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DISSERTATION SUMMARY

Multiple attacks on biological networks

Vilmos Ágoston

Central Laboratory, Biological Research Center, Hungarian Academy of Sciences, Szeged, Hungary

Due to the general applicability of network models network damage has become a widely examined phenomenon in various fields. Scale-free networks have been shown to be relatively insensitive to random damage however, they are rather vulnerable to attacks targeted to their most-connected elements, called hubs (Albert et al. 2000). In several networks cascading failures may occur and the effects of network topology permanent damage on the resistance of networks have been examined.

Most of the studies used a complete elimination of an element from the network to assess network stability. We would like to provide a general answer to the following question: Is the partial inactivation of several targets more efficient than the complete inactivation of a single target? Using various attack strategies against the *E. coli* (Shen-Orr et al. 2002) and *S. cerevisiae* (Milo et al. 2002) transcriptional regulatory networks we found that partial weakening at a surprisingly small number of points can be more efficient than the complete elimination of a single node.

Robust systems, like the molecular networks of living cells are often resistant to single hits such as those caused by high specificity pharmacons. Here we show that partial weakening of the *E.coli* and *S.cerevisiae* transcriptional regulatory networks at a surprisingly small number (3 to 5) of points can be more efficient than the complete elimination of a single network node. We modeled the networks as directed, weighted graphs and tested a variety attack strategies, such as the elimination of nodes (complete inhibition of proteins), weakening of nodes (partial inhibition of a protein) and weakening or elimination of selected interactions and calculated a decrease in the overall communication efficiency of the network. According to this measure, multiple weak hits provided a similar damage than concentrated attack on one point (Ágoston et al. 2005). For example, the removal of a few, strategically selected interactions in the network are more damaging than removing the best connected node (protein) of the network. These results may help to explain why broad specificity, low affinity pharmacons are often more efficient than their high affinity, high specificity counterparts. Multiple but partial attacks mimic well a number of *in vivo* scenarios and may be useful in the efficient modification of other complex systems.

This and the success stories of multi-target drugs and combinatorial therapies led us to suggest that systematic drug-design strategies should be directed against multiple targets (Csermely et al. 2005). We propose that the final effect of partial, but multiple, drug actions might often surpass that of complete drug action at a single target. The future success of this novel drug-design paradigm will depend not only on a new generation of computer models to dentify the correct multiple targets and their multi-fitting, low-affinity drug candidates but also on more-efficient in vivo testing.

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Supervisor: Sándor Pongor
E-mail: vilagos@nucleus.szbk.u-szeged.hu