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Advances in Bulgarian Science



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PROTECTIVE EFFECT OF TYRPHOSTIN AG490, A SELECTIVE KINASE INHIBITOR, ON COLLAGANSE-INDUCED OSTEORTHRITIS

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Abstract. In this work results obtained in the first stage of the project B01/6 "Application of tyrosine kinase inhibitor tyrphostin AG490 in a model of collaganse-induced osteoarthritis" supported by the Fund of Scientific Investigations of the Ministry of Education and Science, Republic of Bulgaria have been presented.

The Janus kinase (Jak)-signal transducer and activator of transcription (STAT) cascade plays a principal role in the signaling of a vast array of cytokines and growth factors which stimulates diverse cellular functions and immune responses. The experiments were designed to evaluate the effects of Jak2 inhibitor, tyrphostin AG490 in collagenase-induced osteoarthritis (CIOA), a mouse model of chronic joint inflammation. CIOA was provoked by intraarticular (i.a.) injection of collagenase in mice and then intraperitoneally (i.p.) treated with different AG490 under schemes. Tyrphostin AG490 inhibited cartilage and bone erosion associated with decreased numbers of double positive CD11b+/Ly6G+ neutrophils and F4/ 80+ macrophages in the synovial fluid and with down-regulation of STAT3, pSTST3 and transforming growth factor (TGF)- β 3 expression in joints. The drug inhibited osteoclast generation in bone and the loss of glycosaminoglycans and proteoglycans.

Key words: tyrphostin AG490, collagenase-induced osteoarthritis; STAT3, TGF-β3, osteoclasts

INTRODUCTION

Tyrosine kinases play a central role in signal transduction through transfer of the terminal phosphate group of ATP to the tyrosine residues on protein substrates, resulting in activation of the substrate. Subsequently, STATs are activated and act as transcription factors [1, 2]. Protein tyrosine kinase inhibitors (PTKIs) are first investigated as anti-cancer agents and then broadly used in clinical trials [3]. Now, they have been evaluated in vari-

ous animal models of multiple sclerosis [4], intestinal inflammation [5], and septic shock [6]. Recently, over 20 drugs that target kinases have been introduced in medical practice and many are currently in preclinical studies [7]. Mitogen-activated protein kinases (MAPKs) and non-receptor tyrosine kinases such as spleen tyrosine kinase (Syk) and JAKs mediate the signaling and transcription of proinflammatory genes triggering the synthesis of many cytokines like interleukine (IL)-1, IL-2, IL-12 and interferons (IFNs) [8]. The in vitro studies revealed several mechanisms of their action, one of them being the inhibition of JAK2 pathway [9, 10] associated with the phosphorilation of STAT1 and STAT3 [11]. Through inhibition of tyrosine phosphorilation and thereby changing cell signaling tyrosine kinase inhibitors can influence multiple inflammatory pathways.

Osteoarthritis (OA) is a chronic joint disorder that requires long-term treatment. Although OA is not considered a classical inflammatory arthropathy because of the absence of marked systemic manifestations of inflammation, proinflammatory cytokines are involved in OA articular cartilage resorption [12,13]. The main characteristics of OA are cartilage degradation, synovial fibrosis, and formation of osteophytes as a response to excessive joint loading or impaired metabolic environment in OA joints. Frequently, osteophytes lead to deformation of the joint, compression of neighboring tissue and decrease of joint function [14]. Tyrphostins represent a novel class of protein kinase inhibitors (PTKIs) initially developed as antitumour agents [15]. Tyrphostin AG490 is a synthetic PTKI which exerts a potent suppressive activity to JAK2 and JAK3 by blocking the constitutive activation of JAK3/STAT, JAK3/AP-1, and JAK3/

MAPK pathways [16, 17]. Also, it is able to induce apoptosis, to suppress proliferation and block IL-6-induced JAK2, ERK2 and STAT3 expression [18].

The aim of the present study was to evaluate the effects of tyrphostin in chronic inflammation in mice, and to examine the mechanisms underlying these effects.

METHODS

Collagenase-induced osteoarthritis and treatment

Male ICR mice (CD-2) background (8-10 week old, weight 20-22 g) were bred in the Animal Facility of the Institute of Microbiology. Osteoarthritis was induced according to the method of Blom et al [19]. After anesthesia (sodium pentobarbital i.p. 50 mg/kg) mice received two i.a. injections (1 U per mice) of collagenase from Clostridium histolyticum (Sigma-Aldrich) at day -2 and 0. Tyrphostin AG490 (2-Cyano-3-dihyroxyphenyl) - N - (benzyl) - 2 - propenamide (Sigma-Aldrich) was dissolved in DMSO and further diluted in saline. One group of mice was treated with AG490 i.p. at a dose of 4 mg/kg for 10 days starting simultaneously with the second collagenase injection (scheme 1, Figure 1A) and one group was treated at a dose of 4 mg/kg for 10 days starting from day 7 (scheme 4, Figure 1A). Another group was treated with 4 mg/kg of AG490 at days 0, 5, and 10 (scheme 2, Figure 1A) and a group was treated with tyrphostin at a dose of 4 mg/kg at days 0, 5 and 10 and with 8 mg/kg at day 18 (scheme 3, Figure 1A). Group injected with PBS at days described in scheme 3 was designated as control.

Histological analyses

Sagital joint sections embedded

in paraffin (6 μ m thickness) were stained with hematoxyline and eosin (H&E), safranin O or toluidine blue. All histological assessments were performed in a blinded protocol. The degree of injury was graded according following characteristics: inflammation, cartilage loss and bone erosion. The 4 score system was used to evaluate each parameter (score 0 – no abnormality; score 4 – severe abnormalities).

Immunohistochemistry

The sections (6 µm) were permeabilized with 0.1% Triton X-100 in PBS for 20 min, washed with PBS and endogenous the peroxidase was blocked with 5% bovine serum albumin/PBS for 1 h at room temperature. After washing, the sections were incubated for 40 min with antibodies against STAT3 (S727, 10 µg/ml), pSTAT3 (S727, 10 µg/ml), and TGF-β3 (10 µg/ml), all from Abcam. Isotype antibodies (anti-mouse IgG or anti-rabbit IgG; Sigma-Aldrich) were used as a background staining control. After washing, the joint sections were incubated for 15 min with combined biotinvlated anti-mouse/anti-rabbit laGs (Abcam). Then streptavidin-peroxidase (1:100 diluted; Biolegend, UK) was added for 10 min. The sections were washed and incubated with DAB solution kit (3',3'diaminobenzididne kit, Abcam, Cambridge, UK) for 10 min and counterstained with Gill's hematoxylin.

Immunoblotting

Synovial fluid cells isolated from healthy or CIOA mice $(1x10^6/ml)$ were pretreated with tyrphostin AG490 (50 μ M) for 20 min at 370C. The ice-cold PBS containing 2 mM sodium orthovanadate was rapidly added to cells and then lysed with buffer containing 1% NP-40, 150 mM NaCl, 50 mmol/l Tris (pH 7.5), 1 mM EDTA, 1 mmol/l PMSF, 2 mM sodium orthovanadate, 1 mM NaF, 80 µmol/L leupeptin, 1 µg/ml aprotinin, 1 µg/ml pepstatin. Cell lysates (30 µg protein) in 2xSDS-PAGE buffer were loaded and separated on 10% SDS/PAGE gel. After transfer and blocking with 5% BSA/PBS buffer for 1h at room temperature, the nitrocellulose membranes were incubated with antibody against phosphorylated Stat3 (phospho S727, 1:1000 diluted, Abcam, Cambridge, UK) or against β-(diluted 1:500, Abcam, actin UK) overnight at 4°C. The immunoblots were washed and incubated with HRPanti-rabbit labeled lgG antibody (1:1000 diluted, GenScript, NJ, USA) for 1 h at RT and developed using chemiluminescent substrate (Sigma-Aldrich, Munich, Germany).

Flow cytometry

Blood was collected by retro-orbital puncture in tubes containing 5 U/mL of heparin and mixed with an equal volume of PBS (pH 7.4). After gradient centrifugation on Histopaque 1083[™] (Sigma-Aldrich) at 1400×g for 40 min at room temperature, peripheral blood mononuclear cells (PBMCs) were carefully collected, washed with PBS and counted. For SF cell collection the skin overlying the ankle was excised. A 30-gauge needle was inserted through the synovial membrane, and the synovial cavity was washed by injecting and immediately aspirating 25 µl of heparinized PBS (5 U/ml) to obtain the synovial lavage and then centrifuged. SF cells and PBMCs were resuspended at 2 x 10⁵/ml in 2% FCS/PBS solution. The cells were incubated for 15 min at 4°C with appropriately diluted antibodies from Biolegend (San Diego, USA) against

mouse Ly-6G (FITC-conjugated; clone 1A8), CD11b (PE-conjugated; clone M1/70), F4/80 (FITC-conjugated, clone BM8), TRAIL (CD253, PE-labeled, Biolegend (San Diego, USA) and IgG isotype controls (BD Bioscience). After with 2% FCS/PBS. washing the samples were analyzed with flow cytometer (BD LSR II) by using BD FAC-(Becton SDiva v6.1.2 Software Dickinson GmbH, San Jose, CA, USA).

Osteoclast differentiation

marrow-derived Bone macrophages (BM) were isolated from the long bones of 6-week-old mice. Bone marrow precursors (2x10⁶/ml) were cultivated with 30 ng M-CSF (GenScript) for 1 day, followed by 50 ng M-CSF for 3 days and then with 50 ng M-CSF+50 ng sRANKL (Biolegend, UK) for 3 days. The cells were cultivated in the presence or absence of different concentrations of tyrphostin AG490 and the specific tartarate-resistant acid phosphatase (TRAP) staining was performed, as described [20]. TRAP activity in the cell lysates was determined using TRAP solution (0.1 M sodium acetate, 1 mM ascorbic acid. 0.15 M KCl. 10 mM disodium tartarate, and 10 mM p-nytrophenil phosphate). The reaction was stopped with 0.3 N NaOH, and the absorbance was measured at 405 nm.

Statistical analyses

Statistical analyses were performed using InStat3.0 and GraphicPad Prism 5.0 (GraphPad Software Inc., La Jolla, CA, USA). Data are expressed as mean ± SD or mean ± SE. The immunohistochemistry data were analyzed using the Mann Whitney Utest. For other data, the differences in mean values between groups were analyzed by unpaired t test. Differences were considered significant when P <0.05.

RESULTS AND DISCUSSION

A number of signal-transducing molecules are associated with the occurrence of excessive tissue mutilations during local or systemic infection and inflammation. The receptor tyrosine kinases are not only cell surface transmembrane receptors, but also act as enzymes possessing kinase activity. Dysregulation of protein kinases is attributable to pathology of a variety of diseases such as cancer, diabetes, autoimmune, cardiovascular, inflammatory, and nervous disorders. Tyrosine kinase inhibitors represent a new approach for better outcome of such conditions. They act directly on cells, not mediators, targeting different pathways simultaneously [21, 22]. The development of OA is attended with progressive loss of articular cartilage and increasing inflammation. Such pathological processes have been observed in various experimental animal models of OA, including CIOA which is characterized with elevated levels of pro-inflammatory cytokines, cartilage and bone erosion and enhanced expression of bone remodeling markers [23].

In the present experiments, immediately after the second injection of collagenase (day 0), mice were treated i.p. with either PBS (control) or with AG490 under 3 different schemes (Figure 1A). Clinical disease activity was observed in all groups, but the mean scores for cell infiltration and cartilage erosion at day 30 were significantly reduced in AG490 treated groups compared to the control group (Figure 1B and C), as the effect on cell infiltration and erosion was superior in scheme 3. The results described below concerned scheme 3 (4 mg/kg at days 0, 5, 10 and 8 mg/kg at day 18). The development of CIOA might be divided into onset (~5 to 7 day), active inflammation with a peak at day 18 and established phase with cartilage and bone erosion, which progress from day 20 to day 30. Part of the mice in each group was killed at day 18. Figure 1D showed that the measurement of body weight did not point on any differences between the groups. The relative popliteal lymph node (PLN) and spleen weights were determined at day 18 and 30 of arthritis. Data showed that the development of joint inflammation was attended with increased PLN in CIOA mice at both time points, significantly inhibited by AG490. Spleen enlargement was limited in tyrphostin- treated mice at day 30 (Figure 1E and F).



Figure 1. AG490 ameliorated cartilage and bone destruction in CIOA mice. A. Different schemes of AG490 administration (*n* = 15 mice per group). B. AG490 inhibited cell infiltration and C. bone erosion. D. Body weight of mice treated under the scheme 3. E. Relative and F. Relative spleen weight. G. and H. AG490 significantly reduced the osteophyte areas in CIOA mice as evident from TGF-β3 immunostaining. I. Joint swelling. Results represent means ± SE, Mann Whitney U test. **P* < 0.05; ***P* < 0.01. Scale bar = 50 µm.

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TGF-β3 BMP2 and are exhealthy in cartilage and pressed play an important role for cartilage repair [14, 24]. They are two bioidentified markers in osteophyte areas in OA, as TGF-β3 appears earlier than BMP2 in osteophytes The notion that BMPs and [25]. TGF-B3 are protective for articular cartilage is now shifted to a notion that they can also play a role in cartilage destruction and osteoarthritis progression. This dual role explanation for provides an the surprising observation that in OA both cartilage anabolism and catabolism might be elevated. We observed increased TGF-B3 expression in the late phase of CIOA and well expressed osteophyte formation, while TGF- β 3 expression was decreased and osteophyte formation

was significantly limited in tyrphostin treated group (Figure 1G and H). Reduced joint inflammation was observed in tyrphostin treated mice (Figure 1I).

Our data showed that CIOA is characterized by а presence of elevated number of neutrophils and macrophages in the synovial fluid (observed with F4/80 and CD11b/Ly6G flowcytometry staining), cells underlying inflammation. the As a result of tyrphostin treatment the number of these cell populations was close to that of healthy mice (Figure 2A and B). We also observed that the pool of PBMCs obtained in the chronic phase of CIOA consisted elevated number of CD11b positive Ly6G cells markedly reduced in a result of AG490 application (Figure 2C).



Figure 2. Effect of AG490 on the number of CD11b+Ly6G+ and F4/80 positive cells. Tyrphostin AG490 was injected under the scheme 3 as described in Fig. 1. Blood and SF were collected at day 30 of CIOA (n = 10 per group in 3 experiments). A. Flowcytometry analyses showed that tyrphostin suppressed the elevation of CD11B+Ly6G+ cells in the SF and B. Decreased the number of F4/80 cells in SF C. Decreased frequencies of CD11b+Ly6G+ cells in blood. Values are means ± SD (n=10 per group in 3 experiments). **P* < 0.05; ***P* < 0.01; *** *P* < 0.001, unpaired t-test.

The importance of Jak/STAT by data the role of ted on arthritis STAT3, showing of pathway in is supporthat blockade

National Scientific Programmes with European Dimensions

STAT3 by overexpression of SOCS3. STAT3-induced inhibitа Jak-STAT of signalling, or supexperimental arthritis [26]. pressed The continuous STAT activation may be of pathogenic significance in the progression and

of arthritis. The maintenance STAT3 phosphorylation is mediof through ated the activation of Janus-like JAK1. kinase JAK2. JAK3, TYK2. and c-Src kinase and is a mark for active inflammatory process.



Figure 3. **A**. Immunohistochemical staining for STAT3 expression in the joint. **B**. Total protein extracts were prepared from synovial cells from control and CIOA mice, and from CIO mice pretreated or not with typhostin AG490 then activated with zymosan. Lysates were analyzed by Western blot using antibodies against phosphorilated form of STAT3. **C**. Graphics presenting STAT3 and pSTAT3 expression in the joint.Data are presented as means ± SD from 3 determinations (n=7 per group). **P* < 0.05; ***P* <0.01, unpaired *t*-test.

CIOA Using model we were able to study the STAT3 and pSTAT3 expression in the arthritic joints and we observed a significant decrease caused by tyrphostin at day 18 (Figure 3A and C). Synovial fluids were obtained and in vitro stimulated or not with zymosan in the presence absence of or AG490. tyrphostin Immunoblotting

showed no activation of STAT3 in SF cells from control mice (Figure 3B). In CIOA mice, a presence of pSTAT3 was detected even without additional activation with zymosan. When SF cells from CIOA mice were additionally activated by incubation with zymosan, a stronger signal was produced which was inhibited in the presence of AG-490.

supposed RA It is that is characterized by synovial cell possibly due accumulation, an to impaired apoptotic mechanism. Early RA is characterized by a low level of synovial apoptosis, while disease durina progression apoptotic mechanism may the be restored [27]. Thus, apoptosis regulation appears to be an important mechanism determining in of chronic the long term course synovitis. However, not manv investigations comprehensively stud-TRAIL and all ied its receptors in the patients with various

of arthritis. Jungel types et al. showed that soluble TRAIL levels are significantly higher in RA syncompared ovial fluid with OA fluid [28]. synovial Here. we demonstrate that CIOA is associated with high expression of TRAIL by synovial cells remarkably abrogated by typhostin AG490 (Figure 4). It would be of interest to further determine whether and how TRAIL is involved in OA pathology. In future experiments the levels of TRAIL in synovial fluid and subpopulations cells expressing of those TRAIL should be defined.



Figure 4. TRAIL is expressed on SF cells from CIOA mice. The representative histograms and values for mean fluorescence intensity (MFI) showed inhibitory effect of tyrphostin AG490 on TRAIL expression.

remodeling involves Bone the synthesis matrix by of bone osteoblasts and resorption its by cells. osteoclast The major role in osteoclast cell differentiation is addressed to receptor activator of nuclear factor kappa ligand В [29]. In vitro, binding of RANK ligand RANKL and with its res-

ults in osteoclastogenesis by monocyte/macrophage progenitor differentiation to osteoclasts and the activation of mature osteoclasts [30]. The effect of tyrphostin A490 on RANKL-induced osteoclast differentiation of bone marrow-derived macrophages was studied in vitro (Figure 5).



Figure 5. Influence of tyrphostin AG490 on osteoclast differentiation *in vitro*. A.
 Photomicrogrphs showing tartarate-resistant acid phosphatase (TRAP) stained mature osteoclasts. B. Tyrphostin AG490 inhibited IL-6 induced osteoclast differentiation. BM cells were pretreated with IL-6 and then stimulated with M-CSF and RANKL in the presence or absence of tyrphostin AG490. C. Figure data present concentration-dependent inhibition of the number of multinucleated cells, D. TRAP activity and E.
 Time-dependent effect of tyrphostin AG490 on the number of multinucleated cells. Data are means ± SD from 3 determinations (n=7 per group). **P* <0.05; ***p* <0.01; ****P* <0.001, unpaired *t*-test.

Substantial inhibition of the generation of multinucleated TRAP-positive cells was detected after cultivation with tyrphostin AG490. The decrease in the number of differentiated osteoclasts and the decrease of TRAP activity were concentration-dependent. At 50 µM AG-490 added, rare multinucleated cells were present (Figure 5A and C). Also, TRAP activity of differentiated cells was significantly diminished by tyrphostin (Figure 5D). The process of osteoclastogenesis might be triggered by IL-6. Two hour pre-incubation of BM cells with IL-6 resulted in a formation of giant cells, in some

cases with more than 10 nuclei. The addition of tyrphostin AG490 at a concentration of 50 µM after cytokine treatment, to a great extent prevented M-CSF+RANKL-induced osteoclast differentiation (Figure 5B). To elucidate the inhibitory effect of typhostin in more detail, we added tyrphostin AG490 at different time periods to BM cells in culture (Figure 5E). Tyrphostin AG490 exposure at a concentration of 50 µM for the entire period of cultivation or during days 0-4 after M-CSF treatment, followed by wash-out and further culture in the absence of tyrphostin AG490, resulted in inhibition

of osteoclast differentiation. However, there was no inhibitory effect when the substance was added at days 4-7.

These findings suggest that tyrphostin AG490 inhibits early M-CSF+RANKL-induced cellular events.



Figure 6. Effect of tyrphostin AG490 on M-CSF+RANKL-iduced BM cell differentiation.
 BM cells were obtained from control and mice with CIOA at day 18, and stimulated with M-CSF+RANKL. A. AG490 lowered the expression of RANKL by BM cells at day 7 of cultivation. B. AG490 decreased the number of F4/80 positive cells.

A variety of systemic hormones, locally produced cytokines and cell to cell interactions regulate osteoclast differentiation and function. Among them macrophage colony stimulating are factor (M-CSF), which is responsible for proliferation and survival of precursors, and receptor activator of nuclear factor κB ligand (RANKL), triggering osteoclast formation and maturation. Designing novel drugs that target RANKL-RANK and their signaling pathways in osteoclasts could give an impetus for new therapies of many diseases associated with bone loss such as arthritis, osteoarthritis and osteoporosis.

At day 7 the cells stimulated with M-CSF and RANKL were collected and subjected to FACS analyses. Data showed that RANKL was expressed on cells from control (MFI=930) and CIOA mice (MFI=850) but the values of the MFI were lower in the presence of AG490 (MFI=640 and MFI=503 for control and CIOA groups, respectively) (Figure 6A). We observed that F4/80 cells consisted of F4/80^{low} and F4/80^{high} populations. Results showed that the percentage of F4/80^{low} population was not influenced by tyrphostin, while less F4/80^{high} population were observed in non-arthritic group (Figure 6B). When cells were obtained from CIOA mice, the frequencies of F4/80^{low} population increased approximately two times, and this elevation was inhibited by tyrphostin. Such suppressive effect of AG490 was also noticed in regard to F4/80^{high} cells in both, control and CIOA groups.

Proteoglycans and glycosaminoglycans are important articular cartilage matrix components considered sensitive to changes in cartilage homeostasis. A great loss of glycosaminoglycans (GAGs) and PGs was observed in arthritis animals while these processes were significantly abrogated in the group treated with AG490 (Figure 7A and B). Bone erosion is based on the generation of osteoclasts within the synovial membrane. This suggests that an intervention that protects bone from attack by inflammatory synovial tissue may be

based on powerful inhibition of osteoclasts. At the late stage of CIOA we observed mature osteoclasts deep in the bone and their number was significantly decreased in AG490-treated mice (Figure 7C).



Figure 7. Tyrphostin AG490 inhibited osteoclast generation in the bone and decreased cartilage loss at day 30 under scheme 3 of CIOA. A. Tyrphostin AG490 reduced glycosaminodlycan thinning (toluidine blue staining). Black arrows indicate destained articular cartilage; red arrows indicate maintained glycan content. Percentage of distained areas showing cartilage loss. B. Tyrphostin lowered proteoglycan (PG) loss (safranin O staining). Black arrows indicate destained articular cartilage and percentage of distained areas. C. Representative TRAP stained joint sections. Arrows indicate TRAP positive cells in CIOA mice and number of osteoclasts (multinucleated TRAP positive cells) in the bone. *P < 0.05, **P <0.01, unpaired *t*-test.

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CONCLUSION

Recently, there have been major changes in the way arthritis is treated. Current biologic agents are all administered by either intravenous infusion or intramuscular injection. Small oral molecules that block the intracellular cytokine signaling pathways represent promising pharmacological а approach, alternative, or additive to the current biologic therapies. A large number of clinical trials have been published reporting positive therapeutic results with tyrosine kinase inhibitors. Present data extend our understanding on the application of AG490 in chronic inflammation and we argue that it may hold promising therapeutic potential against important clinical conditions such as osteoarthritis.

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2. Gyurkovska V., Dimitrova P. and Ivanovska N. *European Journal of Inflammation*, 2014, 12(2): 329-340.

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ПРОТЕКТИВЕН ЕФЕКТ НА ТИРФОСТИН АG490, СЕЛЕКТИВЕН КИНАЗЕН ИНХИБИТОР, ПРИ КОЛАГЕНАЗА-ИНДУЦИРАН ОСТЕОАРТРИТ

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Резюме. Представените резултати са получени през първагодина проект Б01/6 ma на «Приложение на тирозин киназния инхибитор тирфостин AG490 при колагеназа-индуциран модел на ocmeoapmpum», финансиран om «Научни изследвания» Фонд към Министерството на образованието и науката.

Janus киназната (JAK)-сигнал пренасящата U активиращата транскрипцията (STAT) каскада има основна роля при осъществяване на сигнализирането за много цитокини и растежни фактори, които впоследствие стимулират различни клетъчни функции и имунни отговори. Целта на експериментите беше да се установи ефекта на Jak2 инхибитора тирфостин AG490 върху протичнето на колагеназа-индуциран ocmeoapmpum (КИОА), модел на хронично ставно възпаление при мишки. КИОА е предизвикан, чрез вътреставно инжектиране на колагеназа и след третирани това мишките са интраперитонеално с АG490 по различни Тирфостинът схеми. ограничава ерозията на хрущяла и костта, което е свързано С двойнонамаление на броя на CD11b+/Ly6G+позитивните неутрофили и F4/80+ макрофаги в синовиалната течност и подтиска експресията на STAT3, pSTST3 и на растежния фактор TGF-β3 в ставите. Веществото намалява образуването на остеокласти и загубата на глюкозаминогликани и протеогликани в костта.



BULGARIAN ADDED VALUE

NAO "ROZHEN" AND THE BULGARIAN ASTRONOMY

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Abstract. The article describes briefly the history of the Bulgarian National Astronomical Observatory "Rozhen" (NAO). The Government Decision №203/6.05.1967 for building NAO as a part of the Bulgarian Academy of Sciences (BAS) finalizes a long-time period of dreams, plans and efforts of Prof. Nikola Bonev (later academician) and the then young Bulgarian astronomical community. The observatory is equipped with four professional telescopes: 2m Ritchey-Chretien-Coude universal telescope, 50/70 cm Schmidt-camera, 60-cm photoelectric reflector and 15cm solar telescope-coronagraph. The NAO allows observations on a wide range of astrophysical problems, such as: heliophysics, solar system small bodies, comets, stellar physics, extragalactic objects and high-energetic processes in the Universe. NAO is among the top ten continental European observatories and helps Bulgarian astronomers to take part in many international cooperative investigations.

INTRODUCTION

Academician Once Lev Artsimovich (1909 - 1973) characterized the fundamental science as "the best way to satisfy the private curiosity for government's bill". The astronomy is a perfect example. After the first telescopic observations by Galileo Galilei, the millennia long skill to watch by eyes the celestial luminaries quickly was transformed into a fundamental science of extremely important value. During the 19th century the astronomy, being initially a pocelestial-mechanical sitioning and science, gradually was converted into astrophysics - a science possessing the greatest and with the most spectacular physical events laboratory the Universe. That is way the other Artsimovich's phrase "the future [of the physics] belongs to the astrophysics" is not accidental.

The telescope collects light from the luminaries and it is clear, that it's most important characteristics must be the collecting area – the aperture, or usually the diameter of the entrance opening. The efforts to increase the telescopes' size don't stop up to now. Till the mid-20th century the largest telescopes was a result of private initiatives by rich amateurs or private funds. For a long time, the leadership in this field belonged to Great Britain (as the most industrialized country in the past), sometimes to France and then go mainly to the United States. The situation is changed in the mid-20th century with the realizing of astronomy's importance for the technologies too (firstly for military use, but as well and not less important for civil purposes). As a result, the governments' efforts for the development of the astronomical potential of the industrial countries has become dominating. Besides this, the cost of the present-day great astronomical complexes (of order of billion \$) brings forward the international cooperation. Finally, now the world astronomical community (~15000

individuals) features with a dozen of class 8-10 m telescopes, almost the same number class 4-6 m and near hundred instruments of 2-4 m aperture class. The future is connected with the building of the next generation 30-40 m telescopes of 2020-es.

Where in this world competition are we, the Bulgarians? Due to known historical reasons the general development of our country some century and a quarter ago was lagging behind the civilized world. The same was the situation with the astronomy. When Bulgaria resurrects as a national country in 1878, the world knows telescopes of class 1-1.5 m while the only telescope in our lands was Dr. Beron's "Mertz" refractor of only 8-cm diameter...

The following lines are devoted to the 35-anniversary of the formal opening of the Bulgarian modern astronomical base – the National Astronomical Observatory "Rozhen" in Rhodope Mountain.



THE BULGARIAN ASTRONOMY UNTIL MID-20th CENTURY

Despite the deficit of written texts concerning the old-times astronomical practice in our lands, some medieval sources tell us indirectly that there were people that have watched the sky and the events on it. About ten comets were observed from Bulgarians as well as such events like solar eclipses. One of the first Old-Bulgarian authors, Joann the Exarch (10th cen.) devoted a special pages on the Heaven in his compilation from Aristotle and Byzantine writers (Basil the Great and others). In Chpt. 4 of "Hexameron" he complemented the notions about the Heavenly spheres from these authors. We don't know exactly how wide were dispersed the theology's work amongst the people, but e.g. the level of literacy in the Old-Bulgarian capital Tarnovo before the Osman invasion in the late 14th century was quite impressive – more than 30%. The Bogomil's "collective readings" of their apocrypha also tells about the high enough level of Christian enlightenment. But the sources for the intellectual life in medieval Bulgaria are extremely scarce...

The education on physics and astronomy begins a few centuries later, during the Bulgarian Renaissance. In the first public school in Svishtov (1815) only two short descriptive chapters on astronomy were among hundred pages of the Greek schoolbook. Astronomy was in the frame of physics also in the Aprilov-school in Gabrovo (1835). Some short indirect astronomical data can be obtained in the Bulgarian translations of several Russian books on geography, physics and "cosmography" issued in the century. The translations of some children-oriented books were especially important.

The Bulgarian first University, in Sofia (SU), is established in 1888. Since the next year there is a Phys-Math department and astronomy begin to be studied. In 1894 Prof. Marin Bachevarov (b. 1859, educated in astronomy in Moscow) established the Chair of Astronomy and in 1897 - the University's Astronomical Observatory (UAO) in the Sofia's greatest park. UAO was a "temple" of the Bulgarian Astronomy for more than a half century. Equipped in the beginning with Dr. Beron's 8-cm and Prof. Bachevarov's 6-cm telescopes, since 1897 a professional 16-cm Grubb refractor and later (1913) 11-cm refractor were delivered. Other astronomical instruincluded meridian circle ments а (1894), an exact watch (1942-86) and some others.



The University Observatory in 1899 (UAO archive) and the 16-cm Grubb refractor

A DREAM FOR GOOD PROFES-SIONAL OBSERVATORY

The Government Decision № 203/6.05.1967 г. for building NAO as a part of the Bulgarian Academy of Sciences (BAS) finalizes a longtime period of dreams, plans and efforts of Prof. Nikola Bonev (later Academician) and the then young astronomical community. Bulgarian Bonev (1898 – 1979), begun his Bulgarian astronomy work on as Assistant Professor in the SU since 1928. A decade later he is a Professor and he was a head of Bulgarian astronomy more than 40 years. Besides his care to the Astronomical Department of the SU he established also the Section of Astronomy (SA) in the BAS (1953), now - Institute of Astronomy with NAO (IA). Prof. Bonev was the first and most active person in organizing a lobby for building a new big observatory in Bulgaria. He is also an originator of the Bulgarian Astronautic Society in 1957.



Prof. Nikola Bonev (in 1974)

The idea to build a professionobservatory for SU Prof. the al announced Bonev in December 1941 in a "Memorial on a need of further development of the Astronomical observatory" to the University authority: "... we are able and we must build one of moderate size and modern equipped Astronomical observatory, worthy for our central place in the Balkans ..." (UAO archive). Prof. Bonev planned to order from "Carl Zeiss" a 1-m reflector and 40-cm double astrograph. But the plans were abandoned due to the WWII, political changes Bulgaria, etc. Manv in years later Prof. Bonev wrote (in Astronomical calendar for 1973) "... the idea for big modern observatory... was splendidly developed after 9 IX 1944 in the project for National AO with 2-m telescope" (but in fact neither before, nor after the "socialist revolution" the astronomy was among the priorities of the Bulgarian science and governments up to the beginning of the cosmic era!)

Let's go back... Prof. N. Bonev continues to promote the idea to build a new observatory. In 1950 he puts again the same project with 1-m class reflector and 40-cm astrograph and he even attempts efforts to order such instruments in CZ-Jena (being amongst the most famous optical firms in the world, CZ-Jena has already built some 5 exemplars of 1-m reflectors and a dozen of 40-cm astrographs since 1912).

After the "Sputnik-1" lunch in 1957 the "cosmic era" begins for Bulgaria too. A network of 4 stations for visual satellite observations was established and more than a dozen People AO and 6 planetariums were built in Bulgaria since 1960!

NAO "ROZHEN": THE BEGIN-NING

Gradually, the old idea for a new observatory, but already under academic rule, becomes popular in the BAS authorities. In 1958 Prof. N. Bonev reported to the Presidium of the BAS the perspectives for Bulgarian astronomy in the light of need of new AO (BAS archive file F9-3-01-1-16; РД-07-25.06.1963). He explained the need of 1-m reflector and 40-cm astrograph. Being encouraged by the well-disposed to the idea authorities, the Section of Astronomy presents needs of 1.7 million "gold" rubles for import of 1m and 0.4-m instruments for new AO in the period 1961-65 years (F9-1-015p2-3; 1960). The ordered instrument was to be of the new series 1-m CZ telescopes. From the archive notes we come to know that the 1-m for AO at Vitosha Mountain is already ordered in CZ-Jena (East German, DDR). On 05.02.1960 BAS signed a contract with "Zeiss" for production of the instruments. Latter (1961) we ask Zeiss to delay the delivery for 3-4 years due to difficulties and financial the firm agreed. One and a half years latter (May 1963) we renounced the 40-cm astrograph. We keep the order only for 1-m reflector.

The Presidium of BAS stated on 05.06.1963 r. a special Commission for building NAO (with Acad. Assen Datsev as a chair). In a 1963 year report of the Commission a proposal to buy 2-m instead of 1-m telescope appears for first time! (F9-3-03-p06) On Dec, 15, 1965 the Presidium of BAS approved the project for establishing a new AO and buying up a 2-m telescope.

Meanwhile, the search for a suitable site was organized. The initial proposal for observatory at Vitosha (42° 36.1' N, 23° 15.3' E, 1700 m alt.) was rejected because of closeness to Sofia's light pollution. Bulgaria has small, compact territory and the astroclimatic conditions are not so different. In fact our geography belt has a moderate in quality astroclimate. The clear night time is ~30-40%. Some of a dozen proposed potential sites were rejected due to different reasons: low altitude; in vicinity of a big city (Stara Zagora); strong winds (western mountains), etc. The astroclimatic studies were implemented in collaboration with the consultant Dr. Nikolay Kucherov from Pulkovo (he was engaged in the search of site for the Special AO in Caucasus). As a result a site (42°28.6' N, 23° 25'.5 E, 1200 m alt.) near village Plana was approved after several expeditions (Dobrichev & Kovachev, 1966, "Investigation of the astroclimate in Bulgaria", Proceed. of the Astronomy Section, Vol.I p.31). The site in Plana was the favorite for building NAO, but latter was used for establishing a geodetic observatory and station for satellites' observation. The SA begins to prepare plans and administrative acts for building NAO at the Plana's site. The schedule was to complete the montage of the 2-m telescope in 1975 (F9-3-018-p2; 1965). After all these preliminary steps the academic authorities proposed to the Government to fashion the decision for establishing NAO. Finally the Council of Ministers Decision 203/06.05.1967 about establishing of a National astronomical observatory and buying of a 2m telescope from DDR - C. Zeiss, Jena appeared. On Dec 1967 the government specifies a limit of ca. 8 mln levs (4.4 mln converted lv) to buy 2-m telescope with 20-m dome from DDR. CZ already was built three 2-m telescopes: Tautenburg's 1.4/2 m Schmidt on fork mounting (1960) and two classic cassegrains with prime and coude foci on new mounting for Ondrejov (ČSSR) Shemakha and (AzSSR) (1965-68). Meanwhile CZ introduced a new series 2-m telescopes of modern Ritchey-Chretien-Coude scheme (1:4 mirror) having wide-field (~1°) Ritchey-Chretien (1:8) and coude $(\sim 3')$ field, Two exemplars 1:36) foci. were ordered and later mounted: in Bulgaria (NAO, 1979-80) and in Terskol Observatory (Caucasus; 1990).

Meantime. the situation with the choice of the site for NAO was changed. In 1960 the Smolyan dis-Rhodopes trict in the near the south Bulgarian border was established and in 1969 the Council of Ministers puts а Decree about development of Smolyan region. One of the positions was a statement that in Smolyan region an astronomical observatory and a planetarium in the town must be build. According to this new circumstance, in 1970 BAS pre-

(F9-3-94-p19-28), pares а report where a proposal appears to join both projects and to build the academic observatory with 2-m telescope in Smolyan district. Intensive relations between the BAS and the Smolyan district authorities have begun. Soon the scientists from the SA-BAS have organized short-time expeditions for testing the potential sites. Two regions were chosen: peak Mechi chal (Bear peak) SW from Chepelare and the terrain near the chapel "St. Spirit" SE from Chepelare. In the end of 1971 The Council of Ministers approved the change of the site for NAO from Plana to Smolyan region in the Rhodopes. Finally, the Scientific council of SA-BAS decided to affirm as a site for NAO the terrain near the chapel "St Spirit" (41°41'41" N, 24°44'20" E, 1730 m alt.) It is almost perfect decision in topographic sense: relatively flat N-S oriented area with steep slope on south where 2-m dome is built.



NAO "Rozhen" in a topographic map (I.) and the site plan (r.)

The building activities at Rozhen started in 1974. The 20 m wide and 35 m tall (including the dome) tower was designed by Czech architects and constructors.



The dome itself was produced in DDR and is a copy of previously built domes for 2-m Zeiss reflect-The 200-ton dome was deors. livered in NAO in the beginning of 1976 and was mounted in 1977. The 2-m RCC was tested in the factory and rendered to the buyer in the end of 1976. The telescope' montage begun in the spring of 1978 and the "first light" in RCfocus was obtained on 22.11.1978 targeting the well-known globular stellar cluster M15 Pegasus. in Meanwhile DDR in was repaired and modified in order to be translocated in NAO the old 50/70-cm Schmidt-camera of Potsdam Observatory. Together with CZ 60-cm reflect-(suitable or for stellar electrophotometry) the telescope' park of NAO obtain "classic" shape for an astronomical observatory of the second half of 20th century. Later a solar coronagraph with 15-cm aperture was constructed and build in NAO.





The 2-m RCC telescope (I.), 50/70 cm Schmidt-camera (c.) and 60-cm reflector (r.)

The official receiving-giving statement for 2-m RCC telescope was signed on 22.05.1980. Unfortunately, the special tests do not prove the ordered quality of the optics and the conclusion was that the optical system must be changed. It was performed

several years later.

Finally, the regular scientific observations on the 2-m telescope begun since September 1980, half a year before the official opening of the National Astronomical Observatory on March, 13, 1981.



2-m dome and the laboratory corpus (I.) and the domes of other telescopes: 60-cm, solar 15-cm and 50/70 Schmidt (r., from left to right)

NAO "ROZHEN" ON THE WORLD "ASTRONOMICAL" MAP

In order to value the role of NAO for Bulgarian astronomy let us to compare it's characteristics in comparison with other large observatories. The equipment' class of NAO is equal to such European and other facilities, like Asiago in Italy, Crimea Observatories. and Terscol Haute Provence and Pic du Midi (France), Tautenburg (Germany), Schemakha (Azerbaijan), etc. The altitude (ca. 1750 m) is typical for most of the world observatories of 20th century (e.g., Palomar, Mount Wilson, Byurakan,

etc.). The meteorological conditions (~40% clear night time) are typical for the southern Europe climatic belt. Of course, it is far from the best world sites (Chile, Hawaii, Canaries) but is quite enough to perform quality observations for wide range astrophysical programs.

Our NAO still possesses one of the "darkest" night sky in Europe. It is especially important for implementing quality scientific observation. The situation with the light pollution all over the European territory becomes more and more severe. That is why our observatory remains a good "sky watching" place.



Night lights of Europe (2012, I.) and the sky-illumination level map of Bulgaria showing the location of NAO "Rozhen"

Already two generations (some hundred at a whole) scientists have had their education and practice in NAO. Thousands papers published in the international journals and proceedings from Bulgarian astronomers are based mainly on data obtained in NAO. Our astronomers took part in many international cooperative campaigns studying different cosmic oblike cataclysmic, symbiotic, jects, eruptive, eclipsing and other types variable stars; small planets and asteroids investigations - some two asteroids dozen new were discovered using NAO's Schmidt-camera; NAO took part in the world watch campaign to observe the NEO's (Near Earth Objects); extragalactic studies of nearby galaxies, guasars, active galaxies, etc.

CONCLUSION

NAO "Rozhen" is the greatest astronomical *complex* in south-east

Europe. It is well equipped also for performing scientific meetings, schools, symposia, etc. Every summer NAO receives dozens amateur astronomers only not from our country. In the same time the observatory also is a unique tourist annually destination where thousands visitors obtain impression of what is a modern astronomical fahear popular cility, lectures and really see a piece of Bulgarian fundamental science.

Despite it systematic underfunding (alas, like the whole Bulgarian Academy of Sciences), the production of NAO is quite in the world trend and, undoubtedly, the Observatory is a significant investment in the Bulgarian science. The astronomical instruments are large long-lived facilities and we must keep our Observatory at deserved level, develop it and be proud with it existence and role in the Bulgarian intellectual efforts.

Advances in Bulgarian Science

НАО "РОЖЕН" И БЪЛГАРСКАТА АСТРОНОМИЯ

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Резюме. Статията кратко разглежда историята на Националната астрономическа обсервато-"Рожен". Министерското рия постановление №203 от 6.05.1967 г. за изграждане на НАО към БАН увенча дълъг период от мечти, планове и усилия на проф. Никола академик) Бонев (по-късно и младата тогава астрономическа колегия у нас. Обсерваторията е съоръжена с четири професионалтелескопа: 2-м универсален ни телескоп с Ричи-Кретиен и куде

фокуси; 50/70 см Шмит-камера; 60см рефлектор и 15 см слънчев телескоп-коронограф. В НАО има условия за наблюдения по широк клас астрофизически задачи по: хелиофизика, малки планети в слънчевата система, комети, физика на звездите. извънгалактични обекти, високо-енергетични процеси в Космоса. НАО е сред първите десет обсерватории на континен-Европа участвува тална u в множество международни кооперативни изследователски проекти.



MADE IN BULGARIA WITH EUROPEAN SUPPORT

EMBEDDING LANGUAGE TECHNOLOGIES IN A DATA ANALYTICS TOOL

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Abstract. This paper presents a business analytics tool, called BITool, with extended functionalities to process unstructured text: it recognises named entities and extracts numeric values from free text in Bulgarian language. These extensions enable more sophisticated applications of the product and its further tuning to important domains such as public data and patient-related electronic health records. The development was supported by a project funded by the Competitiveness Operational Programme where researchers transferred technologies to small and mediumsized enterprises. The empowered tool and its successful applications prove the feasibility of the approach for doing industrial research in Bulgaria.

INTRODUCTION

Information and Communication Technologies (ICT) enable today all activities of our society – they supply vital components in research, manufacturing, governance and management, services, health, education and transport. ICT growth provides new jobs and markets, opens the door to innovations. Due to this trend, more and more data are generated worldwide, often as a byproduct of digital interactions using data-intensive technologies. The notion of Big Data appeared - a massive volume of structured and unstructured data, too large or too dynamic to be processed by traditional software tools and techniques. The popular "3Vs" features of Big Data were first introduced by Gartner (previously META group): "high Volume, high Velocity, and high Variety" [1]. Wikipedia is an example for big data consisting of unstructured texts, images and hyperlinks; the information gathered via mobile devices with sensors is another example of big data; social networks and large image hosting sites are viewed as big data as well.

Traditional databases hardly cope with big data which often needs embedded tools for pattern detection as well as more sophisticated visualisation facilities to support data exploration. In general big data increased the demands of data analysis tools that are flexible and affordable. The large Volume of big data practically means that knowledge discovery and predicanalytics for establishment of tive trends are the preferred functionality in contrast to databases which deal with searching data items and subsets of data values. Another necessary feature is the speed of processing since big data often appear in real time therefore building on-line services that cope with the Velocity is one of the current challenges in the field. The large Variety of big data generated as text, images, multimedia (audio, video), and various signals requires tools that maintain media and content convergence and data fusion. In Bulgaria the need of specialised big data software will be growing with the emerging data-intensive tasks related to the economic development of the country and the increasing usage of Internet.

This paper presents a tool for data analytics and business intelligence (called BITool) that has been implemented within the project BG161PO003-1.1.06-0023-C0001 "Analysing and identifying dependencies in big data repositories - application for economic and technological analyses" (2012-2015), funded by the **Operational Programme "Development** of the Competitiveness of the Bulgarian Economy" (2007-2013). Two partnering institutions participated in the project: the BITool developer ADISS Lab Ltd. – a small software company, coordinating the project, and the Institute of Information and Communica-Technologies (IICT), tion Bulgarian Academy of Sciences (BAS), as a provider of research expertise in information processing. Here we focus on the

integration of text analysis functionality into BITool in order to extend its capacity to process data described as free text.

The paper is structured as follows. We present the project context and discuss two basic language technologies that were embedded in BITool: Named Entities Recognition (NER) and automatic identification of numeric values of selected entities. Then we overview the application of BITool as software supporting the diabetes register generated in the University Specialised Hospital for Active Treatment of Endocrinology "Acad. Ivan Penchev", Medical University -Sofia. The conclusion discusses the innovation capacity of the tool and presents plans for future work.

PROJECT CONTEXT

"Development of re-The call search and innovation capacity of Bulgarian smalland medium-sized enterprises (SME)" in the Competitiveness Operational Programme supported projects enabling the creation of novel, more elaborated products, that increase the technological and innovation potential of Bulgarian SMEs. Partnership with research organisations was considered vital for implementing original, state-of-the-art ideas and doing know-how transfer in order to align Bulgarian products to the European standards and best practices.

The software product BITool aims to provide fast and effective analysis of enterprise data by visualisation supported at various levels of detail. Initially data can be collected from different sources like databases or text files; from end user's perspective data is stored in a large table viewed as a universal relation. The user can analyse data by grouping them according to some attributes that are considered as dimensions and by defining aggregating functions over some of the remaining attributes viewed as types of facts. Visualisation is supported in two (i) exploration of tree-like modes: structures of grouping attributes and filtering data according to the particular hierarchical node or (ii) exploration of multi-dimensional data i.e. hyperplanes in the *n*-dimensional cube defined by the grouping attributes. The navigation is implemented by click and drag-drop manipulations of graphical objects. By automatic grouping (classification) of selected attributes the user can get a visual idea about the classes of objects constituting the specified dataset. If the table columns correspond to characteristics then the user can select particular columns and split the dataset into groups of objects with similar features. If temporal dimension is included the user can track changes of object characteristics over time by animation. BITool enables the discovery of similar situations over time when a search pattern is specified for a particular period.

The selection of dimensions is dynamic, i.e. the user can start some exploration by choice of certain attributes and later deepen the specification depending on the shown results without necessity to construct the n-dimensional cube once again. The intermediate results can be stored and kept for further explorations by other users. BITool offers most typical features of Business Intelligence software. It can be used as a desktop application or a first step of an Internet service therefore the speed of information processing is essential. The tool is oriented to SMEs that need data analysis but cannot invest in specialised staff and large data warehouse platforms.

The researchers from IICT-BAS, who are experts in computational linguistics, contributed to the project exin automatic analysis pertise of Bulgarian text. As shown above, BITool works on structured information but big data collections often contain free text fields that can be further analysed in order to identify essential facts which are vital for data exploration and the revealing of hidden interdependencies and associations. Having in mind the project applications and the available data sets, two language technologies were of primary importance: automatic identification of named entities in free text as well as automatic extraction of numeric values of preselected parameters from text descriptions.

NAMED ENTITY RECOGNITION IN FREE TEXT

NER is a subtask of the wider area of Information Extraction dealing with automatic identification of entities or facts of interest in textual data. These are mature technologies now widely used in commercial applications. They originated back in 1996 along with the 6th Message Understanding Conference (MUC-6) which was focused on extracting and classifying information about companies and defense related activities from unstructured text. In this task it turned essential to recognise names mentioned in the text such as persons, organisations, locations as well as some numeric expressions like date, time, money, and percent. And this especially important sub-task was called Named Entity Recognition and Classification (NERC) [2] nowadays known as NER. In various domains the entities of interest might be different, e.g. in the financial domain these are markets and players, and in the biomedical domain these are diseases, symptoms, numerical values of examinations etc.

NER is performed after splitting the text into tokens - sequences of characters that are grouped together as semantic units useful for further automatic processing. It includes (*i*) finding names and (*ii*) classification of names by type. Since the features of these entities are often similar, e.g. names of persons, locations and organisations start with an upper case letter and contain tokens, initially all entity candidates are extracted and then they are being classified.

NER systems are sensitive to the particular language and the text genre; they are specifically tailored to the entity types in the application domain. The approaches for tackling NER vary from applying simple rules describing the names, through machine learning algorithms (where more features are supplied to the algorithm which learns to recognise sequences of tokes as entities). to neural networks. The baseline NER accuracy for ordinary English text documents exceeds 90% correct recognition but NER problems

are far from being solved for other informal text styles, such as weblogs and text transcripts from speech conversations, or domain texts in e.g. molecular biology, bioinformatics, and clinical narratives. Recently much attention is paid to the application of neural networks for embedding the words' semantics. Relatively quick progress and significant increase of the recognition accuracy are reported for this approach.

In our project we focused on administrative texts (public data) containing names of persons, organisations and locations as well as on patient records in Bulgarian language. The NER component integrated in BITool is rule based; it uses also lists of names and abbreviations that support the classification. Splitting addresses into subentities is important since it enables recognition of locations and further exploration of facts by municipalities and regions (Figure 1). The NER component can be also used to identify similar names (i.e. names that differ in a few symbols only, mostly in punctuation, see Figure 2) and to correct technical errors like missing spaces.

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Аксаково (REGION)	"rp. Русе , бул.* Липник "№	123"	rp. Pyce	Русе	
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- Асеновград (REGION)	"гр. Стара Загора 6000 ул. "	"Ген. Гурко" 54 , ал. 9"	гр. Стара Загора	Стара Загора	
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Figure 1. Analysis and structuring of addresses: recognition of cities, villages, municipalities, streets

Made in Bulgaria with European Support

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Figure 2. Recognition of organisations' names presented with some variety

It is interesting to note that NER discovers and classifies the entities but this can be also the first step of certain depersonalisation procedure. After identifying names and other personal information the latter can be replaced by pseudonyms or deleted. The right-hand panel in Figure 3 shows a pseudonymised outpatient record represented as a XML file. The ID of the patient (EGN field) and the code of the General Practitioner (called "Practice code") are replaced by pseudonyms; the names of the patient are deleted and question marks are included in the respective positions. Only the name of the city remains in the Address field; the street name and further details are deleted.

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Figure 3. Pseudonymisation of personal identifiers (in blue), anonymisation of names (in orange) and reduction of address to city/village name (in yellow) for patient 496750

EXTRACTING NUMERIC VALU-ES FROM TEXT DESCRIPTIONS

This component was tuned to the extraction of values of clinical tests and lab data from patient records in Bulgarian language. The values are alpha-numeric literals listed in the texts without predetermined order. The extractor recognises at first the indicator (i.e. the name of the tested characteristic) given that the names are not standardised, as well as a value related to the corresponding indicator. There are predefined recognition preferences as shown in Figure 4: the indicator name and value are obligatory (i.e. both have to be found in

the text), the units and interval limits are optional, and the time, condition and explanation of further details are additional features. The units are standardised according to the LOINC nomenclature¹ translated to Bulgarian. We inspected large training corpora of patient records and collected various ways to describe the measurements of these units; after that some recalculation rules were fixed, to cover the data in the corpus. Some selected patient records, written very carefully, were used as a golden standard for accuracy evaluation. The extraction accuracy of 15 indicators exceeded 95% when tested on 6,200 patient records.



Figure 4. Attributes to be identified during the recognition of clinical tests and lab data

The successful recognition of clinical tests and lab data is far from trivial due to specific features of medical language: (*i*) there are many ways to write names (with abbreviations, omitted words in the name, joined words in the name, typos), and no standards or at least preferred variants for writing the names in electronic patient-related files; (*ii*) different separators within the name are used (blanks, commas, dashes, minuses, dots, etc.) but some-

¹ The Logical Observation Identifiers Names and Codes (LOINC) is a standard for recording medical laboratory observations, see *http://loinc.org/international*

times commonly-used separators in the names are omitted; (*iii*) various symbols-separators are used to split the values of different tests but sometimes blanks are omitted; (*iv*) numeric values are recorded in many formats even in one document; (*v*) there are arbitrary replacements of Cyrillic and Latin letters which look identical e.g. the Cyrillic 'c' (pronounced 's') is used for the Latin 'c'. Further domain-specific complications are: the indicator name might contain digits e.g. "17 алфа хидрокси прогестерон" (17-Alpha Hydroxyprogesterone – 17AOHP); the measuring units and signature information are incomplete or wrongly typed in etc. Table 1 illustrates the varieties of writing names of indicators in patient record texts.

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ПЛАЗМЕН КОРТИЗОЛ 8Ч,	ПЛАЗ. КОРТ. 8 Н
ПЛАЗМЕН КОРТИЗОЛ-8ЧАСА,	

Table 1. Nine manners to type in "cortisol at 8 o'clock" in an electronic patient record

The extracting component has its vocabulary (dictionary own of "keywords") and rules for recognition of the elements needed to form the values of interest. The vocabulary covers words and phrases collected from a training corpus of 1,000 patient records; it was constructed semi-automatically with manual editing and irregularity fixing. The automatic text processing is accomplished at several steps:

<u>Step 1: Preprocessing</u>, the text is split to a set of elements. The following tasks are performed at this step: *(i) tokenisation*, when a collection of tokens is constructed; *(ii) transliteration from Latin to Cyrillic letters*. This is done in order to reduce the dictionary of keywords; *(iii) transformation from lower to upper case letters* (to speed up the recognition process); *(iv) unifying the numbers' representation*. A unified format is set for all numeric values, e.g. numbers in the format 'nn,nn' are normalised to 'nn.nn'.

Step 2: Category analysis, a category (indicator name) is assigned to each element of the collection of tokens. This is accomplished as follows: (i) defining the category of each element using the dictionary (some elements can be juxtaposed multiple categories). It might be impossible to assign a category to elements, for instance some to phrases which contain more than one word. If the element is a part of the vocabulary and is included in certain phrase as a first or last special category word. а is assigned to it, thus marking the element for further processing. Examples of assigned categories are: I - denotes an indicator, g – element including a number, m – measuring unit of examination, n - phrase in the description of referential values (for instance: normal to ...); (ii) correcting the spelling errors whenever possible, missing 'левк10,1' e.g. spaces: (wrong, it has to be 'левк 10,1'), but GAD65 is correct; (iii) recognition of numeric values which are presupposed hours; (iv) recognition of medication dose (by the next element, which is supposed to be a dose measure); (v) grouping of tokens into phrases, e.g. "свободен тестостерон" ("free testosterone").

<u>Step 3: Complete test recognition</u>, at this phase the tokens obtained at step 2 are joined into groups using predefined rules. A newly formed group is viewed as an element of the collection too but the groups capsulate their constructing elements. The rule that builds the group assigns a category label to it too. The process of grouping continues until all build-in rules are tried successfully. When all rules fail, it is assumed the all possible categories are constructed.

Let us consider an example of our

rule-based approach to group elements: a rule which assigns the category *Norm* (*N*). The left-hand side of the rule consists of the tokens to be met in the text. The symbols '<' and '>' are used as separators, e.g. <(> denotes the token '('; <v> denotes a number, <s> – a separator. The rule itself is:

and it means the following:

Find an expression which: starts with "(", followed by a phrase signaling referential values <n>, followed by a number <v>, followed by a delimiter <s>, followed by a number <v>, followed by a ")". If all these are present in the given order then this is an expression defining a group of referential values <N>.

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Table 2. Eighteen variants of the rule $\langle ><n><v><s><v><)> => <N>$ which cover the expressions of this kind occurring in a training corpus of 1,000 patient records

Table 2 contains 18 variants of this rule, reflecting the various separators and delimiters learnt from a training set of 1,000 patient records. We found out empirically that the rule works successfully for an experimental corpus of 6,200 patient records.

Figure 5 shows how this rule is applied to the literals '(norm – 8,7-42)' in the text fragment 'testosterone - 3.2 (norm – 8,7-42)'. The tree of analysis is visible in the right-hand panel; it shows how the rule works for the particular phrase.

36

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Figure 5. Analysis of the phrase 'testosterone – 3,2 (norm- 8,7- 42)' in a patient record

APPLICATION

Today BITool is the system supporting the diabetes register at the University Specialised Hospital for Active Treatment of Endocrino-(USHATE) "Acad. logy Ivan Penchev". Medical University Sofia. USHATE was authorised by the Bulgarian Ministry of Health to host an anonymous register of diabetic patients in Bulgaria. This register contains 28 indicators of diabetic patients including age, sex, codes of diagnoses of diabetes and its complications, diabetes duration, risk factors, data about compensation, laboratory results, hospitalisations and prescribed medication. The IICT researchers and BITool developers helped for the automatic construction of this resource using language technologies and business analytics automatically [3]. The register is from Repository generated а of 112 million more than pseudonymised reimbursement requests (outpatient records) submitted to the National Health Insurance Fund (NHIF) in 2012-2014 for more than 5 million citizens, including 436,000 diabetic patients. The outpatient records are semi-structured files in XML format; in each file some tags contain free-text fields with important explanations about the patient: "Status", "Clinical ex-"Anamnesis", aminations" "Therapy". and The BITools functionalities for NER and extraction of clinical data support essentially the outpatient record pseudonymisation as well as the monitoring of significant indicators glycated hemoglobin like (HbA1c) blood sugar values. The oband jective of the register is to improve the healthcare and quality of life of diabetic patients and their families therefore adequate monitoring strategy was needed.

This application, up to the knowledge of the authors, enabled

a unique construction of a medical repository using specific language technologies in large scale, at national level, on an archive of existing patient records without burdening the General Practitioners (GPs) and other medical experts with additional data collection. In Bulgaria the information about diabetic patients was split at various institutions and sources, it was not collected and processed by contemporary information technologies, no databases and registers were available. Therefore no analysis, monitoring and adequate health management decisions were possible. On the other hand building a register by an ordinary approach would be too expensive, slow and ineffective.

The pseudoanonymisation of the outpatient records was performed on primary data in the National Health Insurance Fund; USHATE received only anonymised datasets. Tracking numerous visits of specific patients is possible using the pseudonymised ID of the citizen (EGN). In this way targeted monitoring of particular cases can be done by delivering findings and alerts back to NHIF and other health authorities who can communicate some feedback to the GPs.

The BITool provides fast overviews of this large register in different dimensions. Figure 6 shows the number of diabetic patients in the dimensions age-gender (at certain moment); Figure 7 - the number of diabetic patients per regions. Here BITool operates on the structured information from the NHIF archive: patient pseudonym, region code, age and gender. Further interesting statistics of this kind might concern explorations of diabetic patients per types of diabetes and diabetes complications, per GPs, per types of medication, according to frequency of visits and so on.



Figure 6. Number of diabetic patients grouped by age

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Figure 7. Number of diabetic patients grouped by regions

Extracting and analysing numeric values of important diabetic indicators like the glycated hemoglobin HbA1c, BITool provides explorations of patient status before and after some specific event or a moment of time. Figure 8 shows changes of glycated hemoglobin levels before and after first admission of a specific drug (the latter is presented in the outpatient records by the drug code). The exploration is done for about 400 patients who in certain period had HbA1c higher than 7% (considered normal level) which is the condition to start treatment with this particular drug (the brown area). It is seen that the HbA1c levels significantly decrease (the green area) therefore the therapy implies positive changes after first admission.



Figure 8. Exploring reductions of HbA1c levels after first application of a particular incretin based drug

Advances in Bulgarian Science



Figure 9. Reduction of HbA1c levels after application of incretin based drugs

Figure 9 illustrates the usual output in big data processing – exploration of the tendency in the development of some processes. It displays the number of patients who had changes in the HbA1c levels within the interval [-5,5] units for certain period of time. The tendency is that for most patients the HbA1c level decreased by 1 unit.

CONCLUSION

The product BITool has typical Business Intelligence functionality: it supports the data warehousing processes ETL (Extract, Transform, Load) to integrate data from multiple sources; enables MDM (Master Data Management) as a methodology that identifies the most critical information in the enterprise and provides OLAP (online analytical processing) of multidimensional data cubes. Most data analytics tools have this functionality [4] but the analysis of unstructured texts is beyond the scope of the field. In principle Business Intelligence software is oriented to the needs of large organisations that generate massive volumes of structured information.

Taking into consideration the specific Bulgarian environment where big data only emerge and most information is stored as free text, we designed a simple but efficient strategy how to adopt the BI approach to the needs of Bulgarian public organisations that produce archives and large data repositories. Apparently some extraction structuring functionality and was needed and we implemented it by text analysis tools. Further plans about BITool development concern deepening its capacity to analyse texts in public open data by automatic recognition of nomenclature and catalog entities.

ACKNOWLEDGEMENTS

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ИНТЕГРАЦИЯ НА ЕЗИКОВИ ТЕХНОЛОГИИ В СОФТУЕРЕН ПРОДУКТ ЗА АНАЛИЗИРАНЕ НА ДАННИ

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Резюме. Софтуерният пропозволява BITool дукт бързо и ефективно анализиране на големи количества данни чрез визуализиране на тенденциите за развитие на процеси, които се проследяват наблюдения чрез на данните представени като многомерен куб. Статията представя две надстройки на BITool за автоматичен анализ на свободен текст на български език: разпознаване на наименовани единици и извличане на числови стойности на определени индикатори. Обработката на

информация в текстов вид е съществено разширение на BITool, приложено при автоматичната генерация на анонимен диабетен регистър от архива на Здравната каса. Разработката е осъществена по проект BG161PO003-1.1.06-0023-С0001 "Анализиране и идентификация на зависимости в големи масиви от данни – приложение за икономически и технологични анализи" (2012 - 2015),финансиран по ОП конкурентоспособ-"Развитие на ността на българската икономика" (2007-2013).



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AWARDS

PYTHAGORAS AWARDS '2015 FOR SIGRNIFICANT CONTRIBUTIONS TO SCIENCE*

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The annual Pythagoras awards for significant contributions to science were held on June 18, 2015 during an elegant ceremony in the Royal Hall of Sheraton Sofia Hotel Balkan.

The minister of education and science, Prof. Todor Tanev, begin his welcoming speech at representatives of the academic and scientific community with an allegorically essay of Assoc. Prof. Muntyan about the proverb of Socrates, the Academia and the idea that never dies. "It's a good tradition, that rising the idea of Bulgarian science, minister Tanev says, but also a motivation to development of the youth and all of these people, who are "novices in the temple of science".

Sometimes called "the Bulgarian Oscars for Science" and "Bulgarian

Nobels", the Pythagoras awards are held to scientists, research teams and organization "for contributions and attainments in the field of research". Their establishment is regulated by the Law on Scientific Research Promotion. The main purpose is increasing the prestige of the scientific career and of the scientist profession in the public life. The awards are established in 2009 as successor of the prize "For significant contribution to science" by the Ministry of Education and Science, whose first winner was Academician Dimitar Mishev (2002).

Over 40 scientists from various scientific institutes and higher educational institutions have been nominated for the more prestigious insignia of honour in Bulgaria. Authoritative jury

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chaired by Corresponding Member Konstantin Hadzhiivanov and members Prof. D.Sc. Boris Galabov, Prof. D.Sc. Irina Doychinova, Dr. med. Veliz-Shivarov, Ph.D., Corresponding ar Member of BAS Petar Atanasov, Prof. D.Sc. Rumyana Damyanova and Prof. D.Sc. Chavdar Vasilev - all of them holders of Pythagoras awards from previous years - praised in 6 categories a number of 7 scholars: 4 from the Bulgarian Academy of Sciences (BAS), 2 from the Sofia University "St. Kliment Ohridski" and 1 from the Medical University of Sofia. The selection of proposals for nominations in the various categories are made on the basis of submissions and scientometric indicators – publications and citations for the period of 2013 to 2014, reflected in the international databases of Web of Science, but also on the overall assessment of the scientific contributions of the candidates.

The Grand Pythagoras Prize for young scholar – Pythagoras statuette and money prize of 10 000 BGN - was awarded to Assoc. Prof. Georgi Yord-**Ph.D.**, from the Faculty of anov. Chemistry and Pharmacy at the Sofia University "St. Kliment Ohridski". His research activity is in the field of nanotechnology with application to medioptoelectronics cine, and environmental protection. He develops polymeric based nanoparticles for drug delivery of antibiotics and anticancer agents. Assoc. Prof. Yordanov has contributions in the development of technologies for purification of water from nanoscale pollutants. The results of all these studies in the period of 2013 to 2014 are published in 9 papers (8 of them are in scientific journals with Impact factor) and 3 book chapters (2 of them are issued by CRC Press). The works of Assoc. Prof. Georgi Yordanov, Ph.D., are cited 76

times in the specialized literature during the same period. Assoc. Prof. Yordanov participates in national scientific projects and international European programs in the field of nanotechnology. He is supervisor and adviser of graduates and lecturer of university courses in the field of biomedical and pharmaceutical nanotechnology. He is a winner of 2 bronze medals from international Olympiads in chemistry in India and Denmark, as well as the Young Scientist Award of the Sofia University.

In the category **Grand Prize for successful manager of international projects** the jury bestow two first prizes. Pythagoras statuette and money prize of 5000 BGN were awarded to Prof. D.Sc. Galya Mladenova Angelova and Assoc. Prof. Neli Stoyanova Koseva, Ph.D.

Prof. D.Sc. Galya Mladenova Angelova is head of section "Linguistic Modelling" in the Institute of Information and Communication Technologies at the BAS. She is manager of the project "Advanced Computing for Innovation (AComIn)", in which created new high-performance are methods and algorithms applied in the development of composite and porous materials. Modified are statistically optimized approaches to acoustic holography and an adaptive method for spectral analysis and bistatic aperture; developed are assistive computer interfaces for improvement the quality of life for disadvantaged people, robotic systems for human health, nature-conservation and energy-efficient technologies for processing materials. The project is financed by the Seventh Framework Programme of the European Commission in an amount totaling over 6 million BGN. As a result are published 30 papers in impact factor journals and 67 papers in impact rank journals, submitted are application for 3 patents, the scientific infrastructure of the institute is renovated and a special attention is paid to the young scientists – within the project are prepared 10 PhD dissertations and Postdoctoral Researchers 14 from European countries are appointed. Organized are 21 seminars with presented lectures of 28 foreign visiting scholars, who attended the Institute of Information and Communication Technologies in connection with the project. The results of the research are directed to a number of innovative sectors and to improving the quality of life.

Assoc. Prof. Neli Stoyanova Koseva, Ph.D., is Director of the Institute of Polymers at the BAS. She is manager of the project "Strengthening of the Research Capacity and Innovation Potential of the Institute of Polymers at the BAS for full integration into the European Research Area", funded by the Seventh Framework Programme of the European Commission. The aim of the project is strengthening of the potential for research and innovations in the field of the advanced polymeric materials. Supported are research and innovation activities, which are considered as strategical for the development of the Institute of Polymers and their results are focused to key sectors for the society – public ecology, alternative energy health. sources and efficient use of resources. As a result of the project implementation currently are published 75 papers and are submitted 2 applications for patents. By the members of the project team 90 papers on various scientific forums are presented. Assoc. Prof. Dr. Neli Koseva is supervisor of 6 successfully defended PhD students. She is also manager of 2 other projects under EU programs and funds, as the amount of acquired funds is 6,653 million BGN.

The Prize for established researcher in the field of natural and mathematical sciences - plaque and 5000 BGN money prize – was received by Prof. D.Sc. Stoycho Stoyanov Yazadzhiev, lecturer in the Faculty of Physics at the Sofia University "St. Kliment Ohridski". His research activity is focused on the Einstein's Theory of General Relativity. Among his main contributions in the period of 2013 to 2014 are in the fields of: 1) Exploring fundamental investigations on the problem of dark energy at astrophysical scales and 2) the mathematical understanding of Einstein's equations and their modifications through inclusion of the dark energy. In 2013-2014 Prof. Yazadzhiev published 14 articles in international impact factor journals. He has specialized in the University of Goettingen and in the University of Tuebingen in Germany. He is repeatedly Visiting Professor in prestigious European universities, author and co-author of two textbooks and 125 articles, as 90 of them are published in reputable international journals with impact factor. His works are cited over 1000 times. He is supervisor of 5 successfully defended PhD students. He is also coordinator and an active participant in numerous national and international projects.

The Prize for established researcher in the field of biomedical sciences - plaque and 5000 BGN money prize - was prized to Assoc. Prof. Dr. Radka med. Petrova Kaneva, Ph.D., from the Medical University of Sofia. She works in the field of medical genetics. Her researches are focused on the detection and study of genes associated with progress of various oncological diseases and development of biomarkers for diagnosis and prognosis. She manages and participates in many international projects in the field of biomedical sciences. Assoc. Prof. Kaneva is author of 88 articles, which are cited 1131 times (through the last year – 23 articles and 462 citations). She has 60 participations in national and international scientific forums. She is supervisor of 8 PhD students. She is also a fellow of international organizations, several member of editorial boards of one national and 3 international scientific iournals, Assoc, Prof. Dr. med, Kaneva is holder of the prize "Golden Panacea" for particular contributions in teaching, research and expert activity in the medico-biological field.

The Prize for established researcher in the field of social and humanitarian sciences - plaque and 5000 BGN money prize – was received by Assoc. Prof. Dorotey Naydenov Getov, Ph.D., from the Institute of Literature at the BAS, a prominent expert on Greek paleography and condicology and history of the Byzantine liter-He studies ature. Bvzantine manuscripts, connected with the history of European law, explores the Greek manuscripts in Bulgaria as texts of the Byzantine literature. He is author of 7 books and more than 20 papers, published in Bulgarian, Modern Greek, English and German. In Belgium Assoc. Prof. Getov published a volume with 102 manuscripts and fragments from the Library of Bachkovo Monastery, which is nearly 1000 years old, identifying 3 original manuscripts of one of the founders of the Monastery - Gregorius Pacurianus. He also discovered hundreds of unknown works of Byzantine literature, including 253 manuscripts of anthems, found in Bulgaria, 670 - in Sinai manuscripts and others. Through his comprehensive research work Assoc. Prof. Dr. Dorothey Getov enriches the scientific

resource of contemporary humanities.

The Prize for established researcher in the field of technical sciences - plague and 5000 BGN money prize – was awarded to **Assoc.** Prof. Milen Ivanov Georgiev, Ph.D., from the Institute of Microbiology at the BAS. He focused his studies on the biosynthesis of commercially important molecules of plant origin and development of biotechnological approaches to their sustainable production. Here the main subjects are the natural molecules with anti-inflammatory and anti-neoplastic effect and the development of advanced methods for metabolic engineering. He specializes in Germany and in Netherland. In the period of 2013 to 2014 the results of his researches are summarized in two book chapters and in 20 articles, 18 them in international impact from factor journals. For the same period his works are cited 270 times. He is winner of the BAS's "Marin Drinov" award and of the 2011 Grand Pvthagoras Prize for young scientist.

This year, for the very first time, are awarded prizes for high scientific result by Elsevier and Thomson Reuters, partners of Bulgaria in scientometrics.

Mr. Charles Pallandt, Vice President International Markets at Elsevier. handed the award SciVal for the highest quality of scientific output which means with highest Field Weigted Citation Impact 1.13 in all disciplines for the period of 2012-2014 to the Sofia University "St. Kliment Ohridski". The award was received by the Rector, Corresponding Member of BAS Ivan Ilchev. He thanked to all, who "for years are fighting against the militant illiteracy, but never give up".

The Thomson Reuters manager Mr. David Horky handed the award for articles that occupy first place in the three criteria for high scientific quality – Essential Science Indicators for highly cited, top and hot papers – to the Institute for Nuclear Research and Nuclear Energy at the BAS, represented by the Deputy Director, Corresponding Member Chavdar Stoyanov.

All of the awarded scholars express their gratitude to the Ministry of

Education and Science, which in the worst years for science keeps the tradition to distinguish their achievements and to make them public. The Pythagoras Prize is appreciation not only to the awarded scholars for their remarkable achievements through the last two years, but also to all of the people, who perceived as his life's mission the path of scientific research.

JOHN ATANASOFF AWARD AND PRIZES '2015*



The John Atanasoff Award and Prizes '2015 were awarded for 13th consecutive year by the President of the Republic of Bulgaria Mr. Rosen Plevneliev through an official ceremony on 5th October 2015. The award is named after the eminent scholar of Bulgarian origin John Atanasoff, who invented the first electronic digital computer. It has been handed out since 2003 in support of the personal achievements of young Bulgarian researchers working in the fields of informatics and information technologies.

The John Atanasoff Award '2015 for outstanding achievements in the field of information technologies was awarded to **Dr. Tzeno Galchev**. He holds doctoral degree from the University of Michigan, USA. Dr. Galchev has developed several microsystems that can record the electrical neuronal signals in the brain for the purpose of

Note: The article is prepared based on official information available on the President's website at: https://www.president.bg/cat40/773/Dr-Tzeno-Galchev-is-the-winner-of-the-2015-John-Atanasoff-Award.html&lang=en studying its functionality, with the hope that in the future the same tools can be used to cure a number of different neurodegenerative diseases. Dr. Galchev presented the highlights of his work at a special open-access lecture.

Prizes for outstanding achievements at some of the most competitive international computer sciences Olympiads has received the student **Marin Shalamanov**, and his tutor **Peter Petrov**, as well as the student **Viktor Kirilov** and his teacher **Krasimir Assenov**.

Two new categories to the John Atanasoff Award were introduced in 2015.

Mr. Hristo Stoyanov, first-year

student in Stanford University, USA, received the prize "First steps in computer sciences" for representing Bulgaria in the Intel International Science and Engineering Fair '2015 and for his ranking inside the top 5 of the Research Science Institute contest '2014.

Mr. **Georgi Darzhanliev** and Mr. **Stanimir Nenov** received the prize "John Atanasoff – for projects with social value-added" for their project Pravatami.bg, a platform that aims to improve the understanding of legal matters by the wider public.

The laureates of each category received additional prizes provided by governmental and non-governmental organizations, as well as corporations.

ARTICLES

RECENT PUBLICATIONS OF BULGARIAN SCIENTISTS

Title:	First principles approach to the electronic structure, magnetic anisotropy and spin relaxation in mononuclear 3d-transition metal single molecule magnets
Authors: Source:	Atanasov, M., Aravena, D., Suturina, E., Bill, E., Maganas, D., Neese, F. Coordination Chemistry Reviews, Volume 289-290, Issue 1, 2015, Pages 177-214
Author Affiliations:	Max Planck Institut für Chemische Energiekonversion, Stiftstr. 34-36, Mülheim an der Ruhr, Germany Institute of General and Inorganic Chemistry, , Akad. Georgi Bontchev Street 11, Sofia, Bulgaria
ISSN:	0010-8545
Title:	Cationic triblock copolymer micelles enhance antioxidant activity, intracellular uptake and cytotoxicity of curcumin
Authors:	Yoncheva, K., Kamenova, K., Perperieva, T., Hadjimitova, V., Donchev, P., Kaloyanov, K., Konstantinov, S., Kondeva-Burdina, M., Tzankova, V., Petrov, P.
Source:	International Journal of Pharmaceutics, Volume 490, Issue 1-2, 4 June 2015, Pages 298-307
Author Affiliations:	Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Medical University of Sofia, 2 Dunav Str., Sofia, Bulgaria Institute of Polymers, Bulgarian Academy of Sciences, Akad G Bonchev Str., Bl. 103A, Sofia, Bulgaria Department of Physics and Biophysics, Medical Faculty, Medical University of Sofia, Sofia, Bulgaria Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University of Sofia, Sofia, Bulgaria
ISSN:	0376-5175
Title:	Study of structural break points in global and hemispheric temperature series by piecewise regression
Authors:	Werner, R., Valev, D., Danov, D., Guineva, V.
Source:	Advances in Space Research,Volume 56, Issue 11, 1 December 2015, Pages 2323-2334
Author Affiliations:	Space Research and Technology Institute, Bulgarian Academy of Sciences, Stara Zagora Department, P.O. Box 73, Stara, Zagora, Bulgaria Space Research and Technology Institute, Bulgarian Academy of Sciences, Acad. Gerogy Bonchev Str. Bl. 1, Sofia, Bulgaria
ISSN:	0273-1177

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Title:	Organic cultivation of field pea by use of products with different action
Authors: Source:	Georgieva, N. Nikolova, I., Delchev, G. Spanish Journal of Agricultural Research,Volume 13, Issue 4, 2015, Article number e0906, 13p
Author Affiliations:	Institute of Forage Crops, Department of Technology and Ecology of Forage Crops, Pleven, Bulgaria Trakia University, Stara Zagora, Bulgaria
ISSN:	1695-971X
Title:	Molecular Dynamics Simulation of the Aggregation Patterns in Aqueous Solutions of Bile Salts at Physiological Conditions
Authors: Source:	Mustan, F., Ivanova, A., Madjarova, G., Tcholakova, S., Denkov, N. Journal of Physical Chemistry B, Volume 119, Issue 51, 24 December 2015, Pages 15631-15643
Author Affiliations:	Department of Chemical and Pharmaceutical Engineering, Faculty of Chemistry and Pharmacy, University of Sofia, 1 James Bourchier Avenue, Sofia, Bulgaria
ISSN:	University of Sofia, 1 James Bourchier Avenue, Sofia, Bulgaria 1520-6106
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Authors: Source:	Gencheva, R.V., Stefanova, A.E., Groudev, P.P. Nuclear Engineering and Design, Volume 295, 15 December 2015, Pages 441-456
Author Affiliations:	Institute for Nuclear Research and Nuclear Energy (INRNE), Tzarigradsko shaussee 72, Sofia, Bulgaria
ISSN:	0029-5493
Title:	DNA damage and repair in plants – From models to crops
Source:	Frontiers in Plant Science, Volume 6, Issue OCTOBER, 23 October 2015, Article number 885
Author Affiliations:	Department of Molecular Genetics, Institute of Plant Physiology and Genetics, Bulgarian Academy of Sciences, Sofia, Bulgaria Department of Genetics, University of Silesia, Katowice, Poland
ISSN:	1664-462X
Title: Authors: Source: Author Affiliations:	Two-phonon Raman bands of bilayer graphene: Revisited Popov, V.N. Carbon, Volume 91, 30 May 2015, Pages 436-444 Faculty of Physics, University of Sofia, Sofia, Bulgaria
ISSN:	0008-6223

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Title:	Thin-layer chromatographic study of some reactive dyes and fluorescent brighteners and their intermediates containing stabilizer fragment for textile and polymers
Authors: Source:	Miladinova, P.M. Journal of Planar Chromatography - Modern TLC, Volume 28, Issue 1, 1 February 2015, Pages 6-11
Author Affiliations:	Organic Synthesis Department, University of Chemical Technology and Metallurgy, 8 Kl. Ohridsky str., Sofia, Bulgaria
ISSN:	0933-4173
Title:	Reconstructing eclecticism: Bulgarian economic thought in the Ottoman Empire in the nineteenth century
Source:	History of Political Economy, Volume 47, Issue 4, 1 December 2015, Pages 631-664
Author Affiliations:	CRIISEA, University of Picardie, Amiens, France University of National and World Economy, Sofia, Bulgaria 0018-2702
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Author Affiliations:	Rostislaw Kaischew Institute of Physical Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria Institute of General and Inorganic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria
ISSN:	1002-0721
Title: Authors:	PI-properties of some matrix algebras with involution Rashkova, T.
Source: Author Affiliations:	University of Ruse, Department of Mathematics, 8 Studentska Str, Ruse, Bulgaria
ISSN:	1787-2405
Title:	Lyapunov functions and strict stability of Caputo fractional differential equations
Authors:	Agarwal, R., Hristova, S., O'Regan, D.
Source:	Advances in Difference Equations, Volume 2015, Issue 1, 1 December 2015. Article number 346. Pages 1-20
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ISSN: 1687-1847	University of Ireland, Galway, Ireland

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Title: Authors: Source: Author Affiliations: ISSN:	The international symposium on phytochemicals in medicine and food (ISPMF 2015): An introduction Xiao, J., Georgiev, M.I. Food Chemistry, Volume 186, 1 November 2015, Page 1 College of Food Science, Fujian Agriculture and Forestry University, Fuzhou, Fujian, China Institut für Pharmazie und Lebensmittelchemie, Universität Würzburg, Am Hubland, Würzburg, Germany Laboratory of Applied Biotechnologies, Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, 139 Ruski Blvd., Plovdiv 0308-8146
Title: Authors: Source: Author Affiliations: ISSN:	Interfacial reactions between solid Ni and liquid Sn-Zn alloys Gandova, V. Journal of Mining and Metallurgy, Section B: Metallurgy, Volume 51, Issue 2, 2015, Pages 179-184 University of Food Technologies, Inorganic and Physical Chemistry Department, Plovdiv, Bulgaria 1450-5339
Title: Authors: Source: Author Affiliations: ISSN:	On canonical-type connections on Almost contact complex Riemannian manifolds Manev, M. Filomat, Volume 29, Issue 3, 2015, Pages 411-425 Department of Algebra and Geometry, Paisii Hilendarski University of Plovdiv, 236 Bulgaria Blvd, Plovdiv, Bulgaria 0354-5180
Title: Authors: Source: Author Affiliations: ISSN:	Effects of ursolic acid on contractile activity of gastric smooth muscles Prissadova, N., Bozov, P., Marinkov, K., Badakov, H., Kristev, A. Natural Product Communications, Volume 10, Issue 4, 2015, Pages 565-566 Department of Biophysics, Medical University, 15A Vassil Aprilov Str., Plovdiv, Bulgaria Department of Biochemistry and Microbiology, Plovdiv University, 24 TzarAssen Str., Plovdiv, Bulgaria 1934-578X
Title: Authors: Source: Author Affiliations: ISSN:	On the minimum length of linear codes over F 5 Bouyukliev, I., Kageyama, Y., Maruta, T. Discrete Mathematics, Volume 338, Issue 6, 6 June 2015, Pages 938-95 Institute of Mathematics and Informatics, Bulgarian Academy of Sciences, Veliko Tarnovo, Bulgaria Department of Mathematics and Information Sciences, Osaka Prefecture University, Sakai, Osaka, Japan 0012-365X

Title: Classification of binary self-dual codes of length 40 Authors: Bouyukliev, I., Dzhumalieva-Stoeva, M., Monev, V. IEEE Transactions on Information Theory, Volume 61, Issue 8, August Source: 2015, Article number 7122881, Pages 4253-4258 Author Affiliations: Institute of Mathematics and Informatics, Bulgarian Academy of Sciences, Veliko Tarnovo, Bulgaria Faculty of Mathematics and Informatics, Veliko Tarnovo University, Veliko Tarnov **ISSN:** 0018-9448 Gas chromatography-mass spectrometry for characterization of Title: liquid products from pyrolysis of municipal waste and spent tyres Authors: Pavlova, A., Stratiev, D., Mitkova, M., Stanulov, K., Dishovsky, N., Georgiev, K. Source: Acta Chromatographica, Volume 27, Issue 4, December 2015, Pages 637-655 Author Affiliations: Research Laboratory, LUKOIL Neftohim Burgas JSC, Burgas, Bulgaria Process Engineer Department, LUKOIL Neftohim Burgas JSC, Burgas, Bulgaria University Prof. D-r Assen Zlatarov, Blvd. Prof. Yakimov No. 1, Burgas, Bulgaria University of Chemical Technology and Metallurgy, Blvd. Kliment Ohridski No. 8, Sofia, Bulgaria **ISSN:** 1233-2356

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EVENTS

Scientific Symposium on BENEFICIAL AND PATHOGENIC MICROBES FOR HEALTHIER LIFE AND SAFETY FOODS

The scientific symposium "Benefiand Pathogenic Microbes cial for Healthier Life and Safety Foods" takes place on April, 8-9, 2015 at The Stephan Angeloff Institute of Microbiology in the Bulgarian Academy of Science. Its aim was to explore critical points in application of beneficial microbes - probiotics and the risk of food-borne pathogens, as follows: for safety and functional food; new approaches for prevention the microbial risks in food chain from pathogens; new trends in protection of human and animals health; prophylaxis and therapy of food disorders for wellbeing and health.

Seven oral presentations are presented during the symposium. They are dedicated to various issues, as follows: Foodborne diseases – etiological aspects (by Prof. Hristo Najdenski); Distribution and antimicrobial resistance of Listeria monostrains from foods cvtogenes in Bulgaria (Eva Gyurova, Hristo Daskalov); Beneficial properties of Bulgarian lactic acid bacteria (Svetla Danova); Health benefits of functional probiotic cultures (Stefan Denev. Georgi Beev, Toncho Dinev, Rumyana Moutafchieva, Teodora Georgieva); Expression of some genes involved in the utilization of oligosaccharides and their transport (Ilia Iliev, Iskra Ivanova); Comparative analysis of lactobacilli count in fabricated and (Galina home-made yogurt Satchanska); Forgery and fraudulent practices in the production and trade in food (Yordan Gogov).

A separate panel was designed to poster session and presentations of young scholars.

International conference on MATHEMATICAL METHODS AND MODELS IN BIOSCIENCES (BIOMATH 2015)

This annual conference takes place on June, 14-19, 2015 at the University centre Bachinovo, Blagoevgrad, Bulgaria. It's devoted to recent research in life sciences based on applications of mathematics as well as mathematics applied to or motivated by biological studies.

The conference was opened with Roumen Tsanev plenary lecture by Assoc. Prof. Leander Litov, PhD. Keynote speakers this year were: Ekaterina Auer (University of Applied Sciences Wismar, Germany), Ivan G. Ivanov (Institute of Molecular Biology, Bulgarian Academy of Sciences, Bulgaria), Ivan V. Ivanov (College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, USA), Vlastimil Krivan (Biology Centre CAS, Ceske Budejovice, Chech Republic), Christina Kuttler (Technical University Munich, Zentrum Mathematik, Germany) and Cyril Piou (CIRAD – Département BIOS – UMR CBGP, France).

Within the conference a School for Young Scientists was organized.

10th International Conference on COMMUNICATIONS, ELECTROMAGNETICS AND MEDICAL APPLICATIONS (CEMA'15)

The conference takes place on October 15-17, 2015, at the Technical University of Sofia, International Meeting Center "Helmut Boehme". It is dedicated to all essential aspects of the development of global information and communication technologies and their impact for medicine. The objective of the Conference is to bring together lecturers, researchers and practitioners from different countries, working on the field of communication, electromagnetism and medical applications, computer simulation of electromagnetic field, in order to exchange information and bring new contribution to this important field of engineering design and application in medicine.

The conference program was organized in five sessions and includes 25 presentations of authors from Bulgaria, Japan, Lithuania, Russia and Serbia.

The sessions were chaired by the Professors P. Frangos (NTUA, Athens, Greece), Kalin Dimitrov (Technical University of Sofia, Bulgaria), Rasa Brūzgienė (Kaunas University of Technology, Lithuania), N. Ampilova (St. Petersburg University, Russia) and Dimitar Dimitrov (Technical University of Sofia, Bulgaria).

Most of the participants were from Bulgaria, including a large contingent from the Technical University of Sofia. The speeches presented were the following: Evaluation of experimental results different centrifuges for and for optimization (Tsvetan purposes Kachamachkov, V. Manoev); Mathematical analysis of how spinning under an angle affects the vestibular system of pilots (Tsvetan Kachamachkov); Experimental study of existing centroreal hospital fuges in conditions (Tsvetan Kachamachkov, V. Manoev. D. Dimitrov); Implementation for MEMS in the vestibular system (V. Manoev. Tsvetan Kachamachkov); New research for MEMS in the vestibular system and basic over view of MEMS used TILL now (V. Manoev, Tsvetan Kachamachkov); Clinical results in the treatment of patients with diabetic polyneuropathy with simultanapplication of low-frequency eous magnetic field and mineral water (Vladimir Petrov, Dimitar Dimitrov); 3D model of platform for spinning pilots under an angle and other medical uses (Tsvetan Kachamachkov); Fundamental Study on Measurement of Dielectric Constants of Human Abdomenby Waveguide-Penetration Method (Takahiro Aoyagi); Portable 3-channel real-time EMG acquisition device for use with myoelectric prostheses (Viktor A. Nedialkov); Software for analyzing EMG signals EMGLab (Viktor A. Nedialkov, Dimitar Dimitrov, Kalin Dimitrov); Lower limb EMG signals study from different muscles for potential myoelectric prostheses control (Viktor A. Nedialkov).

2ND INTERNATIONAL CONFERENCE ON NATURAL PRODUCTS UTILIZATION: FROM PLANTS TO PHARMACY SHELF (ICNPU-2015)

The second International Conference on Natural Products Utilization: from Plants to Pharmacy Shelf took place in hotel Novotel Plovdiv, 14 – 17 of October. The ICNPU-2105 meeting was jointly organized by The Stephan Angeloff Institute of Microbiology and Institute of Organic Chemistry with Centre of Phytochemistry, both belonging to the Bulgarian Academy of Sciences.

The ICNPU-2015 conference traditionally focuses on the contemporary trends in prevention and treatment of malignancies, the emerging omics analytical platforms as well as sustainable production and use of natural products.

The international organizing committee of ICNPU-2013 assembled an exciting and diverse program, featuring 19 invited lectures, 51 short oral presentations and 253 poster presentations.

Thanks to the financial support from the Ministry of Education and Science ten young Bulgarian scientists (PhD students and assistants) afforded to attend the ICNPU-2015 and hence presented their thesis and work to the broad scientific community.

The ICNPU-2015 was well attended by 330 participants from 50 difference countries.



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