Modeling of Genetic Networks with Petri Nets

1 Introduction

Petri nets can be used in different ways to model biochemical processes. Here we present one way of modeling of *genetic networks* by means of Petri nets based on [1].

Genetic networks are of utmost importance for the functioning of the cell. The number of genes involved in the network and their interaction is often very complex. Therefore, by making formal models of the networks we try to take advantage of the theory and methodology about Petri nets which is developed in the last more than 40 years. Once we have the models we can use analytical methods or automated verification (like model checking) in order to reason about the behavior of the networks.

2 Quantitative Approach

Genetic networks model interactions between genes. There are two kind of interactions that we need to model: *activation* and *inhibition*. Schematically the activation of a given gene g_1 by some gene g_2 is represented by an arrow line from g_2 to g_1 as in Fig. 1a. The inhibition of g_1 by g_2 is represented by a blunt-end line from g_2 to g_1 as depicted in Fig. 3a.

In the Petri net models that we consider in the sequel the genes are modeled as places (channels) and the events are modeled as transitions (processors). If a place contains one or more tokens this means that the corresponding gene is active. Otherwise, the gene is inactive.

A simple way to model the activation of a given gene g_1 by some gene g_2 is given in Fig. 1b. The arc back from transition t_{g_1,g_2} to gene g_2 ensures that g_2 remains active after it is activated by g_1. The token which is consumed from g_1 in order to activate g_2 is restored back in g_2 after the activation. The marking (state) after the activation is given in Fig. 2.

Similarly, the inhibition of a given gene g_1 by some gene g_2 can be modeled by the net given in Fig. 3b. The gene g_1 is deactivated, i.e., its token is consumed by firing the transition t_{g_1,g_2}, which is enabled by the presence of a token in g_2. The state after the inhibition is given in Fig. 4.

One can see that in the marking given in Fig. 2 the transition t_{g_1,g_2} is enabled and can fire again. As a result we get a marking (state) with two tokens in g_1 and one token in g_2 as in Fig. 5. (Again, the initial token in g_2 was consumed by the firing, but it is also immediately restored.)

Obviously in this way, by repeated firing of t_{g_1,g_2} one can produce an unlimited number of tokens in g_1. In this sense, one could say that the model in Figs. 1 and 2 is *quantitative*. The longer we have an influence by g_2 on g_1 the

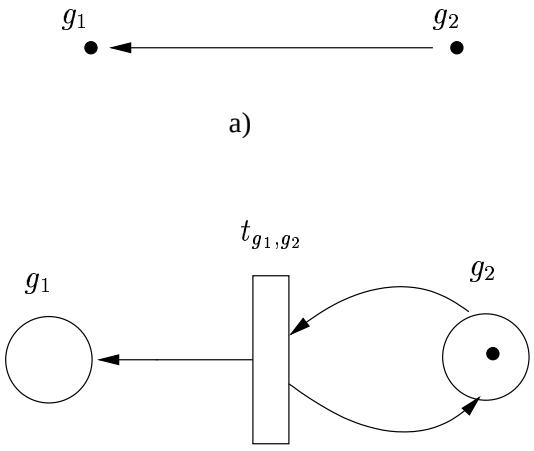


Fig. 1. Activation (quantitative version).

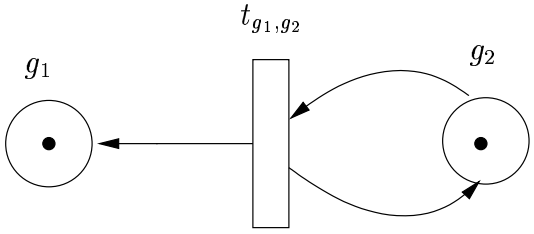
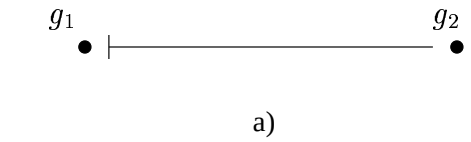
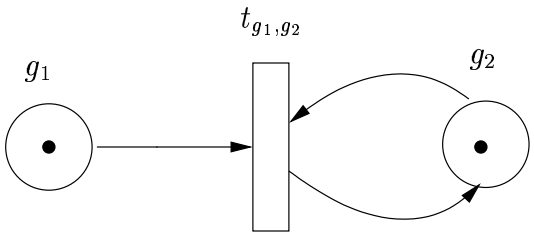


Fig. 2. Activation Petri Net after firing.



a)



b)

Fig. 3. Inhibition (quantitative version).

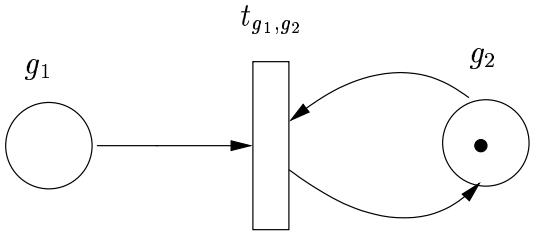


Fig. 4. Inhibition net after firing.

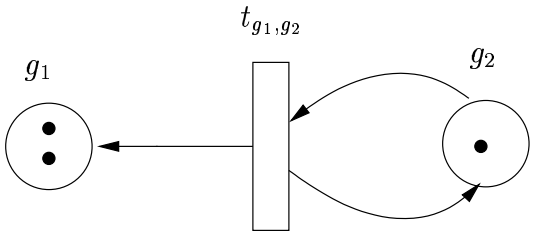


Fig. 5. Activation Petri Net after two firings.

more active g_1 becomes. The quantitative aspect can be also seen if we assume that there is another activator gene g_3 which activates g_1 via a new transition t_{g_1,g_3}. Obviously, now we get tokens in g_1 both via firing of both t_{g_1,g_2} and t_{g_1,g_3}. So, the more activators we have, the more activity of the activated gen we get.

Similarly, if there were more than one tokens in the place corresponding to gene g_1 then one would need more than one steps (i.e. longer activity) by the inhibitor g_2 or more than one inhibitor.

3 Qualitative Approach

The kind of quantitative models from the previous section could be rather difficult to handle. After all, their state space is infinite. Also we are often interested only in the *qualitative* aspects of the networks, i.e., for each gene it suffices to know if it is active or inactive. Therefore, we introduce the slightly more complex solution which has the nice property of having a finite state space.

The solution in case of activation is given in Fig. 6. In the new model each

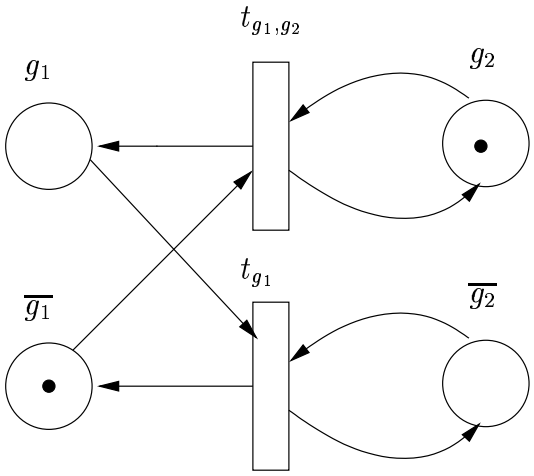


Fig. 6. Activation (qualitative version).

gene is modeled by two places g_i and $\overline{g}_i$ (where $i = 1, 2$). We say that $\overline{g_i}$ is a complement of g_i. In the initial state if g_i contains a token then $\overline{g_i}$ does not and vice versa. Thus, the sum of the tokens in g_i and its complement is exactly one. One can show that this property remains correct after any sequence of transition firings, i.e., in any state which is reachable from the initial state. Moreover, one can show that in all reachable states there is at most one token in each place. For instance, the marking (state) after firing of the net in Fig. 6 is given in Fig.7.

The state space of the net is given in Fig. 8. The state space consists of four

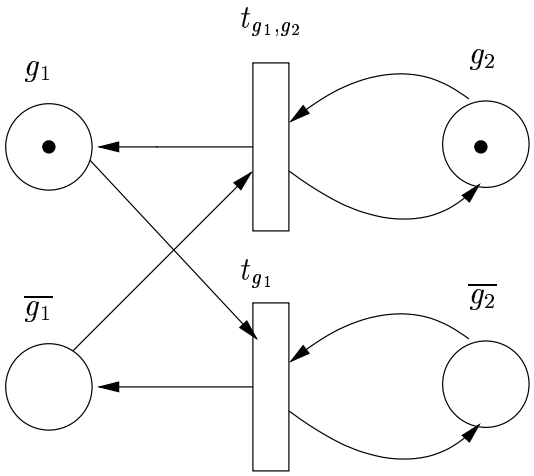
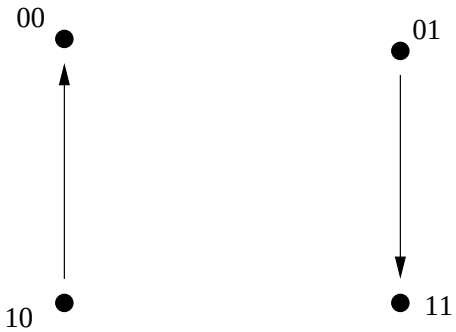


Fig. 7. Activation after firing.



S = {00, 01, 10, 11}
T = {(10,00), (01,11)}

Fig. 8. State space of the activation net.

states corresponding to all possible combinations of states (active or inactive) of g_1 and g_2. A labeling x_1y_2, where $0 \leq x_1, y_1 \leq 1$ of a state denotes that there are x_1 tokens in place g_1 and x_2 tokens in g_2. (The tokens in the complementary places are not given because they are determined by the property that the sum of the tokens in two complementary places always equals 1.) For instance, if we begin in the initial state 01 (given in Fig. 6) by firing t_{g_1,g_2} we can go to the state 11 (corresponding to Fig. 6).

Notice that if we begin with 10 as initial state, i.e., if g_1 is already active, but the activator g_2 is inactive (Fig. 9), than we can go to the state 00. One can

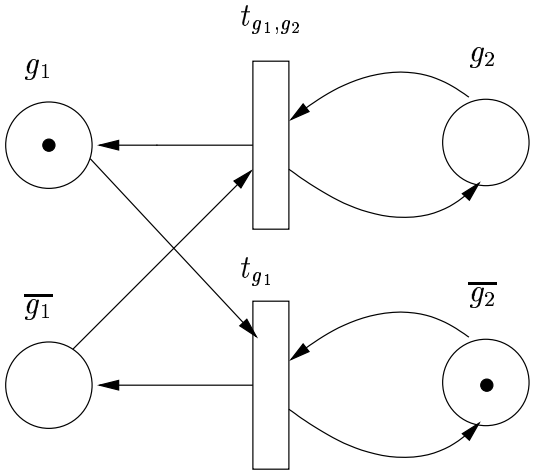


Fig. 9. Spontaneous deactivation/degradation.

interpret this as a spontaneous deactivation or chemical degradation of g_1. This is something which was not the case in the qualitative model. It turns out that such a property could be useful for modeling of complex genetic networks.

From the state space one can also see that the states 00 and 11 are *stable* (also called *steady* or *dead*) states in the sense that no transition is possible from them. Thus, depending on the initial state, the net will eventually stabilize in one of those two states.

The same conservation properties (at most one token per place and the sum of tokens in complementary places exactly one) hold also for the new inhibition model given in Fig. 10. As for the activation case one can also draw the state space for the inhibition net. In this case, instead of spontaneous deactivation we have spontaneous activation of g_1, i.e., transition from state 00 to state 10

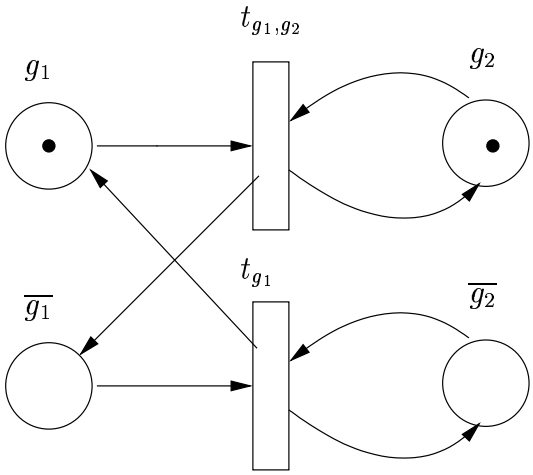


Fig. 10. Inhibition (qualitative version).

4 Construction of More Complex Models

Once we have the activation and inhibition Petri nets in Figs. 6 and 10 respectively, we can construct more complex nets using those two as building blocks.

The first example is a positive activation circuit given in Fig. 11. The circuit consists of genes g_1, g_2, and g_3 which can activate one another in a circular fashion. The Petri net which is obtained by connecting three copies of the activation net in Fig. 6 is given in Fig. 11. If we begin with the initial state 100 as given in Fig. 11 one can reach the steady state 111, i.e., a state where all genes are active. From that state no transition to another state is possible. We leave the drawing of the complete state space to the reader as an exercise.

The second example is the negative circuit given in Fig. 12. Unlike in the positive circuit above, in the negative circuit gene g_3 inhibits gene g_2. Although at first sight the negative circuit looks very similar to the positive one, its behavior is quite different. Namely, beginning with the same initial state 001 one can see a cyclic (oscillatory) behavior of the circuit and there is no steady state, i.e., a state from which there is no transition. Again, the drawing of the complete state space is left an exercise.

References

1. C. Chaouiya, E. Remy, P. Ruet, D. Thieffry, *Qualitative Modelling of Genetic Networks: From Logical Regulatory Graphs to Standard Petri Nets*, Proc. of ICATPN, Lecture Notes in Computer Science 3099, pp. 135-156, Springer-Verlag, 2004.

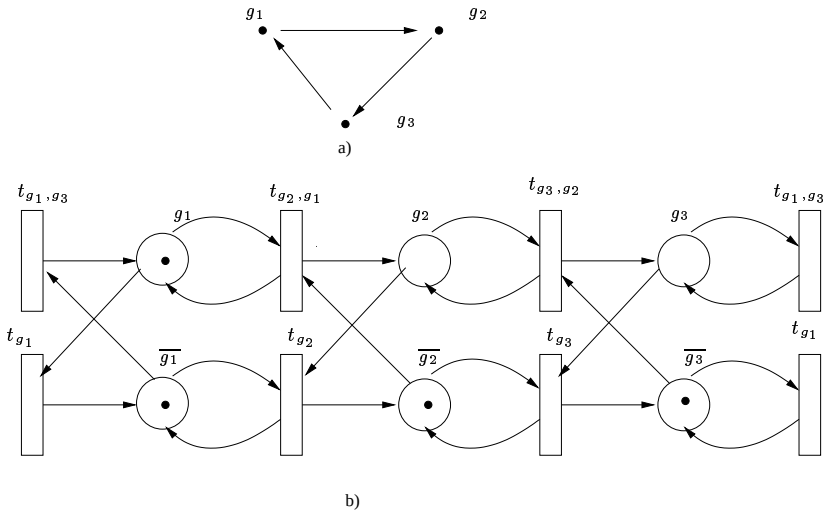


Fig. 11. Positive circuit.

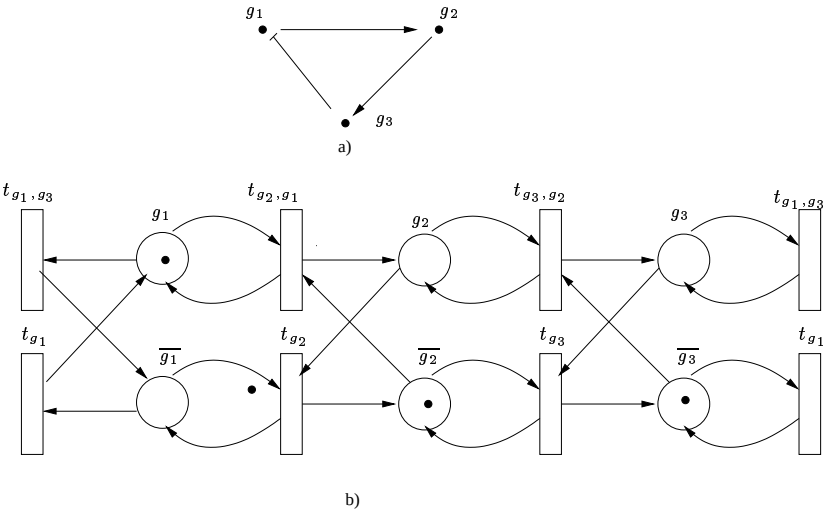


Fig. 12. Negative circuit.