In silico Evolution of Biological Clocks with Genetic Regulatory Networks

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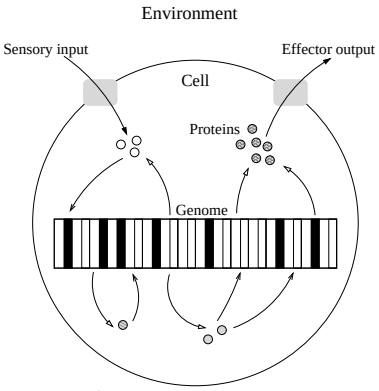
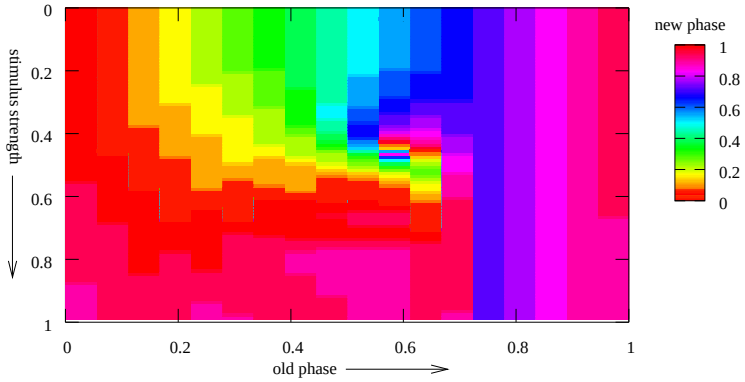
Genetic Regulatory Networks (GRNs) are the control systems of all cells. Their dynamics are of crucial importance in development [4] but also in the ongoing, reactive, metabolism [1]. A characteristic example of such responsive regulation are circadian rhythms, which were present already in early life forms [10]. Following Winfree [10, 11], we ask 1) How is it that biological clocks can adapt, within limits, to perturbations in cycle length, phase shift, and resetting? 2) Why in isolation do they run at internalized rates somewhat different from that of the external cycles? 3) Are these accidents of neutral selective value, or do they have some adaptive significance at the individual level? Evolving artificial genetic regulatory networks (aGRNs) that act as model biological clocks is a natural method to explore these questions.

In our model, every network consists of a number of genes, each having any number of regulatory sites. Gene expression levels are determined by the activation of the corresponding sites and their interaction rules as well as gene type. Abstracting from transduction, environmental input simply raises the level of one protein type while the concentration of another type is read as output (fig. 1A, 2A).

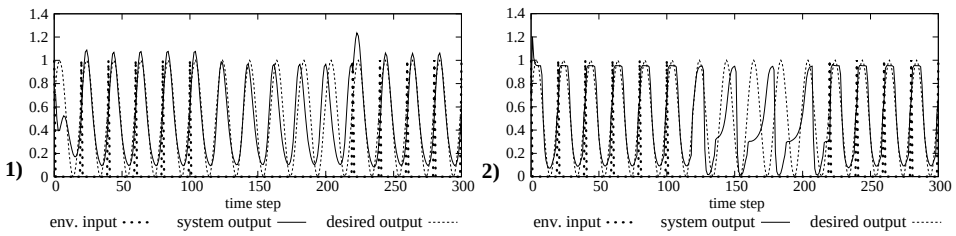
Starting from simple random networks, we use an evolutionary algorithm to arrive at a



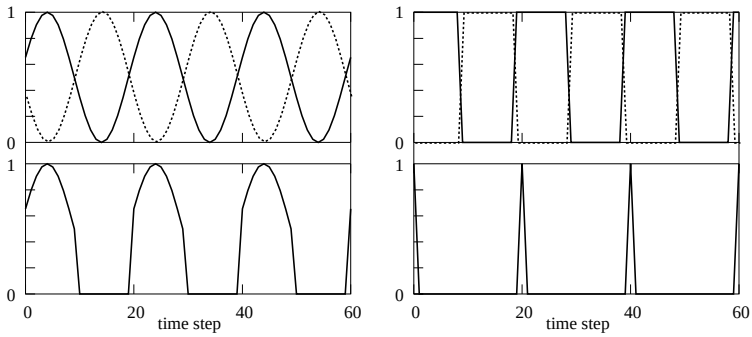
A) Schema of network−environment interaction



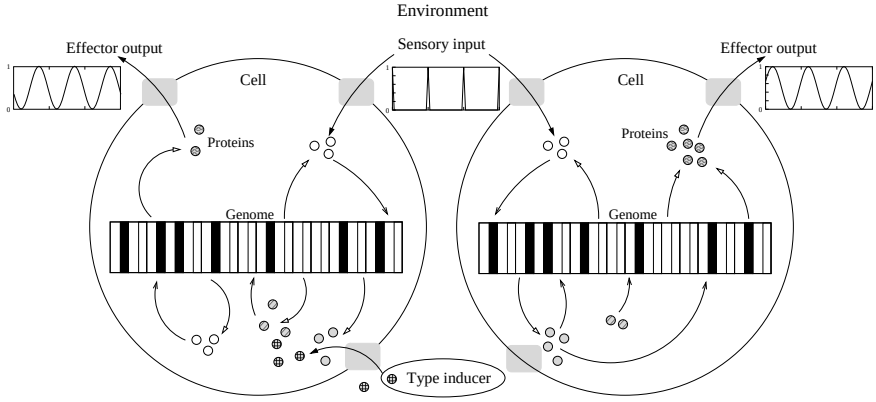
C) Example phase resetting diagram with color coded new phase after disruptive stimulus, after Winfree [10] − note singularity



B) aGRN dynamics revealed when stimulus is missing − external signals are needed to keep in sync



A) Input / desired output functions, with dashed lines (0.5 phase shift) used for differentiation experiments



B) Schema of entity in differentiation experiments, both cells have the same genome and stimulus (apart from type inducer) but have to produce inverse outputs

network whose output closely matches one or two periodic signals. A detailed description of the model and algorithm can be found in [8, 6]. In many cases aGRN dynamics showed internalization of (quasi-) periodic behavior (the less reliable the input during evolution, the more internalization). External stimuli were often only required to keep responses in synchrony, fig. 1B, and (not-selected-for) phase resetting behavior similar to that observed in biological organisms was found (fig. 1C, [10]).

Another very important regulatory mechanism is differentiation: In a multicellular organism, all cells contain the same genome but can take on very different functional roles, depending on signals or differences in the internal chemical composition [5]. We found that it was indeed possible to integrate two different functionalities in one aGRN instantiated in different contexts in a multicellular entity (fig. 2B).

We then investigated whether we could identify significant patterns or prevalent network motifs that had arisen during the evolution process, in order to assess the uniqueness and robustness of the networks that realize particular functionalities.

For network analysis in general and specifically for GRNs, structural, static network occurrence analysis has become quite popular recently [9, 2]. Motifs, subnetwork patterns that occur significantly more often than in random networks, are said to have functional significance and even that network structure of independent origin could evolve convergently [3]. However we find in both groups (one-function clock aGRNs and two-function differentiating aGRNs) motif distribution differences within the groups to be larger than differences

between them [7]. Apparently structural analysis does not allow us to find "the" switch responsible for differentiation, instead this behavior can be variously realized by many different structures. Also, when lesioning one connection from either the most over-represented motif or any random connection, we find no significant difference in impact on function of the aGRN [7]. These results warrant caution for researchers when drawing conclusions from motif analyses.

References

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