Answers to exercises of Chapter 8 (Signal Transduction and Gene Regulation Networks)

1. Given a network of transcription factor genes. You know from the literature that three genes A, B, and C in this network are connected by directed edges {A,B} and {A,C}, which indicate that gene A stimulates the expression of gene B and gene C. You are making an experiment and find that gene A is expressed: that is, the product of this gene, transcription factor A is synthesized and the corresponding protein is detected by a western blot. However, your experiment shows that gene B and gene C are not expressed. Does it mean that the network taken from the literature obviously contains mistakes in regard to the edges {A,B} and {A,C}? If not, what might be the reason for their inactivity? Give your explanation for this apparent contradiction.

There is no obvious mistake in the network taken from the literature. The directed edges {A,B} and {A,C} represent complex relationships between the genes. That is, each edge may abstract several functional steps like transcription, translation, posttranslational modification and so on. The edges {A,B} and {A,C} must be considered as multiple conditional events. The expression of gene A is necessary but not enough to provide the expression of genes B and C. For example, in order to activate the transcription of genes B and C, transcription factor A (i.e., the product of gene A) needs to be modified (e.g., phosphorylated). However, the signal transduction system does not always provide a proper signal for such a modification. Therefore, the possible explanation for the observed experimental phenomenon might be that transcription factor A is expressed, but it is not yet functionally active.

2. Consider the same network as in Exercise 1. Your other experiment indicates that after stimulation of gene A, gene C is expressed as well, but gene B is not expressed. Therefore, the causal link A → B works, while the link A → B is still inactive. Give your explanation for this particular case.

In this case, transcription factor A (i.e., the product of gene A) appears to be present in its active form. Therefore, the lack of expression of gene B is due to other reasons. In higher eukaryotes, transcription factors often function in a cooperative fashion. That is, a particular set of different transcription factors is necessary to initiate the transcription of a particular gene. The presence of all such factors in a set is required. The corresponding sets for gene B and gene C include transcription factor A, but may differ in other transcription factors. The active transcription factor A is necessary but not enough to provide the expression of genes B and C. Therefore, the observed experimental phenomenon may be explained in a way that the set of transcription factors required for the transcription of gene C is completed while that of gene B is not.

3. Given a gene network, consisting of vertices (i.e., genes) and directed edges (causal links between genes). Let us consider vertex v and edges around this vertex. What would provide a stronger impact on the network topology: (a) deleting the vertex v or (b) deleting one of its incoming or outgoing edges? Explain your conclusion.

The topological impact of deleting the vertex v is much stronger than deleting one of its edges. The removal of a vertex destroys all incoming and all outgoing edges around this vertex.

4. When working on Exercises 2 and 3, you may refer to Fig. 8.4. Keep in mind that each edge represents a multiple conditional event that includes more than one functional step. Therefore, an edge indicates the possibility of action, which can be realized under a set of conditions. Note that a complete set of several transcription factors, which cooperatively act on a given gene, is

necessary. Note that each of these transcription factors must be activated via its upstream signaling.

This is a kind of help for answering the questions 1-3 mentioned above.

5. Given a gene network G = (V, E) and given its subnetwork G´ = (V´,E´) centered at gene X. That is, G´ includes gene X, all those genes from which gene X is reachable and all those genes that are reachable from gene X.
(a) What kind of changes in this subnetwork G´ might be expected if all incoming edges of gene X would be deleted?
(b) Which changes in the subnetwork G´ might be expected if all outgoing edges of gene X would be deleted?
(c) Which changes in the subnetwork G´ might be expected if all incoming and all outgoing edges of gene X would be deleted? Would that be comparable with the effect of deleting vertex X?

The subnetwork G´ centered at gene X is the union of two subsets of vertices and edges which are located upstream and downstream of vertex X.
(a) If all incoming edges of gene X are deleted, vertex X has no connection to the "upstream" subset of vertices and edges in G´.
(b) If all outgoing edges of gene X are deleted, vertex X has no connection to the "downstream" subset of vertices and edges in G´.
(c) If all incoming and all outgoing edges of gene X are deleted, vertex X is not connected to both "upstream" and "downstream" subsets of vertices and edges in G´. That is the same as the removing of vertex X from G´.
Depending on the absence or the presence of the cycles which cross vertex X, the impact of removing the edges around X on the integrity of the subnetwork G´ can vary. In the absence of such cycles, the operations mentioned above in (a, b, c) will result in splitting G´ into several (at least two) fragments.