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A computational model for exploratory activity of rats with different anxiety levels in elevated plus-maze

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HIGHLIGHTS

- We model rat's behavior in an elevated plus-maze (EPM).
- We study the behavior of rats under effects of anxiogenic and anxiolytic drugs.
- The virtual rat is an artificial neural network associated with a genetic algorithm.
- Only one parameter is changed to reproduce the behavior of rats under effects of drugs.
- Mann–Whitney test reveals accordance for most variables analyzed.

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ABSTRACT

The elevated plus-maze is an apparatus widely used to study the level of anxiety in rodents. The maze is plus-shaped, with two enclosed arms and two open arms, and elevated 50 cm from the floor. During a test, which usually lasts for 5 min, the animal is initially put at the center and is free to move and explore the entire maze. The level of anxiety is measured by variables such as the percentage of time spent and the number of entries in the enclosed arms. High percentage of time spent at and number of entries in the enclosed arms indicate anxiety. Here we propose a computational model of rat behavior in the elevated plus-maze based on an artificial neural network trained by a genetic algorithm. The fitness function of the genetic algorithm is composed of reward (positive) and punishment (negative) terms, which are incremented as the computational agent (virtual rat) moves in the maze. The punishment term is modulated by a parameter that simulates the effects of different drugs. Unlike other computational models, the virtual rat is built independently of prior known experimental data. The exploratory behaviors generated by the model for different simulated pharmacological conditions are in good agreement with data from real rats.

1. Introduction

The elevated plus-maze (EPM) is a simple experimental apparatus widely used as a pharmacological research tool for anxiety-related studies in rodents (Hogg, 1996). The apparatus consists of a plus-shaped maze with two opposed arms enclosed by walls (enclosed arms) and two opposed arms without walls (open arms). All arms have the same size and are connected at right angle at the central position. The whole structure is elevated 50 cm from the floor.

The standard EPM test consists in putting the rodent at the central position and let it freely explore the maze for 5 min. The standard measures used to characterize the animal's anxiety level are percentage of time spent at and number of entries in enclosed arms. The two main characteristics of the EPM test, which explain its popularity in pharmacological and neurobiological studies, are: (i) it is not required that the animal be trained before the test. Indeed, in most cases it is ideal to use naïve animals, i.e. animals that have never been in the maze before; and (ii) it is not necessary to deprive the animal of any basic resource such as food and water. It is only desirable that the animal be calm when it is placed in the maze.

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The origin of the EPM dates from studies of Montgomery in the decade of 1950 (Montgomery, 1955), in which he analyzed the approach/avoidance conflict in rats during their exposure to a new environment. Montgomery hypothesized that rodent exposure to a new environment causes simultaneous feelings of fear and curiosity in the animal. These feelings are interpreted as adaptive mechanisms of defense to dangerous and unfamiliar stimuli. The idea that the test should last for about 5 min also comes from Montgomery, who observed that often, after 5 min, rats reduce their rate of exploration of the maze because habituation to the environment affects their interest. The first studies that validated the EPM as a test for behavioral and pharmacological research were done in the decade of 1980 (Pellow et al., 1985). After that, several studies have been done to understand the underlying mechanisms of the rat behavior in the EPM (Salum et al., 2003; Walf and Frye, 2007).[1] Most of them are based on the results first obtained by Montgomery (1955), which show that rats spend significantly more time in the enclosed arms than in the open arms of the maze. This behavior is interpreted as resulting from a prevalence of the fear of exposure to new and possibly unsafe environments over the curiosity to explore new environments.

Many studies have been conducted with rats under the influence of anxiogenic or anxiolytic drugs (Pellow et al., 1985; Handley and McBlane, 1993; Dawson and Tricklebank, 1995; Rodgers et al., 1997; Bertoglio and Carobrez, 2002). These studies show that rats under the effect of anxiogenic drugs spend less time in the open arms than control rats, and rats under the effect of anxiolytic drugs spend more time in the open arms than control rats. These results are consistent with Montgomery's theory if one assumes that an increase/reduction of anxiety may be understood as an increase/reduction of *fear*.[2] Methodological information about the experiments with real rats considered here is presented in Appendix A.

A number of computational models for the behavior of the rat in the EPM have been proposed (Salum et al., 2000; Giddings, 2002; Miranda et al., 2009; Tejada et al., 2010; Shimo et al., 2010; Costa et al., 2012). These models have been recently reviewed in Arantes et al. (2013). All of them attempt to simulate the average behavior of naïve male rats in the EPM test. The choice of male rats comes from the experimental observation that the behavior of male rats is different from the behavior of female rats (Steenbergen et al., 1991; Imhof et al., 1993; Marcondes et al., 2001; Elliott et al., 2004; Xiang et al., 2011). In these models, the space of the EPM is discretized and the maze is represented by a network with a central position (or square) and three (Giddings, 2002; Miranda et al., 2009) or five (Salum et al., 2000; Tejada et al., 2010; Shimo et al., 2010; Costa et al., 2012) sequentially connected positions (Fig. 1(a)). The rat is modeled as a computational agent (virtual rat) that moves in the network according to specific rules. In particular, in the models presented in Shimo et al. (2010) and Costa et al. (2012) the computational agent is represented by an artificial neural network (ANN) optimized by a genetic algorithm (GA). The choice of an ANN is motivated by studies that demonstrate that connectionist architectures, like multilayer perceptrons (MLPs), are efficient to reproduce stimulus–response mappings (Ghirlanda and Enquist, 1998). The ANN controls the actions of the agent in a replica of the EPM. Except for the model proposed in Costa et al. (2012), all computational models previously mentioned need data from experiments with real rats in the EPM to be built.

According to Nolfi and Floreano (2000), there are two different approaches for the definition of the fitness function of a GA. In the first approach, the fitness function explores explicitly the abilities and constraints of the agent. In this case, the agent learns how to perform a specific task explicitly defined by the programmer. The first approach was used in Shimo et al. (2010). In the second approach, the fitness function is based on general criteria of the problem. In this approach, the constraints and abilities of the agent emerge due to its interaction with the environment. The second approach is inspired on the process of natural selection in natural agents (Nolfi and Floreano, 2000). It is computationally more expensive than the first approach but, with present day fast and powerful computers, this generally does not represent a major problem. This approach was considered in Costa et al. (2012).

We present here a computational model for the exploratory behavior of the rat in the EPM. The virtual rat is an ANN with weights evolved by a GA. Unlike other computational models mentioned earlier, the virtual rat is built without the use of data from experiments with rats. Data from experiments with real rats are used only to validate the model. The fitness function is based on the approach/avoidance conflict model described by Montgomery (1955). This function is composed by two competing terms. The first term represents the animal drive to explore new positions in the EPM. The second term represents the aversion to dangerous situations relative to the position of the animal in the maze. Our computer model was used to reproduce not only the behavior of control rats, but also the behavior of rats under the effects of anxiogenic and anxiolytic drugs. To the best of our knowledge, only the model presented in Tejada et al. (2010) did the same but with only qualitative agreement between the behavior of virtual and real rats.

2. Methodology

2.1. Virtual EPM

The virtual EPM is divided into 21 positions: five positions in each arm plus the central position (Salum et al., 2000). In our simulations, the virtual rat was allowed to occupy only one of the 21 positions at a time step (Fig. 1(a)). Only transitions for adjacent positions were allowed from one time step to the next. Following Tejada et al. (2009), we used the reduced model of the EPM with 11 positions (Fig. 1(b and c)) to analyze the results. This is justified because in a maze with lighting, smell and temperature under uniform conditions there is no particular reason for the rat to prefer one or another enclosed/open arm (Pellow et al., 1985; Carobrez and Bertoglio, 2005). Thus, for the purpose of analysis of the results, the two open arms are indistinguishable, as well as the two enclosed arms.

2.2. Virtual rat

The computational agent, denoted virtual rat, is controlled by a recurrent multilayer perceptron with only one hidden layer. The network has the Elman architecture (Elman, 1990), i.e. only the neurons of the hidden layer are recurrent. The recurrent connections provide information from previous internal states of the ANN, i.e. they act as an internal memory. The hidden neurons are also important in the decision process.

Sensory units provide perceptual information about the EPM walls, similarly to obstacle sensors in a robot. The number of sensory inputs is 6, being 3 short-distance and 3 long-distance wall sensors. Short-distance sensors detect walls in the range of 10 cm around the actual position of the virtual rat. Long-distance sensors

[1] A search for papers on PubMed using the terms"elevated plus maze" as keyword returns more than 4800 articles in different knowledge areas.

[2] It is interesting to note that, in experiments with real rats, the drugs are inserted in the animals by shots. Since the shot (even without any psychotropic substance) may stress the rat and change its behavior, the control rats receive a shot of saline solution before the experiments to allow comparing them to rats under the influence of drugs fairly.