BioSystems 146 (2016) 35–42

Contents lists available at ScienceDirect

BioSystems

journal homepage: www.elsevier.com/locate/biosystems

Using epigenetic networks for the analysis of movement associated with levodopa therapy for Parkinson's disease

Alexander P. Turner[a,*], Michael A. Lones[b], Martin A. Trefzer[a], Stephen L. Smith[a], Stuart Jamieson[c], Jane E. Alty[c], Jeremy Cosgrove[c], Andy M. Tyrrell[a]

[a] Department of Electronics, University of York, Heslington, York YO10 5DD, UK
[b] School of Mathematical and Computer Sciences, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, UK
[c] Leeds Teaching Hospitals NHS Trust Leeds, West Yorkshire LS1 3EX, UK

ARTICLE INFO

Article history:
Received 3 March 2016
Received in revised form 10 May 2016
Accepted 10 May 2016
Available online 24 June 2016

Keywords:
Epigenetics
Artificial gene regulatory networks
epiNet
Classification
Parkinson's disease

ABSTRACT

Levodopa is a drug that is commonly used to treat movement disorders associated with Parkinson's disease. Its dosage requires careful monitoring, since the required amount changes over time, and excess dosage can lead to muscle spasms known as levodopa-induced dyskinesia. In this work, we investigate the potential for using epiNet, a novel artificial gene regulatory network, as a classifier for monitoring accelerometry time series data collected from patients undergoing levodopa therapy. We also consider how dynamical analysis of epiNet classifiers and their transitions between different states can highlight clinically useful information which is not available through more conventional data mining techniques. The results show that epiNet is capable of discriminating between different movement patterns which are indicative of either insufficient or excessive levodopa.

1. Introduction

Since the beginnings of computer science, there have been many successful attempts at capturing biological models within a computational framework. This field, known as bio-inspired computation, has given rise to algorithms which have been shown to out-perform humans on real world tasks, for instance in object recognition (He et al., 2015). Indeed, many of the computational algorithms that are now state of the art are built upon bio-inspired principles (Oquab et al., 2014; Hinton et al., 2012; Yang et al., 2013; Zhou et al., 2011). The design of bio-inspired algorithms falls on a spectrum. At one end of this spectrum are attempts to capture as much detail from the biological system as possible, to best promote the possibility of emergent behaviour. At the other are intentionally minimalist approaches, using pared-back models that capture only an abstract representation of the biological system. Each of these approaches has advantages, but often the simpler models are functionally complex and capable of capturing real-world biological dynamics (Bull, 2013; Wang et al., 2012).

In this work we use a novel bio-inspired architecture, termed epiNet, which is modelled upon the interactions between genetic and epigenetic processes within biological cells (Turner et al., 2015). Computational modelling of genetic processes, in the form of artificial gene regulatory networks, is nothing new (Lones, 2016). However, the inclusion of epigenetic elements allows for a connectionist architecture with a dynamical topological morphology – that is, the ability for a computational network to autonomously partition itself and select partitions based upon environmental or internal state. This serves two primary advantages. First, it supports task specialisation, where a partition assigned to a specific environmental or internal context is only used in that scenario. Secondly, with minimal analysis it provides a method of characterising a network's behaviour from the ground up, by mapping the functionality of the individual partitions and building up an image of the system's transitions between these partitions. This helps automate the process of model validation. Because of this, we propose that the properties of epiNet lend themselves well to the classification and analysis of real world time series data, where the underlying generative model is often poorly understood.

We describe the application of epiNet to the particular problem of understanding and classifying the movements associated with the neurodegenerative disorder Parkinson's disease when a patient is undergoing treatment with the dopamine replacement drug

* Corresponding author.
E-mail addresses: alexander.turner@york.ac.uk (A.P. Turner), m.lones@hw.ac.uk (M.A. Lones), martin.trefzer@york.ac.uk (M.A. Trefzer), stephen.smith@york.ac.uk (S.L. Smith), stuart.jamieson1@nhs.net (S. Jamieson), Jane.Alty@hyms.ac.uk (J.E. Alty), jezcos@doctors.net.uk (J. Cosgrove), andy.tyrrell@york.ac.uk (A.M. Tyrrell).

http://dx.doi.org/10.1016/j.biosystems.2016.05.005

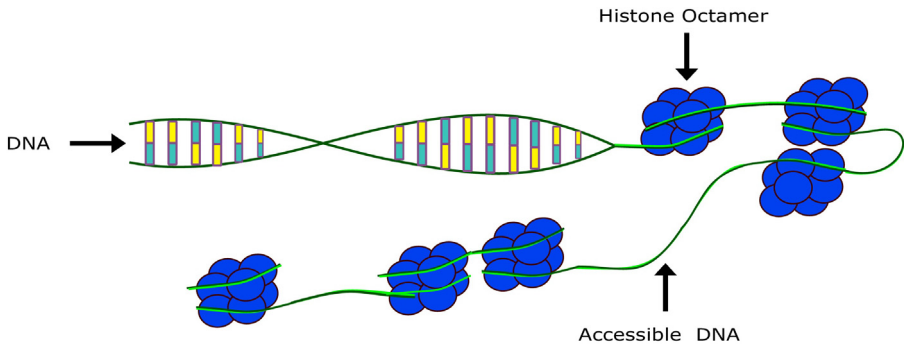

Fig. 1. DNA being wound around histone octamers over 1.67 turns, forming a chromatin fiber.

levodopa. Incorrect dosage of levodopa can have severe manifestations, notably the involuntary and violent muscle spasms known as levodopa-induced dyskinesia (LID). Correct dosage involves finding a balancing point between the removal of Parkinsonian symptoms and the onset of side-effects, providing a challenge to both patients and clinicians alike. In this work, we demonstrate the potential of epiNet by analysing the topological changes and transitions between dynamical states within the model when classifying movement data collected during levodopa therapy. We show that it is possible to provide clinically relevant information about LID, the underlying data and the processes underpinning *why* at any given point epiNet has made a certain decision.

2. Background

2.1. Epigenetics

Epigenetics refers to mechanisms which result in changes in gene expression without altering the underlying DNA (Bird, 2007; Turner, 2001). In Fig. 1, a general eukaryotic arrangement of DNA is illustrated. Within the cell nucleus, DNA is wrapped around a histone octamer over 1.67 turns. This combination of DNA and histones is referred to as chromatin, one of the major epigenetic structures. Chromatin has two prominent biological roles: compressing the size of a DNA strand, and controlling physical access to the DNA. The dynamically varying structure of chromatin allows DNA to move relative to it, allowing the cellular machinery (e.g. polymerase, transcription factors) to access it. Controlling this movement means controlling which genes are actively being transcribed at any given moment. This idea is central to the model used within this paper, where there exists a 'bank' of genes (the genome) which is inactive by default. Then, chromatin reorganises itself relative to the DNA in order to change which genes are accessible to the cellular machinery at any given time.

Additionally, there are other epigenetic marks. One of the most pervasive is DNA methylation, where a methyl group is added to either the cytosine and adenine nucleotides within DNA. In a similar vein to chromatin modifications, methylations typically prevent transcription by physically inhibiting the cellular machinery's ability to straddle the DNA, preventing processes such as transcription (Bird, 2007; Turner, 2001). There are also other epigenetic mechanisms, such as micro RNAs, prions and SRNAs.

2.2. Epigenetic networks

The model used in this work (previously described in Turner et al. (2015)), builds upon a range of previous work from more statically derived genetic and epigenetic functionality (representing genetic networks and static epigenetic marks such as DNA methylation) (Lones et al., 2013; Turner et al., 2014; Reil, 1999; Bull, 2014) to more dynamic models which take inspiration from chromatin modifications (Turner et al., 2013, 2015, 2016). Indeed, the low-level element of epiNet, the artificial gene model, is derived from (Lones et al., 2010), and remains unchanged. This artificial gene is a computational element that takes inputs and processes them using a function, producing a single transformed output. In this paper, we use a sigmoid function, meaning that these low-level elements are similar to perceptrons in artificial neural networks. This function can be parameterised during evolution, allowing the gradient of the function and offset to change for each individual gene, allowing for functions ranging from the typical sigmoid to an approximate step function (Fig. 2). Many of these genes are linked together to form an artificial gene regulatory network, in which certain genes are mapped to external inputs and outputs (Lones et al., 2010).

We have explored several approaches to building epigenetic structures into, or on top of, existing artificial gene regulatory networks (Turner et al., 2013, 2014, 2015). In these models, genes are generally always active unless made inactive by an epigenetic analogue. Additionally, the epigenetic analogues are static and fixed in place and control a small part of the network. With epiNet, by comparison, genes are inactive until turned on by an epigenetic analogue. The epigenetic analogues are then regulated by genes, causing them to move around the genome, switching on and off different parts of the network over the course of time.

The main structure in this model is a genetic structure, consisting of a number of genes (30–100) which exist on a 1-dimensional linear scale (Fig. 3) between [0,1]. These genes are static and are *not* directly executed. Execution of the genes occurs when genes are copied from the genetic structure to the protein network. The protein network functions in a similar way to the networks in (Lones et al., 2010), where it is the structure which directly interacts with an external environment (task) and is executable. However, *which*

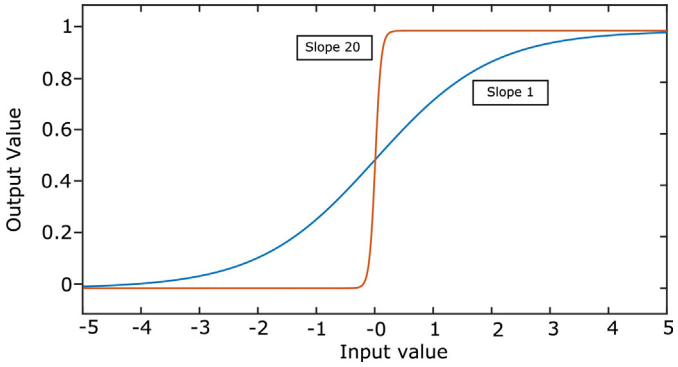

Fig. 2. The changes in the output of the sigmoid function according to different slope parameters, which are optimised for each gene within the network. With a slope of 1, the output can be seen to be a sigmoid with a shallow gradient. With a slope of 20, the sigmoid gradient is steep enough to approximate a step function.