Discrete Applied Mathematics 157 (2009) 2221–2231

Contents lists available at ScienceDirect

Discrete Applied Mathematics

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

Modeling the process of human body iron homeostasis using a variant of timed Petri nets☆

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ARTICLE INFO

Article history:
Received 7 January 2007
Received in revised form 13 June 2007
Accepted 11 June 2008
Available online 1 January 2009

Keywords:
Petri net model
Iron homeostasis
Net analysis
Time dependence

ABSTRACT

The body iron homeostasis is one of the most important processes in the human body. This complex process is not fully understood and until recently only some parts of it have been described in the literature. In our recent papers the main part of the process has been described and a model based on Petri net theory has been proposed. However, in this model any time dependencies occurring in the biochemical process have not been taken into account. In the present paper the model is enriched in the way that durations of biochemical reactions composing this process have been included into the model. A variant of Petri net where with each place a time interval is associated has been used in order to describe these dependencies. The time interval associated with a place corresponds to a time lag of biochemical conditions which must be fulfilled in order to enable a biochemical reaction to start.

1. Introduction

In this paper an extension of the recently proposed model of the human body iron homeostasis is proposed. This complex process plays a crucial role in the human body but it is not fully understood. Until recently, only some components of it have been described in the literature. These descriptions have been given in a rather informal way, i.e. they were not expressed in a language of any mathematical theory. From this follows that they were not very precise. In a series of our recent papers [3,5, 4] the main part of this important process has been described and its model has been formulated in the language of Petri net theory. The model has been analyzed in detail in [5]. However, since for this modeling, a Petri net without time information has been used, the model does not contain any information about time dependencies which are present in the real process and may be crucial for understanding its nature. Although they are not known precisely, they can be estimated by time intervals. In the present paper the core of the model is extended by adding to it time durations of biochemical reactions composing the process. These time durations are modeled by time intervals associated with every place in the net. They should be interpreted as time spans in which the time points of the fulfillment of some biochemical conditions, necessary to enable some biochemical reactions to start, lie. This extension makes the model more realistic since it takes into account more features of the analyzed biochemical process than the previous model, where the time dependencies occurring in the studied phenomenon were not considered.

☆ This research has been partially supported by the EU grant Bioptrain and by the Polish Ministry of Science and Higher Education.

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0166-218X/$ – see front matter
doi:10.1016/j.dam.2008.06.053

Iron is one of the key components of many important biological processes in the human body. It is crucial for many cellular functions and for the proper growth and development of tissues. On the other hand, natural iron is insoluble and can catalyze the formation of potentially damaging toxic oxygen radicals. Hence, an excess of iron may lead to serious diseases. Since humans have a very limited capacity of excreting iron, cells have developed mechanisms of improving iron solubility to control the iron concentrations. However, the signaling pathways and the molecular components involved in this control process are not very well understood. First attempts to build a precise model of it have been made in [3,5,4]. In the present paper an extension of the central part of the model is presented in the language of a variant of timed Petri net.

The Petri nets have been proposed in 1962 by Carl A. Petri in the context of technical systems [27]. Different kinds of such systems were the main area of Petri net applications until the last decade of the 20th century. With the rapid growth of computational biology Petri nets have been also used to model biological systems (cf. [20,30]). Nowadays, they are used for modeling and analyzing various biological processes, e.g. metabolic pathways (cf. [35]), gene regulatory networks (cf. [12]) and signal transduction pathways (cf. [24]). For an overview of biological applications of Petri nets see [17,29].

The analysis approach presented in this paper is mainly based on the net invariants. The definition of these invariants was introduced in [22]. The first biological application of minimal t-invariants to analyze metabolic networks in the steady state was introduced in [33] in the form of elementary modes. In [18] the invariant analysis is proposed and discussed as a validation of a qualitative Petri net model.

The organization of the paper is as follows. In Section 2 the human body iron homeostasis process is described. In Section 3 definitions of the Petri net and its extension used to model the considered biochemical process are presented and analyzed. In Section 4 the Petri net based model of the homeostasis process is analyzed. The paper ends with conclusions in Section 5.

2. Human body iron homeostasis

Iron is an ubiquitous element in the environment and in biology, essential for nearly all living organisms, including human [10]. The mechanisms and factors that influence and regulate human body iron homeostasis are very complicated and still not fully understood phenomena.

After absorption in the small intestine, iron (Fe^{3+}) binds to serum transferrin (Tf). This protein is responsible for its transport from the sites of absorption and storage to the various cells having transferrin receptor-1 (TfR1) on their surface [7]. As a result of this process (i.e. binding Tf(Fe^{3+}) to TfR1) comes into being a complex which is internalized by the receptor mediated endocytosis (RME) into cellular endosomes. Tf binds to the TfR in 2:2 (Tf: TfR subunit) stoichiometry [13]. After the internalization of this complex, iron Fe^{3+} is released from Tf under the endosomal acidic conditions and occurs in the reduced form as Fe^{2+}. Then, in this form iron is transported into the cytosol or mitochondria of the all-proliferative cells (among others the one-nuclear cells, the preerythrocytes and the erythrocytes) and reaches their labile iron pool (LIP) [21].

The LIP is regulated in the most of the cells by iron responsive proteins (IRPs) that sense its level, and in turn control the translation of the TfR and the ferritin in a compensatory manner. A rise in Fe uptake increases the LIP and results in the IRPs inactivation. The latter concomitantly evokes the ferritin synthesis and blocks the TfR synthesis by inducing the TfR mRNA degradation. The LIP is the compartment from which iron is either metabolically drawn into Fe-dependent enzymes, transported into mitochondria for the heme synthesis or incorporated into the ferritin for a secure storage and/or detoxification. How LIP acts depends on the body iron status. If there is a low concentration of the serum iron in the human body, the iron (Fe^{2+}) from the one-nuclear cells LIP is mostly transported out by the protein called ferroportin (Fpn). If the concentration of the serum iron in the human body is high, the iron from the one-nuclear cells LIP is mostly transported out into the ferritin, which acts as the human body iron storage [21].

The erythroid precursors (preerythrocytes) and the red blood cells are other cells, apart from the one-nuclear cells, involved in the body iron homeostasis. In case of these cells, the majority of iron which enters them is transported into mitochondria for the heme synthesis. This phenomenon increases especially due to anemia, when the serum red blood cells and serum iron concentrations are insufficient for the proper function of the human body. In this case synthesis of erythropoietin (EPO), the hormone produced by the kidneys is increased to enhance the erythrocytes production. The red blood cells live in the human body about 120 days and after that period of time they are phagocytosed by the one-nuclear cells. These cells are responsible for the recirculation of the iron derived from the effete red cells so that it may enter the circulation, bind to the Tf, and be transported to the bone marrow for the red blood cells production [26].

The body iron metabolism is changing under the influence of the inflammatory process. It is generally thought that the inflammation alters the one-nuclear cells iron homeostasis, resulting in an increased iron retention and a reduced iron release, thus giving rise to the low iron concentration and anemia, although in the latter event defects in the red blood cells production may be also involved [1].

A protein whose production is modulated in response to the inflammation, the anemia and the hypoxia is the hepcidin [15]. Recently, it has been found that this protein regulates the cellular iron efflux by binding it to the Fpn [2,14]. In the latter phenomenon of inflammatory-induced hepcidin expression, causing an Fpn degradation might account for the iron sequestration within the one-nuclear cells. The influence of the inflammatory process on the human body iron homeostasis what has been described in detail in [4]. In a recently suggested model, for the regulation of the hepcidin expression, the hepatocyte surface HFE (the hemochromatosis protein) competes with the HoloTf(Fe^{3+}) for the binding with TfR1, which is the transferrin receptor-2 (TfR2) competitor [14]. The unbound surface of the HFE and a higher concentration of Tf(Fe^{3+})-TfR2 complex were proposed to increase the hepcidin expression and its release. According to this model, the iron deficiency