Available online at www.sciencedirect.com

ScienceDirect

Procedia Computer Science 120 (2017) 253–259

Procedia Computer Science

www.elsevier.com/locate/procedia

9th International Conference on Theory and Application of Soft Computing, Computing with Words and Perception, ICSCCW 2017, 24-25 August 2017, Budapest, Hungary

Simulation-based identification of optimal combination of drug candidates for spinal muscular atrophy

Recep Duranay[a], Rza Bashirov[a,]*, Adil Şeytanoğlu[b]

[a]*Department of Applied Mathematics and ComputerScience, Eastern Mediterranean University,Famagusta, North Cyprus, Mersin-10, Turkey*
[b]*Department of Biological Sciences, Eastern Mediterranean University, Famagusta, North Cyprus, Mersin-10, Turkey*

Abstract

Spinal Muscular Atrophy is the second leading genetic cause of infant mortality. Homozygous absence of the Survival Motor Neuron 1 gene is the cause of Spinal Muscular Atrophy, while Spinal Muscular Atrophy severity is mainly determined by the number of SMN2 copies. It was reported that the severity of Spinal Muscular Atrophy can be essentially alleviated by an increase of SMN2 mRNA and SMN protein concentrations through inhibiting HDAC – the major molecular regulator of SMN production pathway. Resveratrol, SAHA, TSA and VPA are potential drugs that increase SMN2 mRNA and SMN protein concentrations by inhibiting HDAC. AZA is another potential drug that positively affects SMN protein production by inhibiting methylation of SMN2 gene transcription factors. According to the wet lab experiments use of these chemicals in SMA patients lead to 1.3- to 2.7-fold increase of SMN protein levels.

In the present research, we create deterministic model of SMN production pathway, perform computational validation of underlying pathway by known wet lab observations, and use model checking technique to determine an optimal combination of potential drugs that results in the maximum induction of SMN protein. The simulation results show that SMN concentration can be increased up to 3.84-fold over the control. The current work is conducted in terms of hybrid Petri nets on Snoopy platform. Proposed technique can be easily adapted to other disorders as well.

© 2018 The Authors. Published by Elsevier B.V.

Peer-review under responsibility of the scientific committee of the 9th International Conference on Theory and application of Soft Computing, Computing with Words and Perception.

*Keywords:*Quntitative modeling; hybrid petri nets; spinal muscular atrophy; smn production pathway.

* Corresponding author. Tel.:+90-392-630-1005; fax:+90-392-365-1604.
E-mail address: rza.bashirov@emu.edu.tr

1877-0509 © 2018 The Authors. Published by Elsevier B.V.
Peer-review under responsibility of the scientific committee of the 9th International Conference on Theory and application of Soft Computing, Computing with Words and Perception.
10.1016/j.procs.2017.11.236

1. Introduction

1.1. Motivation

Mutation of the spinal muscular neuron 1 (*SMN1*) gene causes spinal muscular atrophy (SMA) - a genetic disorder resulting in proximal muscle weakness. SMA is amongleading causes of genetic mortality in children. As it is reported in Cherry*et al*. (2014), SMA affects 1 in 11,000 live births. It is known that each SMA patient retains at least one copy of very similar gene called *SMN2*. Because of single point mutation in exon 7,*SMN2* results in only 10% production of full-length survival of motor neuron (SMN) protein,which is insufficient to compensate for the loss of *SMN1*, while almost 90% of the protein made by *SMN2* is missing exon 7, and, thus, cannot be converted into full-length SMN. Anumber of drug candidates, with several currently in clinical trials, were identified to modulate *SMN2* expression. Unfortunately, none ofthemalone issufficiently enoughto cure this disease.This is the pressing motivation for the current work to explore basic molecular interactions in SMN production network in order to predict the optimal combination of the drug candidates that can lead to the maximum induction of SMN. Guided by this motivation, we use Snoopy software, which isdetailed in Heiner*et al*.(2012), to create hybrid Petri net (HPN) model of SMN protein production network and perform simulation-based model checking to predict the combination of potential drugs having desired characteristics.

1.2. Related work

It is reported in Monani *et al*. (2009) that although no drug treatment is available for SMA, several attempts have been made to identify drug candidates that modulate *SMN2* gene as a therapeutic target. In this paper, we review on drug candidates with available qPCR data. Induction of *SMN2* gene expression by histone deacetylase (HDAC) inhibitors is nowadays recognised as the most promising therapeutic strategy for SMA. Several HDAC inhibitors increasing the expression of *SMN2* gene were described in Brichta *et al*. (2003),Avila*et al*.(2007),Hahnen *et al*. (2006),Dayangaç-Erden *et al*. (2009) andHauke *et al*. (2009). In Brichta *et al*. (2003), it was reported that in fibroblast cultures derived from SMA patients treated with therapeutic doses (0.5–500 μM) of valproic acid (VPA), the level of full-length SMN2 mRNA/protein increased 2- to 4-fold. Since VPA is a drug highly successfully used in long-term epilepsy therapy its side effects are well-known. It was observedin Avila *et al*. (2007)that trichostatin A (TSA) treatment in SMA model mice results in increase of full-length SMN protein levels in the brain, liver, and spinal cord by approximately 1.5- to 2-fold. Clinical trials have revealed that various doses of suberoylanilide hydroxamic acid (SAHA), which is also under investigation for cancer treatment, activated *SMN2* gene and inhibited HDAC, resulting in approximately 2-fold increase of SMN protein levels relatively to the control. This observation is described in Hahnen *et al*. (2006). As it is noticed in Dayangaç-Erden *et al*. (2009)1.3-fold increase in full-length SMN protein levels was observed relative to untreated cultures after treatment with 100 μM resveratrol. The *SMN2* gene is subject to gene silencing by DNA methylation. In this sense, inhibition of *SMN2* gene silencing conferred by DNA methylation might represent a promising strategy for drug therapy of SMA. It is notified in Hauke *et al*. (2009) that transcriptional *SMN2* gene activation by the DNA-demethylating drug 5-aza-2'-deoxycytidine (AZA) in *SMN1*-deleted SMA fibroblasts resulted in almost 2-fold increase of full-length SMN protein.

A concept of Petri nets provides a powerful mechanism for modelling and simulating dynamic systems arising in scientific, engineering and industrial domains. Petri nets have been expanded with dozen of extensions in response to increasing demand to represent and analyse biological systems. Over the last two decades Petri nets have been expanded with a dozen of extensions. Petri nets with continuous, hybrid, stochasticand fuzzyextensions have been successfully used for modelling of signalling pathways, metabolic networks and gene transduction networks. In Bashirov and Mehraei (2017) and Bashirov and Akçay (2017)we used hybrid functional Petri net (HFPN) to create and analyse a quantitative model of molecular interactions between major regulators of fetal-to-adult hemoglobin switching network and p16-mediated signalling pathway, respectively.

1.3. Contribution

In the present research we create deterministic model of SMA protein production network by means of HPNs,

Download English Version:

https://daneshyari.com/en/article/6901699

Download Persian Version:

https://daneshyari.com/article/6901699

Daneshyari.com