

# Artificial neural network and deep learning in Sjögren's disease: where we are and where we are going

C. Baldini<sup>1</sup>, G. La Rocca<sup>1</sup>, G. Fulvio<sup>1</sup>, E. Grossi<sup>2</sup>

<sup>1</sup>Rheumatology Unit, University of Pisa;  
<sup>2</sup>Villa Santa Maria Foundation,  
Tavernerio, Italy.

Chiara Baldini, MD, PhD  
Gaetano La Rocca, MD  
Giovanni Fulvio, MD  
Enzo Grossi, MD

Please address correspondence to:

Chiara Baldini  
U.O. di Reumatologia,  
Dipartimento di Medicina Clinica  
e Sperimentale,  
Università di Pisa,  
Via Roma 67,  
56126 Pisa, Italy.

E-mail: chiara.baldini74@gmail.com

Received on September 17, 2023 and  
accepted on November 9, 2023.

*Clin Exp Rheumatol* 2023; 41: 2360-2362.

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EXPERIMENTAL RHEUMATOLOGY 2023.

**Key words:** Sjögren's syndrome,  
artificial neural network

Sjögren's disease (SjD) is a complex and heterogeneous disease characterised by a chronic inflammation of the exocrine glands that leads to a typical ocular and oral dryness (1). The disease is also characterised by fatigue and widespread pain and by a huge spectrum of systemic manifestations, affecting virtually any organ system (2, 3). A minority of patients may also develop non-Hodgkin's lymphoma with a considerable burden on patients' morbidity (4, 5).

Despite the great advances in the understanding of the disease, several unmet needs still remain to be addressed including the early recognition of the disease and the possibility of effective therapeutic strategies (6). Indeed, due to the wide variety of the disease clinical presentation, the diagnosis of SjD can be challenging, and may result in misdiagnosis and late referral to specialists. The diagnostic delay of SjD ranges from 3 to 6 years (7, 8). Moreover, pathogenic mechanisms responsible for SjD have not yet been fully elucidated and there is currently no cure for the disease (9, 10). In fact, there are only treatments that focus on relieving symptoms, generally not able to prevent damage accrual (11). Recent advances in basic and clinical research and novel promising therapeutic strategies are indeed opening new avenues for a personalised medical approach to the disease (12). Therefore, there is a growing interest in patients' sub-phenotyping and biomarkers discovery in order to foster precision medicine in SjD. SjD is a typical example of a disease behaving as a complex system. A complex system is a collection of individual components that act with obscure and mysterious rules, in a manner that is not always predictable and with a strong mutual interconnection whereby the action of one component

alters the context for the action of the others. It follows that a system is complex when its overall dynamics is unpredictable from a local point of view and when these dynamics are different from the sum of the dynamics of its components. The increasing amount of clinical, laboratory, and diagnostic imaging data available in these kinds of diseases requires specific tools able to capture the key properties of the entire ensemble, including the linkages and hubs, and to gather and recombine this information, in a different way from the traditional statistical reductionistic approach, which tends to see things individually, to simplify, and to look at one single element at a time.

We need, for this reason, a special kind of mathematical approach that has, historically, remained cast away from the medical context. The combination of computer science and the new theoretical foundations of complex systems has led to artificial neural networks (ANNs).

What are neural networks? It is not easy to explain in a simple way, but we can say that they are systems of interconnected mathematical equations based on a principle inspired by the highly interactive processes of the human brain. Similar to the brain, neural networks are able to recognise patterns, use data and, above all, learn by examples, just as a doctor does in the initial phase of his or her work.

Artificial neural networks are representation-learning algorithms composed of three processing layers with a finite number of nonlinear units (*i.e.* artificial neurons). The first and the third layer of the network are defined as input and output layers, respectively, while the second layer containing a variable number of artificial neurons called hidden units is able to compute the nonlinearity of a given problem.

Competing interests: none declared.

The learning laws of neural networks rest on very solid mathematical foundations and on relatively recent theories developed over the last 40 years. Towards the end of the 1980s there was an unequivocal demonstration of the ability of neural networks to interpolate any function problem given a sufficient number of hidden units (13).

ANNs gained popularity in problems where the relationships between the variables of interest are very complex (14-16). Based on a set of simple rules, the system attempts to learn using some of the data and apply its "knowledge" in the rest of the available information. Their main feature is the ability to modify their internal structure in response to the data presented (17). Compared to the standard statistical methods used in epidemiology, these models are capable of analysing all signals at the same time and to account for non-linear relationships between all the variables considered (18).

Deep learning (DL) is a specific sub-field of ANNs that employs multiple layers of hidden layers artificial neural networks, allowing to directly process raw data (19) like those contained in digital images and to develop end-to-end predictive models by performing all the processing steps usually involved in the design of a classic ANNs model, including feature extraction and learning. The multi-layered structure of deep neural networks allows them to serve as nonlinear function approximators, able to learn different representations of the input data at multiple levels of abstraction. The literature concerning deep learning has literally exploded in recent years: a clear and comprehensive review was published in 2023 (20).

Intriguingly, ANN and DL techniques have demonstrated to be useful to elaborate prediction models aimed at facilitating timely diagnosis of SjD. Dros *et al.* built a machine learning algorithm based on combined healthcare data to detect the disease in primary care (21). Similarly, random forest and optimal classification tree machine-learning models were also used in 1,647 patients with SICCA syndrome to develop a predictive model to iden-

tify patients at high risk for SjD starting from demographic and clinical patients' features (*i.e.*, age, gender, referral specialist and antibodies positivity) (22). More specifically, if we take into account the diagnostic items for SjD, DL can also predict a focus score >1 in the labial gland biopsies with good accuracy, thus representing a valuable help for assisting pathologists who are not experts in oral medicine, as recently shown in a subproject of the Necessity trial (23). Moreover, DL can also be used to help in the automated segmentation of SGUS images. In the HarmonicSS project more than 1000 SGUS images were collected and four DL techniques for semantic segmentation were assessed (24). Considering the accuracy and speed of these techniques, it was concluded that this approach could have wider applications in assisting SjD diagnosis in clinical practice. Finally, moving towards patients' endotype, Wang *et al.* using a machine learning algorithm based on metabolomics, successfully construct a diagnostic model based on serum aminoacidic and lipidic metabolites that was quite sensitive in distinguishing SjD from healthy controls (25).

Besides the mentioned important steps in SjD diagnosis, at present, the most relevant application of ANN and DL has been demonstrated in the identification of SjD different phenotypic subtypes.

We used Auto Contractive Map (AutoCM), to compute the association of strength of 37 clinical, demographic and histological variables, each with all others. AutoCM allowed us to clearly distinguish SjD patients presenting with predominant glandular manifestations and no or mild extra-glandular features from those with a more severe clinical presentation and we obtained a predictive model for lymphomagenesis based on traditional risk factors that was characterised by a high specificity and sensitivity (26). Analogously, Chatzis *et al.* (4) elaborated a data driven prediction lymphoma model of patients with SjD associated lymphomas, by applying innovative data-driven analysis of clinical features present at the time of SjD diagnosis and found that cryoglobulinae-

mia, focus score and the total EULAR SS Disease Activity Index (ESSDAI) (27) composite index at SjD diagnosis were proven independent MALT lymphoma predictors. In addition, we also applied AutoCM to the evaluation of cardiovascular risk in SjD highlighting the relevance of extra-glandular disease activity and longer disease duration with ischaemic events and peripheral obliterative arteriopathy (28).

Moving towards the endotypic stratification, the application of artificial neural network and machine learning to microarray raw data allowed to identify three different subtypes of patients with SjD; namely, subtype-1 and subtype-3 that were related to cell metabolism, and subtype-2 that had connection with virus infection. Infiltrated immune cells were also different among these three subtypes suggesting a diverse phenotypic expression of the disease and different possible therapeutic strategies (29).

Looking at the past and to all the literature contributions that have been recently produced it seems likely that we are now at the dawn of a new era where novel advanced statistical approaches may open new avenues in the comprehension of a complex and heterogenous disease like SjD.

A burden question is therefore, where are we going? Indeed, we have just started to understand the great potentialities of these novel techniques in analysing large amount of data derived from both the bench and the bedside. These techniques undoubtedly represent crucial tools for the analysis of big data in the ongoing collaborative international projects. Intriguingly, however, the future of these techniques is highly expected in defining SjD individualised therapy. To date the publications that have used artificial intelligence and advanced machine learning techniques to study physio pathogenesis-based treatments in SjD are scarce. A recent systematic literature review aimed at retrieving all articles reporting on the use of advanced statistical analysis applied to the study of systemic autoimmune diseases found only 12 out of thousands of literature abstracts and original papers focused on SjD

but none of them specifically explored pathogenesis-based treatments (30). From this perspective novel advances in artificial intelligence have to be mentioned: we refer to generalist AI otherwise known as foundation models, *i.e.* deep learning models designed in 2017 to handle and produce sequential data, such as natural language. These new systems can adapt to new tasks without requiring retraining, can accept input and produce output using various combinations of data types and can logically analyse unfamiliar medical content. They underpin systems such as open AI's Chat GPT-4 and Google's Bard launched during 2023. In conclusion, some important progress has been made in SjD by applying ANN and DL. In the near future, considering the international efforts in searching for biomarkers and the novel therapies in the pipeline, it is likely that these novel techniques will represent key assets in SjD precision medicine to offer individualised therapies to the patients.

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