1. Raziskovalna organizacija (*Research organisation)*:

Univerza v Ljubljani, *Fakulteta za elektrotehniko*

2. Ime in priimek mentorja (*Name and surname of a mentor*):

Damijan Miklavčič

3. Področje znanosti iz šifranta ARRS (*Primary research field*):

2.06 Sistemi in kibernetika (Systems and cybernetics)

4. Kontaktni e-naslov mentorja (*Contact of a mentor)*:

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5. Kratek opis programa usposabljanja (*Short description of the program)*:

SLO

Raziskovalni program sestavljajo trije podsklopi: i) razvoj strojne opreme, ii) teorija in modeliranje, ter iii) eksperimentalna in uporabna elektroporacija. Vsak sklop se elektroporacije loteva z drugačnega zornega kota in s specifičnimi metodami, vendar so vsi trije podsklopi medsebojno močno povezani. MR bo glede na svojo osnovno izobrazbo delal na enem ali več spodaj opisanih podpodročjih.

i) Razvoj strojne opreme. Učinkovitost elektroporacije je odvisna od električnih parametrov (npr. oblike pulza, amplitude, trajanja). Različne uporabe elektroporacije, kot so genski vnos in zlivanje celic zahtevajo različne vrednosti parametrov pulzov. Pri omenjenih aplikacijah se uporabljajo kombinacije različnih električnih pulzov. Nobena posamezna strojna oprema ne more zadostiti vsem zahtevam. Za uporabo in raziskave elektroporacije so potrebne številne naprave, vključno z nanoporatorji, poratorji za poljubne oblike pulzov, generatorji za dielektroforezo in poratorji s povratno vezavo. Pomemben je tudi razvoj pulznega generatorja za elektroporacijo lipidnih dvoslojev in ustrezne merilne opreme, ki omogoča merjenje sprememb tokov in napetosti vsled elektroporacije planarnega dvosloja oz. celične membrane. Takšen razvoj in nabor naprav nam omogoča, da bomo pri raziskavah elektroporacije še naprej v svetovnem vrhu.

ii) Teorija in modeliranje. Analitični izračuni in numerični modeli porazdelitve električnega polja in toka med celično in tkivno elektroporacijo so uporabni za opisovanje osnovnih procesov elektroporacije in za ocenjevanje različnih vplivnih parametrov. Razvoj novih modelov, ki upoštevajo tako dinamične spremembe membranske in tkivne prevodnosti med elektroporacijo kot tudi pomembne neelektrične pojave, kot npr. transport molekul preko celične membrane in povišanje temperature v tkivu zaradi električnega toka nam bo omogočil preverjanje razumevanja mehanizmov elektroporacije in načrtovanje novih poskusov in najučinkovitejših protokolov za specifične aplikacije. S tem pristopom je moč razvijati in optimizirati tudi elektrode in njihov položaj glede na ciljno tkivo. V zadnjem času je vse večji poudarek tudi na modeliranju kemičnih procesov, ki so bili do sedaj v veliki meri zapostavljeni, čeprav niso nezanemarljivi. Ključni koraki, poleg sklopljenih fizikalno kemičnih modelov, pa predstavljajo v prihodnosti tudi sklalirani modeli, kjer iz modelov na nivoju posamičnih atomov in molekul prenesemo lastnosti in rezultate na nivo membrane in celic, ter iz celičnega nivoja na nivo tkiv z eksplicitno izraženo celično strukturo. Časovna in krajevna resolucija je tu izrednega pomena, tovrstni modeli pa zahtevajo med drugim veliko znanja in iznajdljivosti.

iii) Eksperimentalna in uporabna elektroporacija. Elektroporacijo že uporabljamo v klinični elektrokemoterapiji za izboljšanje vnosa kemoterapevtikov bleomicina in cisplatina v celice pri zdravljenju raka. V zadnjem času preučujemo možnosti uporabe še drugih zdravilnih učinkovin. Elektroporacija postaja pomembna kot nevirusna metoda vnosa

genov. Zanimivo postaja tudi zlivanje celic in ablacija mehkih tkiv z elektroporacijo. Z elektrozlivanjem celic bi lahko zelo učinkovito pridobivali visoke donose zlitih celic, ki jih potrebujemo v hibridomski tehnologiji za proizvodnjo monoklonskih protiteles. Ireverzibilna elektroporacija lahko postane nova ablacijska metoda za odstranjevanje mehkih tkiv, ki obenem ohranja arhitekturo tkiva (npr. pri raku prostate in ablaciji srčne mišice). Elektroporacijo s pridom uporabljamo tudi v biotehnologiji, živilski tehnologiji ter nekaterih t.i. zelenih tehnologijah. Elektroporacija olajša iztiskanje sokov, sušenje rastlinskega tkiva in s tem omogoča prihranek energije, ter ekstrakcijo metabolitov iz mikroorganizmov (mikroalge, kvasovke in bakterije). Elektroporacijo lahko obravnavamo kot platformsko tehnologijo, ki je uporabna v širokem naboru postopkov v medicini, biotehnologiji in živilski tehnologiji.

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The research program consists of three subareas/topics: i) the development of hardware, ii) theory and modeling, and iii) experimental and applied electroporation. Each topic tackles electroporation from a different angle using specific methods, but all three topics highly intertwined. The candidate will – depending on his/her basic education and background - work in one or more of these subareas/topics.

i) The development of hardware. Efficacy of electroporation depends on electric pulse parameters (e.g. pulse shape, amplitude, duration). Different applications of electroporation require different pulses, i.e. gene transfer requires longer pulses or combination of high voltage short and low voltage long pulses; whereas fusion of cells requires combination of sinusoidal dielectrophoretic signal followed by electroporation pulses. No single hardware can meet all the requirements. For various applications and for use in research of electroporation numerous different devices are thus required. Also important is the development of pulse generators for electroporation of lipid bilayer and appropriate measuring equipment, which enables measurement of changes of currents and voltages due to lipid bilayer properties changes. In general development of new devices enables us to continue being among the leading groups in electroporation in the world.

ii) Theory and modeling. Analytical calculations and numerical models of distribution of electric field and mass and heat transfer during cell membrane and tissue electroporation is useful to describe the basic processes of electroporation and to assess effect of different parameters on electroporation. Development of new models that take into account both change of membrane and tissue conductivity during electroporation as well as relevant non-electric processes such as e.g. transport of molecules through the membrane and temperature profiles due to heat generation and dissipation is important in planning new experiments as well as optimizing and developing efficient protocols for specific applications. With this approach, it is possible to develop and optimize the electrodes geometry and their positioning in relation to the target tissue in tumor treatment and/or tissue ablation. Recent modeling efforts also focus on including chemical processes that have so far been largely neglected. New approach that is being developed is a multi-scaling approach where models from the level of atoms and molecules are used in models describing properties and properties at the level of membranes and cells, and the results obtained on this level are carried over to the level of tissues which now have explicit structure. Needless to say temporal and spatial resolution is of paramount importance; however such models require considerable knowledge and ingenuity.

iii) Experimental and applied electroporation. Electroporation used in clinical electrochemotherapy to improve delivery of chemotherapeutic agents such as

bleomycin and cisplatin into cells and thus improving treatment of cancer. Recently we also studied other possible agents for increasing their efficiency like Ruthenium based compounds. Electroporation is becoming an important method for non-viral gene delivery. Fusion of cells and ablation of soft tissue by electroporation is also becoming of great interest. With cell fusion high yields of fused cells that are needed in the hybridoma technology for production of monoclonal antibodies can be obtained. Irreversible electroporation ablation could be a new method for the removal of soft tissue while maintaining tissue architecture (e.g. prostate cancer and cardiac muscle ablation). Electroporation is advantageously used in biotechnology, in food technology, and in some green technologies: electroporation enables extraction of juices by pressing fruits and plant tissues, thereby saving energy; it enables extraction of metabolites from microorganisms (microalgae, yeasts and bacteria). Electroporation can be considered as a platform-technology, which is useful in a wide range of areas from medicine, biotechnology, to food technology.