Modeling hormonally dependent genetic networks

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Usual approaches to regulatory genetic network modeling follow a feed-forward methodology, where the network represents a "black-box" within the cell. The operation of the black box is modeled as an input-output relation and research tries to identify the proper relation that holds for several observed cases; this relation may be expressed in various formalisms (typically boolean networks [1], but also Bayesian networks, etc.).

Our proposal follows a developmental perspective and borrows theoretically from modern accounts of the gene as an information-carrier and as a complex entity and concept [2-5]. These theoretical developments belong to the broad evo-devo trend and attempt to use the gene as a functional biological entity or as a developmental molecular process instead of a well-delimited structural entity encoding for a specific trait.

Within this theoretical context, it is worthwhile to study enhanced relations between genetic network and cellular behavior that include "control in the loop" in the form of memory : in regulatory networks with memory, subsequent activations of the network with the same input vector will yield different output vectors, i.e. the transfer function of the whole network will be itself dynamic. From an external point of view, this may be seen as the network "prefering" some inputs already seen, or "dismissing" them, or in general "specializing" to certain activity pathways. We expect a cell to behave in such a way so as to resist to abrupt changes and to external manipulation, for example by viruses. In a medium term, a genetic network with memory will behave in a more autonomous and prudent manner and it will be less dependent on quick changes in its environment.

From a technical point of view, one way to introduce a sort of memory is to define individual gene functions that are not uniquely defined but that vary for different environmental conditions. One such controlling condition may be the level of an hormone [6]. This model represents the dependence of various genes on external factors that change slowly in comparison with the time scale of the behavior of the gene.

We have studied gene functions that differ according to the level of an external hormone that follows its own dynamics. In this case, long complex (irregular) attractors emerge within the genetic network. We have also studied genetic networks that interact with the hormone in one of the following ways: the hormone does not have intrinsic dynamics but its production is triggered or hindered either by each of the gene functions per hormonal level, or by each of the genes that may be in on or off state. In both of these cases, the networks reach a co-attractor with the hormone (that is, the network state and the hormonal level reach coupled attractors). In the first case, these attractors are very often irregular and longer that usual attractors of RBNs, while in the second case they resemble more the short point and periodic attractors of RBNs. A few higher connectivity

studies (K = number of inputs per gene > 2) and perturbation studies have been performed, that are indicative of enhanced robustness of these models: for example the genetic-hormonal systems appear robust to the exact ranges of the hormonal levels considered per gene but not to their number.

References

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