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SEKSIONI I SHKENCAVE TË NATYRËS

RESEARCH  
26  
KËRKIME



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Bajram Berisha\*,<sup>1</sup>

## NANOPARTICLES AND THE OVARY FUNCTION: THE NEGATIVE EFFECTS ON THE FOLLICULAR DEVELOPMENT AND OVULATION

### Abstract

Recent literature results show that nanoparticles (NP) accumulation damages the physiology of the ovary by disrupting follicular development and the ovulation process during the ovarian cycle. The ovarian cycle is characterized by regularly repeating cellular proliferation, differentiation and transformation patterns accompanying follicular development, maturation and ovulation during the folliculo-luteal transition and corpus luteum (CL) formation. Therefore, any adverse effect of nanoparticles in each of these physiological stages of ovarian function will cause irreparable damage to the reproductive processes, thus causing temporary or permanent infertility of various species. The possible molecular mechanisms of nanoparticle cytotoxicity in the ovary tissue include inflammation, oxidative stress, apoptosis etc. Nanoparticles can enter both follicle cell types (theca and granulosa), affecting their normal function (steroid hormone production), particularly before ovulation. Additionally, exposure to specific nanoparticles can significantly alter levels of gonadotrophins (LH, FSH) and steroid hormones (progesterone, testosterone, estradiol), which causes follicle atresia and anovulation, resulting in reduced fertility. In conclusion this contribution will offer a comprehensive overview of the current state of knowledge regarding the potential adverse effects of nanoparticles on ovary function. In addition, an improved understanding of the molecular mechanisms of nanoparticle toxicity during follicle development and ovulation has an important implication for reproductive health and fertility regulation.

*Keywords:* Nanoparticles, toxicity, folliculogenesis, ovulation, ovary.

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## INTRODUCTION

The interest for studies on the toxicity of nanoparticles (NPs) in the organs and processes of reproduction is growing rapidly. However, there are still mechanisms of action that require more detailed studies and research. The objective of this overview was to discuss recent findings showing that nanoparticle accumulation damages the physiology of the ovary by disrupting follicular development and ovulation process, causing important implications for the reproductive health and regulation of fertility [1, 2].

Nanoparticles – nanoscale dimensions particles (usually smaller than 100 nanometers), currently have been widely used in all aspects of life (medicine, agriculture, pharmacology, and engineering) [2, 3]. The continued increase in the application of nanoparticles in all mentioned aspects of life is raising significant health concerns. Nowadays, nanoparticles can be found in drug delivery systems, clinical therapy and various daily used products such as cosmetics, clothes, food etc. Therefore, in addition to intentional application in medicine, dermal, pulmonary, and gastrointestinal exposures are the three main exposure routes. Despite the differences, all the ways of penetration of nanoparticles in the living organism cause biological damage of different levels.

In particular, the application of nanotechnology in modern medicine is expected to enhance our quality of life through early diagnosis and treatment of diseases and other health problems. Thus, in addition to treating common medical conditions, pharmaceutical nanotechnology for each day and more offers opportunities to diagnose and treat specific health problems, such as neurodegenerative diseases, diabetes, cancerous diseases, etc. However, such a widespread use of nanotechnology and nanoparticles in medicine requires constant care regarding their eventual toxicity [1, 3].

The negative impact of nanoparticles on living organisms depends on the properties of nanoparticles such as shape, size, structure, dosage, material, surface-coating etc. [1, 2, 3]. It is well known that many nanoparticles can pass certain biological barriers and exert toxic effects on various organs, such as the brain, liver, kidney and also ovary and other female reproductive organs [2, 4].

## *The female reproductive system and ovary function*

The female reproductive system consists of the external and internal sexual organs that are in the service and function of the reproduction of new offspring and the preservation of the species. It is already known that the primary female reproductive organ (gonad) is the ovary (pair organs). The ovary is a complex organ that performs two essential reproductive functions, one gametogenic (production of sexual cells) and one endocrine (hormone production). This process requires a perfectly coordinated interplay of various endogenous and exogenous factors.

The ovarian cycle central to reproductive function, is characterized by repetitive cellular proliferation, differentiation, and transformation patterns that include follicular development and ovulation, as well as formation, function, and regression of the corpus luteum [5]. Therefore, in addition to the role of the ovaries in egg cell production, they represent endocrine glands that secrete hormones (mainly estrogen and progesterone), which are essential for normal reproductive development and fertility [6].

### *Folliculogenesis (Follicle growth and development) and ovulation*

In female mammals, the whole number of oocytes (egg cells) are in the ovaries at birth. A follicle represents the structural and functional unit of oocyte and follicular tissue. Folliculogenesis is the process that means recruited primordial follicle grow and develop into tertiary level (Graafian follicle), with the potential to either ovulate their egg for fertilization or to undergo atresia [7]. The ovulation cycle is controlled by a complicated neuroendocrine system consisting of the brain, the adenohypophysis, the ovaries and complex feedback systems as schematically presented in figure 1.

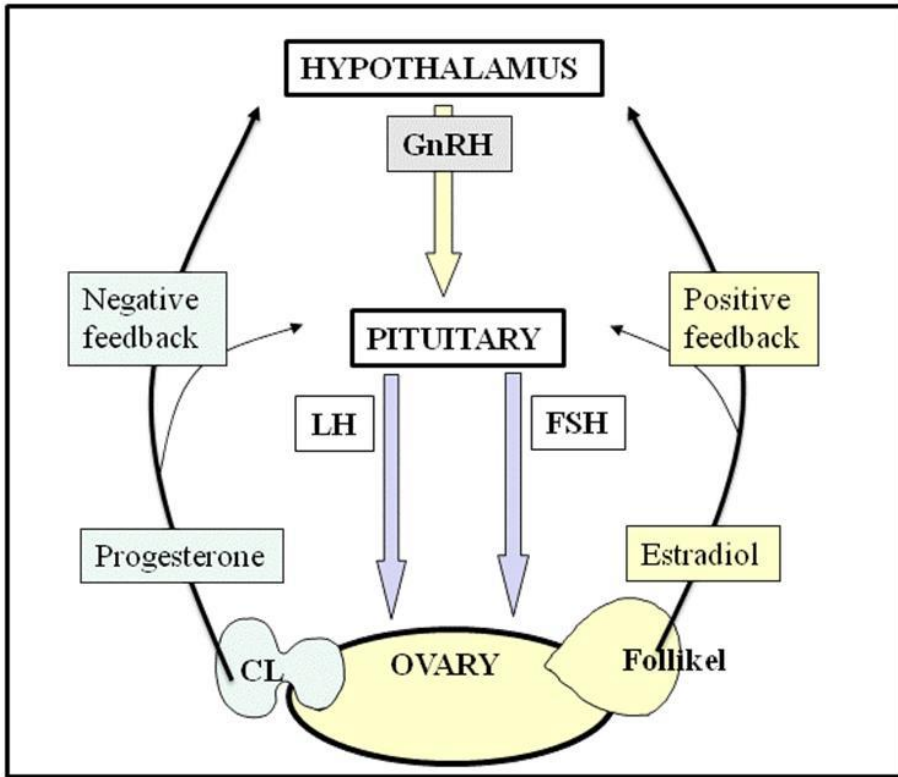
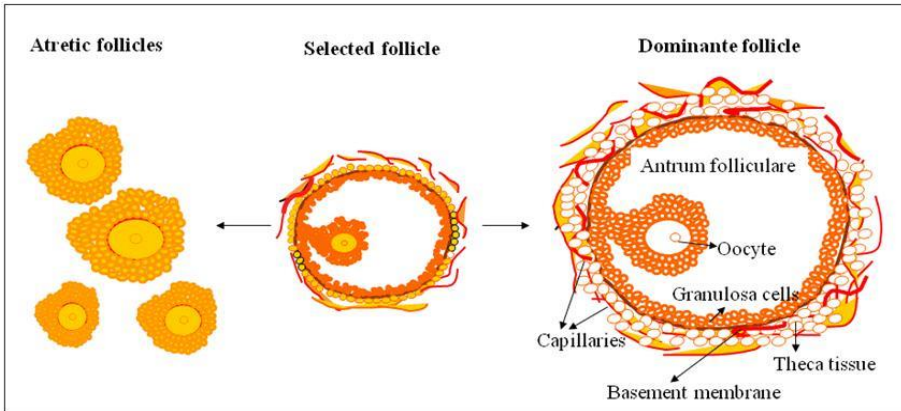


Figure 1. Ovary and hypothalamic-pituitary-gonadal axis, gonadotropins and steroid hormone secretion and feedback mechanisms. Abbreviations: GnRH – Gonadotropin Releasing Hormone, LH – Luteinizing Hormone, FSH – Follicle Stimulating Hormone, CL – Corpus luteum.

Some of the processes that occur here are already very well understood; however, besides the endocrine systems, in the complex of the ovarian physiology, the autocrine and paracrine processes are also involved in [5, 8]. Growth and development of the ovarian follicles (folliculogenesis) involve the recruitment of a cohort of follicles and the selection of a dominant follicle that continues to grow and mature to the preovulatory stage (5, 7, 9-11]. A complex regulatory system must exist to determine which follicles are selected for ovulation (Figure 2).



*Figure 2. Schematic presentation of growth and development of the ovarian follicles (folliculogenesis), involving the recruitment of a cohort of follicles and selection of a dominant follicle until the preovulatory stage (Figure 2 adapted from [52]).*

The ovarian function is mainly regulated by the pituitary gonadotropins FSH (follicle-stimulating hormone), LH (luteinizing hormone) and their receptors. Additionally, it is evident that locally produced factors (paracrine regulation) such as steroid hormones, peptides and growth factors play an essential modulating role in follicular development (follicle recruitment, selection and dominance) and periovulation process [7, 12-15]. Ovulation (the release of an egg from the ovarian follicle) happens as a result of a dynamic interaction between the increase in LH and local follicular factors, including steroid hormones, extracellular matrix proteases, prostaglandins, vasoactive peptides, and numerous growth factors [7, 16-18], localized or secreted in different follicular cells and tissues (Granulosa and theca cells) as schematically presented in Figure 3.

Furthermore, the steroid hormones and prostaglandins appear to be very important regulatory mediator, playing a central role regulating folliculogenesis and ovulation [19-23]. The progesterone and estradiol levels in the preovulatory follicles changes dramatically during the preovulatory phase, suggesting that they play important roles during and after ovulation [20, 24-26].

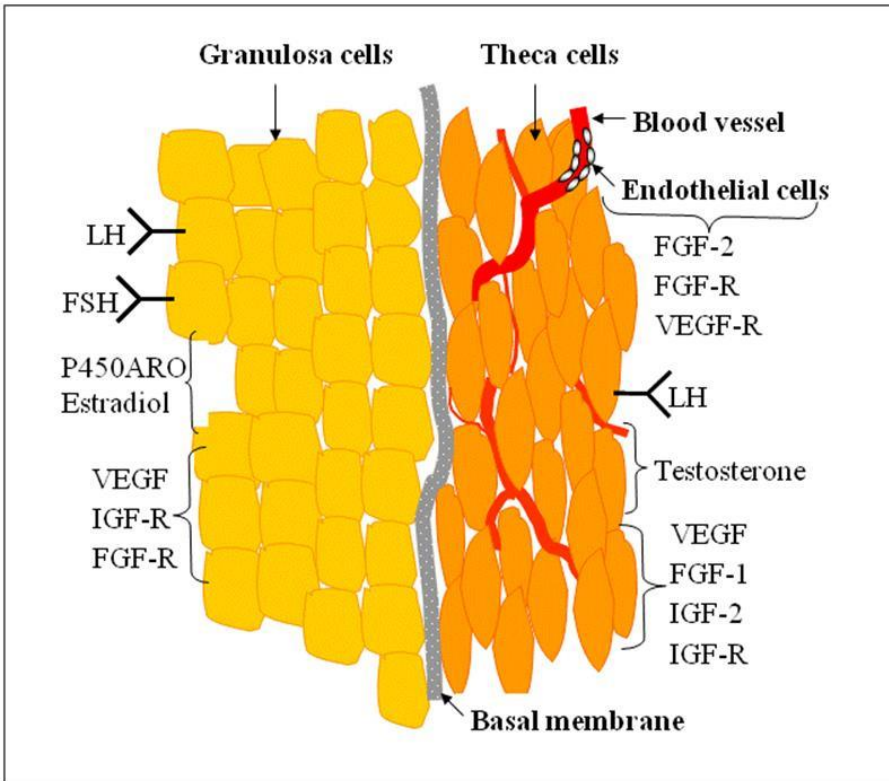


Figure 3. Schematic presentation of proposed actions of intrafollicular hormones (steroids, gonadotropins and enzymes) and different growth factors (and their receptors) in theca tissue, granulosa and endothelial cells of a preovulatory bovine follicle (Modified figure after Berisha & Schams, 2005). Abbreviations: P450ARO – cytochrome P450 aromatase, LH – Luteinizing Hormone, FSH – Follicle Stimulating Hormone, VEGF – vascular endothelial growth factor, IGF – Insulin-like Growth Factor, FGF – Fibroblast Growth Factor, R – Receptor (Figure 3 adapted from [5]).

In addition, the later stage of follicle development, ovulation and corpus luteum formation depends on the growth of new blood vessels (angiogenesis) and establishing a functional blood supply [27-30]. During this folliculo-luteal transition, angiogenesis (the development of a vascular network from existing blood vessels) seems to be the most important regulatory event for ovarian function, which is closely regulated by different endocrine and paracrine angiogenic factors [15, 31-32]. Based on the research results, ovarian angiogenesis is established and is of great importance for follicle development and ovulation. The angiogenic factors, produced by granulosa cells, play a crucial role

in follicular growth via stimulating angiogenesis in the tissue layers of preovulatory follicles [33-34]. It has been reported that angiogenesis in theca follicle layers is dependent on follicle-stimulating hormone (FSH) that induces the expression patterns of HIF1A (Hypoxia Inducible Factor 1 Subunit Alpha) and VEGF (vascular endothelial growth factor) isoforms in granulosa cells [35-36]. In addition, the dominant angiogenic factors regulate final follicle maturation and ovulation and seem essential in early luteal angiogenesis and in corpus luteum formation [15].

Recent publications have focused on applications of nanoparticles in angiogenesis [37-39]. In addition, detailed information about the potential use of nanoparticles in various nanotechnology-based angiogenesis strategies in recent years was described by Dhruva and Shaker [40]. Therefore, an improved understanding of the molecular mechanisms of the biology of angiogenesis has important implications for regulating fertility on the one hand, and the other for treating different angiogenesis-dependent diseases [15, 37-40]. After ovulation, the remaining granulosa cells and theca tissue form the corpus luteum, a temporary endocrine gland that produces one of the most influential female hormone, progesterone. Progesterone regulates the sexual cycle through feedback mechanisms, is also considered an essential hormone during pregnancy [5-6, 41].

### *Pathways of nanoparticles entry into the reproductive system (direct and indirect)*

It has been proven that biomedical or environmental exposure to nanoparticles can result in critical toxicity during sexual development and the functioning of the female reproductive system [2, 4]. In addition to direct toxicity (nanoparticles come into direct contact with cells), indirect toxicity is also an important mechanism of toxicity since nanoparticles do not affect cells at the exposure sites. By releasing signals, mediators cause toxic effects in different cells and tissues [42]. Recent studies have reported the toxic effects of various types of nanoparticles (nanometer oxides, metal nanomaterials, carbon nanoparticles, quantum dots etc.), based on their properties (structures, sizes, shapes etc.) as well as their coating characteristics (inorganic and organic coating) [1, 4, 43-44].

Several biological studies demonstrated that nanoparticles could disrupt hormone secretion, which is essential for sexual development and the normal physiology of the female reproductive system. In addition, studies show that nanoparticles can penetrate cells disrupting their normal structures and their physiology through generation of reactive oxygen species (by increasing oxidative stress), up to placental barrier penetration and accumulation of nanoparticles in various reproductive cells and tissues [4, 45-49].

## CONCLUSIONS

The specific biological studies on the toxicity of nanoparticles in the reproductive processes are proliferating and demonstrated numerous adverse effects on ovary structures and their function. The effects of nanoparticles as shown, damages among others follicular development and ovulation during the folliculo-luteal transition and corpus luteum formation [50, 51]. This evidence indicated that nanoparticles could enter both follicle cell types (theca and granulosa), affecting their normal function, particularly before ovulation and corpus luteum formation. In addition, exposure to specific nanoparticles can significantly affect gonadotrophins and steroid hormones levels, which may cause follicular dysfunction, resulting in corpus luteum insufficiency. The possible molecular mechanisms of nanoparticle cytotoxicity in the ovary include inflammation, oxidative stress, apoptosis etc., but still mechanisms of action require more detailed research [50, 51]. Therefore, any adverse effect of nanoparticles in each of these physiological stages of ovarian function will cause irreparable damage to the reproductive processes, thus causing temporary or permanent infertility in various species.

In conclusion this contribution offers a comprehensive overview of the current knowledge regarding the potential adverse effects of nanoparticles on ovary function. In addition, an improved understanding of the molecular mechanisms of nanoparticle toxicity during follicle development and ovulation has an important implication for reproductive health and fertility regulation.

Note: The results of this review article (with the same title) were presented at the "Trends in Nanotechnology International Conference (TNT2021)" on 30 August 2021, Tirana, Albania. <http://tntconf.org/2021/index.php?conf=21>

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Bajram Berisha

## NANOGRIMCAT DHE FUNKSIONI I VEZORES: EFEKTET NEGATIVE GJATË ZHVILLIMIT TË FOLIKULAVE DHE OVULACIONIT

### Përmbledhje

Rritja e vazhdueshme e aplikimit të nanogrimcave në të gjitha aspektet e jetës bashkëkohore po ngre aktualisht shqetësime të vazhdueshme shëndetësore. Ndikimi negativ i nanogrimcave në organizmat e gjallë varet ndër të tjera nga vetitë e nanogrimcave, si: forma, madhësia, struktura, dozimi, materiali, shtresa e sipërfaqes etj. Aplikimi i nanogrimcave në kohën e sotme mund të gjendet jo vetëm në mjekësi (sistemet e dhënies së barnave dhe terapisë klinike), por edhe në produkte të ndryshme të përdorimit të përditshëm, siç janë kozmetika, veshmbathja, ushqimi, pijet etj. Prandaj, përveç aplikimit të qëllimshëm në mjekësi, ekspozimet dermale, pulmonare dhe gastrointestinale, konsiderohen tri rrugët kryesore të ekspozimit në raport me nanogrimcat. Pavarësisht nga dallimet, të gjitha mënyrat e depërtimit të nanogrimcave në organizmin e gjallë, shkaktojnë dëmtime biologjike të niveleve të ndryshme. Përveç toksicitetit direkt (nanogrimcat vijnë në kontakt të drejtpërdrejtë me qelizat), toksiciteti indirekt është gjithashtu një mekanizëm i rëndësishëm, pasi nanogrimcat nuk prekin qelizat në vendet e ekspozimit, por përmes mediatorëve ndërmjetësues shkaktojnë efekte toksike në qeliza dhe inde të ndryshme.

Shtirirja e studimeve mbi toksicitetin e nanogrimcave në fiziologji dhe veçanërisht në organet dhe në proceset e riprodhimit po rritet me shpejtësi viteve të fundit. Dihet tashmë se shumë lloje të nanogrimcave janë në gjendje të kalojnë disa barriera biologjike dhe të ushtrojnë efekte toksike në organe të ndryshme, si në tru, në mëlçi, në veshkë dhe gjithashtu edhe në vezore dhe në organet e tjera riprodhuese femërore. Prandaj objektivi kryesor i këtij punimi revyjal është diskutimi i gjetjeve shkencore, që tregojnë se akumulimi i nanogrimcave dëmton fiziologjinë e vezores, duke ndërprerë zhvillimin folikular dhe procesin e ovulacionit, dhe duke shkaktuar kështu implikime të rëndësishme për shëndetin riprodhues dhe rregullimin e fertilitetit të specieve të ndryshme.

Rezultatet shkencore të publikuara kohëve e fundit tregojnë se akumulimi i nanogrimcave dëmton fiziologjinë e vezoreve (Ovareve), duke penguar kështu zhvillimin normal të ciklit ovarial. Cikli ovarial, si ngjarje qendrore në fiziologjinë e riprodhimit, karakterizohet nga modele

të përsëritura në mënyrë ciklike të proliferimit, të diferencimit dhe të transformimit qelizor që shoqëron rritjen dhe zhvillimin e folikulave, ovulimin, si dhe formimin, funksionin dhe regresionin e trupit të verdhë (Corpus luteum). Në hulumtimet e viteve të fundit është konstatuar se, përveç sistemeve endokrine, mediatorët autokrinë dhe parakrinë (faktorët e rritjes, citokinet etj.) janë gjithashtu të përfshira në kompleksin e fiziologjisë së vezores. Vezoret, përveç rolit të tyre në prodhimin e gameteve seksuale (qelizave vezë), ato përfaqësojnë gjëndra endokrine të cilat sekretojnë hormone (kryesisht gjestagjene dhe estrogjene), të cilat janë thelbësore për zhvillimin normal riprodhues dhe rregullimin e fertilitetit.

Prandaj, çdo efekt negativ i nanogrimcave në secilën prej fazave fiziologjike të funksionit ovarial do të shkaktojë dëme të pariparueshme në proceset riprodhuese, duke shkaktuar kështu infertilitet të përkohshëm ose të përhershëm të specieve të ndryshme. Në vitet e fundit, disa studime janë fokusuar në aplikimin e nanogrimcave në procesin e angiogjenezës (krijimin e kapilarëve të rinj nga enët ekzistuese të gjakut), si njëri ndër proceset më të rëndësishme në fiziologjinë e vezores. Të kuptuarit më të mirë të mekanizmave molekularë të biologjisë së angiogjenezës, do të ketë padyshim një implikim të rëndësishëm për rregullimin e fertilitetit, por edhe për krijimin e strategjive të reja për trajtimin e sëmundjeve të ndryshme, të cilat varen nga angiogjeneza. Mekanizmat e mundshëm molekularë të citotoksicitetit të nanogrimcave në indin e vezores përfshijnë inflamacionin, stresin oksidativ, apoptozën etj. Ka dëshmi shkencore që tregojnë se nanogrimcat mund të depërtojnë në dy llojet e qelizave folikulare (qelizat theka dhe granulosa), duke ndikuar kështu në funksionin e tyre (pengesa në prodhimin e hormoneve steroidale), veçanërisht në folikulat para ovulacionit. Për më tepër, ka prova të qarta se ekspozimi ndaj nanogrimcave specifike mund të ndryshojë ndjeshëm nivelet e gonadotropinave (LH-hormoni i luteinizimit dhe FSH-hormoni për stimulimin e folikulave) dhe hormoneve steroidale (progesteroni, testosteroni, estradioli), që shkakton atrezinë folikulare dhe pengesa gjatë ovulacionit, duke rezultuar kështu në ulje të fertilitetit.

Si përfundim, ky artikull, ofron një pasqyrë gjithëpërfshirëse rreth gjendjes aktuale të njohurive në lidhje me efektet e mundshme negative të nanogrimcave në funksionin e vezores. Për më tepër, të kuptuarit më të mirë të mekanizmave molekularë të toksicitetit të nanogrimcave gjatë zhvillimit folikular dhe ovulacionit, do të ketë implikim të rëndësishëm për shëndetin riprodhues dhe rregullimin e indikatorëve të fertilitetit.

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## ANTIMICROBIAL RESISTANCE AND LIMITED RESOURCES: A KOSOVA CASE

### Abstract

Antimicrobial resistance (AMR) is one of the major challenges to public health worldwide. The objective of this paper was to present the main challenges and solutions of AMR in the developing world through the Kosova case.

The main challenges of antimicrobial resistance in developing countries are weak governance with limited financial and human resources, over-the-counter sales and lack of regulatory policies on antibiotic use and antimicrobial stewardship. In addition, other political, technological and ecological problems have significant impact on antimicrobial resistance. The Covid-19 was a significant accelerator of antimicrobial resistance worldwide.

Key responses in the developing world would be the implementation of national action plans based on the "One Health" approach; empowering laboratory capacities; improving the surveillance of antimicrobial resistance and antimicrobial consumption in humans, animals and the environment; increasing awareness among population starting from the youngest age; prudent use of antimicrobials in clinical practice and the veterinary sector; infection prevention and control in health care settings and the community; increasing sanitation and immunization coverage and promotion of research and international cooperation.

The AMR is a great challenge for the health care system in Kosova with the "over-the-counter" sale of antibiotics in pharmacies and lack of officially approved antibiotic guidelines as main gaps.

To address the issue of AMR, the Ministry of Health in Kosova completed two national action plans for AMR. The cornerstones of the action plan were antimicrobial stewardship and the "One Health" approach.

*Key words:* Antimicrobial resistance, developing countries, Kosova, One Health

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## 1. FROM FLEMING TO “SUPERBUGS”

Since the discovery of penicillin in 1928, antibiotics have revolutionized the development of medicine [1]. However, their widespread misuse in the human and veterinary sectors resulted in the emergence and spread of antimicrobial resistance (AMR) that can affect everyone, at any age and in any country. Resistant microorganisms today are encountered within acute care facilities, but also in the community and environment [2].

AMR is one of the major challenges of public health worldwide with impact on increasing morbidity, mortality and costs [3]. The largest comprehensive assessment of the global burden of AMR published recently in *The Lancet* estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen–drug combinations in 204 countries and territories in 2019. Results have shown an estimated 4.95 million deaths associated with bacterial AMR in 2019, including 1.27 million deaths attributable to bacterial AMR [4].

According to the World Bank, by 2050, AMR could cost underdeveloped countries more than 5% of gross domestic product and include 28 million more people in poverty lines [5]. O’Neal’s report pointed out that with the current trend of antibiotic misuse worldwide, in 2050, AMR could cause more deaths than cancer (10 million deaths annually) [6]. Therefore, we risk returning to the pre-antibiotic era, where minor wounds and routine diagnostic-therapeutic procedures could be life-threatening for the patient.

The discovery of “superbugs” (*E. coli* and *Klebsiella pneumonia*) in India, that produced an enzyme capable of destroying the most potent antibiotics at our disposal (carbapenems) brought serious concern worldwide [7].

To address the global challenge of AMR, the World Health Organization adopted a global antimicrobial resistance action plan in May 2015 [8]. Furthermore, at the European level, the Council of the European Union adopted European One Health Action Plan against AMR in 2016 [9].

## 2. THE ETIOLOGY OF ANTIMICROBIAL RESISTANCE IS MULTIFACTORIAL

Several factors are responsible for emerging and spread of AMR, but the main one is the misuse or overuse of antimicrobials, particularly in the treatment of upper respiratory tract infections caused by viruses. In recent years, consumption and resistance trends have been escalating in many parts of the world, especially underdeveloped ones [10]. In 50% of prescriptions, antimicrobials are taken unnecessarily, in the wrong dose, or at inadequate duration [11]. Other factors that complement the picture of AMR are insufficient knowledge and awareness of the population and health care workers about the AMR (patient self-medication); lack of infection control resources in hospitals and the community; use of antimicrobials as promoters of animal growth in veterinary medicine; suboptimal dosing, lack of rapid diagnostic tests, and lack of new antibiotic classes in pipeline.

## 3. ANTIMICROBIAL RESISTANCE AND LIMITED RESOURCES

The spread of antimicrobial resistance in developing countries is supported by shortages in all pillars of resistance: governance, surveillance, laboratory capacity, legal regulation, access to antibiotics and intersectoral coordination [12].

Regulatory policies in developing countries are either absent, or solely on paper but not implemented. For example, antibiotics are available “over-the-counter” and in many cases they are dispensed by non-qualified persons working in pharmacies. The implementation of the code of conduct for the pharmaceutical industry during promotional activities is necessary to avoid pressure among prescribers.

Lack of resources and health insurance prevents adequate access of the population to the second or third-line drugs for the treatment of multiresistant infections. Lack of resources also implies difficulties in implementing active monitoring of the resistance rates and monitoring the use of antibiotics.

Limited resources also affect diagnostic laboratory capacities, which are usually deficient. Consequently, developing countries have a higher burden of infections accompanied by more serious clinical impact. Over-prescribing of antibiotics is the justification of doctors in

some institutions of primary care level, which have no laboratory services.

#### 4. ANTIMICROBIAL RESISTANCE AND KOSOVA: FACTS AND FIGURES

AMR is one of the significant challenges for the health care system in Kosovo. The main problems in this area are the inappropriate use of antibiotics, “over-the-counter” sale of antimicrobials from pharmacies (they are available without a physician prescription) and pressure from the pharmaceutical industry. The Administrative Instruction for the Distribution of Antibiotics and Psychotropic Drugs in Kosovo has existed since 2010, but it is not fully implemented [13].

In Kosovo, the antimicrobial resistance surveillance network is managed by the Institute for Public Health. The seven public laboratories of clinical microbiology provide diagnostic support for all public hospitals countrywide, including one academic hospital and 7 general hospitals with a range of 120 to 2167 beds.

WHO Regional Office for Europe during 2012 coordinated the establishment of the surveillance network called CAESAR (Central Asian and Eastern European Surveillance of Antimicrobial Resistance) to assist non-EU countries in building national antimicrobial resistance surveillance [14]. Kosovo is part of this program and has submitted data every year since 2014. CAESAR network collects antimicrobial susceptibility test results from invasive isolates (blood cultures and cerebrospinal fluid). The antimicrobial resistance situation in Europe shows large variations depending on the bacterial species, antimicrobial group and geographical region. Fifty-eight per cent of invasive *Staphylococcus aureus* isolates in Kosovo were MRSA, compared to 14.4% in EU countries. *Acinetobacter spp.* isolates were multiresistant in 91% of cases from invasive samples.

Outpatient data from two comparative studies conducted in Kosovo between 2002 and 2016 among urinary tract isolates of *Escherichia coli* showed increased resistance rates of cephalexin from 2.8% in 2002 to 27% in 2016, whereas ciprofloxacin resistance increased from 1.6% to 19% [15].

## 4.1. Antibiotic consumption

Data for antibiotic consumption were collected in three levels of health care in Kosova: wholesale data, data from all hospitals and data in the primary care level. Total antimicrobial use data of Kosova was analyzed according to the WHO Anatomical Therapeutic Chemical (ATC)/Defined Daily Doses (DDD) methodology and expressed in DDD/1000 inhabitants/day (DID) and total (outpatients and hospital care) antibacterial use was 26.3 DID. Kosova was tenth among countries in Europe for antibiotic consumption [16]. The predominant groups were penicillin (12.8 DID, 48.7% of all antibacterial) and other beta-lactam antibacterial (4.9 DID, 18.7%).

Kosova was a European champion in total parenteral use of ceftriaxone with very high prescription level in primary care settings. Pressure from the pharmaceutical industry and monopoly in distribution resulted in a high prescription rate. On the other hand, very low use of systemic antimycotics and antifungals was noted in Kosova, as compared with other non-EU and EU countries. This can be explained by population structure, where Kosova has the youngest population in Europe with only 8.5% of inhabitants above the age of 65.

Among the 10 most consumed parenteral agents, just two drugs (ceftriaxone and gentamicin) account for over 81% of consumption.

Another WHO publication on antibiotic consumption in Europe, published five years later (December 2018), showed that Kosova has marked a significant decrease in antibiotic consumption by almost 25%. (from 26.3 DID to 20.1 DID). The main factors influencing this decline in consumption are the increased awareness of the population and health care workers about AMR, media pressure, and governmental commitment to address the AMR [17].

Data on antimicrobial use were collected in seven hospitals in Kosova during three consecutive studies. At the hospital level in Kosovo, the use of antibiotics in children was almost twice higher as the EU average (57% vs 36%). In European hospitals lower respiratory tract infections are treated with ceftriaxone only in 8.2% of cases, while in Kosova this antibiotic was used in 82.3% of total cases [18].

During the latest survey in the field of antimicrobial consumption in all Kosova hospitals, from 915 patients included in the study, 520 (56.8%) were using at least one antibiotic on the day of the survey. Third generation cephalosporins were the most prescribed antibiotics



for empiric treatment (34.6%), and surgical prophylaxis (43.1%), followed by aminoglycosides. Antibiotics were administered mainly through the parenteral route (93.8%). Empiric treatment was the main physicians' choice for prescribing (87.1%). In 12.1% of cases antibiotics were prescribed to patients with an undefined site of infection and no systemic inflammation [19].

The third stage of the surveillance of antibiotic consumption was conducted at the primary care level. This survey was retrospective study involving 12 Family Medicine Centres (FMC), in 6 municipality regions of Kosova. A surveillance study showed that 33% of patients received a prescription for antimicrobial agents. The percentage of administration of antibiotics via the parenteral route was 43%. Antibiotic therapy prescription with generic names was seen only in 31% of patients.

## 4.2. Awareness, training and education

Insufficient knowledge of the population for prudent use of antimicrobials poses a significant challenge in abusing antibiotics and AMR. Therefore, a study was conducted to assess the public knowledge, attitudes and practices of antibiotics among Kosovans [20]. The study showed that more than half of respondents (58.7%) had used antibiotics during the last year. A quarter of respondents consumed antibiotics without a medical prescription. The most common reason for usage was flu (23.8%). Healthcare workers were identified as the most trustworthy source of information on antibiotic use (67.2%).

In 2011 Kosova started to mark the European Antibiotic Awareness Day, which then switched to World Antibiotic Awareness Week.

Nowadays, awareness of AMR has switched from adults to school children. Public Health England has prepared an entertaining educational program on antibiotics, hand hygiene and food and translated into many languages. This educational package has already been translated and launched into Albanian (<https://www.e-bug.eu/index.-html#Kosovo>) and is used in all Albanian-speaking regions worldwide.

Communicating with patients is the key to addressing this challenge in primary care. Studies in EU countries have shown that patient satisfaction in primary health care depends more on effective communication than on receiving an antibiotic prescription. In addition,

professional medical advice tremendously impacts on patients' perceptions and attitudes towards their disease and the need to use antibiotics.

In undergraduate studies, the Faculty of Medicine in Prishtina has agreed to include the use of antibiotics and resistance as elective subjects for final- year students.

### 4.3. Infection control

Effective infection control practices reduce the need for antibiotics and prevent the spread of infections caused by multidrug-resistant bacteria in hospitals [21].

As in other developing countries, infection control in Kosovo is challenged by the lack of financial support and political commitment, an inadequate number of trained personnel working in infection control, overcrowded hospitals, and insufficient equipment and supplies.

In the first nationwide Point Prevalence Survey (PPS) of health-care-associated infections (HCAI), prevalence rate was 4.9%. The highest rate was noticed at the tertiary care level in the University Clinical Centre of Kosovo (UCCK) (7.2%). The most common type of HCAI was surgical site infection, representing 35.5% of all reported HCAs. The prevalence of HCAs was highest in surgical departments (46.6%). The median length of stay before the onset of HCAI was 11 days (range: 3–27 days) [19].

### 4.4. Veterinary sector

The treatment with different types of antibiotics to protect the spread of animal losses, often followed by uncontrolled use of these products as growth promoter, which has been prohibited in EU since 2007. There is no systematic monitoring system for infectious diseases or antibiotic consumption implemented in the veterinary sector.

The quality of laboratory food testing in Kosovo is not at the proper level to support food industry demands and meet the consumer's rightful expectations for safe food in Kosovo.

## 4.5. Research and Collaboration

Research and collaboration were another area of importance in the field of antimicrobial resistance and presently Kosova is enrolled in many projects. Several research activities have been successfully implemented with various partners, such as European Commission, WHO, ECDC, Robert Koch Institute, and others.

In the field of AMR in environment, Kosova participated in global surveillance of antimicrobial resistance from sewage in Europe's capital cities. The most common AMR genes identified in the sewage of the capital city Prishtina were *msr* (E), *bla*OXA and *aa*Da (22).

European survey EURECA, which includes 50 hospitals in Europe, showed that Kosova, Serbia, and Greece have the highest rates of healthcare associated sepsis with carbapenem-resistant *Acinetobacter baumannii* among newborns (23).

## 5. COVID-19 AND ANTIBIOTICS

The COVID-19 was the catalyst for the emergence and rapid spread of antimicrobial resistance due to the enormous use of antibiotics at all levels of health care, even in asymptomatic and mild disease cases. However, COVID-19 is a viral infection and is neither treated nor prevented with antibiotics.

Antibiotics are given only in cases where there is clinical confirmation or suspicion of co-infection or secondary bacterial infection. These infections occur mainly in hospitalized patients and those on immunosuppression and are more common in intensive care units.

In the Langford meta-analysis of 7469 studies (25), the prevalence of prescribing antibiotics during the pandemic was 74.6%. Nevertheless, bacterial co-infection was found in only 8.6% of patients and the prescription rate was 9 times higher than the prevalence of bacterial co-infection.

Among the most misused antibiotics during the pandemic in Kosovo was azithromycin in primary care, which increased 7 times; while in hospitals, it was imipenem, which increased 12 folds compared to pre-pandemic use-values.

## 6. SOLUTIONS

Key responses in the developing world would be implementation of national action plans based on “One Health” approach; empowering laboratory capacities; improving the surveillance of antimicrobial resistance and antimicrobial consumption in humans, animals and the environment; increasing awareness among the population starting from the youngest age; prudent use of antimicrobials in clinical practice and the veterinary sector; infection prevention and control in health care settings and the community; increasing sanitation and immunization coverage and promotion of research and international cooperation.

Tackling antimicrobial resistance should start with infection prevention (hand hygiene as simple measure), and increased vaccination and sanitation coverage.

Upgrading laboratory diagnostic services would enable prudent use of antibiotics and help physicians' decisions to initiate, continue, change or deescalate antibiotic therapy. Another very important solution in addressing antimicrobial resistance is Antimicrobial Stewardship Program (ASP).

To address the challenge of antimicrobial resistance, the Ministry of Health of Kosova has initially completed the National Strategy and Action Plan to Combat Antimicrobial Resistance 2011-2015, where 80% of planned activities were successfully implemented. The main successful stories of the initial national action plan were national surveillance data on antibiotic consumption, grants awarded through open call competition, international collaboration and research. In December 2018, the Minister of Health signed a new action plan for antimicrobial resistance for three years (26). The cornerstone of this action plan was antimicrobial stewardship. The support for the laboratory was the largest governmental investment in microbiology capacity in the last 20 years providing state-of-the-art equipment (Next Generation Sequencing, syndromic multiplex PCR, MALDI-Tof, automated blood culture systems and antibiotic susceptibility systems, etc.).

## 7. CONCLUSIONS

AMR in developing countries is a complex problem and all efforts to address this challenge should start with understanding the key drivers of AMR and implementing effective measures. The future interventions

should be focused on the integrated implementation of national action plans, increasing awareness among the population, doctors and stakeholders, preparation of evidence-based guidelines and protocols on antibiotic consumption in health care facilities, implementation of the law that prohibit over-the-counter sale of antibiotics in pharmacies, implementation of the code of conduct for the pharmaceutical industry during promotional activities and implementation of antimicrobial stewardship programs.

AMR phenomenon will always be with us because microbes are always one step ahead. The challenge will be to transform this emergent threat into a manageable problem. Meeting this challenge requires the cooperation of all actors in this field: government, the population, doctors, pharmacists, the media, the pharmaceutical industry, and academia.

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## REZISTENCA MIKROBIKE DHE BURIMET E LIMITUARA: RASTI I KOSOVËS

### Përmbledhje

Rezistenca antimikrobike (RAM) është një nga sfidat kryesore globale të shëndetit publik. Qëllimi i këtij punimi ishte të përmbledhë sfidat dhe zgjidhjet kryesore të fushës së RAM te vendet në zhvillim përmes shembullit të Kosovës.

Sfidat kryesore të rezistencës antimikrobike te vendet në zhvillim janë qeverisja e dobët me burimet e kufizuara njerëzore dhe financiare, shitja e antibiotikëve pa recetë të mjekut dhe mungesat në politikat rregullatore të përdorimit të antibiotikëve dhe kujdestarinë e antimikrobikëve. Problemet e tjera të sferës politike, teknologjike dhe ekologjike kanë ndikim të rëndësishëm në rezistencën antimikrobike. Covid-19 ishte një përshpejtues i rëndësishëm në përhapjen e rezistencës antimikrobike në mbarë botën.

Përgjigjet kryesore të shteteve në zhvillim do të ishin zbatimi i planeve kombëtare të veprimit, të bazuara në qasjen "Një Shëndet (One Health)"; fuqizimi i kapaciteteve laboratorike; përmirësimi i mbikëqyrjes së rezistencës antimikrobike dhe konsumit të antimikrobikëve te njerëzit, kafshët dhe mjedisi; rritja e ndërgjegjësimit të popullatës duke filluar nga mosha më e re; përdorimi korrekt i antimikrobikëve në praktikën klinike dhe në sektorin veterinar; parandalimi dhe kontrolli i infeksionit në institucionet shëndetësore dhe në komunitet; rritja e mbulimit sanitar dhe imunizimit dhe promovimi i kërkimit shkencor dhe bashkëpunimit ndërkombëtar.

RAM është një sfidë e madhe edhe për sistemin shëndetësor në Kosovë, ku mangësitë kryesore janë shitja pa recetë e antibiotikëve në barnatore dhe mungesa e udhërrëfyesve klinikë për përdorimin e antibiotikëve.

Për të adresuar çështjen e RAM, Ministria e Shëndetësisë në Kosovë tashmë ka realizuar dy plane kombëtare të veprimit. Kujdestaria e antimikrobikëve dhe qasja "Një shëndet" ishin shtyllat kryesore të aktiviteteve programore.





Myzafere Limani<sup>\*,1</sup>

**A SURVEY ON THE POSSIBILITIES OF REUSE OF  
FREQUENCY BANDS UHF, VHF AND MILLIMETER  
WAVES FOR WIRELESS COMMUNICATION  
NETWORKS IN THE TERRITORY OF KOSOVO:  
A REVIEW**

**Abstract**

The VHF and UHF frequency bands, traditionally allocated to TV broadcasters, have garnered significant attention from researchers, due to their superior propagation conditions and coverage. Furthermore, with the transition from analog broadcasting to digital television, a considerable amount of spectrum has become available for potential opportunistic use by cognitive radio. These portions of the spectrum, unused by their licensed owners, are known as TV White Spaces. However, it is known that determination of TV white space availability can vary from country to country. Therefore, spectrum measurements are necessary to obtain a better overview of the availability of TV frequency bands and identify potential white spaces. Once spectrum measurements are available, they can be processed to get an actual channel model for the propagation. Furthermore, detection mechanisms can be applied to determine which frequencies are occupied in which locations. This paper provides a comprehensive survey studies performed regarding different aspects of reuse possibilities of TVWS, and also provides a brief overview of the path loss models most commonly used for modelling propagation in TV bands. Finally, some of the detection techniques used in the absence of geo-location databases of TV broadcasters are described, to quantify occupation and usage of these frequencies.

*Keywords:* TV white space, cognitive radio, spectrum measurements, spectrum availability detection, energy detection, detection threshold, the coexistence of networks, propagation model, beam design.

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## INTRODUCTION

The exponential increase in broadband traffic has underscored the need for more efficient and opportunistic use of the available spectrum. Researchers have highlighted the underutilization of licensed portions of the spectrum as a potential opportunity to address the spectrum congestion problem. The electromagnetic radio spectrum is a natural resource and as such is managed by government agencies and policy-makers. Traditionally, the frequency spectrum is divided into chunks and allocated for different services such as radio and television broadcasting, cellular telephony and military and maritime applications. The chunks are then further divided into sub-bands and assigned (licensed) to specific parties for the use, such as television and radio broadcasters and mobile telephone providers. The allocation is done both in the context of a period, where the license is valid for a limited time frame, and in the context of location, where the license is valid for a specific area. While, this kind of spectrum assignment is convenient for regulators and licensees, as it ensures interference-free use of the assigned frequency band, it has raised concerns over its inefficiency. Plenty of research has shown that the spectrum as is managed today, is vastly under-utilized. At the same time, some frequency bands are heavily used at all times, and there are licensed bands that are unoccupied most of the time, even in highly populated urban areas [1].

The use of already licensed portions of the spectrum would be enabled by cognitive radios, which behave as secondary users and use the spectrum whenever the primary users, i.e., the license owners, are not using it. A cognitive radio (CR) is a radio that can change its transmission parameters based on interaction with the environment in which it operates [2]. The use of such radios has been approved by USA and UK regulatory bodies in 2009 and 2012 respectively [3]. The move was motivated by the digital transition in TV broadcasting, which made large swathes of TV spectrum accessible for opportunistic use. This group of vacant channels is known as TV white space (TVWS). However, the availability of TVWS spectrum varies from country to country and depends mainly on the channels chosen for TV broadcasting. The TVWS availability assessment is crucial for each location/country.

Frequency bands corresponding to TVWS spectrum are VHF 30-300 MHz and UHF 300-1000 MHz, except for the channels reserved for emergency transmissions. In Europe, a challenging aspect of TVWS

use is that TV spectrum is not only occupied by fixed TV broadcasting signals but also by licensed Programme Making Special Event (PMSE) devices, e.g., wireless microphones used in small events, concerts or security agencies. PMSE can operate in a licensed or unlicensed basis. Therefore, the detection of such equipment is the subject of a research project [4]. Furthermore, their protection should be guaranteed based on legislative regulations [5].

It is primarily expected that these bands will be used to augment spectrum resources for already existing technologies, such as WiFi, WiMax, etc., when needed, and it's unlikely that TVWS based broadband access will completely substitute them [6]. The two main reasons for using TVWS are the superior propagation characteristics for wireless communication resulting in larger coverage area and the minimal infrastructure requirements, which makes them ideal for rural and undeveloped areas. This is especially convenient for developing countries such as those in Western Balkans. ITU reports show broadband penetration rates are increasing rapidly in these countries [7, 8]. In Albania alone, in the last five years, the number of active mobile broadband subscribers has gone from 8.8 to 52.6 per 100 inhabitants [7, 8]. Furthermore, access through wireless broadband networks through TVWS could be preferred since providing fiber optic connection is not cost efficient for service providers [9]. Nevertheless, the successful implementation of this technology depends on the ability to effectively manage and avoid the possible interference caused to the primary users. This is made possible by with the CR continuously sensing the channel to detect the presence of the primary user. In case of primary user detection, the secondary user has to immediately vacate the channel to avoid causing interference to the primary user. To ensure that primary users are protected at all times, the UK regulator, Ofcom and Federal Communication Commission (FCC) in the USA, have proposed three methods to be used by secondary users: i) beacons, ii) sensing and iii) geo-location with the database.

For the first method, secondary users will only start transmitting if they have already received a beacon signal implying the vacant channel. This requires the infrastructure of beacons to be implemented and maintained which is considered the main drawback of this method [10]. The second method is based on the sensing. The secondary users will sense the spectrum and try to detect the presence of primary users. This is based on the amount of energy received. Operations from secondary users are possible only when they do not detect any primary

signals. The main drawback of this method is the device complexity because cognitive radios besides detecting the signal, must know many other signal characteristics such as modulation and bandwidth [11].

The third technique uses geo-location and databases. The database contains information regarding the spectrum usage in the vicinity during a specific period. Secondary users have to send a query and the database will respond with the list of available frequencies including all transmission parameters that need to be followed for secondary transmission to start. This implies that the database must be kept updated at all times and that secondary users must have geo-location capability. The challenge of utilizing this method is for indoor secondary users where GPS connectivity may not be available due to the signal disruption from buildings, walls, etc., [12]. Alternative outdoor and indoor localization techniques using cellular and wireless network signals are also possible [13]. Techniques that use sensing and geolocation databases have also been proposed and tested [14]. Several trails have been conducted to test several aspects of white space technology, including the white space device and geolocation database interactions, the validity of the channel availability/powers calculations by the database and associated interference aspects on primary services by Ofcom in UK [15]. The opportunities are more appealing for indoor TVWS network usage because of the isolation from the licensed primary transmissions. The best use cases include femtocells and wireless LAN's [16, 17].

The first step towards using cognitive wireless devices, and networks over TVWS are the spectrum measurements in order to understand spectrum usage and availability. Since the measurements depend heavily on the location due to different environments, conducting measurements in each country is crucial. In addition, accurate radio propagation models are the key to determining the actual spectrum availability and its potential for opportunistic use. However, the propagation models vary widely from one area to another because of their dependency on the terrain characteristics. Finally, drawing from a significant amount of literature, various methods for sensing and assessing the availability of TV frequency bands are described, using fixed and adaptive detection thresholds.

## ENERGY ESTIMATION FOR LONG-TERM AND WIDE-BAND SPECTRUM MEASUREMENTS

In energy detection (ED), the received energy (power) is measured in a channel and compared to a threshold  $\gamma$  to assess if signals are present or if only noise was received [1]. Spaulding and Hagen [2] defined spectrum occupancy for ED as the fraction of the measurement time that the detected power  $P$  in a channel exceeds a threshold level. Spectrum occupancy measurements are important to verify the availability of white space for a cognitive radio system, and they are important for radio regulators to see the effectiveness of the frequency allocations. The important issues in these measurements are noise uncertainty, resistance to outliers and sensitivity. One of the bands of interest for occupancy measurements is the 2.400–2.500 GHz Industrial, Scientific, and Medical (ISM) band [3]. In this band, several systems exist such as the popular 802.11 Wireless Local Area Network (WLAN) networks and Bluetooth. There can also be microwave ovens causing interference [18].

The ED is easy to implement and can make detection decision even in a short time (Fig1). However, noise uncertainty can be a significant problem with the ED. It may even lead to a phenomenon called “SNR wall”, where noise uncertainty prevents the detection of weak signals. The noise uncertainty includes thermal noise level changes due to variable temperature and ambient noise (atmospheric noise, galactic noise and man-made noise among others). The man-made noise is caused by unintended radiation from electrical machinery, electrical and electronic equipment and power transmission lines. The power level of this noise varies with the time of day, polarization and frequency. Using adaptive approaches for threshold setting in ED leads to more robustness against the fluctuation of noise floor compared to the typical ED approach with a fixed threshold. In [19], an adaptive threshold was found using a two-step process. First, a reference set was formed from some previously received energy values in different channels and/or time intervals. As there is no guarantee that all of the received energy values are due to only noise, censoring techniques (such as order statistics or the blind and iterative forward consecutive mean excision (FCME) algorithm) are usually used to remove the corrupted energy values (containing also signal components). Then, the found supposedly signal-free energy values were used to calculate the detection threshold. In [20], a longer-term background process was used

to identify frequency bands where only noise is present and the noise variance is estimated from these bands.

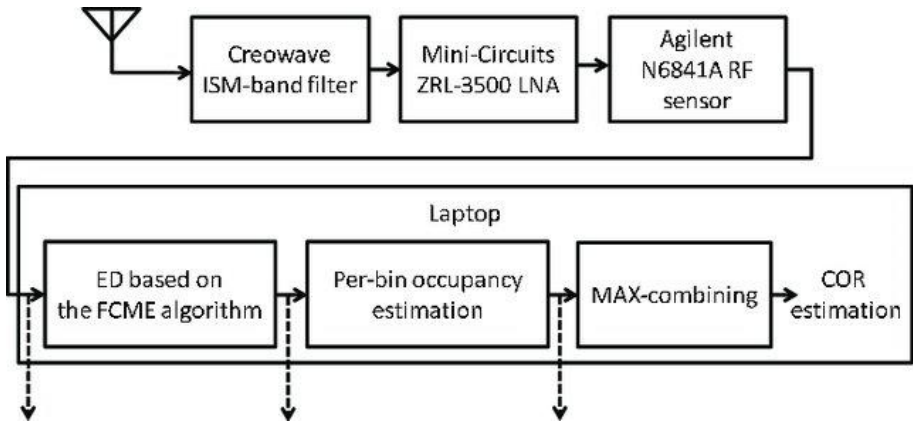


Figure 1. Energy detection measurement process [18].

## NOISE FLOOR ESTIMATION

Practical noise floor estimation should be based on the received samples in many cases. This approach allows noise floor estimation to be done simultaneously with the actual measurements. However, the significant problem with this approach is that it is difficult to find which of the received samples correspond to just noise (the samples we want to locate) and which samples also have signal components (undesired samples). This is important as if the set from which we estimate the noise floor has signal components, the estimated noise floor can be significantly too large even due to one very high-power signal sample.

The Forward Consecutive Mean Excision (FCME) algorithm [21] is a multipurpose iterative method find which of the received samples correspond to just noise. The details of the FCME will not be explained but briefly, an explanation of the outline of the FCME is given. The FCME first rearranges the frequency domain samples (that are in linear scale) in an ascending order according to their energies. After that, the FCME algorithm calculates the mean of a small initial set, which is assumed free of interference. The larger the initial set, the simpler the algorithm because fewer iterations are needed. However, the possibility that the initial set is not clean increases. On the other hand, the smaller the initial set is, the higher the chance that the initial threshold is too small.

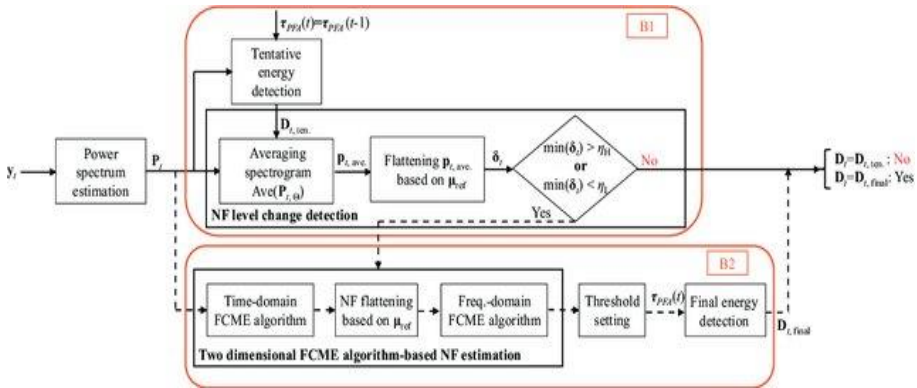


Figure 2. Block diagram of the proposed NF estimation process [22].

Statistics in terms of spectrum occupancy are useful for efficient and smart dynamic spectrum sharing, and the statistics can be obtained by long-term and wide-band spectrum measurements. Noise floor (NF) estimation for energy detection (ED) long-term based and wideband spectrum measurements are important since the NF estimation heavily affects the ED performance and eventually the accuracy of the statistics in terms of spectrum occupancy. Specifically, the following NF estimation problems simultaneously are addressed for the first time in the [22], where spectrum measurement field characterized as (1) slow time varying property of the NF, (2) frequency dependency of the NF, (3) the NF estimation in the presence of the signal, and (4) the computational cost of the NF estimation. Firstly, is applied Forward consecutive mean excision (FCME) algorithm-based NF estimation to deal with the above three problems ((1), (2) and (3)) successfully. Second, NF level change detection is proposed on top of the FCME algorithm-based NF estimation to deal with the fourth problem. The proposed NF level change detection exploits the slow time-varying property of the NF. Specifically, if a significant NF level change is detected the FCME algorithm-based NF estimation is performed to reduce the redundant NF estimations. In numerical evaluations, we show the efficiency and the validity of the NF level change detection for the NF estimation problems and compare the NF estimation performance with the method without the NF level change detection [22].



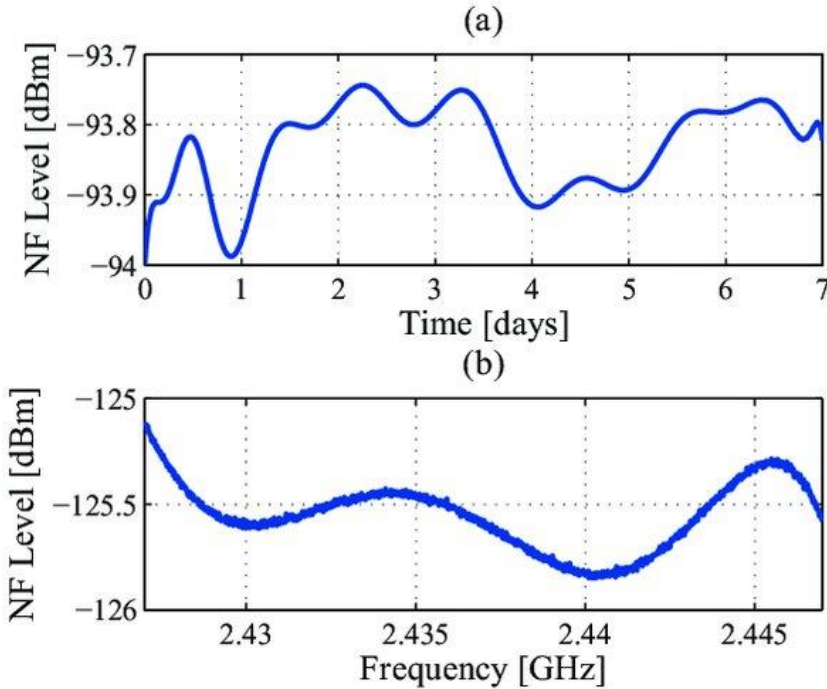


Figure 3. NF setting in the simulations ((a) Assumed NF evolution, (b) Assumed reference NF [22]).

In the paper [22], the authors proposed an efficient NF estimation process (NF level change detection plus FCME algorithm-based NF estimation) for ED-based long-term and wide-band spectrum measurements as shown in Figure 2 and Figure 3. The proposed NF estimation process can deal with slow time-varying property and frequency dependency of the NF, the NF estimation in the presence of the signal, and the computational cost at the same time. Significantly, the proposed process attempts to reduce the computational cost by exploiting slow time-varying NF via the proposed NF level change detection.

## EXPERIMENTAL MEASUREMENTS

Establishing the utilization level of spectrum resources is an essential step in evaluating the true availability of the frequency spectrum, which could potentially become available for opportunistic use. Such assessments typically require extensive measurement campaigns;

to take into account various factors which may affect the availability of spectrum, such as frequency allocation at the national level, and the particulars of the environment and terrain. In the study [23], authors focused on the bands usually reserved for TV broadcasters, since studies show that these bands tend to be less efficiently utilized. In addition, a large set of data obtained from an extensive spectrum measurement campaign conducted over the entire territory of Kosovo is an additional advantage, which enables to attain a comprehensive picture of spectrum availability in TV bands. Spectrum sensing techniques using energy detectors are applied to determine whether the spectrum is utilized. However, due to the significant amount of measurement data collected, machine learning techniques is leveraged to improve the accuracy of the approach, by improving the detection and false alarm rates. As a result, a highly accurate spectrum availability map is obtained which can be in turn used by cognitive radio networks to access the spectrum.

Under-utilization of licensed spectrum, especially in the frequency bands traditionally allocated for TV broadcasting, is a fact that has been well established in the literature [24]. Furthermore, with the transition from analog to digital broadcasting, a substantial spectrum in TV bands is expected to become further available. These bands, often referred to as TV White Space (TVWS), are of great interest due to their superior signal propagation characteristics [25]. While, in most countries, these frequencies remain pre-allocated for TV broadcasting, the opportunistic use by secondary devices has been considered, and allowed, most notably in the USA [26] and UK [27]. Therefore, determining the utilization level of TVWS is essential step in evaluating the true availability of the frequency spectrum, which could become available for opportunistic use. Such assessments typically require extensive measurement campaigns; to take into account various factors that which may affect the availability of spectrum, such as frequency allocation at the national level, and the particulars of the environment and terrain.

The paper [23] presents the results of spectrum measurements over TVWS conducted over a wide area of Kosovo. To the authors knowledge, this is the first study of this scale to be conducted in Kosovo, one of the very few in the Western Balkans region. Similar studies have been performed in Bosnia and Herzegovina [28], Hungary [29], and Macedonia [30]. Applying comparable methodologies to other similar measurement campaigns performed in other countries, a

spectrum occupancy analysis over the Ultra High Frequency (UHF) bands is performed. The detection of activity in a specific channel was evaluated using energy detection techniques based on measured values of received power. To improve the accuracy of the detection process, unsupervised machine learning techniques based on *k-means* clustering were applied, an endeavor made possible by the significant amount of measurement data collected. The authors note that the analysis presented in this work gives an overview of the current spectrum availability, which may change in the future, as TV broadcasting in Kosovo has not yet fully transitioned from analog to digital broadcasting. The goal, however, was to quantify the current utilization levels of the TV spectrum band. The results of the measurement campaign can be used to assess the status of the spectrum use and the availability of the spectrum for other, opportunistic, users. In addition, the outcomes of this extensive analysis can give valuable information to the national regulators about the efficiency of the current spectrum allocations.

When assessing activity in the surveyed spectrum band, an important aspect is the applied detection method. In particular, when energy-based techniques that rely on a pre-determined threshold to decide whether a channel is active or not, the assessment of the noise level becomes critical. In general, for the sake of simplicity, most studies apply fixed thresholds against which the energy of sampled observations is compared. However, a fixed predetermined threshold is not flexible enough to provide an accurate picture of the spectrum availability. To this end, more intricate methods have been studied and presented in the literature. The estimation of the detection threshold without prior knowledge about the signal and noise characteristics is addressed in [32]. Finally, machine-learning techniques have also found potential application in this area. The authors in [33, 34] propose using unsupervised and supervised machine learning techniques on observed samples to determine the activity within a specific frequency channel. A suitable technique based on Hidden Markov Models is instead proposed [35].

The frequency bands under assessment included UHF channels over the 470 – 854 MHz band. The measurement campaign was conducted at 36 different outside locations across the territory of Kosovo. Out of these locations, 14 (around 40%) were in urban/-suburban areas, while 18 were in rural areas. The measurements were performed using the NARDA Selective Radiation Meter SRM-3006, in the spectrum analysis mode, with a frequency resolution of 100 kHz,

and a sweep time of  $\sim 200$  ms. At each location, 10 individual measurements were performed, each lasting 1 minute. The minimum, maximum and average values of the power received were recorded for each measurement. In particular, 7 active transmitters were identified during the measurement campaign. The measurement locations as well as the locations of the 7 TV broadcasters are shown in Fig. 1. The locations were chosen to obtain a sufficient distance resolution from the transmitters. The availability of roads and accessibility also constrained the choice of the locations. Within the city center of Prishtina measurements were taken in several locations within the city center and in the surrounding areas.

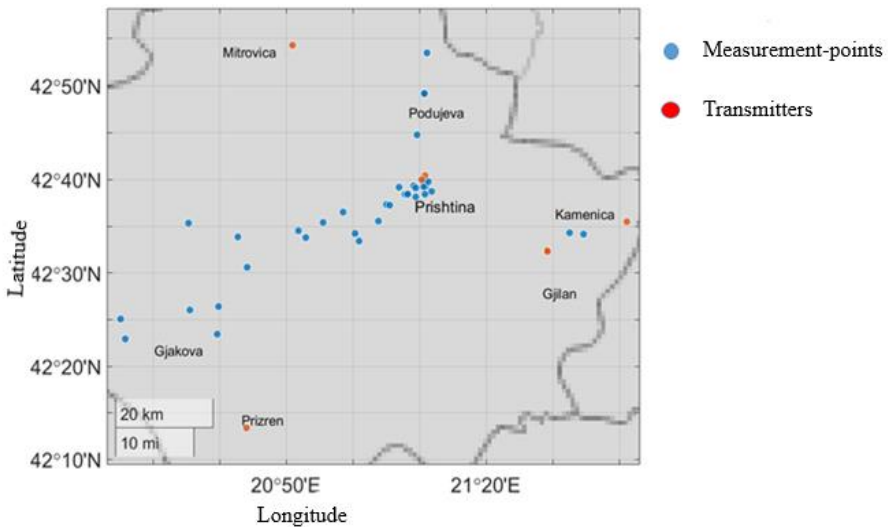


Figure 4. Measurement locations (blue) and TV transmitter (red) positions.

## THE SPECTRUM DETECTION PROBLEM

The theoretical coverage of the TV broadcasters can be established from the official list of licensed transmitters [36], which includes detailed information on antenna locations and characteristics. In particular, we could confirm that seven transmitters from the official list were currently active, on 10 TV channels. Furthermore, previous studies [37], show that the propagation model that best fits the Kosovo environment is the Ericsson path loss model [38]. Calculating the

distance between each measurement location and transmitting antenna, and applying the Ericsson path loss equation, we can derive the estimated received power at each location from each transmitter.

For comparative purposes, the detection using a fixed threshold and double adaptive thresholds (LAD) are performed. This analysis produced availability picture for the measurement locations and frequency band under study. The average occupancy of known active channels over all measurement locations and measurement times are shown in Figure. 5.

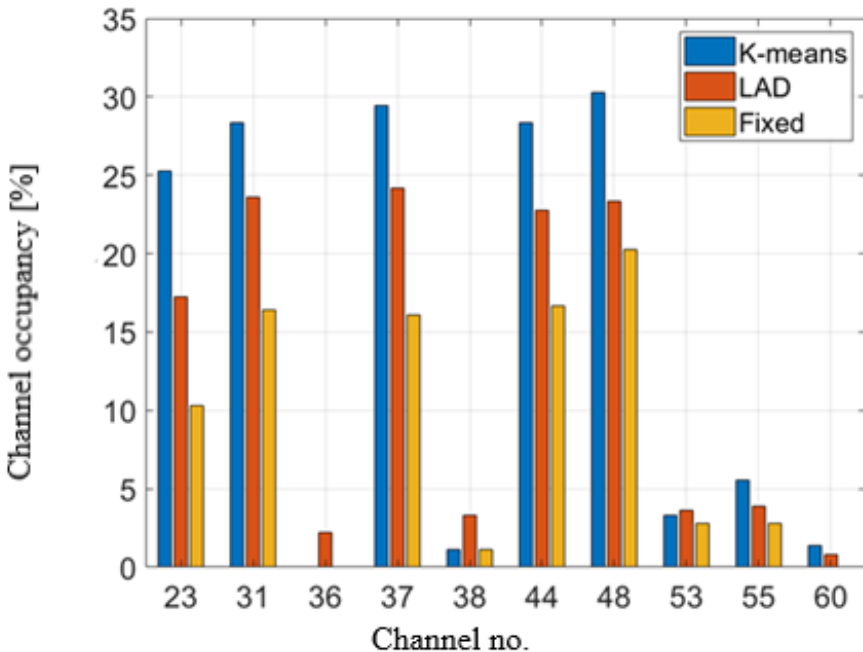


Figure 5. Averaged occupancy over all locations and measurement times for known active channels.

The results show that even known active channels appear unoccupied in more than 70% of the locations. *k*-means can detect the presence of the primary users more often than fixed and LAD methods in most locations. However, LAD can detect primary user presence in some locations that *k*-means does not. It should be noted that LAD is an adaptive method, which tunes its threshold based on the noise level. Therefore it could perform better in noisy locations at higher frequencies since noise is known to increase with frequency. The spectrum occupancy at the different locations in suburban areas over the entire

470-860 MHz band varies between 0-8%, while in rural areas, between 0.02-10%.

## COEXISTENCE IN HETEROGENEOUS WIRELESS NETWORKS IN TV WHITE SPACES

Researchers have highlighted the underutilization of licensed portions of the spectrum as a potential opportunity address the spectrum congestion problem. The use of already licensed parts of the spectrum would be enabled by cognitive radios, which behave as secondary users and use the spectrum whenever the primary users, i.e., the license owners, are not using it. A cognitive radio (CR) is a radio that can change its transmission parameters based on interaction with the environment in which it operates [40]. The cognitive radio network is composed of secondary devices that communicate among themselves; however, the configuration and organization of the network will depend on the technology and standard applied. Cognitive devices for use in TVWS are generally divided into four groups: fixed devices, Mode I personal/portable devices, Mode II personal/portable devices, and sensing only devices. [39]. Fixed devices can transmit up to 4W EIRP (Effective Isotropic Radiated Power). Due to the high transmission power level these devices are not allowed to operate on adjacent channels of the TV channels that are in use and they must have access to database and geolocation capability.

It is envisioned that CR networks will be used for the following applications [41]: (i) Wide area broadband provision to rural areas (ii) Future home networks and smart grids (iii) Cellular communications (iv) Public Safety. CR technology is viewed as an effective solution for the provision of broadband services in rural areas

## COEXISTENCE CHALLENGES FOR CR NETWORKS IN TVWS

Because existing wireless networks are generally designed to work with fixed frequency allocation, coexistence challenges between wireless networks arise when switching to a cognitive radio environment. In addition, because the available spectrum changes rapidly and there are many different QoS requirements for different applications, CR networks have to handle many additional challenges: interference avoidance with primary users, optimal spectrum band selection

for QoS guarantee, seamless communications regardless of the appearance of primary users [32], to name a few. To tackle these challenges, a CR network's coexistence decision mechanism (CDM) must have these four functionalities: spectrum sensing, spectrum decision, spectrum sharing strategy and spectrum mobility, described in detail in [33–36]. The block-scheme of the cycle of cognitive radio functionalities is shown in Figure 6.

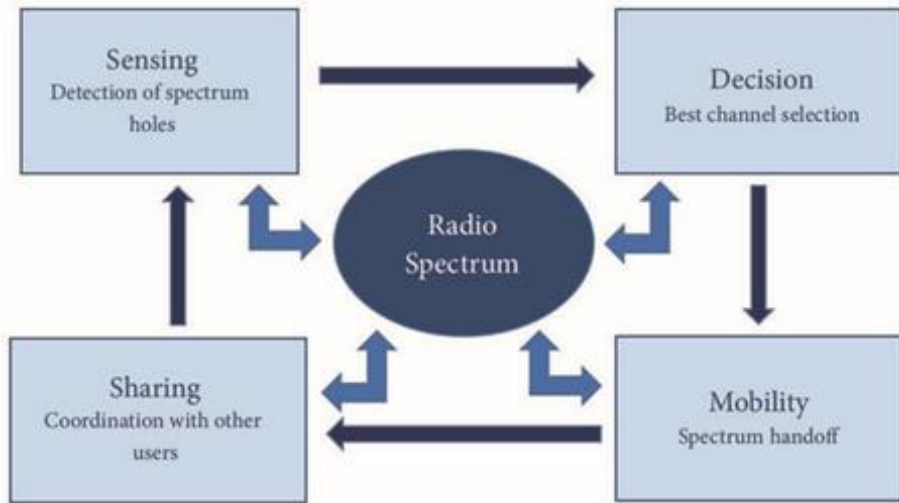


Figure 6. Functionalities for cognitive radio coexistence.

In overlay spectrum sharing, a secondary user may transmit only if the primary user is not active at that time, referred to as the idle period [39]. The secondary user needs to sense the spectrum to detect this idle inactive period. Based on their ability and willingness to collaborate or not, there are two possible ways for different networks to access the spectrum. There are schemes for coexistence that are based on cooperative or no cooperative methods. The cooperative method means that there has to be cooperation and communication between devices or networks that are sharing the spectrum and are within each other's interference range.

Cooperative methods are generally based on the ability to exchange information between networks of similar or different types. This method overcomes the hidden node problem as all the networks are aware of each other's geographical positions. For this method different mechanisms that can be used, such as: TDMA (Time-Division Multiple

Access), FDMA (Frequency-Division Multiple Access) and CDMA (Code-Division Multiple Access). However, considering that spectrum might be shared between heterogeneous networks that have different operational characteristics and requirements, such as: frame rate, guard bands, power allocation, etc., there are many challenges in implementing these techniques. Because of this, adopting a suitable method for all secondary users may not be very useful.

## MMWAVE COMMUNICATION IN URBAN VEHICULAR NETWORKS

Different networks will make the decisions based on their own observations in no cooperative suitable methods. Various strategies are used for these methods such as: DFS (Dynamic Frequency Selection), DCS (Dynamic Channel Selection), power control, listening before the talk, Energy Detection Threshold, etc. Even though this strategy is cheaper and easier to implement, it does not always give the best network performance in terms of throughput and fairness among networks and users

Without coexistence mechanisms, the utilization of TVWS spectrum will be significantly reduced. Without coexistence mechanisms, 92% of the available spectrum is overlapped by neighboring networks [39]. The coexistence mechanisms are categorized into centralized, coordinated and autonomous mechanisms. The difference among these coexistence mechanisms relies on where the coexistence decision is made. The different coexistence mechanisms are presented in Figure 7.

High-definition maps, real-time updates, and on-board multimedia systems are just a few of the applications that make automated vehicles prime consumers of network traffic. Indeed, automotive services –safety and entertainment – are among the reference use cases for next-generation network technologies. Despite the important differences among these technologies, they all share the goal of providing more network capacity to vehicles and drivers.



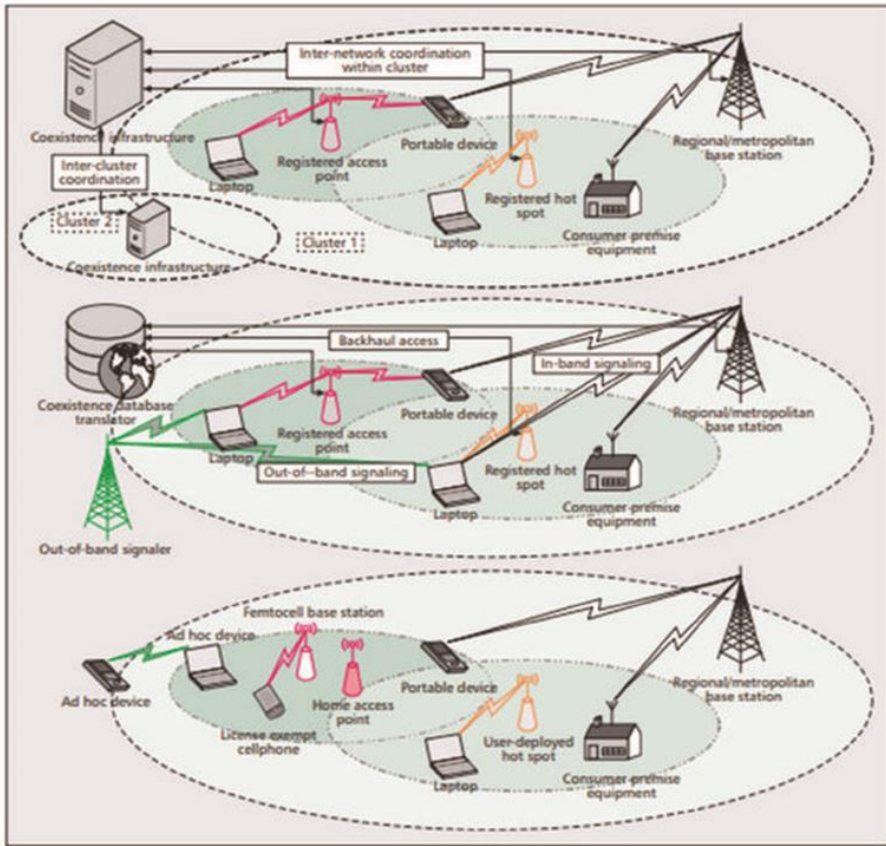


Figure 7. Types of coexistence mechanisms in heterogeneous cognitive networks [42].

Whenever more capacity is needed, millimeter-wave (mmwave) communications are an appealing option [44]. However, on the negative side, mmwave frequencies suffer from harsh propagation conditions, with severe attenuation and high blockage probability. Such severe shortcoming has been addressed mainly by two approaches. On the one hand, mobile network operators plan to backup data transfers served by mmwave links by pairing them with lower-frequency links specially to maintain connectivity through low-frequency control channels, to cope with the unpredictable changes in real-world scenarios and the high sensitivity of mmwave to the presence of obstacles [43]. On the other hand, the design of directional antenna systems, where the available power is concentrated on one or more beams, can significantly help to mitigate the problem. A necessary trade-off in mmwave

communications arises between the directionality gains achieved using beamforming and offered spatial coverage.

This implies that the performance of mmwave networks critically depends on the beam design, i.e., the beams number, direction, and amplitude. Successful beam design requires knowledge about the location of the user(s) to serve, which explains why the earliest and currently, the most mature, mmwave applications target static or quasi-static scenarios. In addition, due to the mobility of the vehicular users, communication in mmwaves is even more sensitive to high Doppler shifts and delays in channel status feedbacks.

The traffic Lights (TL) strategy, proposed in [43], use vehicular mobility constrained not only by the road topology, but also by the state of traffic signals, e.g., traffic lights. Based on such an observation, the TL strategy leverages the available information on traffic light states. It points the beams available at each mmwave base station (gNBs) towards the road segments where the traffic light is red. The TL strategy is more flexible than the static one in that beam directions account for the vehicles' mobility. In addition, it is much more practical than the dynamic strategy, as beam reconfigurations are less frequent, and it does not require any real-time mobility information. Indeed, it is important to stress that, unlike the clustering-based Static and Dynamic schemes, the TL strategy requires no knowledge of vehicular mobility, and can therefore be applied in situations where such information is unavailable or unreliable. The channel gains and performance indicators are based on real-world data. In particular, in approximated channel model the Doppler Effect, shadowing, and multipath fading are considered.

The effective data rate is derived from downlink traffic by using the 4-bit channel quality indicator (CQI) which maps the reported CQI to a particular modulation-coding scheme (MCS) and spectral efficiency value. For the study, the SINR to CQI mapping was performed using the spectral-efficiency based approach reported in [45]. The data rate value depend on the number of gNBs contributing to the useful received signal (constructive interference), and the destructive interference that may come from other gNBs.

The difference in performance between static, dynamic and TL strategies is observed through the signal-to-interference-and-noise ratio (SINR) and data rate achieved by the different strategies, summarized in Figure 8, Figure. 9 and Figure 10, respectively.

Mmwave is a promising technology to enhance the capacity of vehicular networks. However, the performance of mmwave networks depends on the number, alignment, and the width of beams between gNBs and vehicles, which require knowledge of the vehicles' mobility. Instead of relying on real-time mobility information, traffic signals, e.g., traffic lights, which influence mobility itself, is a more promising strategy. Using low-complexity approximate models for the mmwave channel gain and based on their accuracy in realistic scenarios has a priority against more complex, existing models. Based on this innovative mmwave communication models and real-world topology and mobility information, the performance evaluation has provided relevant insights. Leveraging traffic light-state information for beam design results in a network performance that exceeds that of baseline approaches (namely, static beam alignment) and is comparable to that of approaches using real-time mobility information.

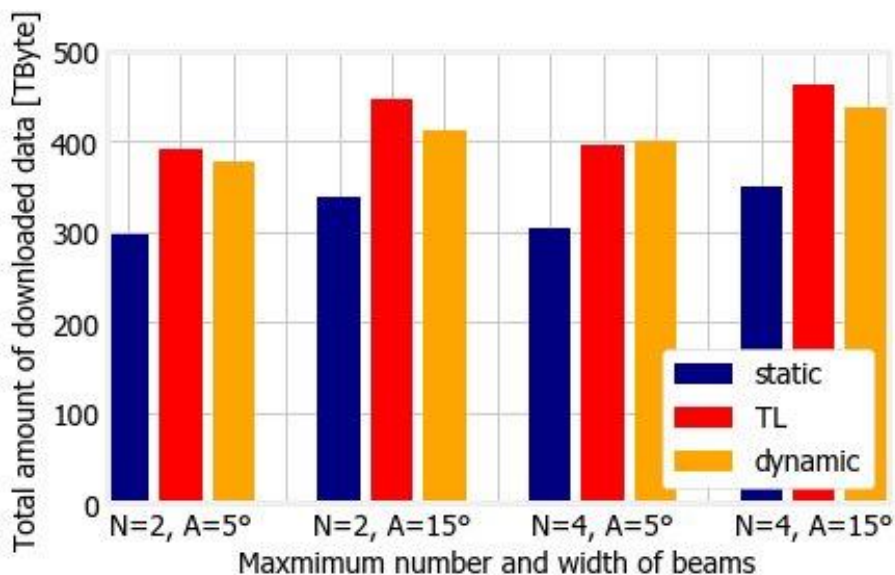


Figure 8. The total amount of downloaded data for different strategies and beam configurations, (i.e., maximum number of beams, beam half-power width).

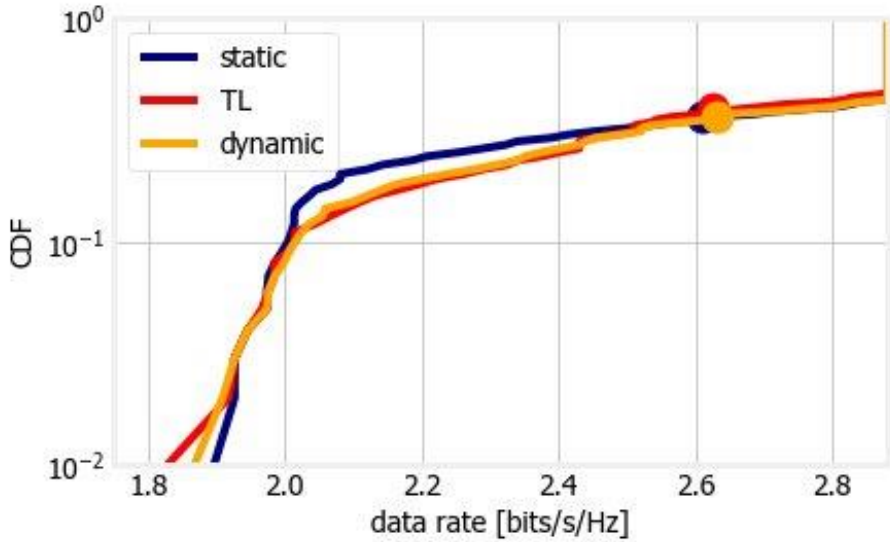


Figure 9. SINR is experienced by served vehicles under different strategies, when there are: two beams (left) and four beams (right) with  $A = 5^\circ$ . The average values are marked by a dot on each curve [43].

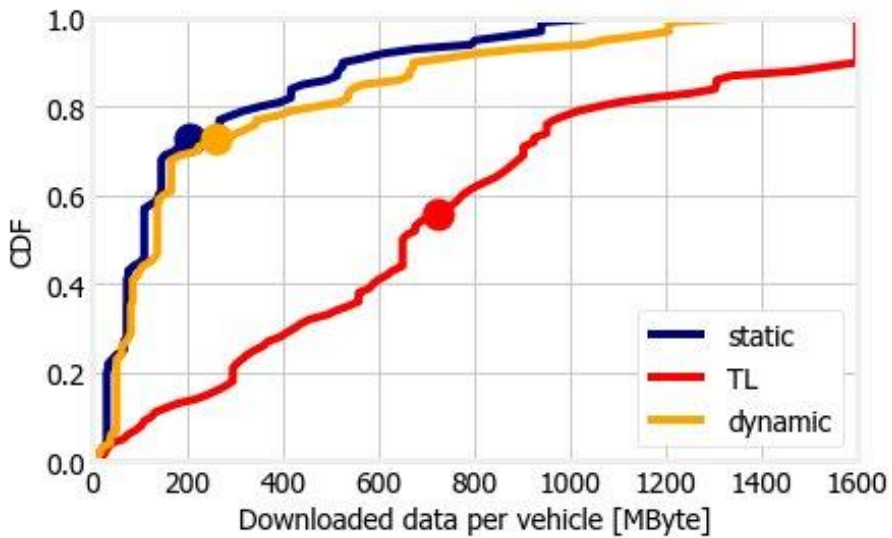


Figure 10. Actual rate experienced by served vehicles under different strategies, when there are: two beams (left) and four beams (right) with  $A = 5^\circ$ . The average values are marked by a dot on each curve [43].

## CONCLUSION

With the transition from analog to digital television broadcasting, a significant amount of frequency spectrum has become available. To take advantage of this, the idea of cognitive devices has been presented, for two main reasons: better use of the spectrum in urban areas and the possibility of wireless communications in rural areas. However, to best realize these two goals, some challenges present in this case must first be addressed. Given that we are talking about licensed frequency spectrum, in addition to detecting the primary user, a severe challenge remains the detection and identification of other secondary devices and networks. Indeed, the problems arising from this issue can be grouped into two categories. The first category is related to the problems resulting from the co-existence of several primary and secondary users, of different technologies, in the same spectrum simultaneously. The second category concerns the problems of the self-co-existence of several secondary users, of other or the same technologies, in the same place. Considering that some of the European and world countries have measured this free spectrum and created the relevant databases, Kosovo joined countries with available database.

The conclusions extracted from the performance evaluation, based on innovative models for *mmwaves* communication patterns, real-world topology and mobility information, have resulted in relevant indicators of network performance that exceeds the baseline approach based on using real time mobility information. Research done within [23] have shown that the occupation of the spectrum in the entire territory of Kosovo does not exceed the value of 10% in any of the measurement points (locations). Moreover, it has been shown that even the known active channels are not occupied for more than 70% in the measured locations. The project findings show that the underutilization of these frequency bands is very large. The analysis results are forwarded to the regulatory authorities to initiate the discussion on the liberalization of these frequency bands for potential opportunistic reuse. The performance of the co-existing networks is presented in terms of these key parameters: frequency band requirements fulfillment rate; degree of neutrality and theoretical capacity.

An accurate model of wave propagation in the channel is developed to evaluate the availability of the spectrum and analyze the potential scenarios for the reuse of this spectrum. The developed model is based on experimental measurements of the spectrum spread over the

entire territory of Kosovo, optimizing and adapting the parameters of known models to the characteristics of the geographical terrain. The model has been extended to urban, suburban and rural areas. The model has been verified with a large amount of data from additional measurements and has shown a high level of accuracy.

Millimeter wave bands are a very promising option for 5G networks, especially for the high speed of demand these networks. Furthermore, millimeter wave communications have also been shown to be very promising candidates for future vehicular networking technologies. Nevertheless, the performance of these wave networks highly depends on various aspects of forward and backward beam management between the base station and the moving vehicle. In this survey, both the beam design aspects and the user association (the moving car) are addressed using the graph-based approach in TL strategy [43]. The system is modeled as a weighted biparity graph, where the problem is treated as a matching problem considering the conflict between users in same spectrum band. Based on the real-world conflict-aware approach and mobility information, our assessment performance has yielded highly relevant content data. The proposed solution significantly outperforms our benchmark scheme utilizing a clustering algorithm. Future work will improve further development of the graphite model for millimeter waves and the interaction between base stations during beam design.

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Myzafere Limani

## HULUMTIMI I MUNDËSIVE PËR RISHFRYTËZUESHMËRINË E BREZAVE FREKUENCORË UHF, VHF DHE VALËVE MILIMETRIKE PËR RRJETET KOMUNIKUESE PA TELA NË TERRITORIN E KOSOVËS: PUNIM REVIAL

### Përmbledhje

Me tranzicionin nga transmetimet televizive analoge në ato digjitale, një numër i konsiderueshëm i spektrit frekuencor është bërë i disponueshëm për shfrytëzim. Për të përfituruar nga kjo, është paraqitur ideja e pajisjeve kognitive, për dy arsye kryesore: shfrytëzim më i mirë i spektrit në zonat urbane dhe mundësia e komunikimeve pa tela në zonat rurale. Megjithatë për të realizuar më së miri këto dy qëllime, së pari duhet të adresohen disa sfida që janë prezente në këtë rast. Duke marrë parasysh se po flasim për spektër frekuencor të licencuar, përveç detektimit të shfrytëzuesit primar, një sfidë serioze mbetet zbulimi dhe identifikimi i pajisjeve dhe rrjeteve të tjera dytësore. Në të vërtetë, problemet që rrjedhin nga kjo çështje mund të grupohen në dy kategori. Kategoria e parë ka të bëjë me problemet që rrjedhin si pasojë e bashkekzistencës së disa shfrytëzuesve primarë dhe sekondarë, të teknologjive të ndryshme, në të njëjtin spektër njëkohësisht. Kategoria e dytë ka të bëjë me problemet e vetë bashkekzistencës së disa shfrytëzuesve dytësorë, të teknologjive të ndryshme apo të njëjta, në të njëjtin vend. Duke marrë parasysh se disa nga vendet evropiane dhe botërore kanë bërë matjen e këtij spektri të lirë dhe i kanë krijuar databazat përkatëse, ka qenë më se i nevojshëm një hulumtim i tillë për Kosovën në mënyrë që edhe ne t'u bashkohemi vendeve të cilat e kanë në dispozicion një databazë të tillë.

Përfundimet e nxjerra nga vlerësimi i performancës, bazuar në modelet inovative [23] për modelet e komunikimit me valë milimetrike, topologjinë e botës reale dhe informacionin e lëvizshmërisë, kanë rezultuar në tregues të rëndësishëm mbi performancën e rrjetit që tejkalon qasjen e bazuar në përdorimin e informacionit të lëvizshmërisë në kohë reale. Hulumtimet e bëra në kuadër të projektit kanë treguar se shfrytëzimi i spektrit në tërë territorin e Kosovës nuk e kalon vlerën prej 10% në asnjërën nga pikat (lokacionet) matëse. Për më tepër, është treguar se edhe kanalet e njohura aktive nuk janë të zëna për më shumë se 70% në lokacionet e matura. Gjetjet e projektit tregojnë se mospërdorimi i këtyre brezave frekuencorë është shumë i madh. Rezultatet e analizës sonë do t'u përcillen autoriteteve rregullatore për të nisur diskutimin për liberalizimin e këtyre brezave frekuencorë për rishfrytëzim të mundshëm oportunist. Performanca e rrjeteve bashkekzistuese paraqitet në terma të këtyre parametrave kyçë: shkalla e përmbushjes së kërkesave të brezit të frekuencës; shkalla e neutralitetit dhe kapaciteti teorik.

Për të vlerësuar disponueshmërinë reale të spektrit dhe për të analizuar skenarët e mundshëm për rishfrytëzim të këtij spektri, është zhvilluar një model i saktë i përhapjes së valëve në kanal. Modeli është zhvilluar në bazë të matjeve eksperimentale të spektrit të shtrirë në të gjithë territorin e Kosovës, duke i optimizuar dhe përshtatur parametrat e modeleve të njohura me karakteristikat e terrenit gjeografik. Modeli është shtrirë në zonat urbane, suburbane dhe rurale. Modeli është verifikuar me një numër të madh të dhënash nga matjet shtesë dhe ka treguar një nivel të lartë saktësie [23].

Brezat e valëve milimetrike janë treguar një opsion shumë premtues për rrjetet 5G, veçanërisht për kërkesën e këtyre rrjeteve për shpejtësi të lartë. Komunikimet me valë milimetrike janë treguar gjithashtu të jenë kandidatë shumë premtues për teknologjitë e ardhshme të rrjeteve të automjeteve. Por, performanca e këtyre rrjeteve varet shumë nga aspekte të ndryshme të menaxhimit të rrezeve përpara ardhëse dhe prapa shkuese midis stacionit bazë dhe mjetit në lëvizje. Në këtë hulumtim janë trajtuar si aspektet e projektimit të rrezeve ashtu edhe lidhja e përdoruesit (makina në lëvizje) me qasjen e bazuar në grafe. Sistemi është modeluar si një graf bipolariteti i peshuar, ku problemi trajtohet si një problem i përputhjes duke marrë parasysh edhe konfliktin në mes të shfrytëzuesve sekondarë në të njëjtin spektër frekuencor. Performanca e vlerësimit [43], bazuar në qasjen e ndërgjegjshme për konflikt në botën reale dhe informacionin e lëvizshmërisë, ka dhënë të dhëna përmbajtësore dhe shumë të rëndësishme. Zgjidhja e propozuar duke shfrytëzuar strategjinë TL dhe modelimin e lartpërmendur, tejkalon dukshëm skemën standarde të bazuar në algoritëm grupimi (cluster) me strategji statike dhe dinamike.

Shfrytëzimi i valëve milimetrike është një teknologji premtuese për rritjen e kapacitetit të rrjeteve të automjeteve. Megjithatë, performanca e rrjeteve të valëve milimetrike varet nga numri, shtrirja dhe gjerësia e rrezeve ndër-mjet NB-ve dhe automjeteve, dhe këto kërkojnë njohuri shtesë për lëvizshmërinë e automjeteve. Në vend të mbështetjes në informacionin e lëvizshmërisë në kohë reale, është propozuar të shfrytëzohen sinjalet e trafikut, p.sh., semaforët, të cilët ndikojnë dhe në një farë mase rregullojnë vetë lëvizshmërinë, dhe si informacione të tilla janë në dispozicion të përhershëm dhe më të besueshëm. Në veçanti, fillimisht është zhvilluar një model i përafërt me kompleksitet të ulët, duke shfrytëzuar një model për karakterizimin e kanalit të valëve milimetrike për verifikimin e saktësisë së rezultateve në skenarë realistë, duke i krahasuar me modelet më komplekse të bazuara në strategji statike dhe dinamike. Më pas është paraqitur një formulim i optimizimit për një dizajn efektiv të rrezes, me një kompleksitet të ulët, zgjidhje heuristike, që ka rezultuar në performancë shumë afër zgjidhjes optimale.

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## AB INITIO EXPLORATION OF CARBON NANOCONES AS POTENTIAL CORROSION INHIBITOR

### Abstract

In an effort to discover new untapped potential inhibitors, a variety of Carbon Nanocones (bare and grafted by carboxyphenyl groups) were investigated as corrosion inhibitors for mild steel in hydrochloric acid-containing aqueous corrosion media. Using Density Functional Theory (DFT), Monte Carlo simulation (MC), and Molecular Dynamics simulation, the adsorption of carbon nanocones (CNC) onto the Fe (110) surface was analyzed. The obtained results provided information at the molecular level on the adsorption capacity, geometry, and adsorption energies of nanocones on the Fe (110) interface. The results demonstrate that carbon nanocones grafted with carboxyphenyl groups suppress corrosion more effectively than the bare ones due to the physical barrier properties of the organic layer that prevent the immediate migration of reducing agents toward the metal surface.

*Keywords:* corrosion, Carbon Nanocone, Density Functional Theory, Molecular Dynamics, Monte Carlo

### INTRODUCTION

The interaction of industrial metals, such as iron, with an aggressive environment containing corrosive species such as chloride ions and oxygen generates corrosion products ultimately shortening the materials lifespan. As a result, a variety of critical sectors [automotive,

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structural engineering, aerospace, oil and gas (energy), etc.] incur substantial losses due to corrosion [1–5]. To limit the magnitude of this process, the use of corrosion inhibitors remains the simplest and the most efficient endeavor. In this sense, a huge portfolio of different molecules is exploited to decrease the corrosion rate of different materials, especially coinage metals in an aqueous acid medium. Therefore the use of corrosion inhibitors continues to be the approach that is both the easiest to apply and the one that is the most effective [1–9]. This way, an extensive portfolio of various compounds is used in order to reduce the rate of corrosion that materials experience. It includes molecules and materials such as: amino acids [10], triazoles [11], ionic liquids [12], triazines [13], green inhibitor molecules [6] [14], polymeric materials [2], purine derivatives [15], quinoxaline derivatives [15], imidazoles [16], quinoline and its derivatives [17], functional and smart coatings [18] [19], natural products-plant extracts [20,21], expired drugs [22], nanomaterials [23,24], etc.

The varied topologies of carbon allotropes have encouraged the synthesis of a wide variety of carbon nanostructures to investigate these substances characteristics. Among the carbon allotrope structures are also carbon nanocones (key intermediate in the nucleation and formation of carbon allotropes such as fullerenes and carbon nanotubes). To our knowledge there is a lack of studies vis-à-vis the possible exploitation of carbon nanocones (CNC) for corrosion protection purposes [25,26]. In general experimental evaluations of corrosion phenomenon are carried out employing a wide range of distinct methods: Potentiodynamic measurements, Tafel slope, Electrochemical Impedance Spectroscopy (EIS), Weight loss measurements, Scanning Electron Microscope (SEM), Atomic Force Microscopy (AFM), Scanning Electrochemical Microscopy (SECM) [2,27–32] etc. These methods have provided new understandings regarding the electrochemical behavior and kinetics of the corrosion process that arises at the interface of materials and corrosive solution, as well as the evaluation of the inhibition performance of various inhibitors and the corrosion rate of materials. Density Functional Theory (DFT) and Molecular Dynamics (MD and MC) are two examples of the types of molecular mechanic's simulations used in these types of investigations. However, despite the fact that these types of research yield a great deal of information, many molecular-level questions can only be answered through highly advanced and effective computational simulations. DFT-derived characteristics include parameters like molecule polarizability and the

difference in electron-donating energy between the HOMO and LUMO levels, the fraction of transferred electrons ( $\Delta N$ ), dipole moment of the molecule, and energy from inhibitor to metal  $\Delta E$  back-donation. All these data have already proven vital parameters for understanding how and why inhibitors interact with the metal surface to exert their corrosion protection ability [33–40]. Moreover, Monte Carlo calculations complaisantly with Molecular Dynamic simulations are dexterous to offer details apropos the adsorption geometry and the adsorption energetics of the molecules onto material surfaces [30–32,41,42]. Because of their inherent stability, carbon nanocones are anticipated to have a longer lifespan than other industrial corrosion inhibitors currently used for corrosion prevention.

## CALCULATION DETAILS

### DENSITY FUNCTIONAL THEORY

DFT computations were executed using the Dmol<sup>3</sup> software from Biovia [18,19]. Meta-Generalized Gradient Approximation (m-GGA) employing the M11-L functional [43] (a dual-range local exchange to afford wide accuracy for both single-configurational and multiconfigurational molecules) and the Triple Numeric quality basis set (including additional polarization functions on all atoms) (TNP) [44] were used for geometry optimizations. The self-consistent-field (SCF) convergence criterion was less than  $1 \times 10^{-6}$  eV. The energy minima were ensured by doing a vibrational analysis to confirm the absence of any imaginary frequencies [21, [45]. The solvent (water) effects in the calculations were included by the Conductor-like Screening Model (COSMO) [33,46,47].

## MONTE CARLO AND MOLECULAR DYNAMIC

### SIMULATION DETAILS

The interaction involving the Fe(110) surface and the Nanocone structures (Figure 2) for the Monte Carlo (MC) and Molecular dynamic (MD) simulation, was done using the Fe(110) (under Periodic Boundary Condition) with a cell size of: 49.64 Å x 49.64 Å x 10.13 Å with the inclusion of a 50 Å vacuum layer at C axis containing inside 2500 water molecules/1 CNC / 25 hydronium + 25 chloride ions. The MD is fulfilled under NVT ensemble [48] at 25°C via 1 fs time step

and a total simulation time of 0.6 ns [28,30,31,37,49]. The temperature control is realized using the Berendsen thermostat MD [5]. The previously prominent COMPASSII force field is used for the simulations MC and MD [50] [28,30,34,35,37,51] [52]. The whole 600 ps of the MD trajectory is used to compute the Radial Distribution Function (RDF) [37,49,51].

## RESULTS

### DFT CALCULATIONS

The  $\sigma$ -profile shows the charge density distribution on the molecule's surface and may be used to determine the solubility of the conjugate in various solvents (in our case water) [53,54].

The sigma-profile charge density curve is constructed using COSMO model calculations. Partially charged atomic nuclei are used in COSMO to depict the electrostatic potential (ESP) [46,47,52,55]. Figure 1 shows that grafted Carbon Nanocone with carboxyphenyl groups are both acceptors and donors of H-bonds at the difference of unmodified Carbon Nanocone. Since water molecules create H-bond acceptor/donor interactions when an inhibitor is dispersed, its dispersion is facilitated by this ability.

The HOMO and LUMO overall spreading and their symmetry contrive as noticeable parameters for adjudicating the activity of a molecule and probing the development of chemical reactions [33,42,56]. The HOMO focuses on the parts of the molecule that have a fondness for providing electrons to electrophilic species while the LUMO point to the zones of the molecule with a high susceptibility to accept electrons from nucleophilic species. The frontier MO's shows that in the CNC inhibitors (Figure 2) HOMO is mainly on one side of the CNC rings with some minor contributions at the terminal ring atoms. For the grafted CNC the HOMO is distributed where the h carboxyphenyl groups higher grafing denisty is located.

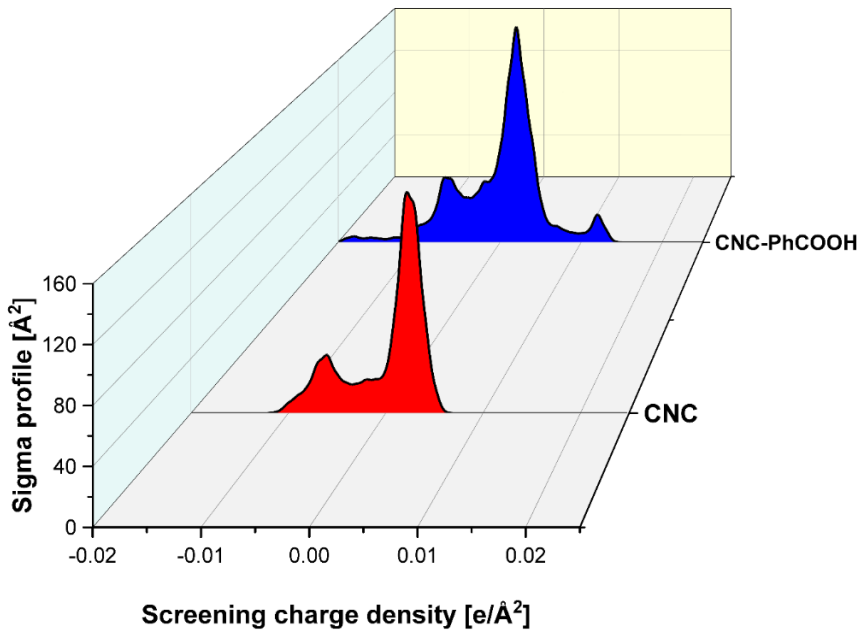


Figure 1.  $\sigma$ -Profile of the inhibitors.

The LUMO density is evenly spread over the CNC structure. The reasonably significant value of HOMO for CNC indicates their aptitude for interacting with the Fe surface by electron-donation and acceptance [34,36,41,57,58].

This reactivity is also evidenced by inspecting their moderately low electron affinity and high ionization potential values, showing an equal propensity in their electron exchange capacity. A moderately high chemical softness (**Table 1**) and low hardness values are also expected values that support these inhibitors as relatively high reactive entities with the adsorptive aptitude when they are in the vicinity of the metal surface.



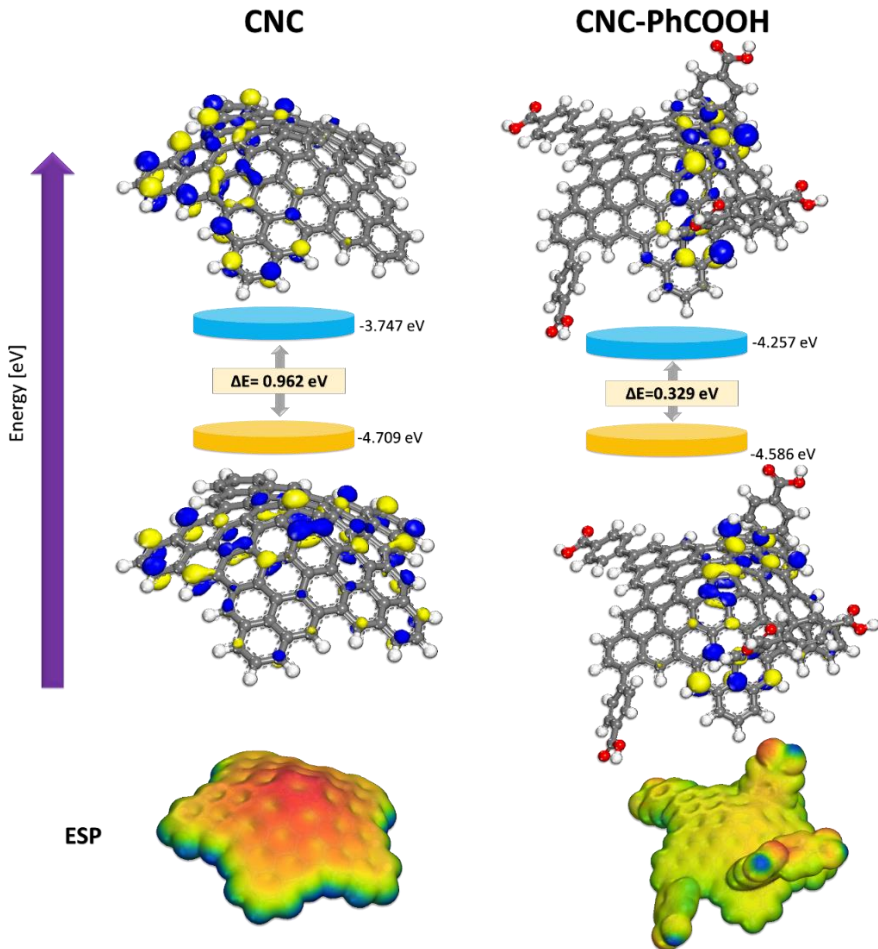


Figure 2. HOMO, LUMO surfaces, and molecular electrostatic potential (MEP) of bare and tethered with carboxyphenyl moieties CNCs (red color represents electron rich areas, whilst blue hue denotes electron deficient parts of the molecule).

Table 1. Calculated theoretical descriptors for CNC inhibitors.

<b>Descriptor</b>	<b>CNC</b>	<b>CNC- PhCOOH</b>
HOMO	-4.7090	-4.5860
LUMO	-3.7470	-4.2570
$\Delta E(\text{HOMO-LUMO})$	0.962	0.329
Ionization energy (I)	4.7090	4.5860
Electron affinity (A)	3.7470	4.2570
Electronegativity (X)	4.2280	4.4215
Global hardness ( $\eta$ )	0.4810	0.1645
Chemical potential ( $\pi$ )	-4.2280	-4.4215
Global softness ( $\sigma$ )	2.0790	6.0790
Global electrophilicity ( $\omega$ )	18.5821	59.4215
Electrodonating ( $\omega^-$ ) power	20.7562	61.6528
Electroaccepting ( $\omega^+$ ) power	16.5282	57.2313
Net electrophilicity ( $\Delta\omega^{\pm}$ )	16.4801	57.2151
Fraction of transferred electrons ( $\Delta N$ )	-1.0374	-3.6216
Energy from Inhb to Metals ( $\Delta N$ )	0.5177	2.1576
$\Delta E$ back-donation	-0.1203	-0.0411

### MONTE CARLO (MC) AND MOLECULAR DYNAMIC (MD) SIMULATIONS

MC and MD simulations are made on the iron metal surface immersed in the simulated corrosion environment that was studied. The configurations of the CNC molecules with the least amount of energy are given in Figure 3 (as chosen above). According to the adsorption geometries of the inhibitor, the presence of oxygen atoms in the CNC-

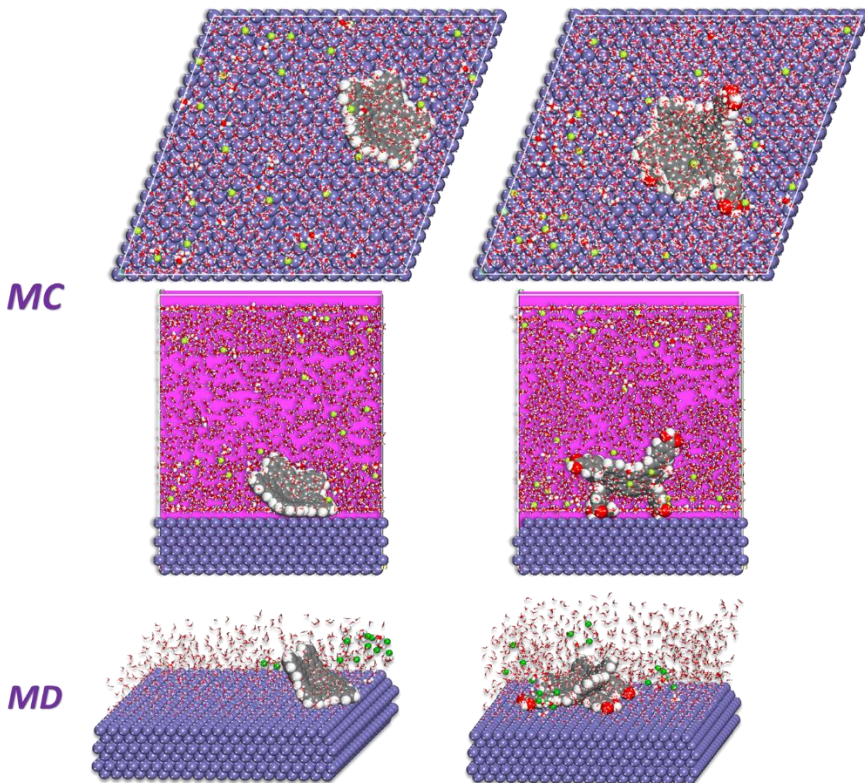
PhCOOH entity is the factor that is responsible for causing this process. This adsorption process is responsible for the establishing an anti-corrosion layer onto the surface of the metal, which safeguards the surface.

A way to quantify the extent of the interaction among inhibitor molecules with the iron surface, is fulfilled over the calculation of the adsorption energies using the following equation:

$$E_{\text{ads}} = E_{\text{total}} - [E_{\text{surface + water}} + E_{\text{CNC or CNC-PhCOOH + surface}}] + E_{\text{water}} \text{ (In the corrosion media)}$$

where:  $E_{\text{total}}$  is the total energy of the system as a result of inhibitor-metal interaction;  $E_{\text{surface + water}}$  and  $E_{\text{CNC or CNC-PhCOOH + water}}$  is system energy in the absence and presence of CNC molecules.

The dispersion of the adsorption energies for the enormous amount of adsorptive configurations produced and calculated by the Monte Carlo method for the CNC inhibitors is shown in Figure 4.



**Figure 3.** MC and MD posethe lowest adsorption configurations for the CNCs inhibitors in the simulated corrosion media on the iron surface under the Periodic Boundary Condition (PBC) model.

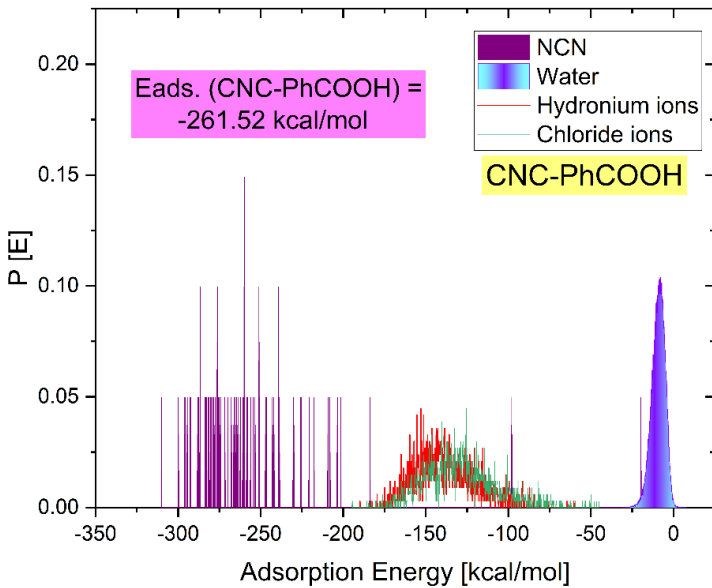
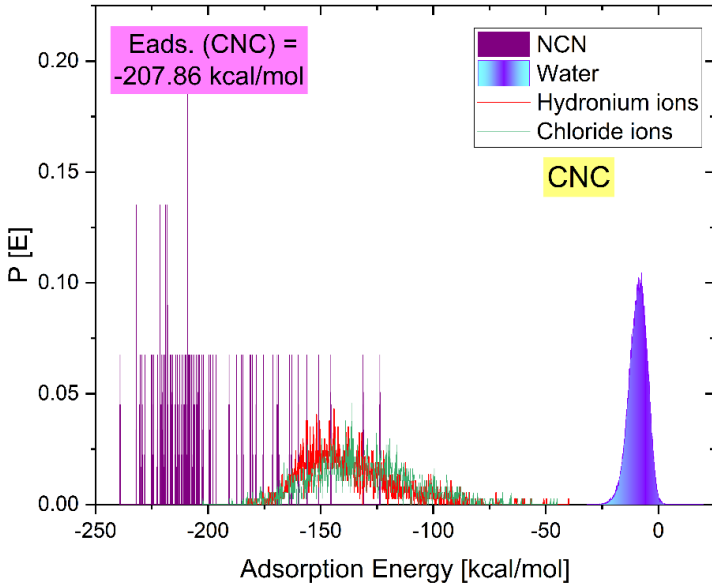


Figure 4. Distribution of adsorption energies for CNC inhibitors onto the Fe(110) surface in vacuum.

These relatively high adsorption energies point toward a strong interaction of the inhibitors onto the MS surface, leading to efficient corrosion protection of iron.

Both MC and MD calculations show that CNC almost flat and adsorbed onto the iron surface. As seen from Monte Carlo calculations (Figure 3), the negative values of the adsorption are suggestive of the spontaneity of the adsorption process [28,35–37]. MD simulations are important as they offer a relatively simple way to trail and capture the dynamics of the adsorption of the studied inhibitors on the metal surface. Furthermore, the addition of the  $-\text{PhCOOH}$  groups onto the CNC structures not only augments its dispersion in water, but also enhances its adsorption capacity toward mild steel, thereby acting as a better corrosion inhibitor.

## CONCLUSION

In this work, several theoretical methodologies were applied, including DFT, MC, and MD, all of which are based on molecular and quantum mechanics. A molecular understanding of how CNC inhibitors interact with iron surfaces to prevent corrosion was made possible by these techniques. Determining how and why these entities interact with the surface, and the corresponding adsorption sites, was made easier with the DFT descriptor calculation. According to Monte Carlo and Molecular dynamics results, when these molecules flat-lay onto the iron surface, they produce a barrier layer that delays the migration of the corrosion species toward the metal surface. The substantial absorption energies support a strong interaction between the CNC and the iron surface,

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## EKSPLORIMI AB INITO I NANOKONEVE TË KARBONIT SI INHIBITORË POTENCIALË TË KORROZIONIT TE ÇELIKU I BUTË

### Përmbledhje

Korrozioni i hekurit dhe çelikut të butë në mjedisë ujore acidike paraqet një ndër shqetësimet kryesore të shumë industrive, të cilat përdorin acidet për procese të ndryshme. Inhibitorët më të mirë të korrozionit konsiderohen substancat, të cilat e zvogëlojnë në masë të madhe korrozionin e metaleve, nuk janë toksike, kanë çmim të ulët dhe përgatiten lehtë. Në një përpjekje për të zbuluar inhibitorë të rinj të mundshëm për mbrojtjen e metaleve industriale, sidomos të hekurit nga korrozioni kur ai gjendet në mjedisë ujore acidike ose bazike në prani të agjentëve të ndryshëm reduktues, në këtë punim janë hulumtuar vetitë inhibitore të nanokoneve të karbonit. Nanokonët e karbonit bëjnë pjesë në kuadër të nanomaterialeve që kanë veti mekanike dhe fizike të jashtëzakonshme për shkak të dimensioneve të tyre shumë të vogla dhe raportit të madh sipërfaqe-vëllim. Vetë emri “nanokone” i karbonit tregon se këto nanomateriale të karbonit kanë formë konike dhe janë shumë stabile. Në këtë punim u hulumtuan vetitë antikorrozive të nanokoneve të karbonit të pamodifikuara, si dhe ato të modifikuara nga grupet karboksifenile kur ato e veshin sipërfaqen e çelikut të butë që zhytet në mjedis ujor, i cili përmban acid klorhidrik. Grupet karboksifenile përftohen zakonisht prej kripërave arildiazonium gjatë reduktimit të tyre me ç’rast përftohen radikalet karboksifenile, të cilat janë specie shumë reaktive dhe e veshin sipërfaqen e nanokonit të karbonit. Në këtë punim u analizua adsorbimi i nanokoneve të karbonit (CNC) në sipërfaqen Fe (110) duke përdorur *Teorinë Funktionale të Dendësisë* (DFT), simulimet *Monte Carlo* (MC) ato të *Dinamikës Molekulare*. Rezultatet e këtyre llogaritjeve mundësuan të kuptohet në nivel bashkëveprimi i nanokoneve të karbonit, qofshin ato të pamodifikuara ose të veshura me grupe karboksifenile me sipërfaqen e hekurit në mënyrë që të pengojnë sa më shumë korrozionin e metalit në një mjedis ujor acidik. Përdorimi i këtyre tri metodave të llogaritjes mundësoi marrjen e informacionit në nivel molekular mbi kapacitetin e absorbimit, gjeometrinë dhe energjitë e absorbimit të nanokoneve në ndërfaqen Fe (110). Metoda DFT mundësoi llogaritjen e parametrave të ndryshëm, si energjitë e orbitaleve HOMO dhe LUMO për nanokonët

e karbonit të pamodifikuara dhe të veshura me grupe karboksifenile, energjitë e jonizimit, afinitetit, vlerën e elektronegativitetit, si dhe vetitë elektrondonore dhe akceptore.

Sipas metodës *Monte Carlo* dhe asaj të *Dinamikës Molekulare* nanokonet e karbonit bashkëveprojnë me sipërfaqe të metalit dhe krijojnë një barrierë fizike që e ngadalëson depërtimin e specieve korrozive dhe ardhjen e tyre në kontakt me sipërfaqe të hekurit. Rezultatet tregojnë se nanokonet e karbonit të modifikuara me grupe karboksifenile inhibojnë korrozionin në mënyrë më efektive sesa ato të pamodifikuara. Arsye për këtë mund të jetë shpërndarja më e mirë e nanokoneve të karbonit në ujë, por edhe prania e molekulës karboksifenile në sipërfaqe të nanokonit të karbonit që e bën atë barrierë fizike më vështirë të depërtueshme. Në bazë të llogaritjeve me metodën *Monte Carlo* u gjet se energjia e absorbimit të nanokoneve të karbonit në sipërfaqe të metalit ishte -208 kcal/mol, kurse për nanokonet e karbonit të veshura me grupe karboksifenile ishte – 261 kcal/mol.



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## SYNTHESIS, STRUCTURAL CHARACTERIZATION AND STEREOCHEMISTRY OF THE BICYCLE ARABINOTHYMIDINE AS A MODIFIED NUCLEOSIDE

### Abstract

Crystals of nucleoside bicycle arabinothymidine (bc-araT),  $C_{12}H_{16}N_2O_6$ , were grown and subjected to X-ray analysis at 173 K. The nucleoside bc-araT exists in only one conformation in the solid state. The furanose ring adopts a C(2')-endo conformation (2E, south-type) and thus gives rise to a pseudorotational phase angle  $P$  of  $143.5^\circ$ . The carbocyclic ring is in a 6'-exo conformation with the hydroxyl group at C(5') in an axial position. The torsional angle  $\gamma$  of bc-araT nucleoside is in a gauche (+sc) orientation, and the orientation of the base (torsion angle  $\chi$ ) is, as expected, anti. The two symmetry independent molecules in the unit cell are linked by a dimer of N-H...O hydrogen bonds.

*Keywords:* crystal structure, nucleoside, bicycle arabinothymidine, conformational analysis.

### INTRODUCTION

#### Chemical context

Our contribution to the field of conformationally constrained oligonucleotide analogs in the past has been on the development of the bicyclo(bc) and tricyclo(tc)-DNA molecular platforms. [1-2] As part of our work on the synthesis and properties of conformationally constrained nucleosides, we became interested in the bicycle ribothymidine (bc-rT) and bicycle arabinothymidine (bc-araT) versions of bc-DNA, the rationale being to identify the influence of the 2'-OH group on

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nucleoside conformation. However, while there exists crystal data of a protected bc-rT nucleoside [2], there is no crystal data available for the bc-araT nucleosides. Here we report on the crystal structural and conformational preferences of bc-araT nucleoside as determined by X-ray and/or NMR.

## EXPERIMENTAL PART

### Synthesis and crystallization

(3'S,5'R)-1-(3',5'-di-O-benzyl-3',5'-ethano-2'-hydroxy- $\beta$ -D-arabinofuranosyl)thymidine (0.050 g, 0.1 mmol) was dissolved in anhydrous MeOH (3 ml), then Pd(OH)<sub>2</sub>/C (70 mg) and 1,3-cyclohexadiene (0.1 ml, 1 mmol, 10 eq.) were added to the solution. The mixture was degassed with Ar for 10 min, flushed with H<sub>2</sub> for 10 min, and then stirred for 1 h at r.t. under H<sub>2</sub> atmosphere. The mixture was then filtered over a Celite pad, the solvent was removed, and the residue was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1) to give compound bc-araT as a white solid. Yield: 0.026 g (85%). Suitable crystals were obtained as colorless rods by recrystallization from methanol.

Table 2. Experimental details.

<b>Crystal Data</b>	
Chemical Formula	C <sub>12</sub> H <sub>16</sub> N <sub>2</sub> O <sub>6</sub>
<i>M<sub>r</sub></i>	284.27
Crystal System, space group	Orthorhombic, P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub> (No. 19)
Temperature (K)	173
a, b, c [Å]	6.8013 (1), 9.1518 (1), 19.4720 (3)
V [Å <sup>3</sup> ]	1212.02 (3)
Z	4
Radiation type	Mo K $\alpha$
$\mu$ (mm <sup>-1</sup> )	0.126
F(000)	600
Crystal Size (mm)	0.26 x 0.37 x 0.44

<b>Data collection</b>	
Diffractionmeter	Bruker APEXII CCD
Absorption correction	Multi-scan (SADABS; Bruker, 2001)
$T_{\min}, T_{\max}$	0.984, 1.000
Dataset	-9: 9; -12: 12; -26: 27
No. of measured, independent and observed [ $I > 2\sigma(I)$ ] reflections	12650, 3252, 3140
$R_{\text{int}}$	0.021
$(\sin \theta/\lambda)_{\text{max}}$ ( $\text{\AA}^{-1}$ )	0.639
<b>Refinement</b>	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.0300, 0.0765, 1.09
No. of reflections	3252,
No. of parameters	185
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ ( $\text{e \AA}^{-3}$ )	0.28, -0.18

TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9:1): Rf 0.21.  $^1\text{H-NMR}$  (300 MHz, DMSO):  $\delta$  149-1.57 (*m*, 1H, H-7'), 1.65-1.80 (*m*, 1H, H-6'), 1.82 (*s*, 3H,  $\text{CH}_3$ ), 1.85-1.88 (*m*, 1H, H-6'), 2.22-2.45 (*m*, 1H, H-7'), 3.79-3.83 (*q*,  $J = 3.21$  Hz, 6.42 Hz, 1H, H-2'), 3.88-3.90 (*d*,  $J = 5.10$  Hz, 1H, H-4'), 3.95-4.10 (*m*, 1H, H-5'), 5.03-5.05 (*d*,  $J = 7.53$  Hz, 1H, 5'-OH), 5.46 (*s*, 1H, 3'-OH), 5.61-5.63 (*d*,  $J = 6.06$  Hz, 1H, 2'-OH), 5.97-5.98 (*d*,  $J = 3.39$  Hz, 1H, H-1'), 7.68-7.69 (*d*,  $J = 1.14$  Hz, 1H, H-6), 11.33 (*s*, 1H, NH).  $^1\text{H NMR-NOE}$  (400 MHz, DMSO): 5.98 (H-1')  $\rightarrow$  3.80 (H-2', 7.9%), 3.90 (H-4', 3.1%).  $^{13}\text{C-NMR}$  (75 MHz, DMSO):  $\delta$  12.6, 30.3, 33.0, 71.7, 77.5, 87.0, 87.9, 88.7, 107.1, 139.0, 150.6, 164.4. HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calculated for  $\text{C}_{12}\text{H}_{17}\text{O}_6\text{N}_2$  285.1081, found 285.1083.

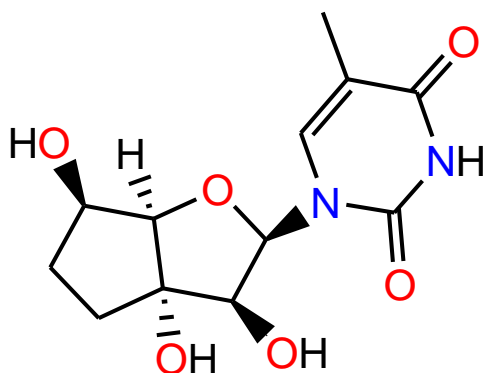
Computer programs: APEX2 and SAINT [15], SHELXT [16], SHELXL2014 [17], ORTEP-3 for Windows [18], Mercury [19], SHELXTL [20] and publCIF [21].

## Refinement

Crystal data, data collection and structure refinement details are summarized in Table 3. The N-bound H atom was located in a difference-Fourier map and refined as riding, with N—H = 0.88 Å, and with  $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{N})$ . All other H atoms were placed geometrically and refined using a riding-atom approximation, with C—H = 0.95–1.00 Å, and  $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$ .

## RESULTS AND DISCUSSION

We were, however, successful to obtain crystals for X-ray analysis of nucleoside bc-araT (Figure 1) which was obtained from (3'S,5'R)-1-(3',5'-di-O-benzyl-3',5'-ethano-2'-hydroxy-β-D arabinofuranosyl)thymidine by removing the benzyl groups via catalytic hydrogenation with Pd(OH)2/C as catalyst. The (3'S,5'R)-1-(3',5'-di-O-benzyl-3',5'-ethano-2'-hydroxy-β-D arabinofuranosyl)thymidine nucleoside was prepared as reported previously.[2]



The obtained crystals were used to prove the anomeric configuration and map the conformational preferences of the bicyclic core structure.

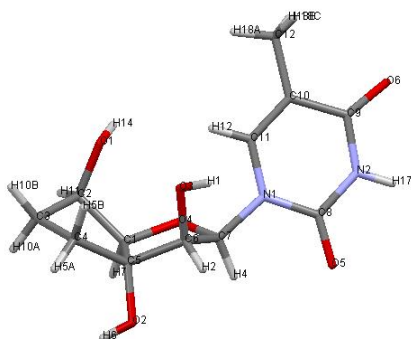


Fig. 1. ORTEP (50% probability ellipsoids) representation of the bc-araT nucleoside. H-atoms are given arbitrary displacement parameters for clarity.

Crystals of bc-araT were subjected to X-ray analysis to map the conformational preferences of the bicyclic core structure. As in the case of bc-dT and other bi- and tricyclic nucleosides [3,4], nucleoside bc-araT exists in only one conformation in the solid state.

The furanose ring of bc-araT nucleoside adopts a C(2')-endo conformation (2E, south-type) and thus gives rise to a pseudorotational phase angle  $P$  of  $143.5^\circ$ . Thus for bc-araT nucleoside, the pseudorotational angle is in the range of  $110$  to  $180^\circ$  [5-7] and agrees with that of the nucleoside bc-dT, which, likewise, was found by X-ray crystallography analysis to adopt an S-type conformation with  $P = 128^\circ$ . [3] The furanose conformation of bc-araT belongs to same class as that of the 2'-deoxygenated derivative (bc-dT), which shows a 1'-exo conformation with a  $P$  of  $128^\circ$ .

The carbocyclic ring is in a 6'-exo conformation with the hydroxyl group at C(5') in an axial position. The confirmation of the carbocyclic ring in the bc-rT nucleoside is more flexible compared to the carbocyclic ring of the bc-araT nucleoside. In addition, the torsional angle  $\gamma$  [O1-C2-C1-C5  $80.9$  ( $11^\circ$ )] of nucleoside bc-araT is in a gauche (+sc) orientation as observed in A- and B-DNA [8,9], and the orientation of the base  $\chi$  [O4-C7-N1-C8  $-122.5$  ( $10^\circ$ )] is, as expected, anti.



Table 1. Pseudorotational phase angles  $P$  and selected torsion angles of bc-araT in comparison to bc-dT, and natural deoxynucleotides in B-DNA conformation. [a] data taken from [3], 1993 [b] data taken from [10].

nucleoside	Furanose pucker	$P$ (deg)	$\delta$ (deg)	$\gamma$ (deg)	$\chi$ (deg)
bc-araT	2'-endo ( ${}^2E$ )	143	138	81	-122
bc-dT <sup>[a]</sup>	1'-exo ( ${}^1E$ )	128	126	149	-113
dN <sup>[b]</sup>	2'-endo ( ${}^2E$ )	144	122	57	-131

*Conformation of bc-araT Nucleoside in Solution.* In order to study the conformational behavior of the bc-araT nucleoside, the experimental  ${}^3J_{HH}$  coupling constants were measured. The bc-araT nucleoside was numbered in the spectral analysis according to Figure 2. The introduced ethylene-bridge was indicated as "3',5'-Ethano".

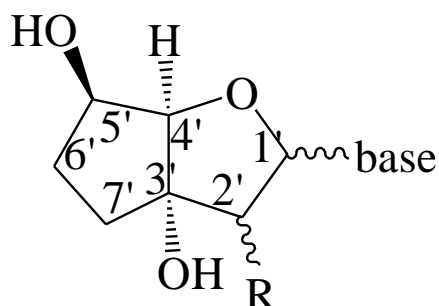


Fig. 2. Numbering of [3.3.0]-bicyclo sugar derivatives in spectral analysis.

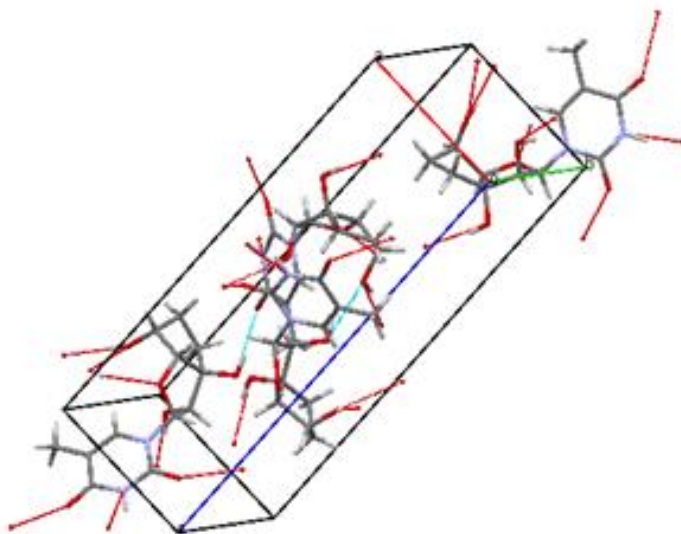
Since the coupling constants for H-C(6') could not be resolved entirely completely, it is impossible to derive a solid conclusion about the value of this torsion angle in solution. However, analysis of the coupling constants for H-C(4') and H-C(5') led to a quantitative statement about the arrangement of the six-membered ring, in the case of the thymine monomer. The  ${}^3J_{H4'H5'}$  coupling constants were found to be 5.1 Hz for bc-araT nucleoside.

Table 2. Coupling constant and calculated angles between H-C4' and H-5'. n.p.: not a possible angle.

compound	value for $^3J_{H4'H5'}$	calculated angles
bc-araT	5.1 Hz	<b>+32<sup>0</sup></b> or <b>+132<sup>0</sup></b> (n.p.)

By application of a Karplus relation connecting the coupling constant  $^3J_{H4'H5'}$  and the torsion angle of H4'H5'[5-7,11-13], four different ranges of the torsion angles for H4'H5' were calculated of which two can be excluded due to the covalent geometry. A possible combination of angles calculated from the Karplus-equation is marked in red in Table 2. Assuming that the carbocyclic ring adopts a chair-like conformation, two conformers are possible, with O(5') being in an axial or an equatorial position. In the former case, H-C(5') is aligned in a staggered fashion to H-C(4'). Hence, the angles to these hydrogens are approximately 30°. The coupling constants for this proton are expected to be between 3 to 4 Hz. The coupling constant  $^3J_{H4'H5'}$  of 5.1 Hz suggests the structure in-between the two possible conformers described above, with a preference for the O(5') in a pseudoaxial arrangement. A complete analysis of the sugar pucker of the bicyclo[3.3.0] skeleton was unfortunately not possible due to the coupling barrier at C(3') and to substantial signal overlap of C(6') and C(7') in the carbocyclic subunit.

The two symmetry independent molecules in the unit cell are linked by a dimer of N-H---O hydrogen bonds. The hydroxyl groups of the two independent molecules are involved an intermolecular O-H---O hydrogen bond and in an intramolecular O-H---O hydrogen bond with the oxygen of the ether moiety (see Figure 3).



*Fig. 3. Partial view of the crystal packing viewed along the b-axis.*

A similar compound, i.e. protected bc-rT and protected bc-araT nucleosides [2] has been reported and shows structures comparable with the title compound. Also, a similar structure, i.e. protected bc-araT [14] was also synthesized. To our knowledge, this is the first crystal structure reported for unprotected bc-araT nucleoside.

## CONCLUSION

During this research we have synthesized a modified nucleoside, which can be used in antisense therapy. At the same time the structure has been determined using spectroscopic techniques such as NMR, MS and X-ray analysis. The furanose ring adopts a C(2')-endo conformation (2E, south-type) while the carbocyclic ring is in a 6'-exo conformation with the hydroxyl group at C(5') in an axial position. The torsional angle  $\gamma$  of bc-araT nucleoside is in a gauche (+sc) orientation, and the orientation of the base (torsion angle  $\chi$ ) is, as expected, anti.

## FUNDING INFORMATION

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SINTEZA, KARAKTERIZIMI STRUKTURAL DHE  
STEREOKIMIA E BICIKLO ARABINOTIMIDINES  
SI NUKLEOSID I MODIFIKUAR

Përmbledhje

Qëllimi i këtij hulumtimi ishte sintetizimi dhe karakterizimi struktural i një nukleozidi të modifikuar, i cili mund të përdoret në terapin antisens. Si pjesë e punës sonë mbi sintezën dhe vetitë e nukleozideve të kufizuara në mënyrë konformacionale, ne u interesuam për versionet e biciklo ribotimidinës (bc-rT) dhe biciklo arabinotimidinës (bc-araT) të bc-ADN-së, me arsyetimin për të identifikuar ndikimin e grupit 2'-OH në konformacionin e nukleozideve. Ndërsa ekziston një e dhënë kristalore e një nukleozidi bc-rT të mbrojtur strukturalisht me grupe mbrojtëse, nuk ka të dhëna kristalore të disponueshme për nukleozidet bc-araT. Këtu ne raportojmë mbi preferencat kristalore strukturale dhe konformative të nukleozidit bc-araT siç përcaktohet nga rrezet X dhe spektroskopia e rezonancës bërthamore magnetike (RBM). Kristalet e nukleozidit bc-araT,  $C_{12}H_{16}N_2O_6$ , janë sintetizuar dhe analizuar me rreze X në 173 K. Nukleozidi bc-araT ekziston vetëm në një konformacion në gjendje të ngurtë. Unaza e furanozës adopton një konformacion C(2')-endo (2E, tipi jugor) dhe kështu krijon një kënd fazor pseudorotacional P prej  $143,5^{\circ}$ . Unaza karbociklike është në një konformacion 6'-exo me grupin hidroksil në C(5') në një pozicion aksial. Këndi torsional  $\gamma$  i nukleozidit bc-araT është në një orientim gauche (+sc) dhe orientimi i bazës (këndi torsional  $\chi$ ) është, siç pritej, anti. Dy molekulat e pavarura nga simetria në qelizën njësi janë të lidhura nga një dimer i lidhjeve hidrogjenore N-H...O.



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## YIELD AND PERFORMANCES OF SEVERAL OF ALFALFA (*MEDICAGO SATIVA* L.) CULTIVARS CULTIVATED IN REGION OF PRISHTINA

### Abstract

A field trial was conducted at the experimental fields of the University of Prishtina, Faculty of Agriculture, Department of Crop science Prishtina in 2018 and 2019. The experimental design was a complete random block (CRB) with four replications. The genetic material of the study was obtained from the Agriculture institute in Ljubljana, Novi Sad, and Osijek. Three alfalfa cultivars: Soqa, Banat, and Osijek 66 were studied. The highest yield for the first year (2018) was obtained for cultivar Soqa on 2956 kg ha<sup>-1</sup> DW, while a lower yield for 2018 was determined for the cultivar Banat VS with a value 2708 kg ha<sup>-1</sup>. For the second year (2019) the highest yield was realized for cultivar Soqa on an average of 3390 kg ha<sup>-1</sup> while on the other side with minimum average values was characterized by the cultivar Banat VS on the value of 2914 kg ha<sup>-1</sup>. The differences were  $d = + 476$  kg ha<sup>-1</sup> dry weight (DW). A two-year investigation for three cultivars of alfalfa growing in agro-ecological conditions in Prishtina will conclude that Cultivar Soqa was shown a higher yield performance compared to the yield performance of Osijek 66 and Banat VS.

*Keywords: alfalfa, yield, locality, year, cultivar.*

### INTRODUCTION

The widespread use of alfalfa (*Medicago sativa* L.) in ruminant livestock diets and the impact of its nutritive value on animal performance has been the impetus for extensive research efforts to discern relationships among harvest interval, plant maturity, and morphology, forage yield, and nutritive value. Several studies have documented the

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general effect of harvest frequency on annual alfalfa DM yield and nutritive value across various environments [1]. Alfalfa (*Medicago sativa* L.) is considered, worldwide, as being one of the most important forage crops. It is cultivated in over 80 countries covering an area of 35 million hectares. Its growth structure is upright with crowns that contain 5–25 stems that grow up to 60 to 90 cm in height [2]. In the West Balkan (WB), the most important legume forage crops are alfalfa (*Medicago sativa* L.) and red clover (*Trifolium pratense* L.), which are mainly used as single N-fixation crops and rarely in mixture with grasses [3]. Alfalfa (*Medicago sativa* L.) is a Fabaceae perennial herb and is an important legume used for forage worldwide. Additionally, it is an important source of nectar and pollen for honeybees in several locations worldwide [4]. It is a cross-pollinated plant, and pollination occurs with the help of insects, wind and other external elements. The honeybees *Apis mellifera* L. and *Apis Florea* F. were found to be the most active pollinators in alfalfa flowers [5]. From all forage crops, which together with meadows have a major contribution in ensuring the forage base, alfalfa crop (*Medicago sativa* L.) occupies an important position. This plant is distinguished by its forage value, vast cultivation area, and high digestibility, and from the point of view of farmers and the world's agricultural scientists considered the "Queen of Fodder Herbs" [6]. Alfalfa monoculture is still prevalent in many European countries, where it is the backbone of organic crop-livestock systems, also significantly contributing to conventionally managed systems [7]. Forage nutritive value partly depends on the availability of nutrients in the plants for animals. Legumes also meet the requirement for greater self-sufficiency of feed proteins at the farm and the country levels [8,9]. It has other superior forage qualities and high yields that livestock can consume as high protein content and it is also rich in minerals and vitamins [10]. While the agronomic studies cited above have documented the general effects of harvest interval and maturity on alfalfa yield and nutritive value across the whole growing season, these studies did not determine how yield changes relative to a nutritive value within the periods of a growing season in which alfalfa is typically harvested [i]. Kosovo has around 1.9 million residents mostly living and work in urban areas. Last 20 years the Kosovar's society faced dramatic changes. Many rural areas have abounded, and consequently the arable lands and animal farms also, but these areas are not used as meadows or as pasture now. Based on actual data, the meadows and pastures cover 224410.83 ha of the total surface of Kosovo. Moreover, just a particular of these surfaces are distinguished clearly as meadows or pastures. The last agriculture census found that 65099.00 ha are

meadows, 11724.27 ha pasture, and 147587.56 ha are not clearly defined [11,12]. In Kosovo, there are two distinguished climate conditions. The Kosovo - area with continental and recognized by extreme temperature (altitudes in this region are from 510-570m) and the Dukagjini area with modified climate conditions with the influence of the Adriatic sea-through river Drini i Bardhë (altitudes are from 350- 450m). Summer temperatures in these regions sometimes reach more than 35-40°C resulting in high evapotranspiration [13,14]. But these surfaces are used alternately depending on farmers' needs. Trends of immigration within or outside the country are quite high and many smallholders abandoned agriculture and farming. The number of small ruminants is decreasing year to year, affecting pastures' disuse, and the reduction of other ruminants has an impact on the common use of meadows [15]. The objectives of the present study were to evaluate the differences between some different cultivated alfalfa for yield traits under agroecological conditions in the Prishtina locality.

## MATERIAL AND METHODS

### Description of the Locations, Soils and Weather

Field experiments were conducted under rain-fed conditions between 2018 and 2019. Field experiments were located at the locality of Prishtina, Kosovo (42° 38' 29" N and 21° 08' 45" E and 570 m. a.s.l.). The soil in Prishtina is classified as vertisol (black soil). The soil analyses were done at the Norwegian University of Life Science, Department of Environmental Sciences, AS, Norway. Soil characteristics are presented in Table 1.

Table 1. Soil characteristics in Prishtina

Location	Depth	CaCO <sub>3</sub>	pH in H <sub>2</sub> O	pH in KCl	Humus (%)	N (%)	mg/100 g soil	
							P <sub>2</sub> O <sub>5</sub>	K <sub>2</sub> O
Pristina	0-30	16.90	7.10	6.58	3.01	0.210	4.2	14.9
	30-60	20.56	7.05	6.74	2.19	0.190	3.7	11.3
	60-90	22.23	7.06	6.42	1.31	0.059	1.7	8.2

Precipitation and temperature data for the location in Prishtina are shown for appropriate years in Table 2. Precipitation was considerably above average at a site in Prishtina for both 2018 and 2019 [16]. Summer temperatures in this region sometimes exceed 35°C resulting in high evapotranspiration.

Table 2. Monthly precipitations (mm) and Temperature oC in Prishtina (HMIK, 2018/19)

Months	Precipitation (mm)		Differences (mm)	Temperatures C		
	2018	2019		2018	2019	Differences
January	93.8	57.6	36	0.1	-4.8	-4.7
February	38.1	41.8	-3.7	8.1	4.9	3.2
March	101.5	12.8	88.7	6.5	9.0	2.5
April	24.3	48.4	-24.1	13.4	10.8	2.6
May	100	81.4	18.6	13.6	15.8	2.2
June	46.5	42.8	3.7	20.8	21.2	0.4
July	106.9	47.5	59.4	22.1	22.9	0.8
August	115.2	33.4	81.8	21.4	23.1	1.7
September	40.9	104.1	-63.2	17.1	18.3	1.2
October	100.1	40.9	59.2	11.7	11.8	0.1
November	120.4	7	113.4	6.5	6.7	0.2
December	2.3	144.3	-142	0.1	3.7	3.6

## Plot Layout and Stand Establishment

The experimental design was a complete random block (CRB) with four replications. The genetic material of the study alfalfa was obtained from the Agriculture institute in Ljubljana, Novi Sad, and Osijek. Three alfalfa cultivars: Soqa, Banat, and Osijek 66 were studied. The cultivars were tall with vertical development characters. The plot size (experimental field EF)  $1.5 \text{ m} \times 5 \text{ m} = 7.5 \text{ m}^2 \times 3 \text{ repetitions} = 22.5 \text{ m}^2$  per cultivars  $\times 3 \text{ Cultivars} = 67.5 \text{ m}^2$  was the total area of the experimental field. The plot yields were converted to the hectare. For hay yield plant samples were dried at 65 C for 48 h until constant weight. All results are converted in DW matter per hectare.

## Statistical analysis

The MINITAB 18 software was applied to analyze the data. Statistical analysis was performed using a one-way ANOVA (for  $P < 0.05$ ). Based on the ANOVA test results, a Tukey test for mean comparison was performed, for a 95 % confidence level.

## RESULTS AND DISCUSSION

Means of alfalfa (*Medicago sativa* L.) cultivars it can be seen in Table 3. There was a significantly high difference between investigated traits considering the yield in dry matter. The highest yield for the first cut for the first year (2018) was obtained for cultivar Soqa on 2956 kg ha<sup>-1</sup> dry weight (DW), while with lower yield was determined the cultivar Banat VS on value 2708 kg ha<sup>-1</sup>. The differences between the cultivars were  $d = +248$  kg ha<sup>-1</sup>. The total experimental average values at all cultivars of alfalfa for the year 2016 was  $X=2806.66$  kg ha<sup>-1</sup> or expressed in relative values was 8.83 % higher for cultivar Soqa. The cultivar Soqa was with higher yield for the year 2018. The values were maximum (3230 kg ha<sup>-1</sup>) and minimum (2820 kg ha<sup>-1</sup>), while for cultivar Banat VS was maximum (2790 kg ha<sup>-1</sup>) and minimum (2650 kg ha<sup>-1</sup>). While for other cultivars Osijek 66 the average value for the yield was 2760 kg ha<sup>-1</sup>. For the year 2019, the highest yield was realized cultivar Soqa an average values of 3390 kg ha<sup>-1</sup>, while on the other side with minim average values was characterized by the cultivar Banat VS on value of 2914 kg ha<sup>-1</sup>.

The differences between them were  $d=+ 476$  kg ha<sup>-1</sup> DW. The total average values for 2019 at the second cut were 3091.73 kg ha<sup>-1</sup> DW. If comparing the cultivar Soqa (3390 kg ha<sup>-1</sup>) with experimental average values (3091.73 kg ha<sup>-1</sup>) the differences were +298.27 kg ha<sup>-1</sup> or expressed in relative values 9.64 % higher for the cultivar Soqa. While the differences between cultivar Banat VS and experimental average values were  $d = - 177.73$  kg ha<sup>-1</sup> or expressed in relative values 5.74 % lower than total average values for the year 2017. The differences for both years 2018 and 2019 for the first cut were  $d = 285.07$  kg ha<sup>-1</sup>, higher significantly for a level of probability 0.05 and 0.01. Results are presented in Table 3 and 4 and figure 1.

Table 3. Descriptive statistics for the yield data at alfalfa cultivars

Yield(kg ha <sup>-1</sup> )DW	Year		Mean	SE	StDev	Variance	CV	Min	Max
Firs Cut	2018	Banat VS	2708	22.9	51.2	2620	1.89	2650	2790
	2019	Banat VS	2914	23.2	51.8	2680	1.78	2850	2990
	2018	Osijek 66	2760	37.8	84.6	7150	3.06	2680	2890
	2019	Osijek 66	2971.2	20.9	46.7	2182.7	1.57	2890	3004
	2018	Soqa	2952	73.4	164.2	26970	5.56	2820	3230
	2019	Soqa	3390	54.9	122.7	15050	3.62	3280	3580
Second Cut	2018	Banat VS	1800	14.1	31.6	1000	1.76	1760	1840
	2019	Banat VS	2018.4	20.9	46.8	2189.3	2.32	1980	2100
	2018	Osijek 66	1963	20.8	46.6	2168	2.37	1890	2004
	2019	Osijek 66	2195.8	59.8	133.7	17873.2	6.09	2009	2340
	2018	Soqa	2079.4	84.5	189	35706.8	9.09	1890	2340
	2019	Soqa	2346.2	66.9	149.6	22377.2	6.38	2150	2541
Third Cut	2018	Banat VS	1508	12.4	27.7	770	1.84	1480	1550
	2019	Banat VS	1708	12.4	27.7	770	1.62	1680	1750
	2018	Osijek 66	1654	24.6	55	3030	3.33	1590	1710
	2019	Osijek 66	1874	21.6	48.3	2330	2.58	1790	1910
	2018	Soqa	1868	24.6	55	3020	2.94	1790	1930
	2019	Soqa	1922	21.5	48.2	2320	2.51	1870	1990

Some results have been reported by some researchers under different conditions and cultivars. Turan et al. [17] reported that the highest yield was obtained from variety CW-3567 (1620 kg ha<sup>-1</sup>). While some results from [18] for hay yield were reported to vary between 18920-24740 kg ha<sup>-1</sup>. During the year 2018 in the locality of Prishtina, the precipitations were relatively higher compared to 2019. Results are presented in Table 2.

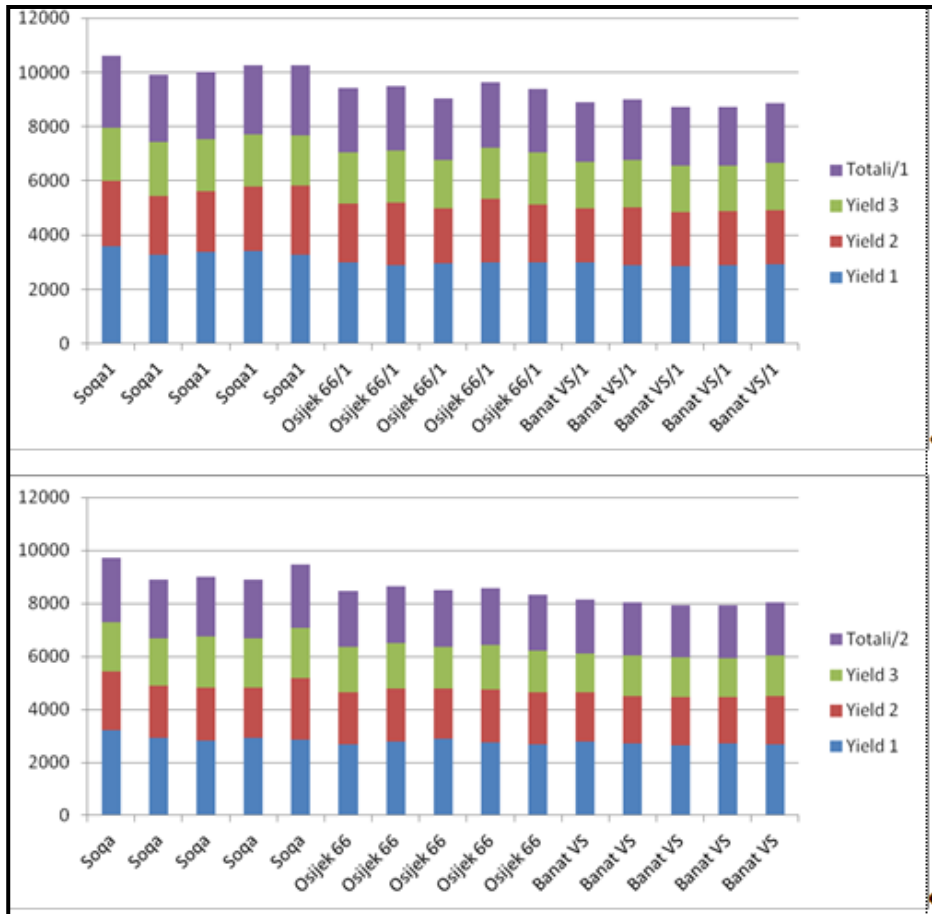


Figure 1. The average yield for 2018 and 2019 year

There were highly significant differences among means of the cultivars; results are presented in Table 4.

Table 4. Analysis of Variance for some cultivars alfalfa

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Factor	2	22995749	11497875	278.80	0.000
Error	87	3587867	41240		
Total	89	26583616			

The second cut with a higher yield for both years (2018-2019) was characterized by the cultivar Soqa (2079.4 and 2346.2 kg ha<sup>-1</sup>) while with lower average values was determined the cultivar Banat VS on values (1800 and 2018.4 kg ha<sup>-1</sup>). The total average values for the second cut in 2018 and 2019 year were 1947.4 respectively 21886.66 kg ha<sup>-1</sup>. If compared with the first cut the all average values, the differences are D (2018) year = 2806.66 (first cut) -1947.4 (second cut) = 859.26 kg ha<sup>-1</sup> higher for the first cut. While for the 2019 year the differences were (3091.73-2186.66 =+ 905.07 kg ha<sup>-1</sup> also higher for the first cut. The total means of alfalfa cultivars for grouping information using the Tukey methods are given in Table 5. All alfalfa cultivars are with higher significance among them for two levels LSD=0.05 and LSD=0.01 of probability.

Table 5. Grouping information using the Tukey method for alfalfa cultivars

Cultivars	The overalls mean	Grouping	
Soqa (2019 year)	3390.0	A	
Osijek 66 (2019 year)	2971.2	B	
Soqa (2018 year)	2952.0	B	
Banat VS (2019 year)	2914.0	B	C
Osijek 66 (2018 year)	2760.0	C	D
Banat VS (2018 year)	2708.0	D	

\*Means of each column followed by the different letters are significantly different.

\*\* indicate  $p < 0.01$  and indicate  $p < 0.05$ .

The third cut for the two years for higher yield characterized the cultivar Soqa on average  $X= 1895 \text{ kg ha}^{-1}$ , while on lower was the Osijek 66 on average yield  $X= 1764 \text{ kg ha}^{-1}$ . The differences between them were  $d = +131 \text{ kg ha}^{-1}$ . Results are presented in Table 3.

## CONCLUSIONS

For two-year investigations (2018 and 2019) for three cultivars of alfalfa growing in agro-ecological conditions in Prishtina will conclude that; Cultivar Soqa was on higher yield compared to the others cultivars Osijek 66 and Banat VS. The ability of the cultivar for higher yields, in this case, cultivar Soqa, we can say, based on our research that shown higher adaptability to the agro-ecological conditions in which they were cultivated.

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Imer Rusinovci, Sali Aliu, Shukri Fetahu dhe Dukagjin Zeka

## RENDIMENTI DHE PERFORMANCA E DISA KULTIVARËVE TË JONXHËS (*MEDICAGO SATIVA L.*) TË MBJELLË NË REGJIONIN E PRISHTINËS

### Përmbledhje

Mënyrat e shumta të përdorimit të jonxhës (*Medicago sativa L.*) në të ushqyerit e bagëtisë dhe ndikimi i vlerave të saj ushqyese në racionet e kafshëve shtëpiake, ka qenë njëra prej arsyeve për përpjekje të gjera hulumtuese – kërkimore, për të dalluar dhe analizuar marrëdhëniet midis intervalit të kositjeve, fenofazave të zhvillimit të bimëve, morfologjisë, rendimentit dhe vlerave ushqyese.

Në Ballkanin Perëndimor, kulturat më të rëndësishme foragjere të bishtajoreve janë jonxha (*Medicago sativa L.*) dhe tërfili i kuq (*Trifolium pratense L.*), të cilat përdoren kryesisht si kultura të veçanta të kultivuara, e shumë më rrallë hasen në përzierje foragjere me barëra të tjera. Jonxha (*Medicago sativa L.*) është bimë shumëvjeçare e familjes *Fabaceae* dhe është bishtajore e rëndësishme foragjere në mbarë botën në të ushqyerit e kafshëve shtëpiake. Përveç kësaj, është një burim i rëndësishëm i nektarit dhe polenit për bletët në shumë vende të botës.

Në 20 vitet e fundit vendi ynë është përballur me shumë ndryshime në sferën e përgjithshme të bujqësisë, përfshirë edhe bimët foragjere në sipërfaqe punuese për nevojat e fermave të kafshëve.

Në bazë të të dhënave aktuale, livadhet dhe kullotat përfshijnë 224410.83 ha të sipërfaqeve të përgjithshme bujqësore të Kosovës, për më tepër, vetëm një pjesë e këtyre sipërfaqeve dallohen qartë si livadhe apo kullota. Regjistrimi i fundit i bujqësisë identifikoi se 65099.00 ha janë livadhe, 11724.27 ha kullota dhe 147587.56 ha nuk janë të përcaktuara qartë.

Në Kosovë dallohen dy rajone kryesore prodhuese: Rrafshi i Kosovës, rajon me klimë të mesme kontinentale i njohur me temperatura ekstreme (lartësitë mbidetare në këtë rajon sillen 510 - 570 m) dhe Rrafshi i Dukagjinit me kushte klimatike më të modifikuara nën ndikimin e lumit të tejdukshëm Drini i Bardhë (lartësitë mbidetare sillen 350 - 450 m). Temperaturat e verës në këto rajone ndonjëherë arrijnë më shumë se 35-40°C duke rezultuar në evaporem (avullim) të lartë. Sipërfaqet punuese të këtyre rajoneve përdoren në mënyra alternative, varësisht nga nevojat e fermerëve. Tendencat e emigracionit brenda dhe jashtë vendit

janë mjaft të larta dhe shumë pronarë të vegjël kanë braktisur bujqësinë dhe blegtorinë. Numri i kafshëve po zvogëlohet nga viti në vit, gjë që po ndikon në mospërdorimin e kullotave, apo edhe përdorimin e ulët të livadheve.

Objektivat e këtij studimi ishin vlerësimi i dallimeve për disa jonxhë të kultivuar të ndryshme për tiparet e rendimentit në kushte agroekologjike në lokalitetin e Prishtinës. Hulumtimet për tre kultivarë të jonxhës janë kryer në fushat eksperimentale të fermës didaktike të Fakultetit të Bujqësisë dhe Veterinarisë në Prishtinë, gjatë viteve 2018 dhe 2019. Dizajni eksperimental ishte bllok i plotë i rastësishëm (CRB) me katër përsëritje. Materiali gjenetik i hulumtimeve ishte me origjinë nga Instituti Bujqësor i Lubjanës, Novi Sadit dhe Osijekut. Janë hulumtuar tre kultivarë të jonxhës: Soqa, Banat VS dhe Osijek 66.

Hulumtimet tona me tre kultivarë të jonxhës (*Medicago sativa* L.) dhanë dallime të konsiderueshme midis tipareve të hulumtuara për rendiment dhe lëndës së thatë. Rendimentin më të lartë për vitin e parë (2018) e ka realizuar kultivari Soqa me 2956 kg ha<sup>-1</sup> materie të thatë (MTH), ndërsa me rendiment më të ulët për vitin 2018 u karakterizua kultivari Banat VS në vlerë 2708 kg ha<sup>-1</sup>. Po ashtu edhe gjatë vitit të dytë të hulumtimeve (2019), rendimentin më të lartë e realizuan bimët e jonxhës të kultivarit Soqa në vlera mesatare 3390 kg ha<sup>-1</sup>, ndërsa me prodhimtari mesatare minimale u karakterizuan bimët e kultivarit Banat VS në vlerë prej 2914 kg ha<sup>-1</sup>. Diferencat ndërmjet tyre ishin  $d = + 476$  kg ha<sup>-1</sup> MTH. Sipas rezultateve të arritura nga hulumtimet e kryera dyvjeçare, për tre kultivarë të jonxhës të kultivuara në kushte agroekologjike të lokalitetit të Prishtinës, arritëm të konstatojmë se kultivari Soqa realizoi performancë më të lartë të prodhimit në krahasim me kultivarët Osijek 66 dhe Banat VS.

Edhe në kositjen e dytë, rendimentin më të lartë për dy vitet e hulumtimit (2018-2019) e realizuan bimët e kultivarit Soqa (2079.4 dhe 2346.2 kg ha<sup>-1</sup>), ndërsa me vlera mesatare më të ulëta u karakterizuan bimët e kultivarit Banat VS (1800 dhe 2018.4 kg ha<sup>-1</sup>). Nëse krahasohen me kositjen e parë të gjitha vlerat mesatare, diferencat janë: viti 2018, kositja e parë 2806.66 kg ha<sup>-1</sup> - 1947.4 kg ha<sup>-1</sup> (kositja e dytë) = 859.26 kg ha<sup>-1</sup> më e lartë në kositjen e parë. Ndërsa në vitin 2019 diferencat kanë qenë (3091.73 - 2186.66 = + 905.07 kg ha<sup>-1</sup> edhe për kositjen e parë. Vlerat totale të kultivarëve të hulumtuar të jonxhës për grupimin e informacioneve me metoda statistikore janë me rëndësi të lartë mes tyre për dy nivelet e probabilitetit (LSD = 0.05 dhe LSD = 0.01).

Enver Hamiti<sup>\*,1</sup>

## POSSIBILITIES OF REUSE OF FREQUENCY BANDS FOR IoT IN SCHOOL BUILDINGS

### Abstract

In this presentation, the data obtained during measurements of electromagnetic power density in typical frequency bands, in one of the largest school buildings in Kosovo, will be presented. The case study is a typical and representative sample, for indicative data. However, the research should be expanded to other educational micro-environments to achieve the full reliability of the data for all bands, from 87 MHz to 5850 MHz. The measurement data show that some frequency bands are completely unused, while in others the traffic is relatively low and creates space for the use of potential devices in IoT, for learning needs. The frequency bands: FM, TV3, TETRA, TV4&5, UMTS and WiMAX, are free, while the two Wi-Fi bands have low-intensity traffic. At this moment, only the bands of mobile systems are characterized by higher traffic intensity.

*Keywords:* Cognitive Radio, Internet of Things, Internet of Mobile Things, CR-based IoT, IoV

### INTRODUCTION

Despite efforts to expand the frequency band for wireless communications, the results of which have culminated in numerous potential developments in the 5G generation, new technologies and current scientific research are moving at a significant speed, in the direction of what is known as *Cognitive radio and the Internet of Things*. These developments, along with those known as machine-to-machine (M2M), are facilitating the daily life of humanity, through mobile connections, raising the emphasis on the "Internet of Mobile Things (IoMT)" [1,2]. IoT is a paradigm that considers the connection of things/objects with wireless or wired connections, based on their unique addressing schemes, and enables an interactive interaction between them.

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In this way, it helps to develop new applications and services for communities, as well as sets the premises for a more "intelligent" world, through "smart" environments: energy, transport, cities, etc. [3-5]. Objects are connected with sensors and communication modules. They can be static or mobile, with a request for connection to energy or not, with the possibility of connection with physical reality, etc. Practically all IoT devices are unstable without cognitive networks, making them connected to CRNs (cognitive radio networks), known as CR-based IoT. Like others similar to these, IoT services are characterized by the essential quality of service parameters: throughput, delay of information packets, reliability, and energy consumption.

CR-based IoT systems extend into multiple environments and will help develop the next generation of intelligent networks, although they are currently in the initial stages of their development [6]. There are many technologies proposed for IoT, wired or wireless. Wireless technologies have significantly higher popularity, due to flexibility and portability. However, the network must support a wide range of data and significant availability of frequency spectrum, as a result of mass services and the fact that these "intelligent" networks exploit the unused spectrum of primary users [7]. Of course, this exploit should be insensitive to primary users and unobstructed by IoT objects.

## CR-BASED IoT APPLICATIONS

The application areas of IoT are numerous and will be useful to many potential users.

### 1. Residential and Home Appliances

Potential applications will be in controlling and managing of various devices in homes and residential facilities. Sensors can be placed in air conditioning equipment, television and other electronic equipment, lighting system control, heating system, and other environmental equipment that are part of access systems (doors, windows, etc.).

### 2. Health care

Sensors of IoT networks will be able to be placed on the body of patients and measure vital parameters for their health, body

temperature, blood glucose level, blood pressure and others. The potential CR-based IoT network will process and carry this information to health workers for further action. Thus, through remote monitoring (Far off monitoring), the response via Wi-Fi will be immediate and health care workers will continuously monitor patients' physical condition, without needing additional equipment or frequency bands.

### 3. Smart Environment

The current circumstances of public safety, whether due to possible technical errors, but in particular, to the violent intentions of the troubled world, declared and undeclared wars, constitute an area of high interest for CR-Based IoT. Of high interest is the control of the emission of CO<sub>2</sub> and toxic gases from factories and means of transport, as well as the identification of potential areas with burning gases. Finally, the control of the basic parameters of the living environment is inevitable: temperature, humidity, air pressure, early detection of earthquakes, warning of precipitation and their measurement, etc. In recent times, public places, especially school facilities are of primary interest, due to aggressive and offensive actions, to ensure a "smart" and protected environment.

### 4. Smart Cities

Urban developments are increasingly dynamic and comprehensive, tending to control and regulate services as independently as possible from humans and the possibility of errors is minimal. However, an extensive range of data must be collected and processed for environmental monitoring, security control and other public security mechanisms, traffic control, etc. The IoV technology enables the control of vehicles through the communications network and embedded systems. It is being developed in three segments: *Vehicles-To-Vehicles*, *Vehicles-To-Infrastructure* and *Vehicles-To-Cloud IoV*. According to predictions, safe and autonomous navigation, according to the will of the users, will be very present and will be developed through the exchange and processing of data between cars, as well as the various sensors placed in them. The current challenge for IoV development remains the frequency spectrum, while CRNs remain a potential opportunity.

## IoT CHALLENGES

The areas of the potential application of CRN are numerous and do not pose a challenge. However, a challenge is the frequency band available and the use of the existing bands with CRNs, implying the development of efficient technologies for what is known as *spectrum sensing*. CRNs should sense unused spectrum from primary users and not block them when they come back to use it. In the case of critical applications, real-time responses are necessary and add complexity to the operation of CRNs. Consequently, allocating frequency bands in coordination with CRNs is a current scientific challenge [7].

Standardization in IoT constitutes a new and current challenge, conditioning its rapid development. A large amount of data and the diversity of devices connected to the IoT cannot function without a regulator of technologies and standards. Technology standards should include network protocols, data collection standards, data security and privacy, etc. [8].

## MEASUREMENT INSTRUMENTS AND STATISTICAL ANALYSIS

Measurements were made with the EME Spy 140 device. The device is a personal exposimeter and measures in 14 frequency bands (87–5850 MHz), which are used for wireless communications. The frequency bands in which the measurements were performed are given in TABLE 1. EME Spy 140 is supported by EME Spy Analysis V3 software. The data stored in EME Spy 140 is transferred to the computer in Excel file format and analyzed with EME Spy Analysis V3. The smallest measured values by the EME Spy 140 instrument vary from band to band (0.05 V/m for FM, 0.01 V/m for TETRA and TV4 and 5, 0.02 V/m for TV3, WiMAX, and Wi-Fi 5G, as well as 0.005 V/m for the remainder). While the maximum value that the instrument measures is 6 V/m for all bands [9]. There are many methods for handling the minimum values detected by the instrument since the exact values can be significantly smaller than them. We have chosen to halve them (eg. All detected values of 0.05 (V/m) have been replaced by 0.25 (V/m)). The overestimation error of the measured values of the electric field will be minimized, either through electric field intensity or electric power density [10], [11]. This method is typical for epidemiological studies.

Table 1. Measured frequency bands of the EME SPY 140

<b>BAND</b>	<b>FREQUENCY</b>
<b>FM</b>	87 - 108 MHz
<b>TV3</b>	174 - 223 MHz
<b>TETRA</b>	380 - 400 MHz
<b>TV4&amp;5</b>	470 - 830 MHz
<b>GSM+UMTS 900(UL)</b>	880 – 915 MHz
<b>GSM +UMTS 900(DL)</b>	925 - 960 MHz
<b>GSM +LTE 1800(UL)*</b>	1710 – 1785 MHz
<b>GSM +LTE 1800(DL)*</b>	1805 – 1880 MHz
<b>DECT</b>	1880 – 1900 MHz
<b>UMTS 2100(UL)</b>	1920 – 1980 MHz
<b>(UMTS 2100(DL)</b>	2110 – 2170 MHz
<b>WI-FI 2G</b>	2400 – 2483.5 MHz
<b>WIMAX</b>	3300 – 3900 MHz
<b>WI-FI 5G</b>	5150 – 5850 MHz

\* In Kosovo the LTE 1800 Re-farming is in use.

## RESULTS OF MEASUREMENTS IN THE SCHOOL BUILDING

Measurements were performed on working days and weekends. The results of the measurements include the spaces inside and outside the "Hasan Prishtina" elementary school. Not wanting to expand the data of the measurements, according to specific days and hours, below are given the processed data extracted from the measurements provide the degree of utilization of different frequency bands in the school, inside and outside the building. According to measurement data, the UMTS 2100 (UL), UMTS 2100 (DL) and WiMAX mobile communication systems are non-functional. The results of FEM-RF power density measurements on FM, TETRA TV3, and TV4 & 5 were negligible. The measured values were limit values in 99.9% of cases. Also, the 99th percentile of the values measured in the schoolyard had the following results: 21.1  $\mu\text{W}/\text{m}^2$  (FM),



1.1  $\mu\text{W}/\text{m}^2$  (TV3), 0.5  $\mu\text{W}/\text{m}^2$  (TETRA), and 0.3  $\mu\text{W}/\text{m}^2$  (TV4&5). Meanwhile, the values measured inside the school were even smaller. It was found that the only active sources of FEM – RF were mobile phone systems, Wi-Fi and DECT. Cellular systems contributed about 94% of the total energy inside the building, and 61% in the schoolyard spaces. At the same time, the Wi-Fi system contributed 3.1% of the total energy in the building and 36% to the schoolyard. Whereas, DECT contributed 3.2%, respectively 2.5% outside the facility. These results were obtained as average values for working days when students and teaching staff were in school. During the weekends, cellular systems contributed 96% inside the building and 54% outside it, while Wi-Fi with 0.9%, respectively 45%. At the same time, the DECT system offers values of 3.1% and 1.1%.

We divided the measured values for the frequency bands of mobile systems on one side, and those of Wi-Fi and DECT on the other. Table 2 and Table 3 give the average values of the EMF-RF power density, which stem from the potential traffic developed in the bands of these systems, inside and outside school buildings [12].

Table 2. Personal exposure to RF-EMF from Wi-Fi bands and DECT inside the school building.

Wi-Fi bands and DECT	Frequency (MHz)	Average power density ( $\mu\text{W}/\text{m}^2$ )	
		Week	Weekend
Wi-Fi 2G	2400 – 2483.5	20	3
Wi-Fi 5G	5150 – 5850	17	2
<b>DECT</b>	<b>1880 – 1900</b>	<b>38</b>	<b>16</b>

Table 3. Personal exposure to RF-EMF from Wi-Fi bands and DECT outside the school building.

Mobile phone bands	Frequency (MHz)	Average power density ( $\mu\text{W}/\text{m}^2$ )	
		Week	Weekend
Wi-Fi 2G	2400 – 2483.5	568	2
<b>Wi-Fi 5G</b>	<b>5150 – 5850</b>	<b>1871</b>	<b>2843</b>
DECT	1880 – 1900	2852	68

The results of the measurements show that the W-Fi and DECT bands are characterized by the very low density of electromagnetic energy in the environment, signalling very low traffic, particularly for the internal school environment. At the same time, the schoolyard seems more charged with electromagnetic energy in these bands and it is supposed to be a consequence of the urban environment, in which the school building is located.

For comparison purposes, Table 4 and Table 5 gives the results of electromagnetic power density measurements, for the bands of mobile phone systems. The results show the presence of electromagnetic energy with significantly higher density than in the previous case [12].

Table 4. Personal exposure to RF-EMF from mobile phone bands inside the school building.

Mobile phone bands	Frequency (MHz)	Average power density ( $\mu\text{W}/\text{m}^2$ )	
		Week	Weekend
GSM +UMTS 900(UL)	880 – 915	9	0
<b>GSM +UMTS 900(DL)</b>	<b>925 - 960</b>	<b>576</b>	<b>262</b>
GSM +LTE 1800(UL)*	1710 – 1785	179	80
GSM +LTE 1800(DL)*	1805 – 1880	140	97

Table 5. Personal exposure to RF-EMF from mobile phone bands outside the school building.

Mobile phone bands	Frequency MHz)	Average power density ( $\mu\text{W}/\text{m}^2$ )	
		Week	Weekend
GSM +UMTS 900(UL)	880 – 915	218	1
<b>GSM +UMTS 900(DL)</b>	<b>925 - 960</b>	<b>1932</b>	<b>1272</b>
GSM +LTE 1800(UL)*	1710 – 1785	890	633
GSM +LTE 1800(DL)*	1805 – 1880	1122	1457

\* Published values at the international level for Wi-Fi bands

The scientific community is interested in Wi-Fi bands, mainly due to the level of electromagnetic radiation which is constantly increasing and potentially affecting human health. However, viewed from the angle of using these frequency bands for **CR\_Based IoT**, these bands offer significant frequency potential in sensitive educational and academic facilities. TABLE 6 shows the summarized results from the scientific works of the field, the authors published as noted below the table and are given in the original form.

Table 6 Personal exposure to RF-EMF from Wi-Fi bands at the international level.

Author	Countries	Mean ( $\mu\text{W}/\text{m}^2$ )
Roser et al., 2017 [8]	Switzerland (school)	1.19
Kurnaz et al., 2018 [9], [10]	Turkey (classroom)	1.28
Fernandez, 2020 [11]	Spain (inside university)	2.55
Vermeeren et al., 2013 [12]	Belgium (Schools area)	6.64
Hardell et al., 2017 [13]	Sweden (School)	3.32
Bhatt et al., 2016 [14]	Greece (School area)	10.7
Hamiti et al., 2022 [1]	Kosovo (School area)	18.5
Vermeeren et al., 2013 [12]	Greece (School area)	21.4
Ramirez-Vazquez et al., 2020 [15]	Jordanian (around the university area)	23.0
Ramirez-Vazquez et al., 2020 [16]	Spain (inside school)	25.3
Ramirez-Vazquez et al., 2020 [15]	Jordanian (university area)	28.8
Hedendahl et al., 2017 [17]	Sweden (from Wi-Fi connection)	66.1
Hamiti et al., 2018 [18]	Kosovo (university)	70.2
Bhatt et al., 2016 [14]	Australia (kindergarten area)	85.0
Verloock et al., 2014 [19]	Belgium (School area)	106
Gallastegi et al., 2018 [20]	Spain (School area)	120

E. Arribas, R. Ramirez-Vazquez and I. Escobar, Comments on “Measurements and Analysis of Personal Exposure to RF-EMF Inside and Outside School Buildings: A Case Study at a Kosovo School”, in *IEEE Access*, 2022, DOI: 10.1109/ACCESS.2022.3198975.

Currently, there are several platforms for managing CRNs and different algorithms for dynamic channel selection in Wi-Fi bands. One of them is the CORAL cognitive radio platform (Cognitive, Radio-Aware, Learning), supporting the algorithm for dynamic channel selection in sectored cells of the Wi-Fi networks [13]. The proposed algorithm utilizes the sensitive information collected by CRNs to continuously adapt the channels assigned to the APs, throughout the network, according to the interference conditions.

## CONCLUSIONS

Based on the results presented in this paper, in particular, the numerical results of experimental measurements in a specific school building, confirm the assumption that multiple frequency bands would pave the way for the implementation of IoT systems in school buildings, either through **CR-based IoT** or allocating free bandwidth for use. In this case, the frequency bands: **FM, TV3, TETRA, TV4&5, UMTS** and **WiMAX** are free, while the two **Wi-Fi** and **DECT** bands have very low-intensity traffic. In this aspect, our aim for continuous monitoring of personal exposure to FEM-RF, through potential IoT devices, especially in objects with higher sensitivity, such as schools, nurseries and other educational or health facilities, is also seen. Almost the same situations we observed compared recently published scientific results at the international level. In particular, we treated and presented the latest results of Wi-Fi bands, as systems of particular interest to CRNs.

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Enver Hamiti

## MUNDËSITË E RISHFRYTËZIMIT TË BREZEVE FREKUENCORE PËR IoT NË OBJEKTE SHKOLLORE

### Përmbledhje

Në këtë prezantim, do të paraqiten të dhënat e fituara gjatë matjeve të dendësisë së energjisë elektromagnetike në brezet frekuencore tipike, në njërin nga objektet më të mëdha shkollore në Kosovë. Rasti i studimit është tipik dhe mostër reprezentative për të dhëna orientuese. Megjithatë, hulumtimi duhet zgjeruar edhe në mikroambiente të tjera, të karakterit edukativ, për të arritur besueshmërinë e plotë të të dhënave për të gjitha brezet nga 87 MHz e deri në 5850 MHz. Të dhënat e matjeve tregojnë që disa breze frekuencore janë tërësisht të përdorura, ndërsa në disa të tjera trafiku është relativisht i ulët dhe krijon hapësirë për përdorim të pajisjeve potenciale në IoT për nevoja mësimi. Brezet e frekuencave: FM, TV3, TETRA, TV4&5, UMTS dhe WiMAX janë të lirë, ndërsa dy brezet Wi-Fi kanë trafik të intensitetit të ulët. Në këtë moment vetëm brezet e sistemeve celulare karakterizohen me intensitet më të lartë të trafikut. Një gjendje e krahasueshme është vërejtur duke i krahasuar rezultatet shkencore të publikuara kohët e fundit, edhe në nivel ndërkombëtar. Në veçanti, ne trajtuam dhe prezantuam rezultatet më të fundit të brezave Wi-Fi, si sisteme me interes të veçantë për CRN-të.

Hulumtimet e mëtejshme, në të cilat do të përfshihet numër më i madh i objekteve shkollore dhe të tjera të karakterit edukativ dhe akademik, do të jetë i mirëseardhur dhe do të riverifikonte pretendimet e dhëna në këtë punim, por edhe më gjerë. Këtu duhet të kemi parasysh që dinamika e zbatimit të rrjeteve IoT është shumë e shpejtë, ndërsa aktualisht rrjetet kognitive janë mbështetësi kryesor i tyre.



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