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Advanced Model

As the IOA function still cannot work well to ensure the linear relationship when the input range spans several orders of magnitude, we search for semilog networks further using the same method.

Identifying Minimal Semilog Networks

We again get the Q-Rank Figure (Figure 1). Topologies that have large Q value are still the minority.

Listed in Figure 2 are all the simplest topologies whose Q value is above 100 that have 4 or less direct links between the three nodes.(Figure 2) There are only one 3-link topology(as the 7th topology in Figure 2) out of all the 7 simplest topologies, and it has exactly the common features of the seven topologies: two positive controls from A node to respectively B node and C node, and one positive control from B to C. We call it the All Activated Network(AAN). The role of different nodes and links will be discussed in the next part.

Mechanisms of Minimal Semilog Networks and Key Parameters Analysis

In order to unravel the mechanism that AAN functions, we analyzed the topology with the ODE equations, and we also get the key parameters in this part.

When the network reaches its steady state,

$$\frac{dX_1}{dt} = \beta_0 - \alpha_1 X_1 = 0$$

$$\frac{dX_2}{dt} = \beta_0 (1 - \lambda_{12} \frac{kIX_1^{\,2}}{K_{12} + kIX_1^{\,2}}) + \beta_m [1 - (1 - \lambda_{12} \frac{kIX_1^{\,2}}{K_{12} + kIX_1^{\,2}})] - \alpha_2 X_2 = 0$$

$$\frac{dX_3}{dt} = \beta_0 (1 - \lambda_{13} \frac{kIX_1^{\,2}}{K_{13} + kIX_1^{\,2}})(1 - \lambda_{23} \frac{X_2}{K_{23} + X_2}) + \beta_m [1 - (1 - \lambda_{13} \frac{kIX_1^{\,2}}{K_{13} + kIX_1^{\,2}})(1 - \lambda_{23} \frac{X_2}{K_{23} + X_2})] - \alpha_3 X_3 = 0$$

Solve the equations,

$$X_1 = \frac{\beta_0}{\alpha_1}$$

$$X_2 = \frac{(\beta_m - \beta_0) \frac{\lambda_{12} kIX_1^{\,2}}{K_{12} + kIX_1^{\,2}} + \beta_0}{\alpha_2}$$

$$X_3 = \frac{1}{\alpha_3} \left\{ \beta_0 + (\beta_m - \beta_0) [\frac{\lambda_{13} kIX_1^{\,2}}{K_{13} + kIX_1^{\,2}} + \frac{\lambda_{23} X_2}{K_{23} + X_2} - \frac{\lambda_{13} \lambda_{23} kIX_1^{\,2} X_2}{(K_{13} + kIX_1^{\,2})(K_{23} + X_2)}] \right\}$$

When $K_{12}, K_{13} >> kIX_1^{\,2} = kI(\frac{\beta_0}{\alpha_1})^2$, $K_{23} >> X_2$, there is

$K_{12} >> \lambda_{12} kX_1^2 (as |\lambda_{12}| < 1), then \frac{\lambda_{12} kX_1^2}{K_{12}} << 1$, so there are

$$X_2 = \frac{\beta_m \frac{\lambda_{12} kX_1^2}{K_{12}} I + \beta_0 (1 - \frac{\lambda_{12} kX_1^2}{K_{12}} I)}{\alpha_2} = \frac{\beta_m \lambda_{12} kX_1^2}{\alpha_2 K_{12}} I + \frac{\beta_0}{\alpha_2}$$

$$X_3 = \frac{1}{\alpha_3} \left\{ \beta_0 + (\beta_m - \beta_0)[\frac{\lambda_{13} kX_1^2}{K_{13}} I + \frac{\lambda_{23}}{K_{23}} X_2 - \frac{\lambda_{13}\lambda_{23} kX_1^2}{K_{13} K_{23}} IX_2] \right\}$$

$$= \frac{1}{\alpha_3} \left\{ \beta_0 + (\beta_m - \beta_0)[\frac{\lambda_{13} kX_1^2}{K_{13}} I + \frac{\beta_m \lambda_{23}\lambda_{12} kX_1^2}{\alpha_2 K_{12} K_{23}} I + \frac{\beta_0 \lambda_{23}}{\alpha_2 K_{23}} - \frac{(\beta_m kX_1^2)^2 \lambda_{13}\lambda_{23}\lambda_{12}}{\alpha_2 K_{13} K_{23} K_{12}} I^2 - \frac{\beta_0 \lambda_{13}\lambda_{23} kX_1^2}{\alpha_2 K_{13} K_{23}} I] \right\}$$

$$= (\frac{\beta_0}{\alpha_3} + \frac{(\beta_m - \beta_0)}{\alpha_3} \frac{\beta_0 \lambda_{23}}{\alpha_2 K_{23}}) + \frac{(\beta_m - \beta_0)}{\alpha_3} (\frac{\lambda_{13} kX_1^2}{K_{13}} + \frac{\beta_m \lambda_{23}\lambda_{12} kX_1^2}{\alpha_2 K_{12} K_{23}} - \frac{\beta_0 \lambda_{13}\lambda_{23} kX_1^2}{\alpha_2 K_{13} K_{23}}) I - \frac{(\beta_m - \beta_0)(\beta_m kX_1^2)^2 \lambda_{13}\lambda_{23}\lambda_{12}}{\alpha_2 \alpha_3 K_{13} K_{23} K_{12}} I^2$$

$$X_3 = a \log I + b$$

As to the object function , we adopt the method of Taylor expansion

$$X_3 = a \log I + b = \frac{a}{2.303} \ln(1 + I - 1) + b \approx \frac{a}{2.303} [(I - 1) - \frac{(I-1)^2}{2}] + b = \frac{a(4I - I^2 - 3)}{4.606} + b$$

Then we can see that the transform of X_3 fits well with the transform of the object function.

Known the reason why the topology is functional in the object function, we need to analyze for the most important parameter in order to provide theoretical support for practice (Figure 3). We also list the parameter changes in Table 1. Among the nine parameters, the essential parameter for the output range is not obvious and that for r is the same condition – we can only see that λ_{13} has no influence on r. Based on an overall consideration, we suggest that in practice a smaller α_3, a larger λ_{12} and a larger λ_{13} should be adopted.

Parameters Tendency of the IOA Networks

It can be seen from the distribution of K and α values that compared to networks with linear response curve, single parameter shows much less tendency. Instead, to establish a semi-log response curve may require the cooperation of multiple parameter values.

Analysis of All Possible Three-Node Networks

Again through the analyses above, we only know that AAN can be functional in Semilog function, but whether the topology is necessary among the more complex networks are still unknown, so we analysis all of the first 74 topologies (Q>100) that are well capable of the Semilog function. (Figure 4)

Analysis of these robust topologies shows that they all contain AAN, so that the very topology is necessary for Semilog function.

Motif Combinations that Improve IOA

To investigate what additional features can improve the functional performance in some more complex and more robust networks than minimal topologies, we clustered the first 74 networks. (Figure 5) The results clearly indicate that apart from the link from A to B, from A to C, from B to C, and from C to C, there should be no positive regulation.

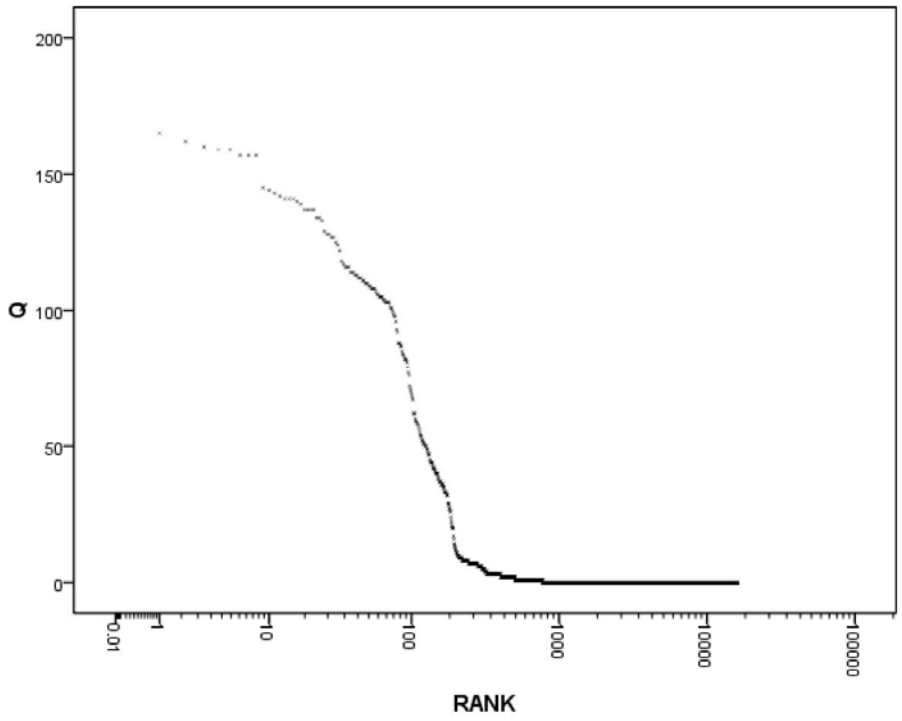

Figure 1 The Q value network topologies Sequence We sort in reverse sequence all the network topologies according to their Q value. X Axis is their ranks, while Y Axis is their corresponding Q values. The figure indicates that topologies that have large Q value are still the minority.

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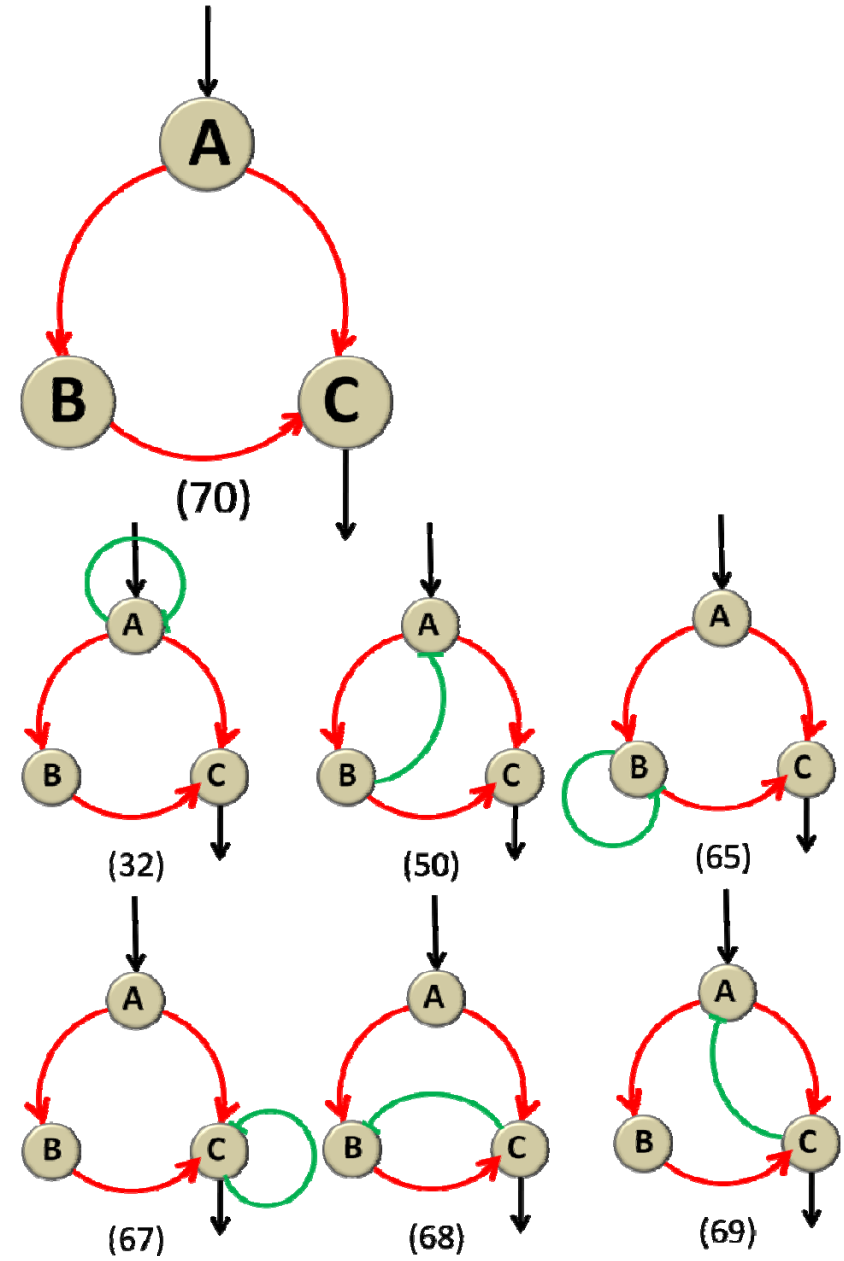

Figure 2 All Functional Networks The numbers below each network are their ranks. The bigger topology has 2 links while the other 6 networks have 3 links. In each network, the green arc with one short straight line at one end stands for repression from the start node to the end node and the red arc with one arrow at one end stands for activation.

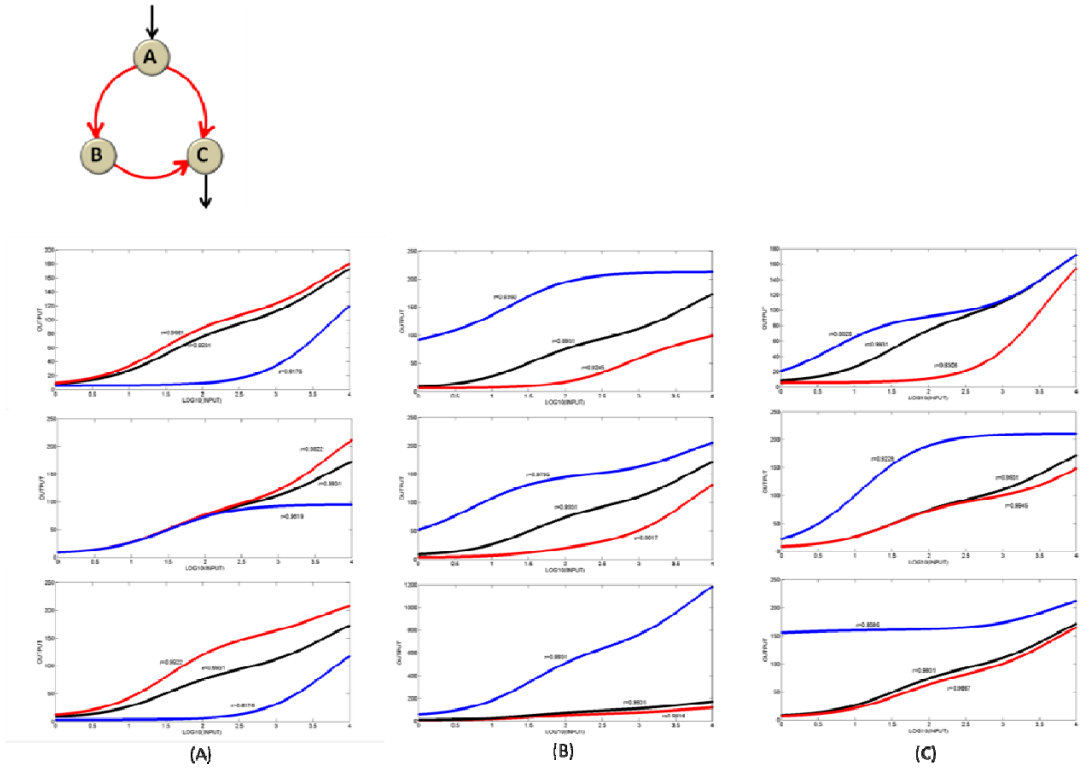

Figure 3 Analysis for key parameters We got all functional sets of parameters of AAN and selected randomly one set and processed it with Matlab to compare the differences once the parameters change. When analyzing one parameter, we only change this very parameter and keep others the same, and when we change the parameter to a lower level, we get the blue line, when to a higher level, we get the red line and the black line is for the unchanged parameter set. Each line has its Pearson Correlation Coefficient r marked in the figure. The X Axis is the concentration of Hg ion as INPUT whose range is 1 to 10000 nM, and the Y Axis is the concentration of node C with the unit of nM. (A) We analyze λ_{12}. λ_{13} λ_{23} from top to bottom. (B) the degradation rate of node A , B and C, respectively, α_1 α_2 α_3 (C) The dissociation rate for each link: K_{12} K_{13} K_{23}.

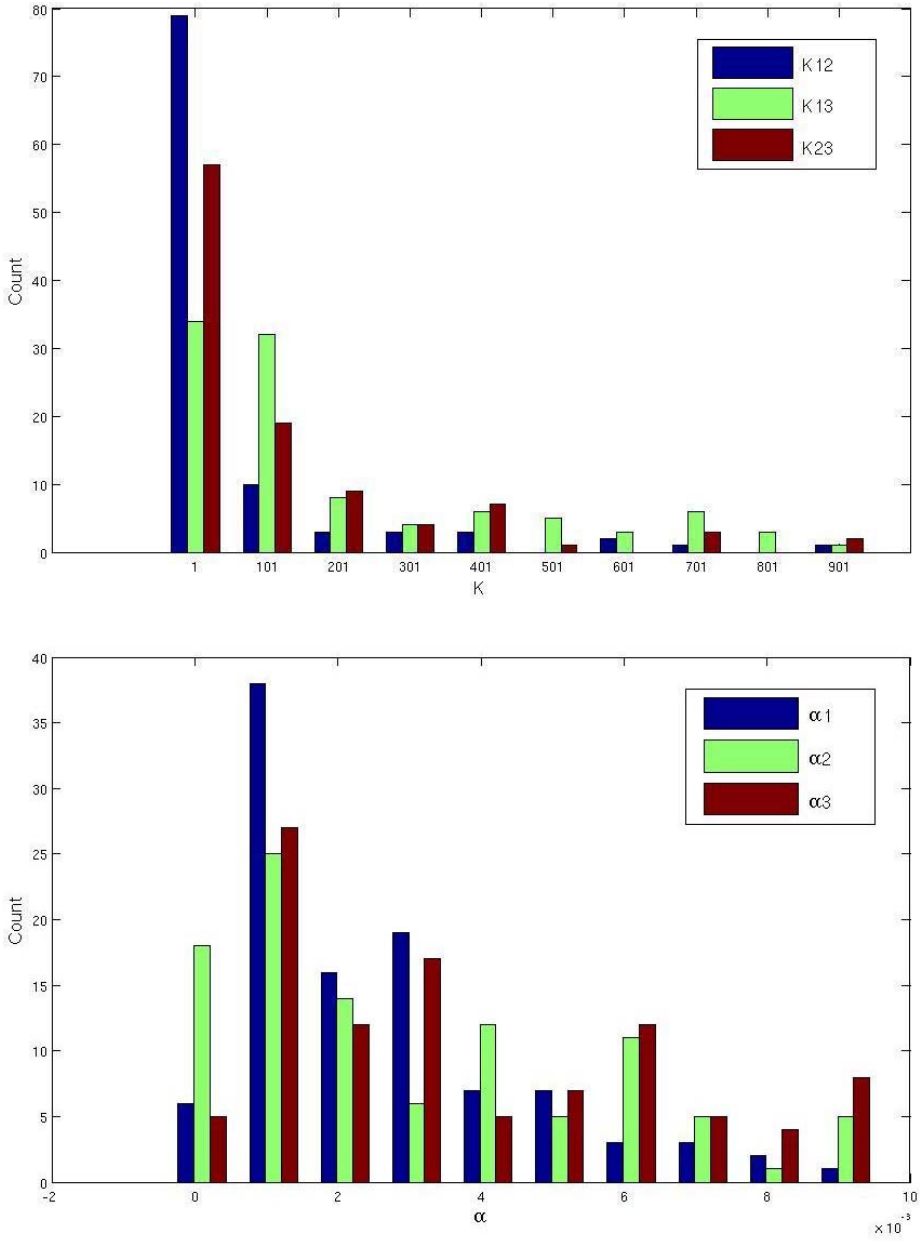

Figure 4 Distribution of parameters which can establish semi-log response curves.

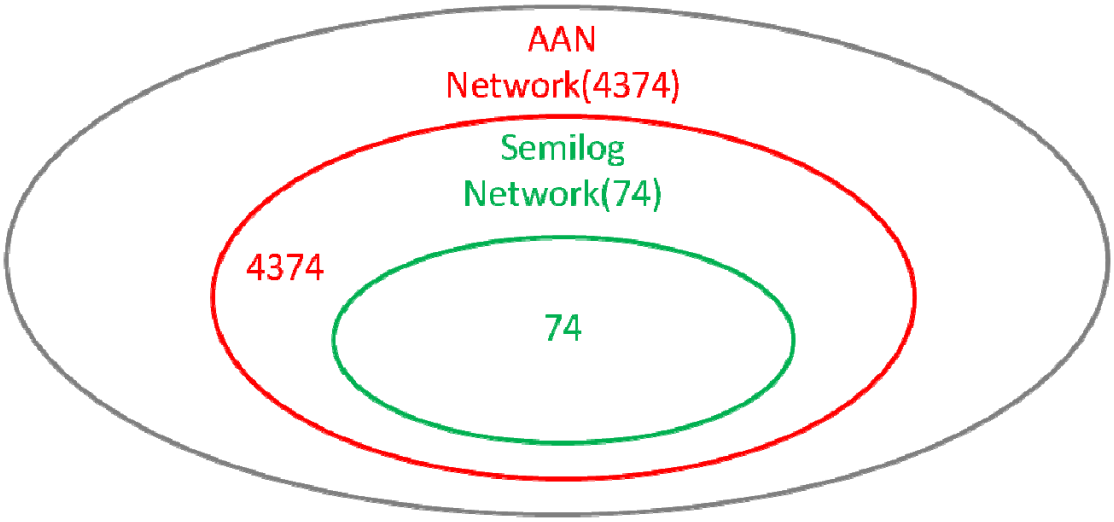

Figure 5 Analysis of the first 160 networks We count all ANNs and the Semilog networks whose Q value is above 100, and discover that all of the Semilog networks are make up of the ANN topology and the topologies contain it.

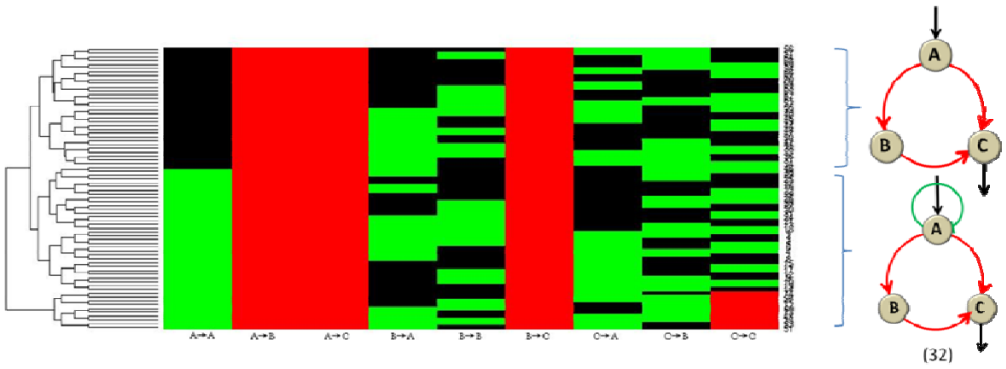

Figure 6 The clustergrams of the networks We use the clustergram command in matlab to get the additional features of the functional networks. The nine vertical rectangle bar stand for nine links in Figure 2 which are, respectively, from A to A, from A to B, from A to C, from B to A, from B to B, from B to C, from C to A, from C to B, from C to C. And red stands for activation, green for repression and black for no regulation. The topologies on the right are corresponding minimal topologies that is shown in the clustergrams on the left.

Table 1 The change of two important characters as the parameters rise

Parameter that changes bigger	NCL	
	Range	r
λ_{13}	↑	↑
λ_{12}	↑	–
λ_{23}	↑	↕

α_1	↓	✣
α_2	↓	✣
α_3	↓	✣
K_{13}	↓	✣
K_{12}	↓	✣
K_{23}	↓	✣

* ↑ has the meaning that the character value rises as the parameter rises. ↓ has reverse meaning. ▬ means that the character value keep relative stability as the parameter changes. ✣ means that only at the unchanged condition the character value is the biggest and any change in parameter results in big change in character value.