An engineering perspective on transcription, translation and their regulation

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https://doi.org/10.18388/pb.2021_520

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Keywords: Mathematical modeling, regulatory networks, DNA information coding, synthetic biology

Acknowledgements: This work was supported by SUT internal grant 02/040/BK_24/1056.

ABSTRACT

Information coded in DNA is replicated, modified and transmitted from the origins of protein-based life. Analogies of these processes to information processing, transmission and storage in computer systems is straightforward and can be utilized both in analysis of biological data and in development of biologically based technical systems. Transcription and translation processes are regulated by extremely complex regulatory networks, providing control of cell growth, cell cycle and cellular responses to stress. As such, they constitute engineering control systems exerting their actions at many levels of time scale and spatial organization. This work presents an engineering perspective on DNA-related information processing and biochemical process control in living cells, followed by a review of two-way crosstalk between engineering and biology.

INTRODUCTION

Understanding of information processing by living cells and regulation of intracellular processes is key to recognizing how specific molecular mechanisms lead to development of various diseases, responses to treatment at a cellular level, and development of efficient treatment procedures. Increasing knowledge of nature-created molecular mechanisms unveils more and more analogies to technical systems. On the one hand, these analogies facilitate adaptation of engineering approaches to analyze intracellular processes, and, on the other hand, they become continuous inspiration for engineers to develop biologically based solutions to technical problems.

Transcription and translation processes can clearly be viewed as translation procedures from information theory point of view. In that context DNA replication constitutes information copying, or transmission. In both cases information redundancy, error detection and correction, and data access control need to be dealt with appropriately, if the information system can be regarded as properly designed. Not surprisingly, all these aspects have been addressed by evolution.

Extremely complex regulatory networks governing molecular processes are another biological engineering marvel. While the concepts of negative or positive feedback loops have existed in the field of molecular biology for quite a long time, other engineering-related control structures in the form of advanced feedforward or hierarchical control have gained wide recognition relatively recently.

The goal of this work is to show aforementioned analogies and thus bring closer two distant worlds – molecular biology, in which heterogeneity and large uncertainty is the norm, and engineering that expects repeatability, reasonable measurement accuracy and structured systems description.

INFORMATION PROCESSING VIEWPOINT

While majority of information theory based approaches in molecular biology research is focused on analysis of the content and meaning of sequences, as well as their retrieval, this work takes an alternative viewpoint, looking at the cell as the information processing system. This allows subsequent utilization of DNA/RNA/protein systems in new technical applications associated with information storage, data compression, data access authorization, retrieval and transmission.

Ambiguity of the nomenclature used is one of the obstacles to overcome in multidisciplinary research and applies also to information science and biology. The term genetic code itself does not rise any questions, though, and is the most natural. Information about amino-acid sequence (for example) in a protein is coded in DNA with an alphabet of four symbols, denoting particular nucleotides. However, biochemical translation of mRNA into protein requires a more

careful discussion. While one may regard this process to be an analogue to translation from the RNA language to the protein language, it seems that this process should be treated as decoding from information science perspective. Additionally, one has to remember that the ribosomes performing this decoding must deal with a highly noisy encoded signal [1]. Moreover, transcription may be viewed as the first decoding step, followed by information processing (e.g. through alternative splicing) and, if the mature mRNA is the end-product of the latter, by the second decoding step leading to the amino-acid sequence.

Both DNA and RNA codes belong to the variable-length codes family. To be of any use, such code should make it possible to define the beginning and the end of a word in the code (or information frame, or packet, in the context of information transmission). There are several ways to achieve this, and in the case of genetic information processing the solution is based on specific marking of these ends. Transcription, the first decoding, is initiated at the TATA box that corresponds to synchronization signal or start code in computer science. As far as signaling the end of the coded word is concerned, there are several mechanisms employed by cells, depending on the cell type. One of these is utilization of a Poly-A sequence marking the end of the gene. That corresponds to the stop bit, or end-of-transmission bit sequence, etc. Similarly, translation, the second decoding, is initiated at the start codon and continued until the stop codon is reached.

To retrieve information for subsequent decoding, it needs to be properly addressed. Gene promoter regions, and, more specifically, the sequences of binding sites play the role of addresses in the discussed biological system. An intriguing fact that many genes share the same sequences in their promoter regions (an interesting analysis can be found in [2]) may be interpreted in two ways from the information processing viewpoint. First, it represents parallel information processing, which requires parallel access to data stored in different sites in memory. Second, it may be treated as broadcast addressing in data transmission, in which information (in this case, about the possible need to initiate transcription) should reach multiple recipients (not necessarily all, as it is possible to define broadcast groups). In that context, information stored in mRNA is always addressed in a broadcast manner.

There is another context, in which one may look at accessing information stored in DNA in the process of transcription. Experimental investigation of transcription initiation shows quite a resemblance to data access authorization. Biochemically, it involves cofactors whose binding is needed [3] and their interplay with the chromatin [4]. It is only recently that new techniques emerged to facilitate observation of DNA accessibility changes through chromatin compaction and phase separation [5].

Another important issue is information compression. In computer science, it is achieved through application of packing algorithms of various efficiency, producing output information coded in a smaller number of bytes, either for its storage or transmission. Compression of DNA data does not change the length of the sequence but the space it requires, and that is achieved through chromatin organization [6], ultimately yielding a similar result. It is worth noting that the density of information stored in DNA is twelve orders of magnitude higher than the density available in electronic memory (1bit per nm^3 versus 1 bit per 10^{12} nm^3, respectively [7]). However, such direct comparison may be misleading, as one should also take into account the environment in which DNA has to be immersed and significant time needed to retrieve information, as compared with electronic devices [8].

CONTROL ENGINEERING VIEWPOINT

Cellular homeostasis, responses to stress, cell cycle and cell behavior in general are governed by complex regulatory networks relying on protein activation, inactivation, degradation, association or dissociation of molecular complexes, shuttling of molecules between cellular compartments, transcription, translation, etc. Understanding the structure and properties of these regulatory networks is necessary in search for controlling them, e.g. in a therapeutic context. This can be achieved with the support of engineering control theory and decomposing extremely complex regulatory networks into simpler subsystems, sometimes called functional motifs [9], and their subsequent analysis.

Feedback loops are the most often mentioned functional motifs of regulatory networks (Fig. 1). Negative feedback is based on either molecules inactivation, degradation, or active transcription or translation inhibition. The simplest negative feedback loop may involve a gene, whose product is its own repressor. In turn, in a positive feedback loop, a molecule increases its own production or activation, so the simplest positive feedback loop would consist of transcrip-

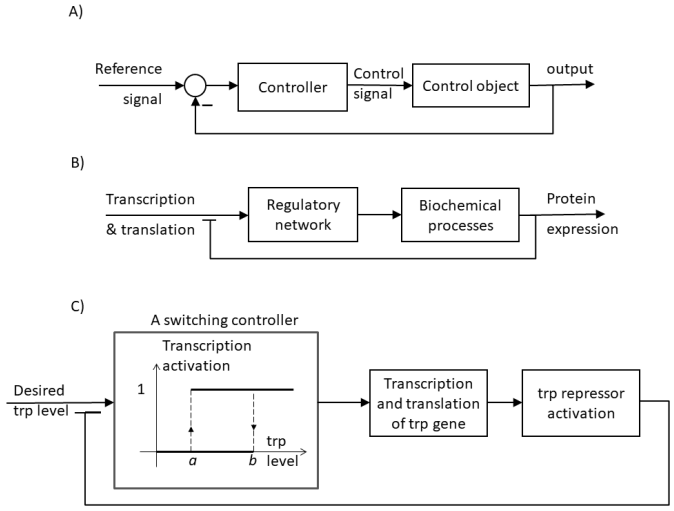

Figure 1. A) A simplified negative feedback control structure; **B)** a related functional motif regulating cellular behavior; **C)** a particular example of autorepression in tryptophane (trp) production in *E. coli*. In technical systems the summing node compares the value of the reference signal with the actual system output. In biochemical systems there is no actual comparison based on subtraction, hence the summing node is replaced by the repression symbol, but the idea remains the same. In trp control system C) the controller is switch-like – if the trp level falls below level a, the transcription is switched on, when it reaches high level b, it is switched off through binding of the repressor activated by trp to its respective operon site.

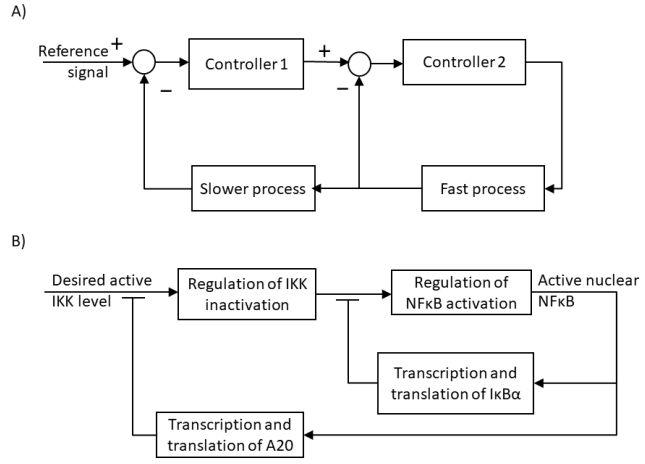

Figure 2. A) Block diagram of a technical cascade control system; **B)** Casacade control structure regulating the NFκB system response, based on early IκBα (early) and A20 (late) genes activation.

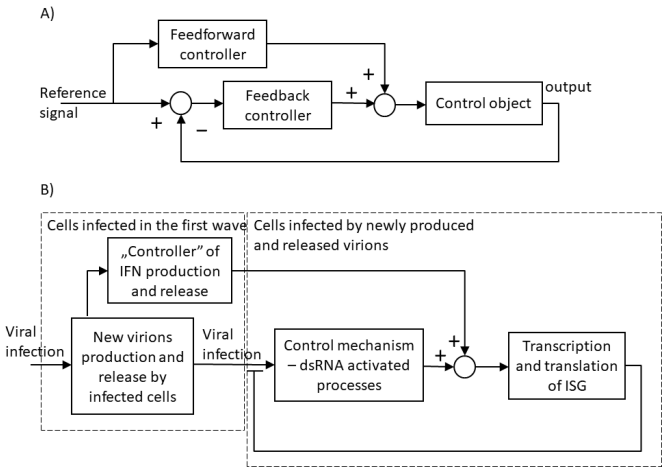

Figure 3. A) Feedforward control structure in technical systems; **B)** feedforward control structure in immune response regulation through type I Interferon (IFN). In B) immune response is activated by dsRNA in infected cells, leading, among others, to production and release of IFN. Binding of this IFN to its respective receptors in neighboring cells helps to prepare them for incoming infection through activation of Interferon Specific Genes (ISGs) thus facilitating their faster response to infection.

tion and translation processes, leading to production of a protein that is a transcription factor of its own gene.

However, analogies between biological and engineering systems go far beyond a simple feedback loop and involve both specific controller type (i.e. the way, in which control signal is formed) and more advanced control structures.

First, and arguably the most frequently analyzed type of a controller in biological regulatory networks is a switch [10], whose technical analogue is referred to as a relay switch and whose simplest implementation in the biochemical networks can be observed in autorepressor loops (Fig. 1B). What is interesting, and so far not explored in this context, is that a relay switch with hysteresis might explain apparently antagonistic (e.g. pro-apoptotic and anti-apoptotic) actions of the same molecular players. Switching control elements are crucial in particular in regulatory networks associated with cell death or cell cycle checkpoints. Moreover, they can be utilized in the search for active drug components that should exhibit high specificity for their target and low affinity to other molecular players [11].

Another type of a controller, used in majority of industrial applications is the so-called PID controller, whose proportional (P), Integral (I) and Differential (D) components are responsible for taking into account the current situation, history of system behavior and future expected behavior predicted on the basis of the current trend, respectively (in an oversimplified, non-technical explanation). While the exact biochemical equivalents of such controller have not been discovered so far, its several variants have been developed and tested with synthetic biology techniques: a simple I controller exhibiting robust perfect adaptation in arbitrary intracellular networks with noisy dynamics [12], a two-component PI controller [13] or a full PID controller [14].

Both in living cells and in industrial applications simple feedback structures are not capable of providing the required system robustness. When a large process to be controlled consists of a series of smaller processes, in technical applications cascade or hierarchical, control is used (there is a difference between these two but the general structure looks the same in both cases). Two controllers are employed there (Fig. 2), one regulating a subprocess, and the other controlling the whole system. Such structure is particularly useful if one of the subprocesses is significantly slower than another, as shown in Fig. 2A, or when it is possible to compensate for disturbances affecting one of the subprocesses. In the latter case, the second controller is designed to attenuate the disturbances effects, before these disturbances affect the second subprocess.

In biological, intracellular setup, such structure is quite common with the easiest examples involving fast subprocesses such as activation or inactivation of proteins and complexes and slow subprocesses requiring transcription and translation. Regulation of early genes expression, whose products are transcription factors for late genes may serve as another example, as it is the case with regulation of the NFκB system (Fig. 2B). Though the term cascade control may be found in some works, such structures are referred to as layered feedback [15], multi-level circuits [16] or hierarchical control [17].

Another control system structure that can be found both in engineering and cellular systems is the feedforward motif. It allows to reduce the time lag in system response to either changes in the reference signal (level of particular molecules desired in a particular situation), or external disturbances, introduced by the feedback structure (Fig. 3). Feedforward has been reported to be one of the most important network motifs that appear in hundreds of signaling networks [18]. However, some misconception can be found in some works (e.g. [19-21]), where two control mechanisms running in parallel (e.g. two alternative pathways activated by the same receptor or the same ligand through different receptors) are considered to constitute a feedforward structure, while, in fact, it is a simple open loop control. While the feedforward

is indeed created by alternative pathways, only one of them must be additionally closed in a feedback loop, as illustrated in Fig. 3A. The feedforward structure depicted in this figure is designed for faster compensation of changes in the reference signal value, which are predetermined, as it is the case with the cyclins in the course of the cell cycle [10], or in the case inflammation, oxidative stress responses or angiogenesis [22] and often involves communication with neighboring cells (Fig. 3B). What needs to be stressed, is that feedforward control, yielding faster transient responses, may lead to poor system behavior if the changes it was designed to cope with have been poorly predicted or the model of their effects on the system is inaccurate (in the case of the technical system). In the case of feedforward regulatory network motif, this corresponds to a disrupted pathway (e.g. in the case of disease-related mutations) and may potentially have fatal consequences [23]. This is particularly evident in interferon dysregulation in viral responses [24], cancer [25], or autoimmune diseases [26]. At the same time, that structure might be effectively utilized in designing immunotherapy [27]. In general, feedback and feedforward control are often analyzed in the context of the interferon-based system [28], cancer [21], metabolic homeostasis or adaptation [29].

The considerations above clearly indicate similarities between cellular mechanisms and control systems, with respect to control structures and type of action of regulatory elements. However, in an attempt to employ engineering knowledge and experience in analysis of intracellular networks one must be aware of two substantial differences. First, except for a very few cases, technical systems act in a purely deterministic way and therefore their behavior and properties can be predicted. Intracellular systems, in turn, exhibit stochastic nature and large heterogeneity may be observed in cell populations, even if the same type of cells is taken into account. Relatively small accuracy of measurements taken in the experiments does not help, either. Furthermore, in multicellular organisms actually a response of a single cell is less important than the response of cell population, or tissue. Therefore, analysis of a single cell control system without taking into account the higher order of organization may be misleading.

CROSSTALK BETWEEN BIOLOGY AND ENGINEERING

HOW ENGINEERING CAN HELP IN GAINING BIOLOGICAL KNOWLEDGE AND ITS PRACTICAL APPLICATION

Different signal transduction pathways are activated in the cell as the result of stress conditions or therapeutic actions, leading to activation of genes and mechanisms responsible for survival and adaptation. Regulation of these signaling pathways is critical for growth, development and response to the treatment of cancer and other human diseases as well as immune system responses to infections. Although many pathways determining cellular responses have been extensively studied and there is rich literature devoted to them, many control mechanisms have not been discovered yet and exploiting existing knowledge in development of new therapies is very difficult. Efforts to uncover the structure of regulatory mechanisms governing intracellular processes and intercellular communication and interactions are hampered by high costs of experiments, uncertainty of measurements and multiple interactions between systems under consideration. On the other hand, control engineering that tackles similar problems in technical field provides plentiful of solutions. Finding analogies between these fields should facilitate much faster progress in molecular biology and medicine, supporting analysis of experimental results, *in silico* analysis of biological hypotheses as well as experiment planning This is why employing engineering knowledge and methods becomes more and more important in supporting biological research [30], helping to investigate unknown mechanisms regulating responses to various stress factors, interactions between specific signaling pathways, or phenomena like cellular signal memory [31]. Moreover, engineering methods, such as sensitivity analysis, may facilitate discovery of molecular targets for new drugs [32], a process which requires mathematical modeling of regulatory networks, molecular dynamics modeling, artificial intelligence-based tools and IT hardware and software infrastructure (Fig. 4). Mathematical modeling of dynamical responses of biochemical regulatory networks supports experimental work in many ways. Bifurcation analysis may explain why experiments that follow the same

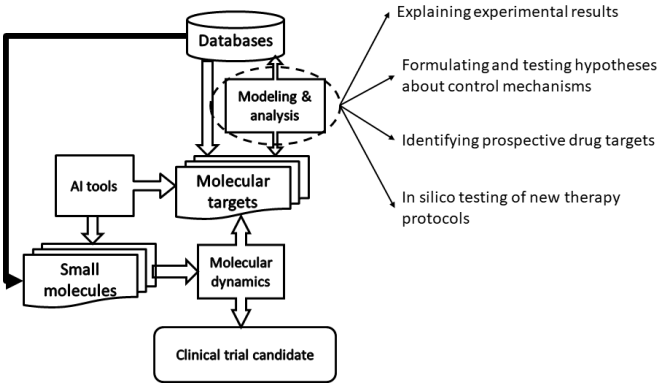

Figure 4. Engineering support in new drug development.

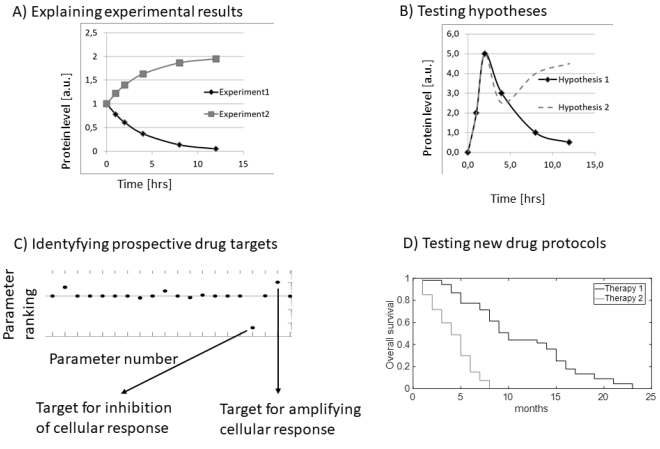

Figure 5. Mathematical modeling support in molecular biology. **A)** through bifurcation analysis it is possible to explain completely different results in seemingly the same experimental setup; **B)** simulation-based verification of hypotheses about unknwn regulatory mechanisms can indicate those worth further experimental validation (Hypothesis 1) as the other does not lead to results observed experimentally; **C)** sensitivity analysis of signaling pathways unveils potential drug targets by indicating parameters, unanimously associated with biochemical processes and their molecular participants; **D)** *in silico* testing of virtual patients response to treatment allows to find a protocol exhibiting the highest efficacy.

procedure may yield qualitatively different effects through indicating a parameter, whose even slightest change might produce contradictory results (Fig. 5A). In uncovering previously unknown control mechanisms, regulating cellular responses, simulation helps to reject hypotheses that would not be able to result in dynamics observed experimentally (Fig. 5B) thus saving resources for more promising experiments. Sensitivity analysis, in turn, shows change of which parameters yields largest changes in cellular responses (Fig. 5C). As each parameter in mathematical model is unanimously associated with a single process, and this, in turn, with molecular players involved, such investigation turns out prospective drug targets. Finally, as mathematical models can describe responses to treatment in a heterogeneous population of patients, in-silico based studies on virtual pool of patients serve as a safe tool to test alternative treatment protocols (Fig. 5D).

BIOLOGICALLY INSPIRED ENGINEERING SOLUTIONS

The crosstalk between engineering and biology is two-way. Just as engineering may help in answering biological questions, biology becomes inspiration for new technological developments in what might be treated as purely engineering area (information storage, information processing and computation) as well as in a combination of both in the form of a relatively new field of synthetic biology.

In hindsight, information storage seems to be the most natural application of biology in engineering. It does not make a big difference if information is coded in a binary system, with zeroes and ones, or in a nucleotide-based code with A,C,G and T symbols (that could be represented by 00, 01, 10 and 11 anyway). Implementation of DNA-based information storage requires proving its ability to perform basic operations like writing, reading and storing information for some time and providing its reliability through error detection and correction mechanisms. A lot of research has been conducted in this field, proving that data can be safely archived in the form of DNA and then retrieved with error-correcting codes used for providing reliability of such data storage [33,34]. However, in addition to complex error correction algorithms, substantial data redundancy is usually required to maintain data integrity [35]. In order to deal with these problems new research is still going on [36], with significant breakthroughs [37,38]. Nonetheless, it should be noted that this application is meant more for data backup than for fast access and temporary data storage. Using still images and video films as data sources, it was sown that data-carrying chromosome was stable through 100 generations, thus demonstrating stable replication for multiple data retrievals, similar to optical discs, with a potential to be used in data multiplication and distribution [39].

As multiple biochemical processes take place at the same moment in the living cell, looking at the cell as a powerful parallel data processor seems to be a natural consequence of successful approaches to store information in DNA, leading to emergence of a new biomolecule-mediated computing concept. Theoretically, it could yield anything between 10^8 and 10^{14}-fold increase in data processing speed, with 10^{10}-fold reduction of energy consumption [7]. Though industrial-scale general-purpose DNA integrated circuits have not yet materialized, they are the subject of research of many groups trying to develop multilayer DNA-based programmable gate arrays (DPGAs) [40] that would correspond to field-programmable gate arrays (FPGA), so common in current electronic technology. In the meantime, application-specific DNA- or RNA-based computational solutions are proposed, e.g. for password generation [41], or securing (encrypting) data with DNA steganography [42,43].

In addition to utilizing biology in information processing, engineering and biology work in concert to design and produce various synthetic biology applications, from basic genetic circuits *in vitro* and in cells to metabolic engineering in cells to biosynthesize complex molecules of economic value [44]. These applications include bacterial biosensors [45], synthetic transcription factors that control beneficial transgene expression thus advancing cell and gene therapy [46], synthetic receptors, a synthetic biology tool that can precisely control the function of therapeutic cells and genetic modules [47].

Development of engineered biological regulatory networks is based on the so-called transcriptional genelet circuits, first simple ones, then merged to create more complex networks to provide timely responses to upstream stimuli and coordination of downstream signal expression [48]. Such genelets have been shown to facilitate design and implementation of bistable circuits, feedforward and feedback circuits, pulse generating circuits and potentially be scaled up to regulate and functionalize complex biological systems [49]. An interesting fact is that depending on the circuit type, the circuitry works either at protein or RNA levels. At the molecular level, the key components of these systems are protein segments, called inteins, that can excise themselves from the protein while re-ligating the remaining segments (exteins) [50,51].

Arguably the most promising applications of synthetic biology is in diagnostics and treatment in medicine. So far, synthetic gene circuits have already been found to recognize disease-associated signals and either attenuate them, or facilitate desired responses from the immune system. That way they can be utilized in improving the potency and safety of therapeutic cells and target chronic diseases [52]. One of the most striking examples of industrial-scale implementation of genetic engineering and application of control knowledge to optimize the production process inside cells is yeast modification to produce human insulin and insulin analogues [53].

Apart from clinical applications, biotechnology industry should also benefit significantly from synthetic biology developments in other areas, starting from unicellular organisms, and then proceeding to multicellular organisms. For example, engineering plants to possess novel traits could address global problems, from climate change to food security [54].

CONCLUSIONS

The idiosyncratic review of similarities between biological and engineering systems clearly shows that researchers in both fields may benefit from closer cooperation, preceded by a careful setup of nomenclature used. Methods developed in control and information theory may help in understanding intricacies of biological systems, from the way useful information is encompassed by seemingly unnecessary DNA fragments to different and sometimes contradictory experimental results that are not caused by some failure of experimental procedures, to uncover of novel regulatory mechanisms that have escaped explanations so far. On the other hand, biological systems that are robust and sensitive at the same time, may inspire technology to create innovative products.

Having said that, one must remember that the world viewed by researchers in engineering and in life sciences is characterized by completely different features. Engineers, while acknowledging measurement uncertainties and stochastic disturbances that may appear, expect rather deterministic system behavior and high repeatability. Biologists, on the other hand, are accustomed to high noise and ambiguity. To facilitate better understanding and cooperation between these two groups, they need to learn each other language. Additionally, engineering experience is not enough and must be accompanied with sound biological knowledge of a person with a technical-background who tries to support biologists, or for successful development of new solutions.

REFERENCES

1. Rosen G (2006) Examining coding structure and redundancy in DNA. IEEE Engineering in Medicine and Biology Magazine 25(1): 62-68
2. Aptekmann AA, Bulavka D, Nadra AD, Sánchez IE (2022) Transcription factor specificity limits the number of DNA-binding motifs. PLoS One 17(1): e0263307
3. Smith NC, Matthews JM (2016) Mechanisms of DNA-binding specificity and functional gene regulation by transcription factors. Curr Opin Struct Biol 38: 68-74
4. Kumar A, Chan J, Taguchi M, Kono H (2021) Interplay among transacting factors around promoter in the initial phases of transcription. Curr Opin Struct Biol 71: 7-15
5. Mansisidor AR, Risca VI (2022) Chromatin accessibility: methods, mechanisms, and biological insights. Nucleus 13(1): 236-276
6. Parmar JJ, Padinhateeri R (2020) Nucleosome positioning and chromatin organization. Curr Opin Struct Biol 64: 111-118
7. Shu JJ, Tan ZH, Wang QW, Yong KY (2023) Programmable Biomolecule-Mediated Processors. J Am Chem Soc 145(46): 25033-25042
8. Hossein SM, De D, Das Mohapatra PK (2020) DNA sequence compression using RP/GP2 method with information storage and security. Microsystem Technologies 26(7): 2159 - 2172
9. Tyson JJ, Novák B (2010) Functional motifs in biochemical reaction networks. Ann Rev Phys Chem 61: 219–240
10. Tyson JJ, Novák B (2022) Time-keeping and decision-making in the cell cycle. Interface Focus 12(4): 20210075
11. Mansouri M, Fussenegger M (2023) Small-Molecule Regulators for Gene Switches to Program Mammalian Cell Behaviour. Chembiochem 11: e202300717
12. Aoki SK, Lillacci G, Gupta A, Baumschlager A, Schweingruber D, Khammash M (2019) A universal biomolecular integral feedback controller for robust perfect adaptation. Nature 570(7762): 533-537
13. Frei T, Chang CH, Filo M, Arampatzis A, Khammash M (2022) A genetic mammalian proportional-integral feedback control circuit for robust and precise gene regulation. Proc Natl Acad Sci USA 119(24): e2122132119
14. Filo M, Kumar S, Khammash M (2022) A hierarchy of biomolecular proportional-integral-derivative feedback controllers for robust perfect adaptation and dynamic performance. Nat Commun 13(1): 2119
15. Hu CY, Murray RM (2022) Layered feedback control overcomes performance trade-off in synthetic biomolecular networks. Nat Commun 13(1): 5393
16. Gao Y, Wang L, Wang B (2023) Customizing cellular signal processing by synthetic multi-level regulatory circuits. Nat Commun 14(1): 8415
17. Meijer LHH, Joesaar A, Steur E, Engelen W, van Santen RA, Merkx M, de Greef TFA (2017) Hierarchical control of enzymatic actuators using DNA-based switchable memories. Nat Commun 8(1): 1117
18. Zhou J, Sun T, Jin S, Guo Z, Cui J (2020) Dual Feedforward Loops Modulate Type I Interferon Responses and Induce Selective Gene Expression during TLR4 Activation. iScience 23(2): 100881
19. Sehgal V, Ram PT (2013) Network Motifs in JNK Signaling. Genes Cancer 4(9-10): 409-413
20. Fujita Y, Komatsu N, Matsuda M, Aoki K (2014) Fluorescence resonance energy transfer based quantitative analysis of feedforward and feedback loops in epidermal growth factor receptor signaling and the sensitivity to molecular targeting drugs. FEBS J 281(14): 3177-3192
21. Wong RWJ, Ong JZL, Theardy MS, Sanda T (2022) IRF4 as an Oncogenic Master Transcription Factor. Cancers (Basel) 14(17): 4314
22. Wang H, Hartnett ME (2016) Regulation of signaling events involved in the pathophysiology of neovascular AMD. Mol Vis 22: 189-202
23. Tang D, Wang H, Billiar TR, Kroemer G, Kang R (2021) Emerging mechanisms of immunocoagulation in sepsis and septic shock. Trends Immunol 42(6): 508-522
24. Lopez L, Sang PC, Tian Y, Sang Y (2020) Dysregulated Interferon Response Underlying Severe COVID-19. Viruses 12(12): 1433
25. Chen Z, Giotti B, Kaluzova M, Vallcorba MP, Rawat K, Price G, Herting CJ, Pinero G, Cristea S, Ross JL, Ackley J, Maximov V, Szulzewsky F, Thomason W, Marquez-Ropero M, Angione A, Nichols N, Tsankova NM, Michor F, Shayakhmetov DM, Gutmann DH, Tsankov AM, Hambardzumyan D (2023) A paracrine circuit of IL-1β/IL-1R1 between myeloid and tumor cells drives genotype-dependent glioblastoma progression. J Clin Invest 133(22): e163802
26. Newton R, Shah S, Altonsy MO, Gerber AN (2017) Glucocorticoid and cytokine crosstalk: Feedback, feedforward, and co-regulatory interactions determine repression or resistance. J Biol Chem 292(17): 7163-7172
27. Yu R, Zhu B, Chen D (2022) Type I interferon-mediated tumor immunity and its role in immunotherapy. Cell Mol Life Sci 79(3): 191
28. Ji L, Li T, Chen H, Yang Y, Lu E, Liu J, Qiao W, Chen H (2023) The crucial regulatory role of type I interferon in inflammatory diseases. Cell Biosci 13(1): 230
29. Liu Y, Birsoy K (2023) Metabolic sensing and control in mitochondria. Mol Cell 83(6): 877-889
30. Kardynska M, Kogut D, Pacholczyk M, Smieja J (2023) Mathematical modeling of regulatory networks of intracellular processes - Aims and selected methods. Comput Struct Biotechnol J 21: 1523-1532
31. Kalliara E, Kardynska M, Bagnall J, Spiller DG, Müller W, Ruckerl D, Śmieja J, Biswas SK, Paszek P (2022) Post-transcriptional regulatory feedback encodes JAK-STAT signal memory of interferon stimulation. Front Immunol 13: 947213
32. Kardynska M, Smieja J, Paszek P, Puszynski K (2022) Application of Sensitivity Analysis to Discover Potential Molecular Drug Targets. Int J Mol Sci. 23(12): 6604
33. Grass RN, Heckel R, Puddu M, Paunescu D, Stark WJ (2015), Robust Chemical Preservation of Digital Information on DNA in Silica with Error-Correcting Codes. Angew Chem Int Ed 54: 2552-2555
34. Meiser LC, Antkowiak PL, Koch J, Chen WD, Kohll AX, Stark WJ, Heckel R, Grass RN (2020) Reading and writing digital data in DNA. Nat Protoc 15(1): 86-101

35. Xu C, Zhao C, Ma B, Liu H (2021) Uncertainties in synthetic DNA-based data storage. Nucleic Acids Res 49(10): 5451-5469
36. Ding L, Wu S, Hou Z, Li A, Xu Y, Feng H, Pan W, Ruan J (2023) Improving error-correcting capability in DNA digital storage via soft-decision decoding. Natl Sci Rev 11(2): nwad229
37. Zhang Y, Ren Y, Liu Y, Wang F, Zhang H, Liu K (2022) Preservation and Encryption in DNA Digital Data Storage. Chempluschem 87(9): e202200183
38. Akash A, Bencurova E, Dandekar T (2024) How to make DNA data storage more applicable. Trends Biotechnol 42(1): 17-30
39. Chen W, Han M, Zhou J, Ge Q, Wang P, Zhang X, Zhu S, Song L, Yuan Y (2021) An artificial chromosome for data storage. Natl Sci Rev 8(5): nwab028
40. Lv H, Xie N, Li M, Dong M, Sun C, Zhang Q, Zhao L, Li J, Zuo X, Chen H, Wang F, Fan C (2023) DNA-based programmable gate arrays for general-purpose DNA computing. Nature 622(7982): 292-300
41. Mahendran A, Chatterjee S, Vijayarajan V (2018) Password generation mechanism using DNA and RNA processing. J Computat Theor Nanoscience 15(6-7): 2184 - 2188
42. Cun Q, Tong X, Wang Z, Zhang M (2023) A new chaotic image encryption algorithm based on dynamic DNA coding and RNA computing. Visual Computer 39(12): 6589 - 6608
43. Malathi P, Praneeth K, Phani Teja GVS, Rohith KRB, Nayana K T (2023) DNA Steganography using RNA codons and Amino acids 14th Int Conf Computing Communication and Networking Technologies (ICCCNT) Delhi, India, IEEE str. 1-7
44. Ornelas MY, Cournoyer JE, Bram S, Mehta AP (2023) Evolution and synthetic biology. Curr Opin Microbiol 76: 102394
45. Chiang AJ, Hasty J (2023) Design of synthetic bacterial biosensors. Curr Opin Microbiol 76: 102380
46. Bhatt B, García-Díaz P, Foight GW (2023) Synthetic transcription factor engineering for cell and gene therapy. Trends Biotechnol S0167-7799(23): 00284-6
47. Teng F, Cui T, Zhou L, Gao Q, Zhou Q, Li W (2024) Programmable synthetic receptors: the next-generation of cell and gene therapies. Signal Transduct Target Ther 9(1): 7
48. Schaffter SW, Schulman R (2019) Building in vitro transcriptional regulatory networks by successively integrating multiple functional circuit modules. Nat Chem 11(9): 829-838
49. Li Y, Arce A, Lucci T, Rasmussen RA, Lucks JB (2023) Dynamic RNA synthetic biology: new principles, practices and potential. RNA Biol 20(1): 817-829
50. Anastassov S, Filo M, Chang CH, Khammash M (2023) A cybergenetic framework for engineering intein-mediated integral feedback control systems. Nat Commun 14(1): 1337
51. Sarmiento C, Camarero JA (2019) Biotechnological applications of protein splicing. Current Protein Peptide Sci 20: 408–424
52. Teixeira AP, Fussenegger M (2023) Synthetic Gene Circuits for Regulation of Next-Generation Cell-Based Therapeutics. Adv Sci (Weinh) 21: e2309088
53. Kjeldsen T, Andersen AS, Hubálek F, Johansson E, Kreiner FF, Schluckebier G, Kurtzhals P (2023) Molecular engineering of insulin for recombinant expression in yeast. Trends Biotechnol 24: S0167-7799(23)00286-X
54. Bull T, Khakhar A (2023) Design principles for synthetic control systems to engineer plants. Plant Cell Rep 42(12): 1875-1889