Chapter 7

Role of Density Functional Theory in "Ribocomputing Devices"

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http://dx.doi.org/10.5772/intechopen.80491

Abstract

Molecular computing devices composed of biological substances, such as nucleic acid and ribonucleic acid plays a key role for the logical processing of a variety of inputs and viable outputs in the cellular machinery of all living organisms. These devices are directly dependent on the advancement in DNA and RNA technology. RNA nanoparticles can be engineered into a programmable and logically acting "Ribocomputing Devices"; a breakthrough at the interface of nanotechnology and synthetic biology. It opens a new path to the synthetic biologists to design reliable synthetic biological circuits which can be useful as the electronic circuits. In this emerging field, a number of challenges persist; as how to translate a variety of nucleic acid based logic gates developed by numerous research laboratories into the realm of silicon-based computing. So in this chapter we will discuss the advances in ribonucleic acid (RNA) based computing and it's potential to serve as an alternative to revolutionize silicon-based technology by theoretical means. Also the results of the calculated parameters with computational tools using Density functional theory and the designed device circuits will be analyzed.

Keywords: genetic information, logic gates, toehold switches, energy landscapes, RNA nanoparticles

1. Introduction

RNA nanotechnology is the modern and recent field of science which applies the application of top-down or bottom-up approaches to build the artificial architectures of RNA at the nanoscale. The pioneer work on "RNA nanotechnology" was carried out by eminent Scientist Prof. Dr. P. Guo et al. [1–4] RNA nanotechnology involves the characterization of the physical, chemical and biological properties of artificial RNA scaffolds in computing devices.

These molecular computers are natural and/or artificial devices in which macromolecules, including proteins and nucleic acids mediate necessary functions. The three basic operations are similar to the computer operations as: sensing inputs, processing the inputs and generating specific outputs. The schematic representation of RNA nanoparticles with different constructed motifs are given in **Figure 1**.

Nature has given us the best computer in the form of living cell. These cells generate enormous amount of signals (inputs) using a broad range of environmental factors, example: temperature, pH, pressure, nutrients, signaling chemicals, macromolecules, etc. [5–7]. Biological systems have the ability to adapt to new information from an altered environment. They can be self-assemble and self-reproduce, which might provide some economic advantages. Recently Eminent Prof. Alexander A. Green group has designed the ribocomputing devices in which RNA molecules were used as input signals and protein as the output signal. AND, OR, and NOT logic results were obtained from the self-assembly of input and gate RNAs in the

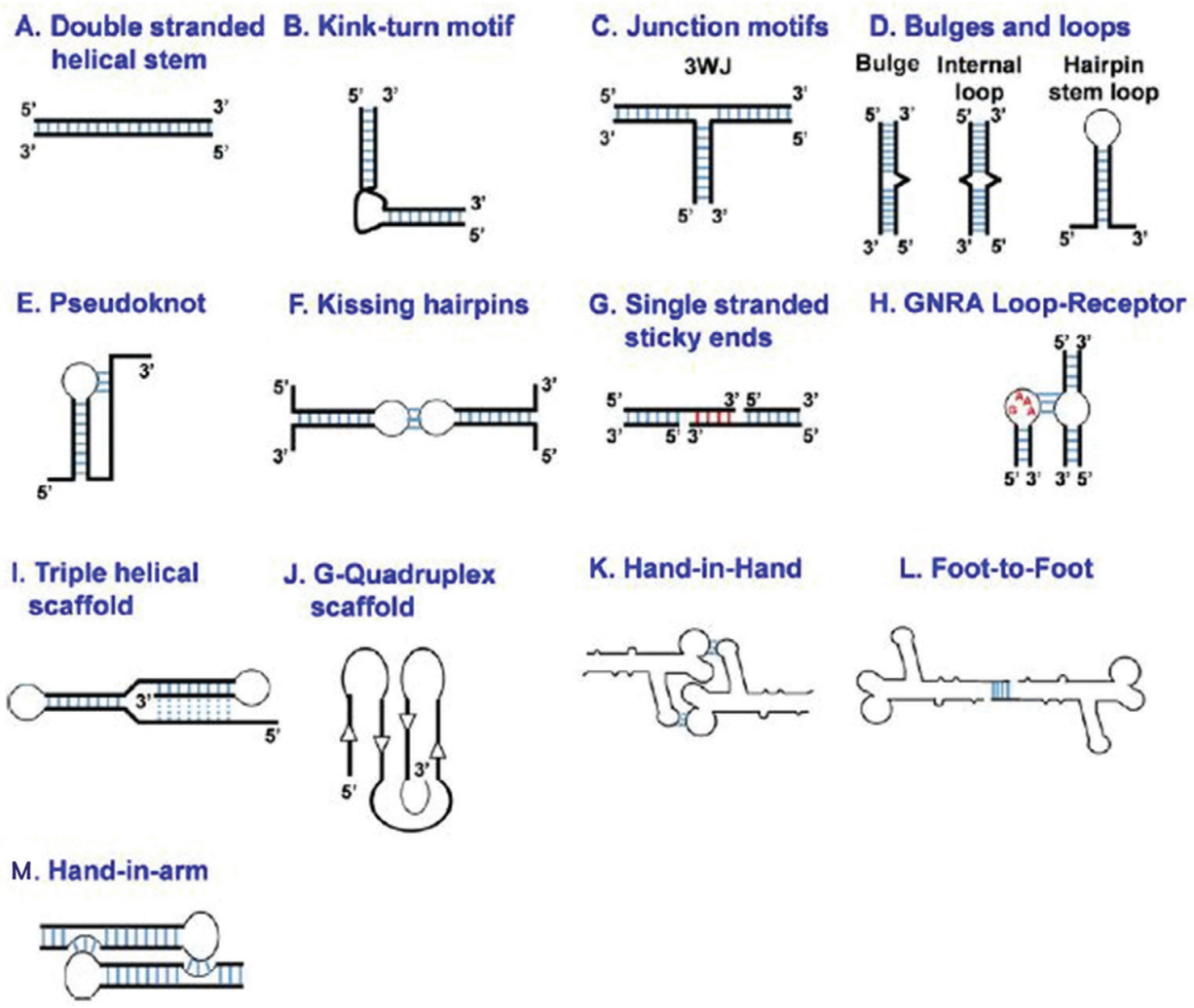

Figure 1. Schematic representation of RNA nanoparticles with different constructed motifs. Adapted with permission from Ref. [96].

device. Gate RNA was used to carry out the signal processing. These devices were operated at the post-transcriptional level and used an extended RNA transcript to co-localize all circuit sensing, computation, signal transduction, and output elements in the same self-assembled molecular complex. The advantage of these systems was the reduction in diffusion-mediated signal losses, lowered metabolic cost and improved circuit reliability. These devices utilized programmable RNA molecules, allowed effective in silico designs, composed of precisely designed synthetic RNAs networks, worked at the post-transcriptional level, minimized delays and improve the reliability of signal transduction. Further these circuits co-localized to integrate multiple circuit functions within a single transcript gate RNA [8]. The input RNAs can interact cooperatively with one another to activate the gate RNA for AND logic or they can prevent for NOT logic. Toehold switch designs, which translate an output gene only if a cognate trigger RNA is expressed in the cell, were also optimized to evaluate the AND logic gate for the ribocomputing devices [9].

Now the question arises why there is a need to replace the silicon based technology?

The capabilities of digital electronic devices have increased in lock-step with Moore's Law, which states that the number of transistors in a microchip will double approximately every 2 years [10]. This will also end up reaching a limit, as the unending quest to miniaturize transistors, which also come to a halt due to the quantum tunneling effect [11]. When the distance of a gate is scaled down about 10 nm, its electrons will jump spontaneously from source to drain, and the control over the flow of electricity will be lost. To overcome this problem, it is possible to either increase the size of microchips or fabricate them as stacking microchips. Even then it will only delay the stalemate.

Further, there are few critical challenges to make a transistor at the atomic level: (i) the accuracy of computing will be affected, because the wires in the circuit will become too close and they will affect each other; (ii) the heat generated in such a small area with too many concentrated transistors will greatly affect the functions of the transistors; (iii) the energy consumption to cool the circuit board would be too high to be a burden. Also the chip temperature will impact the circuit reliability, energy consumption and system cost.

So the next option is to use the biomolecules, including DNA, RNA and proteins as the major elements in logic gate operations. The enzymatic selectivity (processing of specific chemical function) of biomolecules give them an advantage over silicon-based computing with both specificity and usability in an intracellular environment. As most of the biological reactions controlled by specific enzymes are interconnected with other functional inputs, it is possible to fabricate DNase- and/or RNase-based informational processing units. These units can be scaled-up to fabricate artificial biocomputing networks possessing variety of logic functions.

Replacing the silicon computing devices with the molecular computers has the following other advantages: these devices are subjected to the universal physical laws, have a small mass-to-volume ratio and move in viscous media rather than in a vacuum or air. Though they cannot store momentum, kinetic energy or thermal energy for a significant period of time due to their extremely small size, and must operate isothermally. Molecular computing has an enhanced ability to provide parallel computation. These systems can self-assemble and

self-reproduce, which might provide some economic advantages. Moreover, cells can be engineered to sense and respond to environmental signals, even under extreme conditions such as: high temperature, high pressure, radioactivity or toxic chemicals, and have the ability to adapt to new information for a changed environment. The ultimate goals of biocomputing are the monitoring and control of biological systems. The diagnosis of diseases, drug screening and to understand the experimental systems can be done by monitoring. It is also necessary to observe the environment to detect multiple disease indicators [11, 12], and cell based biosensors using logic gates to detect arsenic, mercury and copper ion levels [13]. Another utility is to control development, cell differentiation and re-programming, which mainly depends on gene regulatory networks [14, 15], tissue engineering and tissue regeneration [16], and to control the immune system and malign growth. Logic based biological devices are also executed to detect cancer cells (e.g. small-cell lung cancer, prostate cancer, HeLa cells), and to induce selective apoptosis of these cells [11, 17, 18].

The concept of DNA molecular computation was demonstrated by Prof. Leonard Adleman, in which the ability of synthetic DNA oligonucleotides were used to solve a seven-point Hamiltonian path problem by performing a sequence of logical operations [19]. Since then, the possibility of developing a new generation of molecular logic gates and molecular computers based on the advantages of DNA molecules has started [20–29]. The DNA molecules were chosen as they are amenable to well-regulated, programmable folding, and have the unique ability to store genetic information. The massive parallel computation power and colossal memory capacity [30, 31] were also the salient features of DNA technology, though improvement in specificity of interaction and chemical stability is still to be taken into account. DNA self-assembly properties through WC base interactions can also lead to the formation of a variety of structures (tiles) [32–34]. The studies have also been carried out on the nucleobase stacking pairs and coinage metal clusters to observe the Boolean operations [35]. However, the limitations in the application of DNA-based computation is the intolerable level of execution time in performing logic gates operation and in some circuits, it require more time to reach a stable state to achieve the final value (three-layer see-saw circuits). Another challenge is the limitation of functional proteins required for catalyzing the reactions. So the field of RNA technology has been explored. RNA can be served as the polymeric material to build varieties of structures which included nanoparticles, polygons, bundles, membranes, micro sponges and arrays. The different modifications for stable RNA nanoparticles are shown in **Figure 2**. The vital significance of RNA nanotechnology relies on application of RNA biopolymers at the atomic level. In RNA, the base pairing of nucleotides can be canonical as well as non-canonical and the tertiary interactions of RNA mediate multi-way junctions, bulges and internal hairpin loops. Apart from that RNA is thermodynamically more stable due to relatively low in energy. Now RNA is considered as a subdivision of nucleic acid nanotechnology due to its diverse functions.

The reason for taking the RNA is twofold: RNA (i) possesses the structural properties of DNA and (ii) mimics the functional properties of proteins [36–40]. Interestingly the device design and the role of DFT used for DNA technology can implement to RNA nanoparticles also due to some similar structural properties. So here we will discuss the role of DFT in RNA technology based on the previous studies being carried out on the DNA technology. RNA nanoparticles also include the following properties based on these factors: introducing

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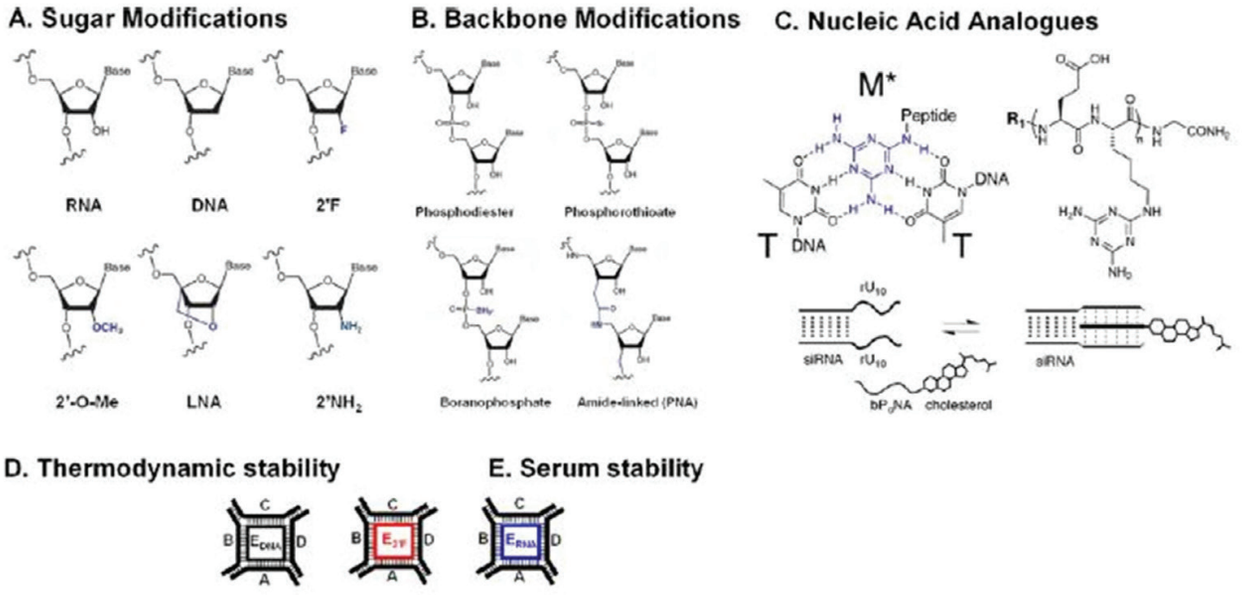

Figure 2. Different modifications for stable RNA nanoparticles (A) sugar modifications (B) backbone modifications (C) nucleic acid analogs (D) thermodynamic and (E) serum stability. Adapted with permission from Ref. [96].

chemical modification into nucleotides without significant alteration of the RNA property in folding and self-assembly; tuning the immunogenic properties of synthetic RNA constructs for in vivo applications; role of 2D, 3D, 4D structure and intermolecular interaction of RNA molecules; developing methods to control shape, size, and stoichiometry of RNA nanoparticles; regulation and processing functions of RNA in cells; cost in RNA production by biochemical synthesis; and safety of using RNA due to its therapeutic modality for cancer and other diseases without affecting the other organs.

RNA molecules have main role of passing information from genome to proteome in all living creatures. The discovery of non-coding RNAs revealed that RNA performs more versatile functions, including gene expression and regulation. The pictorial representation of beacons and resistive biomemory in RNA nanotechnology applications is given in **Figure 3**. The RNA molecules are involved in computational algorithmic processes, including RNA editing (RNA sequence alternation) [36] and RNA-based regulatory networks [35, 36]. In previous studies carried out on RNA computational systems, the inputs were small RNA elements or motifs, and the output was the mRNA [35–37].

There are various classes of RNA functional molecules, such as ribozymes, RNA aptamers, riboswitches, miRNA and siRNA, orthogonal ribosomes [38, –39] that enable the fabrication of RNA-based nanoparticles to advance the modern nanotechnology [40–42]. The recent advances are endonuclease CRISPR (Clustered regularly interspaced short palindromic repeats) associated Cas9 [43] and the bacterial CRISPR pathway [44], which enables predictable programming of gene expression. Recent efforts in genome mining and programmable RNA based switches have increased the number of parts which further enable predictable design of deeply layered logic circuits. These biological circuits required digital-like characteristics as Boolean logic gates with all or nothing responses.

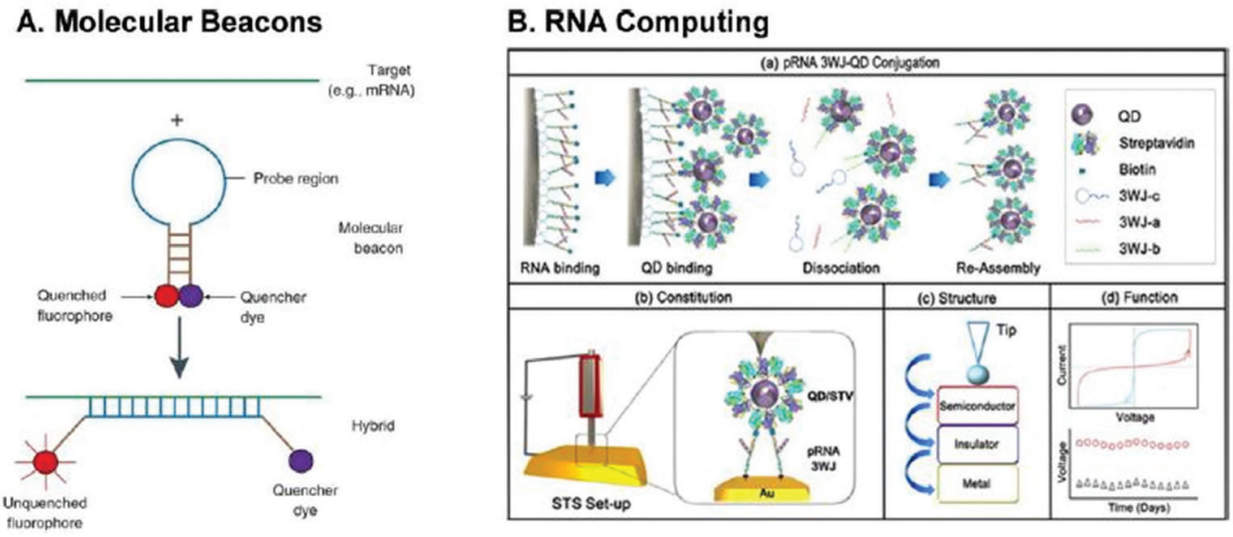

Figure 3. RNA nanotechnology applications in beacons (A) and resistive biomemory (B). Adapted with permission from Ref. [96].

2. Application of RNA nanotechnology in computation (in vivo)

RNA nanotechnology emphasizes its critical role in the process of catalysis in cell signaling and sensing functions. RNAs use the concentrations of specific chemical species as signals to implement the functions of logic to build up the network of multiple layers Boolean networks. Then these molecular computers were able to operate and communicate directly in a biological environment [45, 46] or work inside a living cell [47]. A plasmid with a specifically encoded DNA was inserted and external program was used to control the computation inside the host cell. The mRNA was used to encode a fluorescent protein and the target sequences for small interfering RNA (siRNA) with control level of fluorescence exhibited by the cell. Another in vivo computation programming was observed by a response to both endogenous and exogenous molecular signals. In this work, combination of ribozymes and RNA aptamers were used [48, 49].

The concept to utilize the cleaving ability of ribozyme to a specific molecule with the computational work was carried out using the concentrations of two proteins as input and output, implemented by studying the mechanism of ribozyme-aptamer molecules using yeast. In another study it was shown that the individual mammalian cells were capable of executing the basic arithmetic functions in a robust manner. A memory module (toggle switch) was designed [50] and a scalable factor (transcriptional/post transcriptional) was used to construct a synthetic regulatory circuit with a HeLa cancer cell 'classifier' to sense the expression levels of a customizable set of endogenous microRNAs to trigger a cellular response that matches the predetermined profile of interest [51]. In gene circuit engineering, RNA mediated regulation employs three major mechanisms, cis-acting RNA structure related modulation of translation, catalytic RNA or ribozyme-mediated cleavage of target transcripts and trans acting antisense small RNAs-mediated regulation of translation [52]. The experimental design

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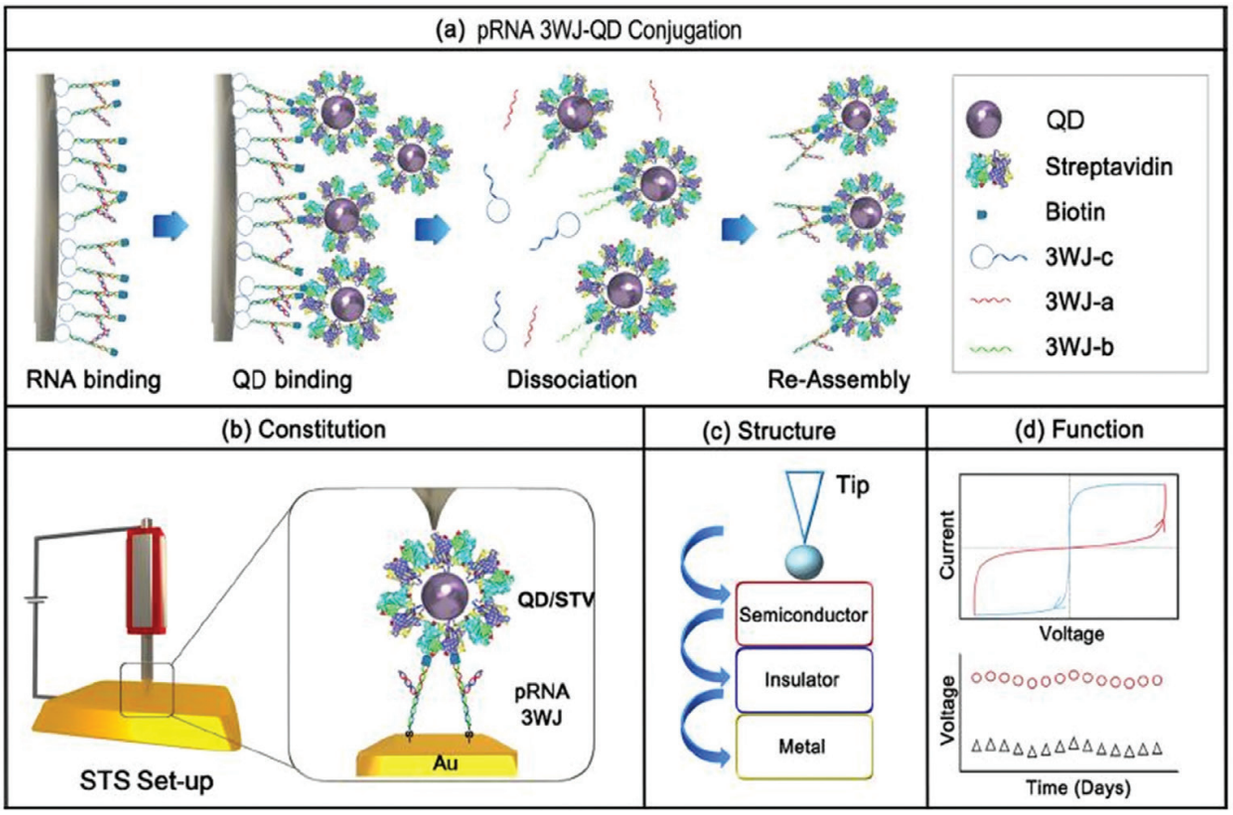

Figure 4. Schematic diagram of the experimental design method for the QD/STVQD/STV/Bio-3WJ chimera nanoparticle (a) site-specification, (b) constitution, (c) expected structure, and (d) function. Adapted with permission from Ref. [96].

method for the QD/STVQD/STV/Bio-3WJ chimera nanoparticle is given in **Figure 4**. RNA bioelectronics can lead to bio computer devices; as information storage devices, logic gates, field effect transistors and computation systems. An autonomous bio molecular system has been suggested to logically regulate the gene system. The system has been used for prostate cancer state detection. The basic diagnostic rule is that if the specific gene related to prostate cancer is over expressed, then ssDNA bind to their mRNA and exhibits the protein synthesis. The logical output is the release of ssDNA with modulation of gene expression, defined by the two states "positive and negative" [12]. An RNAi logical evaluator has also been used to perform Boolean operations for human kidney cells [47] and intracellular device in single mammalian cell.

3. Role of DFT in RNA nanotechnology

The RNA junction database [53], NanoTiler [54], RNA2D3D algorithms [55], RNA dynamics [56, 57] are used to build RNA nanoparticles that incorporate individual RNA motifs to defined user specifications. The energy landscape perspective of bio molecular dynamics provides a quantitative framework to consistently integrate theoretical concepts and experimental observations. Recognizing the potential of this approach, there has been decades of investigation

into the character of protein folding landscapes and now the recent developments occur in the field of bionics. At theoretical level, the objective is to construct appropriate potential energy functions in order to explore the thermodynamic and kinetic behavior of the system. The discrete path sampling (DPS) procedure [58, 59] was employed to explore the energy landscape of the DNA G-quadruplex by HiRE-RNA force field. In order to fold proteins on physiological timescales, the energy landscape associated with folding should possess only small traps, relative to the energetic gap between the folded and unfolded ensembles. So, these landscapes should be minimally frustrated. These software's can demonstrate the biophysical and biochemical activities and also able to answer the complex analytical questions. The designed hybrid systems as (RNA–RNA, RNA–DNA, RNA–PS DNA etc.) are optimized and the reaction pathways, triggering and charge transfer mechanism can be carried out by DFT and TDDFT methods. NUPACK program [60] is used to calculate the thermodynamic analysis of inputs. Generally, three different theories can be used to analyze the results: density functional theory (DFT), and moving on to many-electron GW [61] methods as well as GW-inspired DFT + Σ [62] calculations. Further complex band structure (CBS) calculations are used to estimate the tunneling decay constant Σ, and Landauer-Buttiker transport calculations are used to compute the transmission spectra directly. Various effects such as device contact geometry, metal/molecule interfaces, molecular anchoring and side groups, inelastic effects, molecular conformation, and stochastic fluctuations are responsible for the results. So the parameters related to these effects are also taken into account. It is anticipated that the lowest conductance histogram peak correspond to single molecular junctions, while higher conductance peaks are attributed to junctions having multiple molecules linking the gold electrodes.

Electron transport mechanisms can be categorized as: coherent tunneling and incoherent hopping [63]. Along with these parameters, thermal transport and thermoelectric properties are also important [64, 65]. The transport properties estimated by GW formalism are calculated in previous studies [66, 67]. The transmission is based on two parameters Seebeck coefficient and thermo-electric figure of merit; and is very sensitive to energy and k-resolution of the calculations. The DFT + Σ method is considered to be more appropriate method to calculate the conductance, but is only applicable to system with small polarizability of molecule and broadened resonance [68, 69]. Another promising method time dependent density functional theory (TDDFT) is used to measure the wavelengths (absorption and emission) for fluorescence, and time dependent current-density functional theory (TDCDFT) for the measurement of the current–voltage characteristics. The conductance of systems is analyzed with the help of dynamical exchange−correlation correction [70–72]. The software tools TranSIESTA [73] and SMEAGOL [74] are used to calculate the electron transmission spectrum using the non-equilibrium Green's function (NEGF) method and SCARLET [75, 76] for the scattering-state method.

The complex band structure calculations are used to investigate tunneling in DNA strands [77]. Further studies were carried out for pyridine-gold junctions, which show less variation in conductance values [78–80]. These studies can provide us useful insights for the RNA-Au junctions also.

Single-molecular junctions are also the potential candidates for thermoelectric applications due to large phonon mode mismatch at the metal molecular interface and tunable electronic

conductance properties [81–83]. The thermopower S, a derivative of the electron transmission at the Fermi level E_F, and proportional to the logarithmic F is another important transport property which measures the charge carrier type and thermoelectric responses. The transport of electron spin in molecular wires, and the effects of solvent properties can also studied using DFT [84–86] and DFT + Σ [87] calculations. Few calculations have also been carried out on the charge transfer in short duplexes DNA/DNA and DNA/RNA with virtually equivalent sequences [84–86]. G09 [88] and Turbomole [89] software's can been used to carried out the calculations using the implicit water solving model (COSMO) (the Conductor like screening model) [90] or PCM (polarizable continuum model) [91]. The DFT method can also be used to study the charge transfer mechanisms, delocalization nature of orbitals, base stacking, electronic coupling and conformational flexibility. Tersoff potential is preferred for carbon nanotubes-nucleotides-metal cluster interactions [92].

4. Conclusion

Scientists have demonstrated how living cells can be induced to carry out computations in the form of tiny robots or computers. Synthetic gene networks have been used to construct a wide range of biological devices, including molecular counters, oscillators, toggle switches, logic gates, cell classifiers and analog signal processors [93–95]. On a long-term scale, we believe that merging the research activities with a focus on the RNA as crucial molecular machinery for the cell will provide unprecedented insights into central molecular aspects of the RNA function and dynamics, ultimately enabling us to generate an integrated view of the molecular picture of the processes tuned by the RNA nanoparticles. Many natural limitations to the engineering of biological computers still remain. How do we eliminate or reduce noise in nucleic-acid based computing? An increase in the number of elements in RNA- and DNA-based logic operations is accompanied by a drastic increase in noise [96, 97]. The common approaches for noise reduction may include following: (i) better optimization of individual logic gates, (ii) utilization of network topology [98, 99] and (iii) for even larger networks, the introduction of new network elements to suppress the redundancy of the elements, thereby improving the signal-to-noise ratio. Also, the biochemical reaction time is also a critical aspect in working with a scalable circuit, which needs to be solved. With continued technological advances, it is now time to establish the rigorous physical and chemical understanding of RNA dynamics. Using the theoretical infrastructure developed in the context of protein folding, the field is positioned to extend the application of energy landscape techniques to the study of the large assemblies. Through close integration of computation and experimentation, it will be possible to dissect the complex interplay of structure and energetics during RNA function. We anticipate that such endeavors may ultimately reveal physical principles that govern biological dynamics. Finally we have a long way to go to understand nano-molecular computers in sufficient detail to be able to "reverse engineer" an existing molecular computer or design a relatively new one.

RS acknowledges the financial assistance by the DST WOS-A (SR/WOS-A/CS-69/2018). RS is also thankful to her mentor Dr. Shrish Tiwari, Bioinformatics Department, CSIR-Centre for Cellular and Molecular Biology, Hyderabad for the support.

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References

[1] Shu D, Moll WD, Deng Z, Mao C, Guo P. Bottom-up assembly of RNA arrays and superstructures as potential parts in nanotechnology. Nano Letters. 2004;**4**:1717-1723. DOI: 10.1021/nl0494497

[2] Shu Y, Cinier M, Shu D, Guo P. Assembly of multifunctional φ29 pRNA nanoparticles for specific delivery of siRNA and other therapeutics to targeted cells. Methods. 2011;**54**:204-214. DOI: 10.1016/j.ymeth.2011.01.008

[3] Zhang F, Lemieux S, Wu X, St.-Arnaud S, McMurray CT, et al. Function of hexameric RNA in packaging of bacteriophage φ29 DNA in vitro. Molecular Cell. 1998;**2**:141-147. DOI: 10.1016/S1097-2765(00)80123-9

[4] Hendrix RW. Bacteriophage DNA packaging: RNA gears in a DNA transport machine (minireview). Cell. 1998;**94**:147-150. DOI: 10.1016/S0092-8674(00)81413-0

[5] Acker H. Mechanisms and meaning of cellular oxygen sensing in the organism. Respiration Physiology. 1994;**95**:1-10

[6] Daly K, Darby AC, Hall N, Wilkinson MC, Pongchaikul P, Bravo D, et al. Bacterial sensing underlies artificial sweetener-induced growth of gut lactobacillus. Environmental Microbiology. 2015;**18**(7):2159-2171. DOI: 10.1111/1462-2920.12942

[7] Green J, Paget MS. Bacterial redox sensors. Nature Reviews. Microbiology. 2004;**2**:954-966. DOI: 10.1038/nrmicro1022

[8] Green AA, Kim J, Ma D, Silver PA, Collins JJ, Yin P. Complex cellular logic computation using ribocomputing devices. 2017;**548**:117-133. DOI: 10.1038/nature23271

[9] Green AA, Silver PA, Collins JJ, Yin P. Toehold switches: De-novo designed regulators of gene expression. Cell. 2014;**159**:925-939. DOI: 10.1016/j.cell.2014.10.002

[10] Livstone MS, van Noort D, Landweber LF. Molecular computing revisited: A Moore's law? Trends in Biotechnology. 2003;**21**:98-101. DOI: 10.1016/S0167-7799(03)00005-2

[11] Keyes RW. Physical limits of silicon transistors and circuits. Reports on Progress in Physics. 2005;**68**:2701-2746. DOI: 10.1088/0034-4885/68/12/R01

[12] Benenson Y, Gil B, Ben-Dor U, Adar R, Shapiro E. An autonomous molecular computer for logical control of gene expression. Nature. 2004;**429**:423-429. DOI: 10.1038/nature02551

[13] Gil B, Kahan-Hanum M, Skirtenko N, Adar R, Shapiro E. Detection of multiple disease indicators by an autonomous biomolecular computer. Nano Letters. 2011;**11**:2989-2996. DOI: 10.1021/nl2015872

[14] Lewandoski M. Conditional control of gene expression in the mouse. Nature Reviews. Genetics. 2001;**2**:743-755. DOI: 10.1111/j.1600-6143.2006.01685.x

[15] Wang B, Barahona M, Buck M. A modular cell-based biosensor using engineered genetic logic circuits to detect and integrate multiple environmental signals. Biosensors & Bioelectronics. 2013;**40**:368-376. DOI: 10.1016/j.bios.2012.08.011

[16] Peter IS, Faure E, Davidson EH. Predictive computation of genomic logic processing functions in embryonic development. Proceedings of the National Academy of Sciences. 2012;**109**:16434-16442. DOI: 10.1016/j.cub.2008.02.061

[17] Khademhosseini A, Langer R, Borenstein J, Vacanti JP. Microscale technologies for tissue engineering and biology. Proceedings of the National Academy of Sciences of the United States of America. 2006;**103**:2480-2487. DOI: 10.1073/pnas.0507681102

[18] Morelli AE, Thomson AW. Tolerogenic dendritic cells and the quest for transplant tolerance. Nature Reviews. Immunology. 2007;**7**:610-621. DOI: https://doi.org/10.1159/000346507

[19] Adleman LM. Molecular computation of solutions to combinatorial problems. Science. 1994;**266**:1021-1024. DOI: 10.1126/science.7973651

[20] Wang K, Tang Z, Yang CJ, Kim Y, Fang X, Li W, et al. Molecular engineering of DNA: Molecular beacons. Angewandte Chemie (International Edition in English). 2009;**48**:856-870. DOI: 10.1002/anie.200800370

[21] Cornett EM, Campbell EA, Gulenay G, Peterson E, Bhaskar N, Kolpashchikov DM. Molecular logic gates for DNA analysis: Detection of rifampin resistance in *M. tuberculosis* DNA. Angewandte Chemie (International Edition in English). 2012;**51**:9075-9077. DOI: 10.1002/anie.201203708

[22] Ogawa A, Susaki Y. Multiple-input and visible-output logic gates using signal-converting DNA machines and gold nanoparticle aggregation. Organic & Biomolecular Chemistry. 2013;**11**:3272-3276. DOI: 10.1039/C3OB40313K

[23] Okamoto A, Tanaka K, Saito I. DNA logic gates. Journal of the American Chemical Society. 2004;**126**:9458-9463. DOI: 10.1021/ja047628k

[24] Penchovsky R. Engineering integrated digital circuits with allosteric ribozymes for scaling up molecular computation and diagnostics. ACS Synthetic Biology. 2012;**1**:471-482. DOI: 10.1021/sb300053s

[25] Zhang C, Yang J, Xu J. Circular DNA logic gates with strand displacement. Langmuir. 2010;**26**:1416-1419. DOI: 10.1021/la903137f

[26] Qian L, Winfree E. Scaling up digital circuit computation with DNA strand displacement cascades. Science. 2011;**332**:1196-1201. DOI: 10.1126/science.1200520

[27] Weitz M, Kim J, Kapsner K, Winfree E, Franco E, Simmel FC. Diversity in the dynamical behaviour of a compartmentalized programmable biochemical oscillator. Nature Chemistry. 2014;**6**:295-302. DOI: 10.1038/nchem.1869

[28] Winfree E. Algorithmic self-assembly of DNA: Theoretical motivations and 2D assembly experiments. Journal of Biomolecular Structure & Dynamics. 2000;**17**(1):263-270. DOI: 10.1080/07391102.2000.10506630

[29] Barish RD, Rothemund PW, Winfree E. Two computational primitives for algorithmic self-assembly: Copying and counting. Nano Letters. 2005;**5**:2586-2592. DOI: 10.1021/nl0520381

[30] Ajo-Franklin CM, Drubin DA, Eskin JA, Gee EP, Landgraf D, Phillips I, et al. Rational design of memory in eukaryotic cells. Genes & Development. 2007;**21**:2271-7226. DOI: 10.1101/gad.1586107

[31] Goldman N, Bertone P, Chen S, Dessimoz C, LeProust EM, Sipos B, et al. Towards practical, high-capacity, low-maintenance information storage in synthesized DNA. Nature. 2013;**494**:77-80. DOI: 10.1038/nature11875

[32] Aghebat Rafat A, Pirzer T, Scheible MB, Kostina A, Simmel FC. Surface-assisted large-scale ordering of DNA origami tiles. Angewandte Chemie (International Edition in English). 2014;**53**:7665-7668. DOI: 10.1002/anie.201403965

[33] Wei B, Dai M, Yin P. Complex shapes self-assembled from single-stranded DNA tiles. Nature. 2012;**485**:623-626. DOI: 10.1038/nature11075

[34] Wei B, Vhudzijena MK, Robaszewski J, Yin P. Self-assembly of complex two-dimensional shapes from single-stranded DNA tiles. Journal of Visualized Experiments. 8 May 2015;**99**:e52486. DOI: 10.3791/52486

[35] Srivastava R. Nucleobase pairs—(M_2 clusters and M_2^{2+} cluster ions (M = Ag, Au, Cu) interaction: A DFT and TDDFT Study. Submitted to Scientific Reports

[36] Guo P. The emerging field of RNA nanotechnology. Nature Nanotechnology. 2010;**5**: 833-842. DOI: 10.1038/nnano.2010.231

[37] Guo P. RNA nanotechnology: Methods for synthesis, conjugation, assembly and application of RNA nanoparticles. Methods. 2011;**54**:201-203. DOI: 10.1021/nn200989r

[38] Qiu M, Khisamutdinov E, Zhao Z, Pan C, Choi JW, Leontis NB, et al. RNA nanotechnology for computer design and in vivo computation. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering. 2013;**371**:20120310. DOI: 10.1098/rsta.2012.0310

[39] Grabow WW, Jaeger L. RNA self-assembly and RNA nanotechnology. Accounts of Chemical Research. 2014;**47**:1871-1880. DOI: 10.1021/ar500076k

[40] Afonin KA, Grabow WW, Walker FM, Bindewald E, Dobrovolskaia MA, Shapiro BA, et al. Design and self-assembly of siRNAfunctionalized RNA nanoparticles for use in automated nanomedicine. Nature Protocols. 2011;**6**:2022-2034. DOI: 10.1038/nprot.2011.418

[41] Afonin KA, Bindewald E, Yaghoubian AJ, Voss N, Jacovetty E, Shapiro BA, et al. In vitro assembly of cubic RNA-based scaffolds designed in silico. Nature Nanotechnology. 2010;**5**:676-682. DOI: 10.1038/nnano.2010.160

[42] Khisamutdinov EF, Bui MN, Jasinski D, Zhao Z, Cui Z, Guo P. Simple method for constructing RNA triangle, square, pentagon by tuning interior RNA 3WJ angle from 60 degrees to 90 degrees or 108 degrees. Methods in Molecular Biology. 2015;**1316**:181-193. DOI: 10.1007/978-1-4939-2730-2

[43] Jasinski D, Haque F, Binzel DW, Guo P. Advancement of the emerging field of RNA nanotechnology. ACS Nano. 2017;**11**:1142-1164. DOI: 10.1021/acsnano.6b05737

[44] Zegans ME, Wagner JC, Cady KC, Murphy DM, Hammond JH, O'Toole GA. Interaction between bacteriophage DMS3 and host CRISPR region inhibits group behaviors of *Pseudomonas aeruginosa*. Journal of Bacteriology. 2009;**191**:210-219. DOI: 10.1128/JB.00797-08

[45] De Silva AP. Molecular computation: Molecular logic gets loaded. Nature Materials. 2005;**4**:15-16. DOI: 10.1038/nmat1301

[46] Miyoshi D, Inoue M, Sugimoto N. DNA logic gates based on structural polymorphism of telomere DNA molecules responding to chemical input signals. Angewandte Chemie (International Edition in English). 2006;**45**:7716-7719. DOI: 10.1002/anie.200602404

[47] Rinaudo K, Bleris L, Maddamsetti R, Subramanian S, Weiss R, et al. A universal RNAi-based logic evaluator that operates in mammalian cells. Nature Biotechnology. 2007;**25**:795-801. DOI: 10.1038/srep00641

[48] Breaker RR. Engineered allosteric ribozymes as biosensor components. Current Opinion in Biotechnology. 2002;**13**:31-39. DOI: 10.1016/S0014-5793(03)01160-8

[49] Suess B, Weigand JE. Engineered riboswitches: Overview, problems and trends. RNA Biology. 2008;**5**:24-29. DOI: 10.4161/rna.5.1.5955

[50] Auslander S, Auslander D, Muller M, Wieland M, Fussenegger M. Programmable single-cell mammalian biocomputers. Nature. 2012;**487**:123-127. DOI: 10.1038/nature11149

[51] Lou C, Liu X, Ni M, Huang Y, Huang Q, et al. Synthesizing a novel genetic sequential logic circuit: A push-on push-off switch. Molecular Systems Biology. 2010;**6**:350. DOI: 10.1038/msb.2010.2

[52] Xie Z, Wroblewska L, Prochazka L, Weiss R, Benenson Y. Multiinput RNAi-based logic circuit for identification of specific cancer cells. Science. 2011;**333**:1307-1311. DOI: 10.1126/science.1205527

[53] Bindewald E, Grunewald C, Boyle B, O'Connor M, Shapiro BA. Computational strategies for the automated design of RNA nanoscale structures from building blocks using NanoTiler. Journal of Molecular Graphics & Modelling. 2008;**27**:299-308. DOI: 10.1016/j.jmgm.2008.05.004

[54] Bindewald E, Hayes R, Yingling YG, Kasprzak W, Shapiro BA. RNA junction: A database of RNA junctions and kissing loops for three-dimensional structural analysis and nanodesign. Nucleic Acids Research. 2008;**36**:D392-D397. DOI: 10.1093/nar/gkm842

[55] Martinez HM, Maizel JV, Shapiro BA. 2008 RNA2D3D: A program for generating, viewing, and comparing 3-dimensional models of RNA. Journal of Biomolecular Structure & Dynamics. 2008;**25**:669-683. DOI: 10.1080/07391102.2008.10531240

[56] Kasprzak W, Bindewald E, Kim TJ, Jaeger L, Shapiro BA. Use of RNA structure flexibility data in nanostructure modeling. Methods. 2010;**54**:239-250. DOI: 10.1016/j.ymeth.2010.12.010

[57] Paliy M, Melnik R, Shapiro BA. Molecular dynamics study of the RNA ring nanostructure: A phenomenon of self-stabilization. Physical Biology. 2009;**6**:046003. DOI: 10.1088/14783975/6/4/046003

[58] Wales DJ. Discrete path sampling. Molecular Physics. 2002;**100**:3285-3305. DOI: 10.1080/00268970210162691

[59] Wales DJ. Some further applications of discrete path sampling to cluster isomerization. Molecular Physics. 2004;**102**:891-908. DOI: 10.1080/00268970410001703363

[60] Dirks RM, Bois JS, Schaeffer JM, Winfree E, Pierce NA. Thermodynamic analysis of interacting nucleic acid strands. SIAM Review. 2007;**49**:65-88. DOI: 10.1137/060651100

[61] Hedin L. New method for calculating 1-particle greens function with application to electron-gas problem. Physical Review. 1965;**139**(3A):A796-A823. DOI: 10.1103/PhysRev.139.A796

[62] Quek SY et al. Length dependence of conductance in aromatic single-molecule junctions. Nano Letters. 2009;**9**(11):3949-3953. DOI: 10.1021/nl9021336

[63] Nozaki D et al. Disorder and dephasing effects on electron transport through conjugated molecular wires in molecular junctions. Physical Review B. 2012;**85**(15):155327. DOI: 10.1103/PhysRevB.85.155327

[64] Aradhya SV, Venkataraman L. Single-molecule junctions beyond electronic transport. Nature Nanotechnology. 2013;**8**(6):399-410. DOI: 10.1038/nnano.2013.91

[65] Lee W et al. Heat dissipation in atomic-scale junctions. Nature. 2013;**498**(7453):209-212. DOI: 10.1038/nature12183

[66] Strange M et al. Self-consistent GW calculations of electronic transport in thiol- and amine-linked molecular junctions. Physical Review B. 2011;**83**(11):115108. DOI: 10.1103/PhysRevB.83.115108

[67] Darancet P. et al. Ab initio GW electron-electron interaction effects in quantum transport. Physical Review B. 2007;**75**(7):075102. DOI:10.1103/PhysRevB.75.075102.

[68] Quek SY, Khoo KH. Predictive DFT-based approaches to charge and spin transport in single-molecule junctions and two-dimensional materials: Successes and challenges. Accounts of Chemical Research. 2016;**138**(24):7791-7795. DOI: 10.1021/ar4002526

[69] Rumetshofer M, Dorn G, Boeri L, Arrigoni E, Linden WV. First-principles molecular transport calculation for the benzenedithiolate molecule. New Journal of Physics. 2017;**19**:103007. DOI: 10.1088/1367-2630/aa8117

[70] Vignale G, Kohn W. Current-dependent exchange-correlation potential for dynamical linear response theory. Physical Review Letters. 1996;**77**(10):2037-2040. DOI: 10.1103/PhysRevLett.77.2037

[71] Sai N et al. Dynamical corrections to the DFT-LDA electron conductance in nanoscale systems. Physical Review Letters. 2005;**94**(18):186801. DOI: 10.1103/PhysRevLett.94.186810

[72] Kurth S, Stefanucci G. Dynamical correction to linear Kohn-Sham conductances from static density functional theory. Physical Review Letters. 2013;**111**(3):030601. DOI: 10.1103/PhysRevLett.111.030601

[73] Brandbyge M et al. Density-functional method for nonequilibrium electron transport. Physical Review B. 2002;**65**(16):165401. DOI: 10.1103/PhysRevB.65.165401

[74] Rocha AR et al. Spin and molecular electronics in atomically generated orbital landscapes. Physical Review B. 2006;**73**(8):085414. DOI: 10.1103/PhysRevB.73.085414

[75] Choi HJ, Cohen ML, Louie SG. First-principles scattering-state approach for nonlinear electrical transport in nanostructures. Physical Review B. 2007;**76**(15):155420. DOI: 10.1103/PhysRevB.76.155420

[76] Choi HJ, Ihm J. Ab initio pseudopotential method for the calculation of conductance in quantum wires. Physical Review B. 1999;**59**(3):2267-2275. DOI: 10.1103/PhysRevB.59.2267

[77] Wang H, Lewis JP, Sankey OF. Band-gap tunneling states in DNA. Physical Review Letters. 2004;**93**(1):016401. DOI: 10.1103/PhysRevLett.93.016401

[78] Venkataraman L et al. Single-molecule circuits with well-defined molecular conductance. Nano Letters. 2006;**6**(3):458-462. DOI: 10.1021/nl052373

[79] Quek SY et al. Mechanically controlled binary conductance switching of a singlemolecule junction. Nature Nanotechnology. 2009;**4**(4):230-234. DOI: 10.1038/nnano.2009.10

[80] Quek SY et al. Amine-gold linked single-molecule circuits: Experiment and theory. Nano Letters. 2007;**7**(11):3477-3482. DOI: 10.1021/nl072058i

[81] Wang RY, Segalman RA, Majumdar A. Room temperature thermal conductance of alkanedithiol self-assembled monolayers. Applied Physics Letters. 2006;**89**(17):173113. DOI: 10.1063/1.2358856

[82] Mahan GD, Sofo JO. The best thermoelectric. Proceedings of the National Academy of Sciences of the United States of America. 1996;**93**(15):7436-7439. DOI: 10.1073/pnas.93.15.7436

[83] Humphrey TE, Linke H. Reversible thermoelectric nanomaterials. Physical Review Letters. 2005;**94**(9):096601. DOI: 10.1103/PhysRevLett.94.096601

[84] Pilevarshahri R et al. Spin transport in higher n-acene molecules. Physical Review B. 2011;**84**(17):174437. DOI: 10.1103/PhysRevB.84.174437

[85] Bhattacharya S, Akande A, Sanvito S. Spin transport properties of triarylamine-based nanowires. Chemical Communications. 2014;**50**(50):6626-6629. DOI: 10.1039/C4CC01710B

[86] Liang SH et al. Organic magnetic tunnel junctions: The role of metal-molecule interface. Physical Review B. 2012;**86**(22):224419. DOI: 10.1103/PhysRevB.86.224419

[87] Gorjizadeh N, Quek SY. Interface effects on tunneling magnetoresistance in organic spintronics with flexible amine-Au links. Nanotechnology. 2013;**24**(41):415201. DOI: 10.1088/0957-4484/24/41/415201

[88] Frisch MJ et al. Wallingford CT: Gaussian, Inc.; 2009. (Software)

[89] Furche F, Ahlrichs R, Hättig C, Klopper W, Sierka M, Weigend F. Turbomole. WIREs Computational Molecular Science. 2014;**4**:91-100. DOI: 10.1002/wcms.1162

[90] Klamt A, Schüürmann G. COSMO: A new approach to dielectric screening in solvents with explicit expressions for the screening energy and its gradient. Journal of the Chemical Society, Perkin Transactions. 1993;**2**(5):799-805. DOI: 10.1039/P29930000799

[91] Tomasi J, Mennucci B, Cammi R. Quantum mechanical continuum solvation models. Chemical Reviews;**105**(8):2999-3094. DOI: 10.1021/cr9904009

[92] Srivastava R. Chapter 13. Novel Optoelectronic devices. 2017. DOI: 10.5772/67527. ISBN: 978-953-51-5219-4

[93] Jasinski D, Khisamutdinov EF, Lyubchenko YL, Guo P. Physicochemically tunable polyfunctionalized RNA Square architecture with fluorogenic and ribozymatic properties. ACS Nano. 2014;**8**:7620-7629. DOI: 10.1021/nn502160s

[94] Khisamutdinov EF, Jasinski DL, Li H, Zhang K, Chiu W, Guo P. Fabrication of RNA 3D nanoprisms for loading and protection of small RNAs and model drugs. Advanced Materials. 2016;**28**(45):10079-10087. DOI: 10.1002/adma.201603180

[95] Lee L, Yagati AK, Pi F, Sharma A, Choi JW, Guo P. Construction of RNAi quantum dot chimera for nanoscale resistive biomemory application. ACS Nano. 2015;**9**(7):6675-6682. DOI: 10.1021/acsnano.5b03269

[96] Li H, Zhang K, Pi F, Guo S, Shlyakhtenko L, Chiu W, et al. Controllable self-assembly of RNA tetrahedrons with precise shape and size for cancer targeting. Advanced Materials. 2016;**28**(34):7501-7507. DOI: 10.1002/adma.201601976

[97] Fedichkin L, Katz E, Privman V. Error correction and digitalization concepts in biochemical computing. Journal of Computational and Theoretical Nanoscience. 2008;**5**:36-43. DOI: 10.1166/jctn.2008.004

[98] Privman V, Arugula MA, Halamek J, Pita M, Katz E. Network analysis of biochemical logic for noise reduction and stability: A system of three coupled enzymatic and gates. The Journal of Physical Chemistry. B. 2009;**113**:5301-5310. DOI: 10.1021/jp810743w

[99] Privman V, Strack G, Solenov D, Pita M, Katz E. Optimization of enzymatic biochemical logic for noise reduction and scalability: How many biocomputing gates can be interconnected in a circuit? The Journal of Physical Chemistry. B. 2008;**112**:11777-11784. DOI: 10.1021/jp802673q