dialysis delivery system that incorporates adaptive and logic controls. Integrating monitoring vital signs with parameters of dialysis will produce large data sets that will require predictive models with complex calculations and, possibly, ML methods to deliver better decisions and increase patients' safety 48,49 (Nadkami GN, 2016; Ketchersid T. 2013).

Is AI the future for therapy and decision problem solving in medicine or it is science fiction?. A vision of potential applications of AI in medicine.

To discuss the future potential of AI in medicine, it is necessary to assess its current standing, as described in previous sections. AI is the field of computer science that studies the automatic generation of intelligent behavior from a computational point of view. The term "intelligent behavior" is usually defined in terms of how difficult it would be for a human to perform a given task 50 (*Russell, 2009*). Computational problems that are historically considered part of AI include reasoning, knowledge discovery, planning, learning, natural language processing, perception and the ability to move and manipulate objects.

ML, a subfield of AI, has experienced an unprecedented boom in the 2010's, particularly in the form of DL 51 (*Goodfellow, I2016*). This progress is intimately tied to the increased computational power of processing units. Many of the algorithms popularized during this period were developed decades earlier, but their full potential was not realized until the advent of commercially available graphical processing units (GPUs) that made it possible to efficiently parallelize computation. Automatically generating intelligent behavior that is comparable to that of humans has been a long-standing goal of AI. There are many recent publications that claim to achieve or surpass human-level performance in various areas of AI, such as image segmentation 52 (*Zeng, T., 2017*), concept learning 53 (*Lake, B.M., 2015*), and speech recognition 54 (*Xiong 2016*). With respect to medicine, achieving human-level performance is not only of academic interest, but effectively determines when an AI algorithm may perform its task better than a human would. Several studies indicate that AI algorithms may already surpass humans in clinical tasks such as predicting lung cancer 55 (*Yu 2016*), skin cancer 56 (*Esteva 2017*), and the risk of heart attacks 57 (*Weng 2017*). This trend is bound to continue in the future, with some clinical tasks performed more efficiently and accurately using AI.

With this background in mind, it is evident that AI holds a great potential for clinical tasks in medicine. However, much research on AI for medicine has been carried out in academic settings. For AI systems to have an impact on the diagnosis and treatment of the general population, it would be necessary to implement and integrate such systems in the public healthcare domain. As we discuss below, such a large-scale implementation of AI systems in medicine is far from straightforward. The problem of interpretability has already been discussed, but there is also a host of other issues that we describe below.

A prerequisite for the implementation of AI systems in medicine is to ensure that the appropriate infrastructure is in place. Specifically, patient data should be properly collected, labelled and organized, and measurements performed by digital tools that are directly connected to the network, such that patient records are automatically updated and maintained. Such a digital reform is under way in many countries 58 (*The Economist, 2017*), but there is still plenty of work to be done. An important limitation of ML algorithms is that they need access to large amounts of high-quality data. Although open access to data is becoming more common in academics, there are many incentives in medicine for keeping data private: companies want to maintain an edge over their competition; hospitals may not want to compromise the privacy of its patients, etc. Most likely, it would be necessary to propose and implement new regulations regarding how medical data is created, maintained and shared. A related problem is to ensure that sensitive patient information is not divulged in data records used to train ML algorithms. Patient records are usually anonymized to leave out sensitive information in order to guarantee

the privacy of patients. However, as ML algorithms become increasingly powerful, they can also be used to predict the missing information in patient records. Hence, anonymization may not be sufficient on its own, and additional techniques are necessary to ensure that anonymized patient information cannot be reconstructed.

If AI algorithms are used to make clinical decisions, this raises both ethical and legal questions. Who is liable in case something goes wrong, the developer of the AI system or the hospital? What should an AI algorithm do in case it is faced with two unattractive options? Ethical dilemmas of this type are frequently discussed in the context of self-driving cars 59 (*Bonnefon, J., 2015*), e.g. what should an autonomous car do if it is faced with the decision of hitting a pedestrian or hurting its own passengers? The Ethics Commission at the German Ministry of Transport and Digital Infrastructure recently published the world's first ethical guidelines for autonomous driving 60 (*BMVI. 2017*), and similar initiatives would be needed for medicine.

If discriminatory bias is present in historical data records, then ML algorithms simply learn to reproduce this discriminatory bias. There are several examples in the news of ML algorithms that discriminate: an algorithm implemented by Google to display job ads presented men with higher-paying job offers than women 61 *Independent, 2015*), and an algorithm for predicting crime rates in the U.S. unfairly associated a higher risk with African-Americans than with other ethnical groups 62 (*Business Insider, 2016*). It is easy to imagine clinical situations in which decisions may be considered discriminatory, so this is another aspect of AI that has to be taken into account.

Another problem is that implementing AI systems in healthcare can be viewed by doctors as *trespass* on their domain of expertise, and perhaps even as a threat to their job security. Given the current state-of-the-art in AI, most doctors should be safe: AI algorithms excel at specialized tasks for which they have been trained, but they lack the ability to draw conclusions, integrate information and perform high-level reasoning. In addition, doctors can provide patients with a sense of comfort and human empathy that would be very difficult to reproduce in an artificial system. However, there are specialist doctors such as radiologists whose job mainly consists in analyzing images to diagnose patients. These specialists would directly compete with AI algorithms that perform the same task. Even in these cases, however, there is a danger in relying too much on AI algorithms, since the human knowledge might eventually become lost, an effect known as "automation bias".

In the short term, we believe that the proper way to integrate AI in medicine is to view AI algorithms as tools that doctors can use to make more informed decisions. In this sense, it is important to develop applications that present the outcome of AI algorithms in an explanatory way that doctors can understand and interpret. On the one hand, doctors would have to accept that there are certain tasks that AI algorithms perform better. On the other hand, doctors would be ultimately responsible for the final decisions taken regarding diagnosis and treatment.

It is difficult to speculate in how AI will transform medicine in the long term. One area of AI called life-long learning studies the problem of AI systems that evolve over time and adapt to new challenges and tasks that they were not originally designed for. Such a system would more closely resemble a human's ability to switch between tasks and draw on previous experience to

solve new tasks more efficiently. This research is still in an early stage, and it will likely be many years before such systems are ready to be implemented in real-world applications. One can imagine deploying a team of autonomous nanobots in a human body that automatically learn to perform new tasks over time, with the aim of ensuring the well-being of the patient.

CONCLUSIONS AND FUTURE TRENDS.

ESRD patients depend on technology for living. The evolution of dialysis therapy has been characterized by the search for safer devices with more efficient and clinically tolerable treatments.

Data analytics, delivered by AI and ML is likely to play an important role in medical decision making for patient monitoring of dialysis efficacy and safety. However, MDSS are still far from the mainstream of medical practice.

One challenge for AI methods is the potential lack of interpretability and/or comprehensibility of the data models they generate due to the impossibility to describe the relationship between the observed data and the resulting outcomes due to its complexity. This problem can only be overcome by achieving a synergy between machine and human experts in which both tap into each other's expertise to increase their own.

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FIGURE LEGENDS

Figure 1: Interpretability cycle, considering a number of *actors*, including: the data and/or corresponding models and the ML interpretation tools, on one side (the *machine* side), and the cognitive processing based on a model of the reality to be interpreted, on the other side (the *human* side). The cycle allows for data and model adaptation according to human interpretation (Adapted from 14 [*Vellido, A., 2012*]).