Modelling finite and infinite behaviour of cancer stages using Büchi and finite automata

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Cancer is an incurable disease in which abnormal cells multiply uncontrollably and infect the surrounding tissues and organs of the body. A Büchi automaton is a finite automaton that operates on infinite input words. This article presents normal cell division and cancer progression using the finite automata and Büchi automaton respectively. It will help in understanding the intricacies of cancer, and can ultimately benefit in designing an effective treatment that can slow down the progression of cancer.

Keywords: Büchi automaton, cancer progression, cell division, doubling, replication.

WORDS are the fundamental paradigm of formal language theory. In ω-languages, words are defined by an infinite sequence of letters. Reactive systems involved in non-terminated computations can be represented by the language of infinite words. Most of today's software systems (operating system, air-traffic control system, satellite control systems, telephone switching network, microprocessor, web and embedded applications) are designed to provide services without interruption to the users. Any temporary unavailability is considered a critical failure. These reactive systems can be modelled using Büchi automata. Automata on infinite objects are used for specification and verification of non-terminating program. Their behaviour can be described by infinite streams of input, states and actions.

The human body consists of millions of tiny cells, which divide and multiply over time. New cells form and replace older and damaged cells. A large clump of abnormal cells is called a tumour, and as it progresses it becomes cancer. Cancer generates trillions of abnormal cells that grow and multiply uncontrollably. These affected cells attack neighbouring tissues and extend to other body organs and can lead to death, if they are not treated in time.

Ribba *et al.*[1] applied the hybrid cellular automaton model (a multiple scale individual-based framework) for assessing and improving chemotherapy treatment for cancer patients. To better understand the cancer process, Hunahan and Weinberg[2] proposed a conceptual framework with six hallmarks which occur as integral components of all forms of cancer. Bowles and Silvina[3] designed a cancer automata framework for determining the growth of cancer, affected lymph nodes and to diagnose the presence of metastasis. Additionally, they used model checking as an investigation technique for providing an effective treatment plan.

Giannakis and Andronikos[4] used ω-automata and stochastic Büchi automata to represent the infinite behaviour of the protein folding process. Loohuis *et al.*[5] introduced the concept of cancer hybrid automata for modelling the cancer progression process. Furthermore, they explored the concept of automatic verification of consistency, causal connection, unreachable and unstable states and correspondingly proposed a therapy plan. Alur and Dill[6] proposed the concept of timed automata to model the behaviour of real-time systems and applied the concept of timed automata for automatic verification of systems.

Abott *et al.*[7] extended the work of Hunahan and Weinberg[2], and investigated the interactions of the six hallmarks in the form of a model called CancerSim. Furthermore, they described the process of CancerSim implementation of the hallmarks in an agent-based simulation. CancerSim enables a modeller to study various aspects of developed tumours and develop ways to alter their progression by various parameters. Motivated by the applications of Büchi automata, we have designed a Büchi automaton to represent the cancer progression process. Normal cell division, doubling and DNA replication are represented by finite automata. When a mature cell continues to divide itself an infinite amount of times, it leads to cancer which can be represented by the Büchi automaton. Earlier, various researchers modelled the cancer progression process, but the concept of infinite cell division was not considered.

The paper is organized as follows: The following section describes the preliminaries related to finite automata, omega-regular expression, Büchi automata and the specific acceptance conditions. We then model the cancer progression process using Büchi automaton and finally present our conclusions and the possible future scope.

Preliminaries

Let Σ be an alphabet and Σ^* is the free monoid generated by using concatenation operation on Σ. An empty string

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is denoted by ε and $\varepsilon \in \Sigma^*$. Null language is denoted by ϕ, and it does not contain any string. The string $w = a_1a_2a_3 \ldots a_n$ consists of finite symbols taken from Σ and length of w is denoted by $|w|$. Σ^ω denotes a set of all infinity strings over Σ. An ω-string is an infinite sequence of symbols $a_1a_2a_2 \ldots$ from Σ.

Definition 1 (ref. 8 and 9): Let Σ be an alphabet; then the regular expression can be defined using following rules:

(i) Primitive regular expression: ε, ϕ and $a \in \Sigma$ are regular expressions.
(ii) If r_1 and r_2 are regular expressions representing regular languages L_1 and L_2 respectively, then
  (a) Union operation: $r_1 + r_2$ is a regular expression representing regular language $L_1 \cup L_2$.
  (b) Concatenation operation: r_1r_2 is a regular expression representing regular language L_2L_2.
  (c) Kleene closure: r† is a regular expression representing regular language L†.

Example 1: Consider $\Sigma\{0,1\}$ then

$$\Sigma^* = \{\varepsilon, 0, 1, 00, 01, 10, 11, \ldots\}.$$

Example 2: Consider $\Sigma = \{0, 1\}$ then

0 is a regular expression representing the regular language $\{0\}$.
1 is a regular expression representing the regular language $\{1\}$.
$0 + 1$ is a regular expression representing the regular language $\{0, 1\}$.
0^* is a regular expression representing the regular language $\{\varepsilon, 0, 00, 000, \ldots\}$.
0^*1 is a regular expression representing the regular language $\{1, 01, 001, 0001, \ldots\}$.

Definition 2: Deterministic finite automaton[8] is a quintuple $(Q, \Sigma, \delta, q_0, F)$ where Q is a finite nonempty set of states, Σ is an alphabet, $Q \times \Sigma \to Q$ is a transition relation, $q_0 \in Q$ is a start state and $F \subseteq Q$ is a set of final states.

Example 3: Figure 1 represents the deterministic finite automaton $(Q, \Sigma, \delta, q_0, F)$ for the regular expression 0^*1 where $Q = \{q_0, q_f\}$, $\Sigma = \{0, 1\}$, δ, q_0, $F = \{q_f\}$. The string $w = 001$ is accepted because the determinestic finite automaton processes the input string $q_0 \xrightarrow{0} q_0 \xrightarrow{0} q_0 \xrightarrow{1} q_f$ and reaches the final state.

Definition 3: ω-regular expression[10] s over an alphabet Σ can be defined using the following grammar:

$$s \to \phi | r^\omega | rs_1 | s_1 + s_2,$$

where r is a regular expression.

Definition 4 (ref. 11): The language $L_\omega(s)$ is inductively defined as follows:

$$L(\phi) = \phi,$$

$$L(r^\omega) = (L(r))^\omega,$$

$$L_\omega(rs_1) = L(r)\cdot(L_\omega(s_1)),$$

$$L(s_1 + s_2) = L(s_1) + L(s_2).$$

Definition 5 (ref. 10): A non-deterministic Büchi automaton A is a quintuple $(\Sigma, Q, q_0, \delta, F)$ where Σ is an alphabet, Q is a finite set of states, $q_0 \in Q$ is a start state, $\delta = Q \times \Sigma \to Q$ is a transition relation and $F \subseteq Q$ is a set of accepting states.

An infinite run ρ over infinity string w is defined by $\mathrm{Inf}(\rho) = \{q | q = q_i$ for infinitely many $i\}$.

An infinite run ρ_i is accepted by Büchi automaton if $\omega \in \Sigma^\omega$ visit the set of final states infinitely often, i.e. $\mathrm{Inf}(\rho_i) \cap F \neq \phi$.

Example 4 (ref. 10): Processing of an input string $w = 010101010101\ldots$ for the Büchi automaton shown in Figure 2 is $q_0q_1q_2q_fq_0q_1q_2q_fq_0q_1q_2q_f \ldots$ and $\mathrm{Inf}(\rho) = \{q_0, q_1, q_2, q_f\}$.

Example 5: Figure 3 represents the non-deterministic Büchi automaton corresponding to ω-regular expression $(0 + 1)^*0^\omega + (0 + 1)^*(01)^\omega$.

For an input string $w = 0101000\ldots$

$$\mathrm{Inf}(\rho_1) = \{q_0, q_0, q_0, q_0, q_1, q_1, q_1, \ldots\} = \{q_1\} \text{ and}$$

$$\{q_1\} \cap F = \{q_1\}$$

$$\mathrm{Inf}(\rho_2) = \{q_0, q_0, q_0, q_0, q_0, q_0, q_0, \ldots\} = \{q_0\} \text{ and}$$

$$\{q_0\} \cap F = \phi.$$

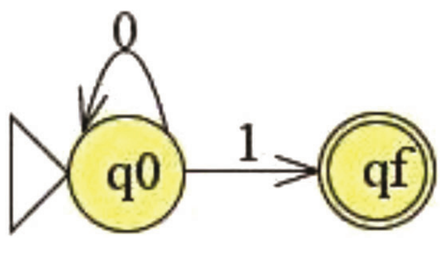

Figure 1. Deterministic finite automaton for regular expression 0*1.

The input string $w = 0101000\ldots$ is accepted, because $\mathrm{Inf}(\rho_1) \cap F \neq \phi$.

Representation of cancer cell formation using Büchi automaton

In this section, various stages of cell division and cancer progression are represented using finite automata and Büchi automaton respectively. Cell growth, replication, doubling and divisions are stages in the normal cell cycle[12,13] as shown in Figure 4. In replication, a cell is divided into two new daughter cells which contain the same genetic information as the parent cell. Cell division refers to the growth of the cell, and it divides the parent cell into daughter cells. After maturing, normal cells do not multiply. Cancer is the result of errors in DNA. Cancer cells are like infinity loop in programing. An infinity loop program uses the resources until the computer system crashes. Similarly, cancer cells keep growing and dividing themselves until they use all the system resources. The infinite properties of the biological cancer progression process are characterized and represented in Figure 5.

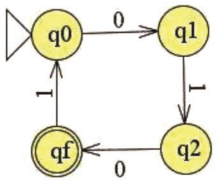

Figure 2. Büchi automaton accepting a string $w = 010101010101\ldots$

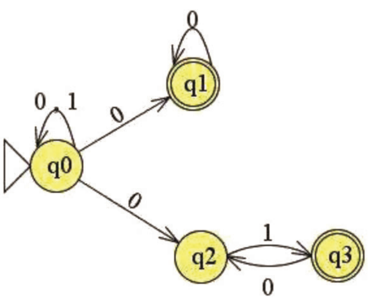

Figure 3. Büchi automaton for $(0 + 1)^*0^\omega + (0 + 1)^*(01)^\omega$.

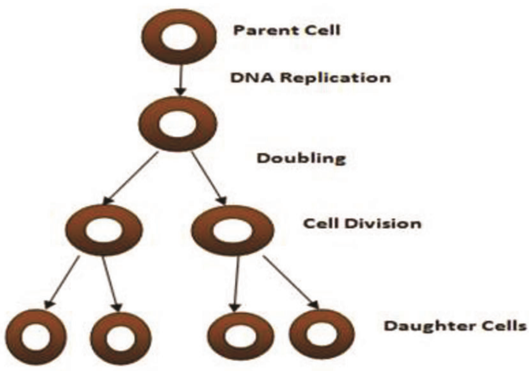

Figure 4. Normal cell-division process.

Normal cell division takes place if the growth factor is positive, whereas cancer cell division takes place in both cases (positive or negative) of the growth factor availability and leads to an abnormal state as shown in Figure 6. Table 1 depicts various symbols used to represent the Büchi automaton.

Modelling of initial stages of cancer division using finite automata

Cancer progression is modelled using discrete states (cancer phenotypes) of Büchi automaton. Finite automata can represent various stages of normal cell division.

(1) Finite automaton for the replication process: In the replication process, DNA makes a copy of itself prior to cell division. This can be described by the regular expression $di\ du\ e\ s(di\ du\ e\ s)^*$ where di, du, e and s represent centriole disengagement, centriole duplication, centriole elongation and centriole separation respectively. The replication process is shown in Figure 7.

(2) Finite automaton for the cell doubling process: In the cell doubling process, cell doubles itself for cell division. This can be described by the regular expression $ghdc(ghdc)^*$ where g, h, d and c represent growth, chromosome duplication, doubling and cytokinesis respectively. The cell division process is shown in Figure 8.

(3) Finite automaton for the cell division process: In the cell division process, a cell divides itself and forms two daughter cells with the same genetic material and roughly half of the cytoplasm. This can be described by the regular expression $grdiv(grdiv)^*$ where g, r, d, i and v represent growth, replication, doubling, membrane indentation and cell division respectively. The cell division process is shown in Figure 9.

Büchi automaton for cancer progression

Büchi automaton of cancer progression can be constructed by merging various stages (growth, replication, doubling and cell division) of the cell division process.

Table 1. Various symbols used for stages in cancer progression

Full name	Symbol	Full name	Symbol
Growth	*G*	Centriole disengagement	*Di*
Positive growth	*Gp*	Centriole duplication	*Du*
Cytokinesis	*C*	Centriole elongation	*E*
Replication	*R*	Centriole separation	*S*
Doubling	*D*	Chromosome duplication	*H*
Division	*V*	Membrane indentation	*I*

Figure 5. Cancer formation process.

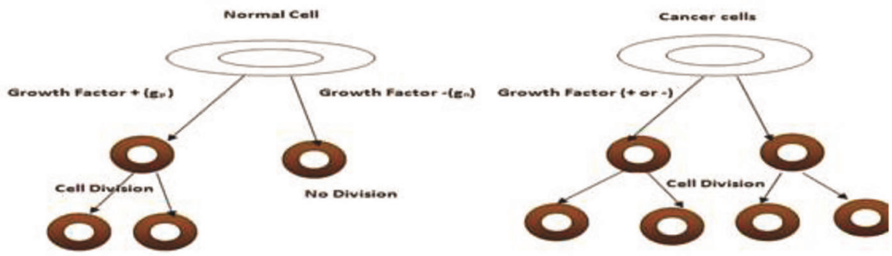

Figure 6. Cell division in normal and cancer cells.

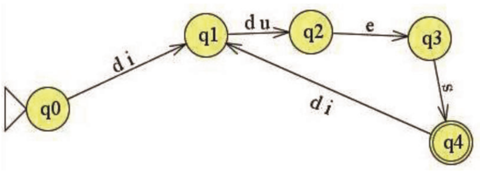

Figure 7. Finite automaton representing replication process of cell division.

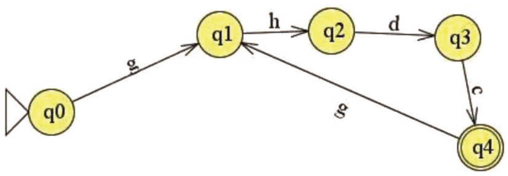

Figure 8. Finite automaton representing doubling process of cell division.

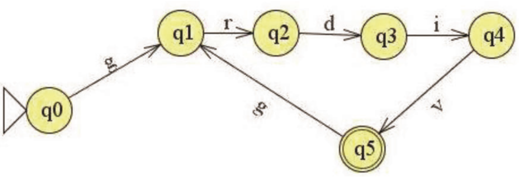

Figure 9. Finite automaton representing normal cell division process.

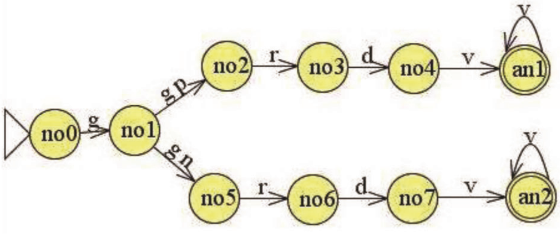

Figure 10. Büchi automaton representing various stages of cancer progression.

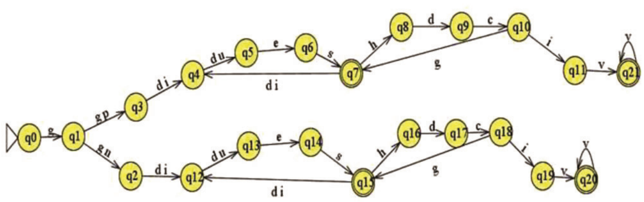

Figure 11. Detailed Büchi automaton for cancer progression process.

(1) Generalized Büchi automaton for the cancer cell division process: Figure 10 depicts the Büchi automaton for the cell cycle and cancer formation process. States labelled with *no*0, *no*1, *no*2, *no*3, *no*4, *no*6, *no*7 and *no*8 represent the normal states reached after growth, replication and the doubling process. States labelled with *anor*1and *anor*2 represent the abnormal states where cell division takes place many times, irrespective of growth factor (positive or negative) and leads to cancer. The final states, *anor*1 and *anor*2, generate a large number of daughter cells by division of the parent cell. This process can be represented by $g\ gp\ r\ d\ v(v)^{\omega}\ tg\ gn\ r\ dv(v)^{\omega}$ omega-regular expression.

(2) Detailed Büchi automata for cancer progression: Figure 11 represents the detailed Büchi automaton with the inclusion of all the stages of a cancer cell during the formation process. In this process, the cell cycle starts with the growth phase, followed by centriole disengagement, centriole duplication, centriole elongation and centriole separation. Chromosome duplication then takes place, followed by doubling, cytokinesis and membrane indentation. At last, cell division takes place infinitely many times and leads to cancer.

Conclusion

We designed finite automata for representing replication, doubling and the cell division process of a normal cell.

Buchi automaton was designed to represent the infinite behaviour of the cancer progression process. These models can be used to design an effective treatment plan for patients and ultimately help to slow down the progression of cancer. Potential directions for future research include the design of an in-depth Buchi automaton for cancer progression and design of transducers for representing the cancer progression process.

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