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NOISE AND OSCILLATIONS IN BIOLOGICAL SYSTEMS: MULTIDISCIPLINARY APPROACH BETWEEN EXPERIMENTAL BIOLOGY, THEORETICAL MODELLING AND SYNTHETIC BIOLOGY

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Rapid progress of experimental biology has provided a huge flow of quantitative data, which can be analyzed and understood only through the application of advanced techniques recently developed in theoretical sciences. On the other hand, synthetic biology enabled us to engineer biological models with reduced complexity. In this review we discuss that a multidisciplinary approach between this sciences can lead to deeper understanding of the underlying mechanisms behind complex processes in biology. Following the mini symposia "Noise and oscillations in biological systems" on Physcon 2011 we have collected different research examples from theoretical modeling, experimental and synthetic biology.

Keywords: Systems biology; synthetic biology; nonlinear dynamics.

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1. Introduction

Recent decade can be associated with a real revolution in molecular biology. Sequencing of human genome, pioneering steps in understanding the role of miRNAs in genome processing, epigenetics studies, and increased complexity in all aspects of molecular biology, from genome to protein turnover, all this become possible due to rapid progress of high throughput technologies which provided unprecedented flow of information from experimental studies. It soon became clear that we have more data that we can analyze and understand with classical approaches to data analysis and theoretical modeling. The overflow of bio-information can be treated only with sophisticated and newly developed techniques for statistical analysis and numerical modeling. Fortunately, rapid progress in data mining was accompanied with equally fast development of computer hardware, nonlinear dynamics and numerical techniques which moved theoretical modeling on a new *niveau*.

Modeling can be not only numerical - one can use synthetic biology to construct biological synthetic models of more complex real systems. This is especially true for synthetic genetic networks which operate almost independently from the rest of cellular machinery and hence provide us with a test system of reduced complexity. Such synthetic genetic networks allow to study complicated interaction of gene expression in more precise way. And again, recent decade manifested itself in pioneering construction of genetic switches, oscillators or logical networks. Due to this factors, the flow of information between theoretical modeling, experimental and synthetic biology is especially interesting nowadays and make multidisciplinary approaches really productive. We analyze briefly this flow in Fig.1.

In this review, following the mini symposia "Noise and oscillations in biological systems" at the conference Physcon 2011 in León, Spain we have collected examples which use this multidisciplinary approach to apply theoretical modeling to understand functioning of more complex systems in experimental and synthetic biology.

2. Delayed Coupling Theory of Vertebrate Segmentation (S. Ares, L.G. Morelli, A.C. Oates, and F. Jülicher)

The body plan of all vertebrate animals has a segmented organization that is reflected in the repeated arrangement of vertebra and ribs. This structure forms during the development of the organism by a process called segmentation. The segments —called *somites*— form sequentially along a linear axis, one by one, with a precisely controlled timing, Fig. 2A. The timing of vertebrate segmentation is set by a genetic clock. This clock is realized by oscillations of the levels of certain proteins in individual cells.

The spatio-temporal patterns of genetic oscillations have been described by coupled sets of phase oscillators which are arranged in space.[1] The state of a single oscillator is characterized by the phase $\theta_i(t)$, where i labels the oscillator. The

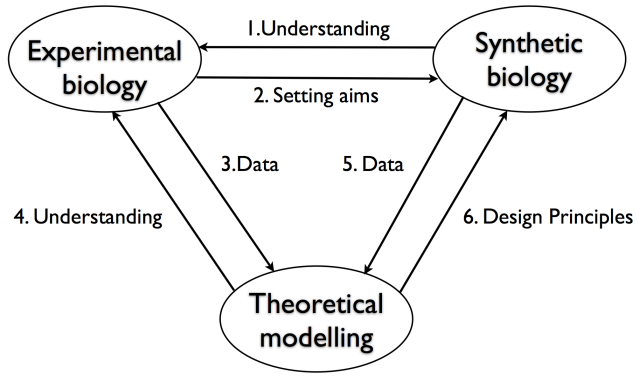

Fig. 1. The vice versa benefit between theoretical modeling, experimental and synthetic biology. 1: synthetic biology works with small genetic networks of reduced complexity and, hence, greatly contributes to understanding of more complex natural systems by proving the general design principals suggested by mathematical models, 2: experimental biology with medical applications set aims for synthetic biology e.g. by asking for target molecules, 3,5: experiments provide data for theoretical modeling to parametrize the model and validate model predictions, 4: modeling contributes to understanding and helps to set up new experiments, 6: modeling develops design principles for synthetic biology.

dynamic equations for the phases are given by

$$\dot{\theta}_i(t) = \omega_i(t) + \frac{\varepsilon_i(t)}{n_i} \sum_j \sin\left[\theta_j(t-\tau) - \theta_i(t)\right], \tag{1}$$

where the sum is over all neighbors j of cell i. Here, ε denotes the coupling strength and τ is the time delay involved in coupling. After initial transient dynamics, the system settles in a spatio-temporal limit cycle with collective frequency Ω which obeys the relation $\Omega = \omega_A - \varepsilon \sin(\Omega\tau)$. This implies that changes in coupling strength or delay would lead to changes in oscillation period, Fig. 2B, and thus in variations of the wavelength of cyclic gene expression patterns as well as the resulting segment length, Fig. 2C-D. These predictions have been confirmed experimentally and have led to the discovery of the first mutants with altered collective period, so called period mutants.[2] This example shows how the analysis of effective theoretical descriptions can motivate the design of experimental perturbations, and lead to the discovery of interesting biological phenomena.

3. Mixed Feedback Loops Greatly Improve the Tunability of Genetic Oscillators (E. Nicola, S. Ares, and L.G. Morelli)

As mentioned in the introduction, biological cells are composed of thousands of different genes, proteins, metabolites and other chemical substances. All these components interact with each other inside the cell in a myriad of different ways, and the

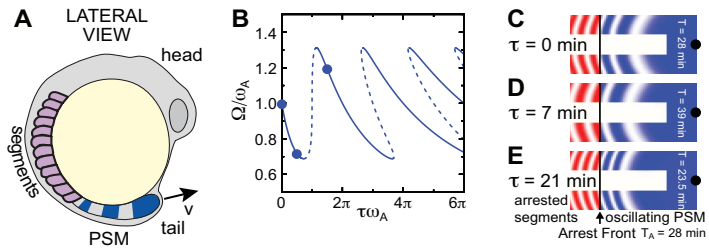

Fig. 2. (A) Schematic lateral view of a zebrafish embryo. (B) Dimensionless collective frequency Ω as a function of time delay τ of coupling for parameters obtained from zebrafish experiments. Solid and dashed lines indicate stable and unstable solutions, respectively. Blue dots correspond to the three cases shown in panels (C-E). (C-E) Snapshots of numerical solutions of the model given by Eq. (1) in a two-dimensional geometry for different time delays as indicated. Color intensity indicates the value $\sin\theta$ of the phase θ.

output of these interactions regulates many cellular functions. However, this complicated network of interactions seems to be modular. A recurrent type of module or motif appearing in gene regulatory networks is characterized by its oscillatory behaviour on the levels of gene expression.[3] Novák and Tyson have shown that, when modules with small numbers of components are considered, only a handful of different motifs can oscillate.[3,4]

Modules of gene regulatory networks often include feedback loops which vastly enrich their dynamics. These feedback loops can be either negative or positive.[3] A pure negative feedback loop can result in oscillations. On the opposite, a pure positive feedback may lead to multi-stability, typically resulting in a toggle-switch (i.e. bistability). In a recent publication Tsai et al. have recognized that oscillatory motifs combining positive and negative feedback loops seem to be more common in biology than simpler oscillators built on single negative feedback loop.[5] Based on a extensive numerical study of many different models of biological oscillators, they suggest that motifs combining positive and negative feedback loops are more robust and that they offer the potential of tuning the properties of the oscillations. In contrast, single negative feedback loop oscillators are much less flexible, in particular regarding the range of frequencies in which they can oscillate.

We aim to explore the reasons that make genetic oscillators based on mixed positive and negative feedback loops more flexible. We propose a family of simple models that include mixed feedback loops and perform a detailed bifurcation analysis of these motifs. Our analysis of this family of generic models of genetic oscillators reveals that very general mechanisms underlie the tunability of the oscillations. Overall, our study shows that simple mathematical models can be used, together with thorough theoretical analysis as provided by the theory of bifurcations, to identify key mechanisms underlying the complex behaviour observed in more detailed models of oscillatory genetic networks.

4. Modeling Approaches of the Circadian Clock and Light Entrainment in Zebrafish (R. Heussen, A. Zaikin, and D. Whitmore)

A circadian clock is the daily time-keeping mechanism found in a wide variety of organisms, which allows them to anticipate and thus adapt to environmental fluctuations. Circadian rhythms can free-run in constant conditions, but are usually entrained by environmental cues, often light, and in most higher organisms a central circadian pacemaker is present. Understanding these clocks is of great interest as a host of biological processes is affect by them. In this respect, zebrafish is an attractive vertebrate model due to its similarities to mammalian clocks, coupled with the lack of a central pacemaker and direct light sensitivity of fish organs and embryonic cell lines.[8] Thus they represent a complete clock system within a single cell and could provide great insight into the yet poorly understood processes of entrainment.[6]

On a population scale, core clock component transcription output can be investigated using transgenic luciferase reporter genes. Different cell lines, each with a specific clock reporter gene construct, allow to look at various transcriptional activities with high time resolution under different light regimes or pulses. In the more costly experiments with single cells, it has been shown that global signal fluctuations up to non-oscillating averages stem from desynchronization of cells, while their individual oscillators persist.[7,9] Here, a single light pulse shifts the phase of individual cells to become synchronized again. The raw data can subsequently be quantified in order to determine features and extract essential information. For one, variable responses of cell cultures and unaccounted factors that mask the circadian rhythm can be removed by detrending, for example by applying a 24-hour moving average method. The data can be further analyzed using the Hilbert transform to obtain the circadian rhythm amplitude, period, the phase of oscillations, as well as the dampening due to desynchronization. However, even with this information it can prove difficult to spot the underlying mechanisms and any emergent properties. Here, a mathematical model can reduce the complexity of such systems and thus the cost of simulation, while still allowing accurate predictions. Oscillators are frequently modeled using gene regulatory networks characterized by negative feedback with time delay. Furthermore, the noisy and random events at the microscopic level can be reflected with mathematical random or stochastic processes.

While the mechanisms behind entrainment require more investigation, the modeling of circadian clocks of several species has already significantly shed light on how these oscillations arise. Importantly, systems biology does not just focus on the individual components, but seeks to discover instances of emergence. In this way the dynamics of interactions can be captured and compared with experimental data, to not only improve the theoretical grasp of a system, but also to make experimental work more effective and to pin point unexpected predictions as starting points for future investigation.

5. Symmetry and Synchronization in Models of Antigenic Variation (K. Blyuss)

This work employs methods of equivariant bifurcation theory to study the dynamics of the interactions between antigenic variants and the human immune system during immune escape. Using the example of antigenic variation in malaria, we investigate the effects of symmetry on possible dynamical regimes and (de)synchronization of antigenic variants. The results of the analysis are quite generic and can also be applied to the studies of various multi-strain diseases.

Many known parasites, such as *Plasmodium falciparum* (causative agent of malaria), *African Trypanosoma*, HIV, *Haemophilus Influenzae* etc. use antigenic variation to achieve antigenic escape.[10] This method relies on the ability of parasites to continuously change the surface markers (antigens) they present on the cell surface, which allows them for a long period of time to remain undetected by the immune system of their hosts. Although many aspects of the dynamics of antigenic variation have been studied, the effects of symmetry have remained largely unexplored.

When considering models of antigenic variation from a perspective of equivariant bifurcation theory (i.e. theory of dynamical systems with symmetry), it is possible to gain an insight into classification and stability of steady states using symmetry properties of the coupling matrix between different antigenic variants.[11] Isotypic decomposition of the phase space and equivariant Hopf theorem allow one to find analytical expressions for the boundary of Hopf bifurcation for the fully symmetric steady state, as well as identify particular symmetry of the bifurcating solution.[12] On the other hand,[13] H/K Theorem provides a systematic approach to classifying periodic solutions with different types of symmetry.[11]

Due to the genericity of obtained results, they can be applied to a wide range of models of host-parasite interactions, where the symmetry of interactions between antigenic variants gives clues about the expected types of behaviour, their stability and symmetries. The same approach can be used to study the dynamics of multi-strain infections, where the symmetry properties of interactions between strains provide significant insights into stability and symmetries of different types of solutions.

6. Noise-induced Rhythmicity in the Circadian Clock (E. Ullner)

In higher organisms, circadian rhythms are generated by a multicellular genetic clock that is entrained very efficiently to the 24-hour light-dark cycle. Most studies of these circadian oscillators have considered a perfectly periodic driving by light. Naturally organisms are subject to non-negligible fluctuations in the light level all through the daily cycle. Interestingly higher organisms respond to artificial constant light conditions over several days with a kind of phase transition from the free running rhythmic to an arrhythmic behaviour. The constant light intensity determines the transition.

We investigate how the interplay between light fluctuations and intercellular coupling affects the dynamics of the central clock. We model the central circadian clock as a collective rhythm of a large ensemble of nonidentical, globally coupled cellular clocks modeled as Goodwin oscillators. Based on experimental considerations,[14] we assume an inverse dependence of the cell-cell coupling strength on the light intensity, in such a way that the larger the light intensity the weaker the coupling.

The system offers access to interesting questions from the biological viewpoint and the dynamical systems side. The phase transition from the rhythmic to the arrhythmic behaviour and the critical light intensity are essential for the coherence resonance (CR), a noise-induced effect known from the dynamical system theory. The phase transition can be observed only in the overt rhythm that we model by the mean response of all individual circadian oscillators. We study the influence of noise on the quality of the overt rhythm and consider the synchronization and the coherence of the mean-field. Our results show a noise-induced rhythm generation for constant light intensities at which the clock is arrhythmic in the noise-free case.[15] Importantly, the rhythm shows a resonance-like phenomenon as a function of the noise intensity. Such improved coherence can be only observed at the level of the overt rhythm and not at the level of the individual oscillators, thus suggesting a cooperative effect of noise, coupling, and the emerging synchronization between the oscillators.

From the biological viewpoint the CR offers a test tool for the light dependent coupling hypothesis. The CR in the discussed system relies on the hypothesis of light dependent coupling. Experimental results of a noise-induced rhythmicity for constant light intensities at which the clock is arrhythmic in the noise-free case would strengthen the biological relevant hypothesis of light dependent coupling amongst the individual oscillators. The mathematical model originates form the biological problem, makes use of a noise-induced phenomena and gives a protocol for experimental testable predictions that can be used to strengthen the biological derived hypothesis of light dependent coupling amongst the many basic circadian oscillators building the central clock. The discussed circadian model gives an example for the vice versa beneficial connection between biology and mathematical modeling.

7. Stochastic Bifurcations in Biological Systems (A. Zakharova and A. Koseska)

The dynamical structure of genetic networks determines the occurrence of various biological mechanisms, such as cellular differentiation. However, the question of how cellular diversity evolves in relation to the inherent stochasticity and intercellular communication remains still to be understood. In order to address this problem, we have generalized the deterministic systems theory to stochastic dynamical systems,[16] and hence investigated the complexity of genetic networks' behaviour in terms of stochastic bifurcations.[17] This theoretical consideration allows to obtain

a comprehensive picture of the dynamics of stochastic cellular networks. In particular, we have shown that the expression of given proteins of interest is defined via the probability distribution of the phase variable, representing one of the genes constituting the system. Moreover, we have shown that under changing stochastic conditions, the probabilities of expressing certain concentration values are different, leading to different functionality of the cells, and thus to differentiation of the cells in the various types.

8. Stabilising the Artificial Cell Differentiation in the Coupled Repressilator (M. Fryett and E. Ullner)

Synthetic genetic networks are very important for a general understanding of biological design principals and for future applications.[18] In particular, the coupled repressilator is a prototype due to it's simplicity yet rather complex dynamics.[19] The basic model consists of a set of coupled differential equations for each cell which provide very rich and multi-stable dynamics due to phase respulsive coupling. Depending on the cell density and the initial conditions,[20] the system expresses an oscillatory regime, inhomogenous limit cycle (IHLC), inhomogenous steady state (IHSS) and homogenous steady state (HSS). The IHLC and IHSS are of particular interest since they can be seen as artificial cell differentiation (ACD) in isogenetic populations.

In any microbiological system we expect to see intrinsic noise and we have to be able to test the robustness of the deterministic models by inducing noise.[27] In particular, it would be interesting to see if the IHLC and IHSS exist within a noisy environment. Intrinsic noise can be simulated in the coupled repressilator model by applying the Gillpesie algorithm.

Taking the parameter set of the deterministic model and applying Gillespie to that model yields very noisy results due to the low numbers genes (and mRNA molecules) and the dynamical regimes are indistinguishable (Fig. 3 left).[20] To overcome the destructive high intrinsic noise level we apply two strategies. First we reduce the intrinsic noise by increasing the number of plasmids within each cell thus increasing the number of genes and thence the number of mRNA molecules. Secondly, bifurcation analysis shows that the HSS and IHSS/IHLC regimes are close together and the intrinsic noise pushes the system in randomly and very frequent in different co-existing state. The bifurcation analysis revealed that a change in the cell membrane permeability increases the distance between these basins of attraction and stabilizes the ACD. The stochastic Gillespie simulations of the altered model show a significant stabilization of the ACD (Fig. 3 right) in the noisy environment and the IHLC/IHSS are expressed much longer in time and clearly distinguishable.

9. Effect of Noise and Asymmetry on Decision Making in Gene Regulatory Networks (N. Nene and A. Zaikin)

Cell fate commitment, or attractor selection, has only recently been shown to be also dependent on the speed at which external signals induce changes on tran-

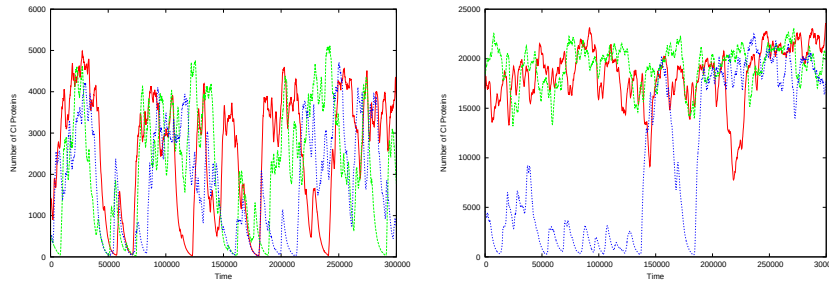

Fig. 3. Stochastic simulation of three coupled repressilators. Each color shows the dynamics of the *CI* protein in different cell. Left: Intrinsic noise dominated the system for the parameter set taken from the deterministic model. Right: Increasing the plasmid number and changing the cell permeability according to the bifurcation analysis reduce the noise and stabilise the ACD. The genetically identical cells behave differently under the same environmental condition. The red and green cells express over long time a high *CI* protein level whereas the blue cell expresses a low *CI* protein level but a high *LacI* protein level (data not shown).

scriptional landscapes, a mechanism known as *Speed-dependent Cellular Decision Making* (SdCDM).[21] This has extended the already widely proven importance of external signal characteristics such as amplitude and duration on phenotype selection. SdCDM has been observed in genetic decision switch models (see Fig. 4A) and it depends on the time-dependent asymmetry between external signals. In the simulations of Fig. 4, illustrating the mechanism reviewed here, the signals $S_{1,2}$ had simple linear profiles where only the rising times to the same final steady state amplitude caused the transient selective driving force to arise. This induced a transition into a region of bistability where decision making stemmed from the system converging to one of the available stable states. An inherent aspect to SdCDM is the fact that the signals are most efficient in selecting a desired attractor, in the face of fluctuations, when the sweeping speeds through the critical region are smaller, i.e. when the characteristic rising times are larger (see Fig. 4B).[21] As in canonical models of *nonequilibrium* statistical physics, the probability of noise forcing a jump across the potential barrier separating the desired end states is reduced when the system goes through its critical region slowly, thus helping memory of the transient external asymmetry to be retained. For additional effects when both the intensity of fluctuations and the time-scale separation between processes in the circuit of Fig. 4A are increased see Ref. 21. The SdCDM mechanism shows the importance of considering the theory of dynamic bifurcations in addition to other techniques more extensively explored in biological circuits,[21] such as large deviation and sample-paths approaches,[22] in order to understand cell fate decision. This *endeavour* contributes to the clarification of real selectivity mechanisms present in cells that execute competing differentiation, proliferation or apoptosis programs. One can hypothesize that evolution has selected for embryonic development with an optimal cellular differentiation speed. The conditions leading to deviations from this optimal route, the onset of pathologies and their potential treatment, constitute

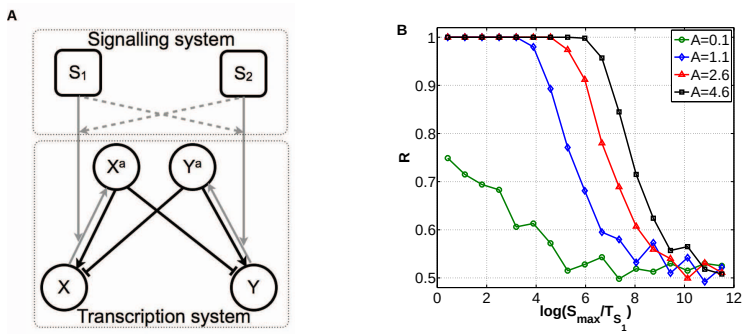

Fig. 4. Integrated genetic switch and SdCDM. (A) Circuit representation: Nodes represent proteins, regulated by signals S_1 and S_2, and X and Y transcription factors that can be phosporylated to generate X^a and Y^a. Black and grey lines represent protein-gene and protein-protein interactions, respectively. (B) Fraction of cells R converging to a selected state ($(X, Y) = (H, L)$) versus signalling sweeping speed (controlled by the signal rising time T_{S_1}) and maximum asymmetry A between S_1 and S_2 in the presence of fluctuations. Here the maximal asymmetry $A = \max(\Delta S(t)) = S_{\max}\left[1 - (T_{S_1}/T_{S_2})\right]$. The values of all parameters associated with transcription or translation processes were assumed to be symmetric in order to focus on the bias provided by the external signals.[21]

still an important open question to which the observation of speed-dependent effects is an important contribution.[21]

10. Discussion

The greatest challenge facing the systems biology research community is the translation of knowledge accumulated in Statistical Physics, Nonlinear Dynamics and Applied Mathematics into effective methods to understand effects in complex biological systems. Let us discuss main trends recently utilized along this strategy, which became possible due to the development of main principles behind modeling of genetic or protein systems.

Real advance of Nonlinear Dynamics has been understanding of chaotic behaviour, self-organization principles,[23] and on the other hand synchronization between interacting systems.[24] The adjustment of rhythms due to an interaction, the essence of synchronization, has been found in huge variety of different cellular and molecular systems. Recently the synthetic gene network with global intercellular coupling has been engineered that is capable of generating synchronized oscillations in a growing population of cells.[25] Interestingly, the principles governing the behaviour of nonlinear systems are similar in genetic and neural networks including also manifestation of stochasticity.[26]

Stochasticity can be found on all levels of molecular and cellular organization, in particular, gene expression occurs in random way under the influence of intrinsic and extrinsic fluctuations which can be measured experimentally.[27] These measurements established a quantitative foundations for modeling noise in genetic networks

and led to numerous theoretical studies. The key question of these studies was how noise which is inherently present in genetic systems and is essential for heterogeneity enable genetic networks to function in robust and reliable way. Moreover, studies of stochastic and coherence resonances, ratchets and noise-induced transitions have shown that counterintuitively noise may lead not only to disorder but to ordering in nonlinear systems. This noise-induced order has been found in numerous biological systems and is certainly utilized by nature in real time or as a evolutionary adaptation.[28])

Network theory is an another source of knowledge and methods for the study of genetic and protein network systems. Inferring regulatory and pattern formation interactions between genes or interacting elements from genomics, transcriptomics or proteomics data is of paramount importance to systems biology. How genetically regulated patterns are organized, how to identify links or couplings between network elements, what is the minimal topology to perform the required function and still work in the robust and reliable way, what is the direction of coupling and which principle underlie the oscillations, synchronization, scale-free behaviour - all these questions are just the few where developed methods of network analysis can help use in understanding the complex biological systems.[29]

Discussion about the translational research will be incomplete without taking note of new approaches to analysis of information processing on intra- or intercellular level interpreting a cell or genetic motif as a single dynamical node able to perform state-dependent computations.[30] Living cells need to continuously sense and process external information in an adaptive manner and in multiple time scale using genes and proteins as a reservoir of dynamical elements coupled each other in recurrent networks, similar to those existing in neural or artificial neural systems. The goal of this research direction is not only to understand signatures of this primitive intelligence on cellular level but also to construct synthetic intelligence systems using gene or DNA interactions.[31]

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