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Predicting the physiological response of *Tivela stultorum* hearts with digoxin from cardiac parameters using artificial neural networks

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ABSTRACT

Multi-layer perceptron artificial neural networks (MLP-ANNs) were used to predict the concentration of digoxin needed to obtain a cardio-activity of specific biophysical parameters in *Tivela stultorum* hearts. The inputs of the neural networks were the minimum and maximum values of heart contraction force, the time of ventricular filling, the volume used for dilution, heart rate and weight, volume, length and width of the heart, while the output was the digoxin concentration in dilution necessary to obtain a desired physiological response. ANNs were trained, validated and tested with the dataset of the *in vivo* experiment results. To select the optimal network, predictions for all the dataset for each configuration of ANNs were made, a maximum 5% relative error for the digoxin concentration was set and the diagnostic accuracy of the predictions made was evaluated. The double-layer perceptron had a barely higher performance than the single-layer perceptron; therefore, both had a good predictive ability. The double-layer perceptron was able to obtain the most accurate predictions of digoxin concentration required in the hearts of *T. stultorum* using MLP-ANNs.

1. Introduction

Digoxin is a glucoside belonging to the group of digitalis, compounds obtained from *Digitalis purpurea* plant. These compounds are widely used as drugs for the treatment of congestive heart failure and atrial tachyarrhythmia (Wilkerson et al., 1980; Yang et al., 2012; Ziff and Kotecha, 2016). The pharmacological mechanisms of digoxin in the heart are well known (Ziff and Kotecha, 2016; Smith, 1988). Its biochemical effect consists in inhibit the enzymatic activity of the Na^+/K^+-ATPase in cardiomyocytes (Ziff and Kotecha, 2016; Smith, 1988; Dawson and Buckley, 2016). A physiological response in the heart occurs as a result of this inhibition: the maximum contraction force of the heart muscle and ventricular filling rate increase (known as positive inotropic effect), and heart rate is decreased (known as negative chronotropic effect) (Ziff and Kotecha, 2016; Smith, 1988; Dolphen and Lesne, 1980; Berman et al., 1980). Because of this effect, the digitalises are called cardiotonic drugs.

The Pismo clam (*Tivela stultorum*) is a species of bivalve mollusk (which means it has two valves) of the Veneridae family. Their geographical distribution extends from Half Moon Bay, California, USA, to Magdalena Bay, Baja California Sur, Mexico, along the west coast of the three Californias, as well as Socorro Island, Colima, Mexico (Fitch, 1950; Skoglund, 1991).

The molluscan hearts are composed of auricle and ventricle. Similar to vertebrates, each compartment is constituted of myocytes that contract simultaneously and as mammals, values of blood pressure along the cardiovascular system of mollusks are distinct with the highest in the ventricle. The most important characteristic is that as the human heart, the endocardial surface is considered to be similar to those of smooth muscles in mammals (Collins et al., 2006; Kodirov, 2011). The heart rate in Mollusca can reach values comparable to humans (60 bpm) and this can be altered in response to temperature changes and other stress factor as heavy metals, acetylcholine and other compounds (Bini et al., 2006; Kodirov, 2011). Because of their physiological and pharmacological response to digitalis, the heart of *T. stultorum* has been validated as a biological model for pharmacology, both in its biochemical (Cuéllar-Roehri, 1991) and physiological response (Guerra Rivas, 1994).

On the other hand, tissues from mollusks (Cuéllar-Roehri, 1991; Guerra Rivas, 1994), dogs (Wilkerson et al., 1980; Murphy et al., 1987), chickens (Wernke and Cacini, 1990), guinea pigs (Schäfer et al., 1985; Del Valle-Mondragón et al., 2008), rats (Goldstein et al., 2006; Eyer et al., 2012), and other animals have been used to quantify parameters of pharmacodynamics, pharmacokinetics and

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digitalis toxicity. All these analyses involve considerable sacrifice of animals to fulfill this purpose.

An *in silico* model that predicts the amount of drug needed to obtain a specific physiological response could complement the *in vivo* models; thus, the sacrifice of animals and laboratory experiments would be reduced. For this reason, an approximate prediction of the concentration of digoxin necessary to obtain a desired effect in the cardiac activity can be of great interest in the field of pharmacology.

Artificial neural networks (ANNs) are a computational method whose design and operation is based on the behavior of biological neurons in the human brain. These networks consist of several interconnected basic units called neurons, where each connection has a weight. Unlike other computational methods, the ANN is not programmed, but learns by finding relationships and similarities between the input data of the network. These inputs are multiplied by the weight of each neuron, similarly, this signal passes through a transfer function defined for each neuron, and thus each generates an output that goes along with the output of the other neurons to the next layer of the network. This process is repeated for the next layer until it reaches the end of the network. The value obtained is compared with the expected value and the error is calculated, then the neurons change their weights so that the error is reduced, and the whole process is repeated until the error is minimized (Agatonovic-Kustrin and Beresford, 2000).

The perceptron is a topology of ANN, although it can also be understood as the basic unit of the neural network; the artificial neuron. The perceptron sums all input signals and multiplies the sum by the randomly initialized weight values. At first, the perceptron lacks the ability to distinguish complex input patterns; however, through a learning process (training) it acquires this capability (Ponce Cruz, 2010). Multi-layer perceptron (MLP) is a topology of ANN that has shown a good performance to recognize patterns of complex systems, solving problems of non-linear relationships and make accurate predictions (Agatonovic-Kustrin and Beresford, 2000; Ponce Cruz, 2010; Mateo Jiménez et al., 2011; Gobburu and Chen, 1996; Yamamura, 2003; De Matas et al., 2010; Chen et al., 2011). MLP-ANNs consists of at least three layers: the input layer, which has as many neurons as inputs of the network; the hidden layer, which has the activation function on the neurons; and the output layer, that gives the output.

ANNs have been widely applied in the field of pharmacology. The neural network systems have been used for the analysis of pharmacokinetics parameters and the pharmacodynamics of danshensu (Chen et al., 2011), cyclosporine (Camps-Valls et al., 2003), Repaglinide (Haidar et al., 2002) agonist bronchodilator $\beta 2$ (De Matas et al., 2010), nitrendipine (Belič et al., 2005), ill patients (Yamamura, 2003), drug formulation (Takayama et al., 2003), dose-response prediction (Mager et al., 2005), prediction of poisoning of patients treated with digoxin (Camps et al., 2000; Albert et al., 2010), design of systems for the controlled release of drug doses (Chen et al., 1999), cell culture parameters prediction for the production of biopharmaceuticals (Takahashi et al., 2015), detection of congestive heart failure (Masetic and Subasi, 2016), among other applications.

In this paper, data were obtained from experiments *in vivo* from the physiological response of hearts of *T. stultorum*. All experiments were performed in the laboratory of Pharmacology and Toxicology of Marine Sciences Faculty. The experiments consisted in evaluating the before and after effects of adding a specific concentration of digoxin. Subsequently, various ANNs models using MLP topology were built. These ANNs were trained with data from in vivo experiments to predict the concentration of digoxin necessary to be used in a dilution that causes a physiological response in the cardiac ventricular activity of *T. stultorum*.

The aim of this work is to develop a predictive model that describes the pharmacodynamics relationship between the concentration of digoxin and the physiological response of the ventricle of *T. stultorum*, based on biophysical parameters of cardiac activity. The variables used for prediction were: maximum and minimum value of heart contraction force, ventricular filling time, volume used for dilution, heart rate, weight, volume, length and width of the heart.

2. Materials and methods

2.1. Data set

Readings from the activity of 25 heart ventricles of *T. stultorum* were provided by the Laboratory of Marine Pharmacology, where the force of heart muscle contraction was measured over time, making a distinction between the time before and after adding concentrations of digoxin. Four signals features were taken from the heart signals, with one recording for each maximum of contraction force, and the rest of the input variables were provided; thus, resulting in a data set of $10,614 \times 9$ values.

2.2. Preparation of information

The readings contained raw data from a force transducer, saved using the LabChart software (ADInstruments Pty Ltd, Bella Vista, New South Wales, Australia). To make use of the data, they were exported to a file in text format (.txt), and then they were imported and stored as vectors using the MATLAB 8.5 R2015a software (MathWorks Inc., Natick, MA, USA). They were separated into three vectors, one for each channel and one for time readings. Regions with a lot of noise or blank data were discarded. LabChart readings were made at a frequency of 1 kHz, which means that each second of sampling contains a thousand data of measured force. To reduce the amount of data, a larger granularity of one out of 100 was applied, thus reducing the amount data down to 10 out of 1000 per second. A t test was performed to verify that the new data set was statistically equal to the original set (Table 1). Null hypothesis was $\mu_1 - \mu_2 = 0$, where μ_1 is the average of N original heart lectures and μ_2 represents the average of n granulated heart lectures.

Significant biophysical parameters were extracted from the cardiac activity readings according to Guerra Rivas (1994) using a MATLAB script. Each local maximum of the readings was taken as a maximum of force of muscle contraction, and every local minimum as a minimum of force of muscle contraction. The filling time was taken as the time it takes the ventricular chamber to fill and to empty blood fluid, that is, the time between beats. The heart rate was taken as the number of beats per minute. The rest of the input variables were provided through the *in vivo* experiments. Sizes of data sets are being $10,614 \times 9$ values used to train, validate, and test the ANNs. The input data of the ANN were standardized to z values (Mean = 0, standard deviation = 1) using the formula (Eq. (1)):

$$z_n = \frac{x_n - \bar{X}}{\sigma_x} \tag{1}$$

where z_n is the standardized value of the observation n, x_n is the original value of the observation n, $\bar{X}$, and σ_x are the mean and standard deviation of the variable X, respectively. Output data were normalized in the range $[-1, 1]$, with the following formula (Eq. (2)):

$$X_i = \frac{x_i - \left(x_{\max} + x_{\min}/2\right)}{\left(x_{\max} + x_{\min}/2\right)} \tag{2}$$

where X_i is the normalized value of the observation i, x_i is the original value of the observation i, and x_{min} and x_{max} are the minimum