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RESEARCH ARTICLE

Computational model for monitoring cholesterol metabolism

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Abstract A non-deterministic finite automaton is designed to observe the cholesterol metabolism with the states of acceptance and rejection. The acceptance state of the automaton depicts the normal level of metabolism and production of good cholesterol as an end product. The rejection state of this machine shows the inhibition of enzymatic activity in cholesterol synthesis and removal of free fatty acids. The deficiency in human cholesterol metabolism pathway results in abnormal accumulation of cholesterol in plasma, arterial tissues leading to diseases such as hypercholesterolemia, atherosclerosis respectively and formation of gallstones. The designed machine can be used to monitor the cholesterol metabolism at molecular level through regulation of enzymes involved in the biosynthesis and metabolism of cholesterol for the treatment of diseases incident due to the respective metabolic disorder. In addition, an algorithm for this machine has been developed to compare the programmed string with the given string. This study demonstrates the construction of a machine that is used for the development of molecular targeted therapy for the disorders in cholesterol metabolism.

Keywords Cholesterol metabolism · Enzymes · Molecular targeted therapy · Non-deterministic finite automata

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Introduction

An interdisciplinary research which interconnects both the field of mathematics and biology is a developing study. Computational biology deals with the modeling of biological systems through mathematical approach. The field of computing calculates different levels of notion together and constructs the corresponding automation in a form of machine by dealing with both the simulated and natural information processes (Denning 2005). The knowledge of perfect designing and implementation procedure for enhancing the approach to the biological process is supposed to be a vital target for synthetic biology (Marguet et al. 2007). A complete framework for the construction of computational models of bio-systems is yet to be formulated (Blakes et al. 2011). Modeling biological systems from the molecular to organismal scales are to be extensively studied (Banerji 2013). The emergence of biochemical pathways occurred due to the impact of the series of reactions between different bio-molecules which comprised to form a pathway (Banerji 2014).

The identification of basic biological processes can be achieved by developing a framework for different interaction levels between bio-molecules (such as DNA, RNA and protein), networks and cells (Dhar and Giuliani 2010). On the other-hand, algorithmic systems biology which integrates both the models and experiments can be applied to influence the scope of scientific field (Priami 2009). Based on this, the structural organization of biological context with hierarchical nature was projected with a 'chassis construct' was designed using a scheme of algorithms (Dhar and Giuliani 2010).

The results from the bio-computing based on mathematics have a significant role in solving biological problems. Based on this idea, Kari (1997) has used mathematical

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methods relating the biological concepts to explore the computational biology. Benenson et al. (2001) introduced simulation of bio-molecular process using finite automaton with two states and two symbols which was experimentally tested in vitro. Further, the non-deterministic finite state automaton based on DNA strands was described by Nowak and Plucienniczak (2008). In which, the DNA molecules are analyzed whether they are described by specified regular expression using automaton. A computational model for the extraction of human erythropoietin from the collection of proteins using finite automaton was constructed by Selvakumar et al. (2013). Muhammad et al. (2013) constructed a push-down automaton to monitor the glycolysis process in cancer cells.

The biosynthesis of cholesterol equals to three-fourth of the body cholesterol. The cholesterol consumption in diet accounts to one-fourth of the total cholesterol. Cholesterol is synthesized mainly in liver, intestine, skin and endocrine glands. Cholesterol is a progenitor for life assisting steroid hormones and a vital substance for cellular integrity. Cholesterol in diet and synthesized in the body can be stored in the form of cholesteryl esters. The cholesteryl esters can be converted to free cholesterol through enzymatic reactions and further can be metabolized to gain energy in liver. In addition, the cholesterol is synthesized in the form of lipid rich core chylomicron particle in human intestine (Bennion and Grundy 1975; Dietschy and Gamel 1971). The lipid-rich core consists mainly of triglycerides and also small amounts of cholesterol ester. In addition, it has a surface coat containing protein (including specific apoproteins), phospholipids and free cholesterol. The triglycerides with a surface apoprotein, phospholipids and free cholesterol pass into the capillary system. The endothelial cells of the capillary beds containing the enzyme called lipoprotein lipase. The triglycerides are hydrolysed by lipoprotein lipase (LPL) and release the free fatty acids.

The monitoring procedure based on non-deterministic finite automaton (NFA) is used to enhance the diagnostic procedures and conventional treatment in cholesterol metabolic disorders. This application assists the development in the targeted therapy through scrutinizing the expression level of the enzymes and its functional activity.

Automata

Generally devices that are used to transform information from one form to another based on definite procedure are called automata (Muhammad et al. 2013). It deals with the logic of computation with respect to the simple machines. It is a mathematical model of a system with distinct inputs and outputs (Hopcroft and Ullman 1979). Automata are the abstract models of machines that perform computations on an input by moving through a series of states. At each state of the computation, a transition function determines the next state on the basis of a finite portion of the present state. As a result, once the computation reaches an accepting state, it accepts the sequence of symbols called strings. This is an approach to implement the computing devices with the acceptance of regular expressions.

Non-deterministic finite automata (NFA)

An alphabet is a finite non empty set of symbols. Symbols are denoted by small letter or digit. A string is a finite sequence of symbols. (e.g. $\Sigma = \{a,b\}$, here Σ is an alphabet; a, and b are symbols; and abbb, abab, ababab are strings) (Hopcroft and Ullman 1979). The set of strings over the given alphabet is called a formal language.

Definition A non-deterministic finite automaton is a five tuple, $R = (\Sigma, Q, q_0, F, \delta)$ where Σ is the input alphabet, Q the set of states, $q_0 \in Q$ the start state, $F \subseteq Q$ the final states and $\delta : Q \times \Sigma \rightarrow 2^Q$ transition function.

Two major elements in finite automata are states and inputs. Here the change of state is fully governed by the input and the current state. The state moves from one place to another place due to the input and reaches the final state. The input mechanism can move only from left to right and it can read exactly only one symbol on each step (Selvakumar et al. 2013). For example, a non-deterministic finite automata (NFA) was designed to monitor the nitrogen metabolism and examined the ammonia detoxification involving the enzymes (as input) of urea cycle. Such a machine assists in scrutinizing the completion of urea cycle for degradation of ammonia into urea which is then excreted. This computational model also suggests the regulation of the enzymatic activity which can serve as a therapeutic application focusing on molecular targeted treatment for urea cycle disorders (UCD), brain damage and other related deficiencies due to ammonia toxicity (Ali et al. 2014).

Cholesterol biosynthesis

The initial reaction of cholesterol biosynthesis (Fig. 1) involves the formation of mevalonate from Acetoacyl-CoA and Acetyl-CoA by a series of reactions with the formation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). This reaction is followed with the conversion of HMG-CoA catalysed by HMG-CoA reductase, which requires two moles of cofactor NADPH to form mevalonate. Mevalonate is then catalysed by mevalonate kinase and phosphomevalonate kinase for yielding 5-pyro phosphomevalonate. After the two successive phosphorylation, isopentenyl

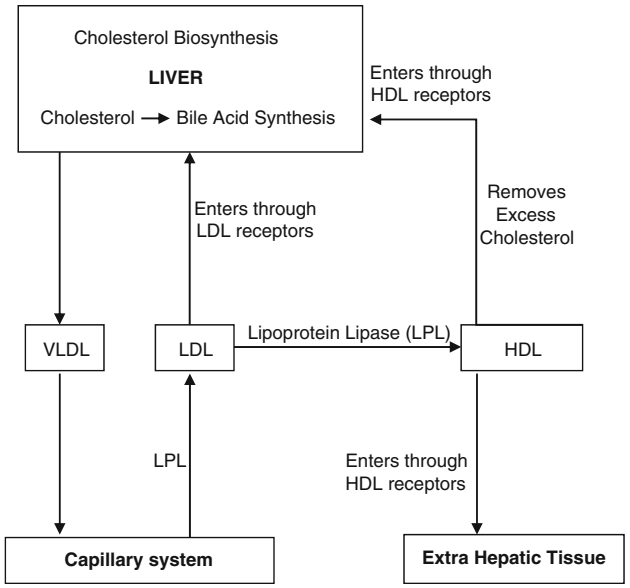


Fig. 1 Overview of cholesterol metabolism and transport

pyrophosphate (IPP) is produced by ATP-dependent decarboxylation reaction.

Isopentenyl pyrophosphate is then condensed with a molecule of DMPP yielding geranyl pyrophosphate (GPP). Farnesyl pyrophosphate (FPP) is produced when GPP condenses with another IPP molecule. Two molecules of FPP are catalyzed by NADPH-dependent enzyme, squalene synthase yielding squalene. Lanosterol is generated from squalene in the presence of the enzyme lanosterol synthase. Lathosterol is then converted to lanosterol through a series of reactions. Further lanosterol is catalysed by lathosterol dehydrogenase to produce 7-dehydrocholesterol (DHC7). Finally, cholesterol is synthesised from 7-dehydrocholesterol in the presence of 7-dehydrocholesterol dehydrogenase (DHCR7) catalysing reaction (Herman 2003).

Cholesterol transport

The hydrophobic (insolubility in aqueous solutions) nature of cholesterol requires special mechanisms for its transport and excretion (Fig. 1). The packaging of cholesterol with lipoproteins is required for plasma transport, biliary excretion and absorption in the intestinal cells (Grundy 1978). The cholesterol esters are transported in low density lipoprotein (LDL). The high plasma LDL cholesterol ratio contributes to the coronary atherosclerosis (Mead and Ramji 2002). The activity of the enzyme LPL catalyses to remove the free fatty acids resulting in decreased amount of cholesterol and increased level of lipoprotein to form high density lipoprotein (HDL). HDL is known as good cholesterol as it removes cholesterol from other extra hepatic tissues to the liver yielding bile acid through cholesterol metabolism.

Computation process of finite automata

A programmable machine is designed to check the process of cholesterol metabolism. It is a new approach to implement the computing devices with the acceptance of regular expressions. A machine is constructed with the non-deterministic finite automaton to accept a string of enzymes. In NFA, the state of acceptance is defined as to accept the string of enzymes and it attains the final state. If the machine cannot accept the string at any cause, it can be defined as the state of rejection (Muhammad et al. 2013).

Here the molecules are denoted as states and are represented as below:

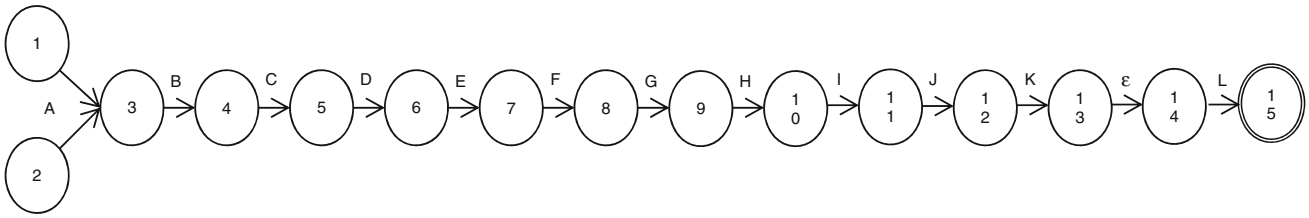
States: Acetoacyl-CoA (1), Acetyl-CoA (2), HMG-CoA (3), Mevalonate (4), Mevalonate phosphate (5), 5-Pyrophospho mevalonate (6), Isopentenyl pyrophosphate (7), Geranyl pyrophosphate (8), Farnesyl pyrophosphate (9), Squalene (10), Lanosterol (11), 7-Dehydrocholestreol (12), Cholesterol (13), Very low density lipoprotein (14), High density lipoprotein (15).

Here the enzymes are considered as inputs and are represented as below:

Inputs: HMG-CoA synthase (A), HMG-CoA reductase (B), Mevalonate kinase (C), Phosphomevalonate kinase (D), Mevalonate pyrophosphate decarboxylase (E), Geranyl pyrophosphate synthase (F), Farnesyl pyrophosphate synthase (G), Squalene synthase (H), Lanosterol synthase (I), Lathosterol dehydrogenase (J), 7-Dehydrocholesterol dehydrogenase (K), Lipoprotein lipase (L).

In the transition diagram (Fig. 2), ε transition is a spontaneous transition that does not use any input. The automaton simply decides to change states without reading any symbol. There is no input from state 13 to 14, instead a transporter is involved. The sequence of symbols called string is accepted with ε transition. Transition function of non-deterministic finite automata for the state of acceptance is shown in Table 1.

In case of rejection state (Table 2), this designed machine could not read the input symbol and therefore the process stops. During such condition, the cellular cholesterol level can be regulated by any of the following enzymes involved in the cholesterol metabolism in order to re-initiate the process. Subsequently, the re-initiated process can be used as a therapy for the metabolic disorders of cholesterol.



Molecules:

Acetoacyl-CoA (1), Acetyl-CoA (2), HMG-CoA (3), Mevalonate (4), Mevalonate phosphate (5), 5-Pyrophospho mevalonate (6), Isopentenyl pyrophosphate (7), Geranyl pyrophosphate (8), Farnesyl pyrophosphate (9), Squalene (10), Lanosterol (11), 7-Dehydrocholestreol (12), Cholesterol (13), Very low density lipoprotein (14), High density lipoprotein (15)

Enzymes:

HMG-CoA synthase (A), HMG-CoA reductase (B), Mevalonate kinase (C), Phosphomevalonate kinase (D), Mevalonate pyrophosphate decarboxylase (E), Geranyl pyrophosphate synthase (F), Farnesyl pyrophosphate synthase (G), Squalene synthase (H), Lanosterol synthase (I), Lathosterol dehydrogenase (J), 7-Dehydrocholesterol dehydrogenase (K), Lipoprotein lipase (L)

Fig. 2 Transition diagram for cholesterol metabolism

Table 1 The procedures and transition functions of NFA for "Acceptance"

Transition function	Explanation
δ (1,A) = 3	Start from the current state 1 with input A, and then it goes to the state 3
δ (2,A) = 3	Start from the current state 2 with input A, and then it goes to the state 3
δ (3,B) = 4	Start from the current state 3 with input B, and then it goes to the state 4
δ (4,C) = 5	Start from the current state 4 with input C, and then it goes to the state 5
δ (5,D) = 6	Start from the current state 5 with input D, and then it goes to the state 6
δ (6,E) = 7	Start from the current state 6 with input E, and then it goes to the state 7
δ (7,F) = 8	Start from the current state 7 with input F, and then it goes to the state 8
δ (8,G) = 9	Start from the current state 8 with input G, and then it goes to the state 9
δ (9,H) = 10	Start from the current state 9 with input H, and then it goes to the state 10
δ (10,I) = 11	Start from the current state 10 with input I, and then it goes to the state 11
δ (11,J) = 12	Start from the current state 11 with input J, and then it goes to the state 12
δ (12,K) = 13	Start from the current state 12 with input K, and then it goes to the state 13
δ (13,ε) = 14	Start from the current state 13 with input ε, and then it goes to the state 14
δ (14,L) = 15	Start from the current state 14 with input L, and then it goes to the state 15

Table 2 The procedures and transition functions of NFA for "Rejection"

Transition function	Explanation
δ (1,A) = 3	Start from the current state 1 with input A, and then it goes to the state 3
δ (2,A) = 3	Start from the current state 2 with input A, and then it goes to the state 3
δ (3,R) = 3, $\forall$ R $\neq$ B	In this transition, the current state is 3 and if it could not get an input B, then it remains in the state 3

According to the literature, the expression level and the activity of certain enzymes can be controlled like HMG CoA reductase (HMGR) which catalyses the rate-limiting step of metabolism. Further, the first genetic defect named as mevalonic aciduria of the cholesterol biosynthetic pathway is due to deficiency of the enzyme mevalonate kinase which was identified in 1986 (Houten et al. 2000; Kelley and Herman 2001; Waterham 2002). This enzyme can also be regulated at the genetic level as a treatment for that disorder. The deficiency of a critical enzyme called familial LPL for the removal of triglycerides and lipid transport, is characterized by very severe hypertriglyceridemia usually presents in childhood. This enzyme can also be normalized at the expression level for the targeted treatment. The conversion of FPP to squalene catalyzed by squalene synthase is the first committed step in the cholesterol synthesis is a significant target for therapeutic interference (Pandit et al. 2000).

Based on the process of this machine, we have developed an algorithm to check whether the two strings are equal or not. In this algorithm, the string given by the user is used to compare the existing string (ABCDEFGHIJKεL). This procedure is applied to monitor the regular enzymatic process from Acetyl-CoA to high density lipoprotein in cholesterol metabolism.

Algorithm

Step 1: Begin

Step 2: Declare array variables a and b

Step 3: Declare variables i, j and c

Step 4: Initialize variables

c ← 0

a[size] ← string

Step 5: Get string from the user and assign it to b

Step 6: **For** i ← 0 and j ← 0 **until** i and j ← end of string **do**

Begin

If a[i] ≠ b[j]

c ← c+1

End

Step 7: **If** c = 0

Display strings are equal

Else

Display strings are not equal

Step 8: End

Conclusion

Cholesterol biosynthesis is regulated by the plasma and dietary cholesterol. Cholesterol also acts as an important constituent of bile, released from the gallbladder, where it is oxidized into bile acids to enhance digestion and absorption of dietary fats. The ongoing researches in cholesterol metabolism focuses on the condition of hypercholesterolemia, where decreased HDL and increased LDL levels augment risk of cardiovascular disease (Grundy 1978). In the present study, the designed machine developed with an algorithm suggests targeting the up or down regulation of the enzymes that are associated with the aberrant build-up of cholesterol in blood plasma, tissues of artery and biliary tract. Subsequently, the machine is also used to monitor and assists in molecular targeted therapy for diseases such as hypercholesterolemia, atherosclerosis and gallstones.

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Conflict of interest The authors declare no conflict of interest.

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