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Editorial

Scientific advances in complex systems of biophysical interest

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In recent years, in the study of systems of biophysical interest, complex system approaches are assuming greater and greater importance. Such systems are composed by many elements that interact each other through non-linear relationships with cooperative phenomena, emerging properties, feedback loops that make the evolution of the system behavior determination over the time a complex task. In fact, due to the interactions, the entire system behaviour cannot be simply determined starting from the behaviour of the constituent components. In this framework biophysical systems are to be considered, for excellence, complex systems. The aim of this Special Issue is to collect new experimental and theoretical findings together with advanced methodologies and approaches for investigating the structural and dynamical properties systems of biophysical interest.

In charge of Guest Editors, we are honoured to present 11 paper that represent remarkable additions to the research literature.

More specifically, the paper entitled “Endoplasmic reticulum localization of phosphoinositide specific phospholipase C enzymes in U73122 cultured human osteoblasts” by Matteo Corradini, Marta Checchi, Marzia Ferretti, Francesco Cavani, Carla Palumbo and Vincenza Rita Lo Vasco highlights how different PLC enzymes were demonstrated to be involved in the differentiation of osteoblasts and differently localize in the nucleus, cytoplasm or both depending on the isoform. In particular, the amino-steroid molecule U-73122 inhibits the enzymes belonging to the PLC family and promotes off-target effects. In order to evaluate possible off-target effects of the molecule in human osteoblasts, the Authors investigated the expression of *PLC* genes and the localization of PLC enzymes in cultured human osteoblasts (hOBs) in the presence of low dose U-73122. The obtained results confirm that all *PLC* genes are transcribed in hOBs except for PLC δ3 in quiescent hOBs at seeding. Confirming literature data excluding toxicity of U-73122 on cell survival, the results also indicate that U-73122 did not significantly affect the transcription of *PLC* genes. It acts upon the localization of PLC enzymes,

as PLC enzymes are detected in cell protrusions or pseudopodia-like structures, at the nuclear or the plasma membrane, in membrane ruffles and/or in the endoplasmic reticulum [1].

The review paper entitled "A review of molecular biology detection methods for human adenovirus" by Neelabh Datta highlights how in humans particularly in children, adenovirus is one of the most common viruses that cause respiratory illnesses. The author points out how rapid detection of antiviral antibodies or viral antigens in clinical samples can be achieved by molecular diagnostic techniques like PCR, Real-Time PCR, LAMP, mPCR-RLB, PCR-ELISA, Tem-PCR, Gene Chip, and so on. Some of the molecular diagnostic methods are relatively economical, exceedingly sensitive and explicit. There are several commercially accessible molecular diagnostic techniques that enable their use in clinical laboratories all over the world. In this contribution, the principles, characteristics, and applications of molecular biology surveillance methods commonly used in labs and clinics for the detection of human adenoviruses are examined and highlighted [2].

Thee review paper entitled "Improvement in growth of plants under the effect of magnetized water" by Etimad Alattar, Eqbal Radwan and Khitam Elwasife highlights how the magnetic field can change the polarity characteristics and hydrogen-bond structure of water; therefore, magnetized water can affect plant growth and development. Magnetized water is hexagonal water created by passing water through a specific magnet that can activate and ionize water molecules to change its structure. This review highlights the use of magnetized water in the agricultural sector to enhance plant growth and food productivity. The authors discuss the impact of magnetized water on seed germination, vegetative growth, fruit production, soil and pigments of treated plants. Plant growth and development can be improved both qualitatively and quantitatively via irrigation with magnetized water. It can promote seed germination, seedling early vegetative development, improvement of the mineral content of fruits and seeds, the enzyme activity of the soil, improved water use efficiency, higher nutrient content, and better transformation and consumption efficiency of nutrients; it can also mitigate soil salinity. Furthermore, magnetized water had a substantial good influence on the mobility and uptake of micronutrient concentrations. Also, irrigating plants with magnetized water resulted in a considerable increase in chloroplast pigments and photosynthetic activity. Magnetizing low-quality water can be considered as an alternative tool to overcome the problem of scarcity and shortage of water resources. As a result, magnetic treatment of irrigation water could be a promising technique to boost agricultural production while also being environmentally beneficial in the future [3].

The paper titled "Natural bond orbital analysis of dication magnesium complexes $[Mg(H_2O)_6]^{2+}$ and $[[Mg(H_2O)_6](H_2O)_n]^{2+}$; n=1-4, by Ganesh Prasad Tiwari, Santosh Adhikari, Hari Prasad Lamichhane and Dinesh Kumar Chaudhary highlights how the metal ion is ubiquitous in the human body and is essential to biochemical reactions. The study of the metal ion complexes and their charge transfer nature is fruitful for drug design and may be beneficial for the extension of the field. In this regard, investigations into charge transport properties from ligands to metal ion complexes and their stability are crucial in the medical field. In their work, the DFT technique has been applied to analyze the delocalization of electrons from the water ligands to a core metal ion. At the B3LYP level of approximation, natural bond orbital (NBO) analysis was performed for the first five distinct complexes $[Mg(H_2O)_6]^{2+}$ and $[[Mg(H_2O)_6](H_2O)n]^{2+}$; n = 1-4. These complexes were optimized and examined with the higher basis set 6-311++G(d, p). In the complex $[Mg(H_2O)_6]^{2+}$, the amount of natural charge transport from ligands towards the metal ion was 0.179e, and the greatest stabilization energy was observed to be 22.67 kcal/mol. The donation of the p orbitals in the hybrid orbitals was increased while approaching the oxygen atoms of H_2O ligands in the 1st coordination sphere with the magnesium ions.

The presence of water ligands within the 2nd coordination sphere increased natural charge transfer and decreased the stabilizing energy of the complexes. This finding may be due to the ligand-metal interactions [4].

The paper entitled "Effect of Rs5746136 genotypes on SOD activity and biomarkers levels in breast cancer patients" by Hadi Sajid Abdulabbas and Yasir Haider Al-Mawlah highlights how Oxidative stress factors are among the most common carcinogens, Superoxide dismutase enzyme-2 (SOD2) is an endogenous antioxidant involved in the scavenging of superoxide anions. The Authors study aimed to investigate the effect of the SOD2 gene polymorphism (rs5746136) on SOD activity and biomarker levels in breast cancer patients. This study aimed to investigate the effect of SOD2 gene (rs5746136) polymorphisms on SOD activity and biomarkers levels in breast cancer patients. The spectrophotometry methods were used to detect malondialdehyde (MDA) and Catalase (CAT), Superoxide dismutase (SOD), and Glutathione (GSH) levels, which reflect antioxidant capacity, and the genotypes of rs5746136 were detected utilize PCR and RFLP. According to the current findings, the GA genotype of the control group was the most common (70%), followed by GG and AA genotypes (26.7% and 3.3%) respectively. In the patient group, the most common genotype was GG (45.6%), followed by the GA genotype (42.8%) and then the AA genotype (11.4%) The frequency of heterozygous genotype G/A compared to the homozygous genotype (G/G) [OR = 0.3571, 95% CI = 0.1375–0.9277, P = 0.0345]. The AA genotype is significantly associated with an increased risk of developing BC [OR = 2.00, p = 0.5403, CI: 0.2175–18.3883]. No significant differences were found in frequencies of the A allele between patients and control groups [OR = 0.7872, 95% CI = 0.4198–1.4762, P = 0.4558]. In addition, there are modest (P 0.05) relationships between serum biochemical parameters levels and rs5746136 genotype in breast cancer patients, but a substantial association between serum SOD activity and GSH concentration and GA and GG rs5746136 genotype in the control group. In conclusion, the current investigation suggests that the AA genotype of (rs5746136) in the MnSOD gene may be associated with an increased risk of breast cancer. The chosen SOD2 variants (rs5746136) play a crucial role in controlling the activity of the SOD enzyme [5].

The paper entitled "Screening revealed the strong cytotoxic activity of *Alchemilla smirnovii*and *Hypericum alpestre*ethanol extracts on different cancer cell lines" by Mikayel Ginovyan, Svetlana Hovhannisyan, Hayarpi Javrushyan, Gohar Sevoyan, Zaruhi Karabekian, Narine Zakaryan, Naira Sahakyan and Nikolay Avtandilyan highlights how compounds of plant origin are considered promising alternative approaches in the development of medicines for the prevention and treatment of cancer. The large diversity of herbal species still requires careful exploration as a source for new anticancer compounds. The goal of the study was to screen different herbal extracts traditionally used in Armenian folk medicine for their cytotoxic effect against some cancer cell lines, and to find the prospective plant species among them. The cytotoxicity of the plant ethanol extracts was evaluated with MTT test against HeLa (human cervical carcinoma) and A549 (human lung adenocarcinoma) cells. Antioxidant properties were assessed with DPPH free radical scavenging assay. Five of the tested ten herbal extracts exhibited significant growth-inhibiting activity on HeLa cells. Moreover, *Alchemilla smirnovii* and *Hypericum alpestre* extracts also showed potent cytotoxicity on human lung adenocarcinoma cells. These two plants possessed high antiradical activity as well. Their DPPH stoichiometric values were 0.4234 and 0.14437 respectively, meaning that 1 μg of plant extract brought the reduction of DPPH equal to the respective stoichiometric values in μg. Thus, *A. smirnovii* and *H. alpestre* extracts expressed themselves as potent cytotoxic and antioxidant agents and could have

promising anticancer potential. Further evaluation of their *in vivo* anticancer properties has much interest [6].

The paper entitled "Growth inhibition of cultured cancer cells by *Ribes nigrum* leaf extract" by Mikayel Ginovyan, Agnieszka Bartoszek, Izabela Koss-Mikołajczyk, Barbara Kusznierewicz, Pierre Andreoletti, Mustapha Cherkaoui-Malki and Naira Sahakyan includes data on the possible selective cytotoxic effect of extract of *Ribes nigrum* L. growing at high Armenian landscape. For this purpose, different non-cancer (microglial BV-2 wild type (*Wt*), acyl-CoA oxidase 1 (ACOX1) deficient (*Acox1-/-*) and cancer (human colon adenocarcinoma HT29 and human breast cancer MCF7) cell lines were applied. *R. nigrum* leaf ethanol extract showed a growth inhibition effect towards HT29 and MCF7 cells started from 6 h of treatment at the concentration of 0.5 mg/mL DW. The lowest concentration (0.125 mg/mL DW) of the investigated extract expressed cytotoxicity after 72 hours following cancer cell treatment. In contrast to the cancer cells, in the case of the tested non-cancer cells, cytotoxic effect was not observed at the applied concentrations. The extract sub-cytotoxic concentration, in this case, was reported to be the 1 mg/mL DW. Further investigations are needed to confirm the selective cytotoxicity and possible action mechanisms of the leaf extract of *R. nigrum* [7].

The paper entitled "Encapsulation of flavours into *Yarrowia lipolytica* active yeast cells. Fluorescence study of the lipid droplets morphology and steryl/sterol balance during the shock" by Thi Minh Ngoc Ta Cynthia Romero-Guido, Thi Hanh Phan, Hai Dang Tran, Hanh Tam Dinh and Yves Waché highligths how yeast are a powerful material for the encapsulation of compounds. Usually, yeast used as capsules are inactivated by the encapsulation treatment, which is stressful to cells. However, if kept active, cells can bring their own activity in addition to the encapsulated compound. The Authors have observed previously that lipid-grown *Yarrowia lipolytica* were more resistant to encapsulation. The objective of the present study was to identify physiological markers involved in this resistance. This paper focuses on the role of intracellular lipid droplets (LDs) and of the ergosteryl content to protect cells during the lactone treatment. Lipid-grown cells were more resistant to lactone and the presence of LDs before the shock increased significantly the resistance. The ergosteryl esters from the LD pool were hydrolysed to release ergosterol able to strenghten the plasma membrane during the shock. For cells devoid of LDs, membrane ergosterols were esterified concomitantly with LDs growth, resulting in a membrane weakening. By using *pox3*-mutant strains, 258 which possesses numerous and small-sized LDs, the Authors observed the original behaviour: these mutants showed no increased resistance and their LDs exploded in the cytoplasma during the shock. These results point out the role of LDs in cell resistance to amphiphilic stresses as a storage compartment as well as in ergosterol homeostasis [8].

The paper entitled "Efficiency of GrowDex® nanofibrillar cellulosichydrogel when generating homotypic and heterotypic 3D tumor spheroids"by Perumalsamy Balaji, Anbazhagan Murugadas Lauri Paasonen, Sellathamby Shanmugaapriya and Mohammad A. Akbarsha highligths how in recent times, homotypic and heterotypic 3D tumor spheroid (HTS) models have been receiving increasing attention and come to be widely employed in preclinical studies. The present study is focused on the generation of homotypic (A549 and MDA-MB-231, separately) and heterotypic (A549 + NIH/3T3; MDA-MB-231 + NIH/3T3) 3D tumor spheroids by using GrowDex® nanofibrillar cellulosic (NFC) hydrogel as the scaffold. Light microscopic observations and F-actin staining confirmed the formation of spheroids. The proliferation efficiency indicated an expansion of cell population and an increase in spheroid size over time. The distribution, interaction pattern and influence of fibroblasts on the epithelial cell types were observed in terms of the size and shape of the HTS against homo-spheroids.

An interesting observation was that, with an increase in the size of HTSs, many more fibroblast cells were found to occupy the core region, which, perhaps, was due to the faster growth of tumor cells over normal cells. Thus, normal and tumor cells, especially with origins from two different species, can be cultured together in 3D format, and this can potentially enhance our knowledge of tumor microenvironments and cell-cell interaction. These spheroids could 222 be used to improve microphysiological systems for drug discovery and to better understand the tumor microenvironment [9].

The paper entitled "Regulation of gene expression in *Nicotiana tabacum* seedlings by the MKASAA peptide through DNA methylation via the RdDM pathway" by Larisa I. Fedoreyeva, Tatiana A. Dilovarova, Boris F. Vanyushin, Inna A. Chaban and Neonila V. Kononenko highlighs how DNA methylation is involved in the protection of the genome, the regulation of gene expression, splicing, and is associated with a serious reprogramming of plant development. Using fluorescence microscopy, it was shown that the MKASAA peptide penetrates through the root system of *Nicotiana tabacum* tobacco, mainly into the cap, meristem, and elongation zones. In the cell, the peptide is localized mainly on the nuclei. In tobacco seedlings grown in the presence of the peptide at a concentration of 10–7 M, an increase in the expression of DNA methyltransferases, especially DRM2, which methylates previously unmethylated DNA sites, is observed. In the presence of the peptide in the roots and leaves of tobacco, the level of global DNA methylation increases. An increase in DNA methylation occurs via the RdDM pathway. Presumably, the peptide binds to siRNAs, forming giant particles that remodulate chromatin and facilitate the entry of DNA methyltransferases. An increase in the level of DNA methylation is accompanied by silencing of the genes of the *GRF*, *KNOX*, and *EXP* families. Suppression of gene expression of these families is accompanied by significant morphological changes in tobacco seedlings. Thus, the short exogenous MKASAA peptide is involved in global morphological and genetic changes in tobacco seedlings [10].

The paper entitled "Bubble mediated polymerization of RNA and DNA" by Roman Marks highlights how research dedicated to trace rotational motion of bubbles in saline water revealed that these may generate either single cationic or cationic/anionic motions, including spliced double helix flow. In all cases, the aggregated ionic flows propagate in spiraling as well as rotational manner. However, if bi-ionic or double helix motion is generated, the flow is oppositely directed and has opposite electric charges. Next, the assembled flow is forced to pirouette within the bubble vortex. During that processing the narrowing of spiraling flow takes place and result in increase of revolutions to even millions per second. As a result, a significant friction is induced between revolving ionic hydrates allowing continuous detachment of electrons from covalent atomic shells of electropositive elements. Then, free electrons may be attracted by electronegative elements that are dissolved in seawater. Afterwards, that negatively charged elements may undergo electrical condensation around cationic centers of revolutions. That explain a unique mechanism which operates when negatively charged phosphate compounds and pentagonal blocks found in RNA and DNA as ribose as well as pentagonal rings in nitrogenous bases A and G are being winded. The compensative anionic flow and revolutions may conduct winding of hexagonal blocks found in nitrogenous bases A, G and C, T or U. These assume to gather more positive charge needed to bridge negatively charged sugar molecules in nucleic acids. Thus, the continuity in generation of electronegative compounds and spiral manner of arranging them within the sub-bubble vortices should be regarded as a mechanism responsible for precise, rotational-electric polymerization of elongated macromolecules of RNA/DNA architecture. Reported research refers mainly to physical processes activated by rising bubbles thus should be confronted with other experimental methods used in genetics, microbiology and chemistry [11].

In conclusion, the present *Special Issue* furnishes a representative sampling of some findings that in the wide range of research under the general heading *Scientific advances in complex systems* of biophysical interest have recently attracted a lot of interest.

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