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Analiza in napovedovanje dinamike celjenja električno stimuliranih in konzervativno zdravljenih kroničnih ran

DOKTORSKA DISERTACIJA

MENTOR

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Zahvala

Za strokovno vodstvo in pomoč pri nastajanju disertacije se iskreno zahvaljujem mentorju in predstojniku Laboratorija za biokibernetiko na Fakulteti za elektrotehniko, izrednemu profesorju Damijanu Miklavčiču, ki je potrpežljivo spremljal in z nasveti usmerjal moje delo.

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Kazalo

Povzetek

Klinične raziskave tako počasnih procesov, kot je celjenje kroničnih ran, so dolgotrajne in naporne. Zato je 390 kliničnih primerov celjenja kroničnih ran zbranih v podatkovni bazi pomembno dolgoletno delo več raziskovalcev, terapevtov in specialistov. Zbrani podatki o poteku celjenja več sto kroničnih ran omogočajo že s standardnimi statističnimi pristopi določitev značilnih parametrov, ki vplivajo na potek celjenja. Najpogosteje so raziskovalci iskali le vpliv načina zdravljenja na hitrost celjenja, ker jim takrat majhno število podatkov ni omogočalo kompleksnejše analize, v kateri bi obravnavali še druge, mogoče celo vplivnejše parametre. Trenutna količina podatkov pa nam je omogočila ravno to kompleksnejšo analizo problema kroničnih ran, pri kateri smo uporabili tudi manj standardne pristope, ki omogočajo odkriti iz množice podatkov tudi tisto znanje, ki bi s standardnimi statističnimi pristopi ostalo skrito v množici medsebojnih odvisnosti parametrov. Tako pridobljeno znanje nam pomaga k boljšem razumevanju problematike, pomaga pri izbiri in načrtovanju načina zdravljenja ter s tem vodi k hitrejšemu okrevanju bolnika.

V prvem sklopu našega dela smo ugotovili, da je za spremljanje poteka celjenja dovolj redno tedensko merjenje površine rane oz. njenih medsebojno pravokotnih diagonal, če obliko rane aproksimiramo z elipso. Oblika rane ne igra pomembne vloge pri analizi dinamike celjenja. Ugotovili smo, da ima časovni potek spreminjanja normirane površine zakasnjen eksponencialni potek. Matematični zapis zakasnjene eksponencialne krivulje smo označili za najsplošnejšo strukturo matematičnega modela. Parametre modela smo iskali za vsak primer kronične rane posebej. Dokazali smo, da lahko parametre modela določimo že s štiritedenskim opazovanjem poteka celjenja rane in pri tem ne naredimo značilne napake pri oceni časa do zacelitve. To dejstvo lahko s pridom uporabimo za napovedovanje časa do zacelitve po vsaj štiritedenskem obdobju opazovanja poteka celjenja.

Področje kroničnih ran je glede vrednotenja učinkov zdravljenja zelo neusklajeno. Zato smo analizirali dosedanje načine vrednotenja učinkov zdravljenja na hitrost celjenja ran in predlagali najustreznejši način. Mero hitrosti celjenja smo definirali kot prirastek tkiva od roba rane proti središču v milimetrih na dan. Tako definirana hitrost celjenja je neodvisna od začetne velikosti rane (površine in oblike), kar nam omogoča primerjavo hitrosti celjenja ran različnih začetnih velikosti. Za njen izračun potrebujemo čas do zacelitve rane. Ker mnoge rane niso bile opazovane do zacelitve, ga lahko ocenimo iz zakasnjenega eksponencialnega modela po štirih tednih opazovanja spreminjanja površine rane.

S tako definirano mero hitrosti celjenja smo na kliničnih podatkih dokazali značilno hitrejše celjenje kroničnih ran stimuliranih z izmeničnim električnim tokom od ran, zdravljenih

konzervativno ali z nameščenimi neaktivnimi elektrodami. Med skupinama konzervativno zdravljenih ran in ran, zdravljenimi s placebom, nismo našli značilnih razlik. Uspeh stimulacije z enosmernim električnim tokom je bil primerljiv z uspešnostjo zdravljenja z izmenično električno stimulacijo in boljši od uspešnosti konzervativnega zdravljenja ali zdravljenja s placebom. Razlika ni bila statistično značilna, vzrok pa je lahko v nehomogeni skupini ran stimuliranih z enosmernim električnim tokom, ki združuje različne postavitve stimulacijskih elektrod.

Način zdravljenja pa ni najvplivnejši parameter na hitrost celjenja kroničnih ran. Na hitrost celjenja vplivajo tudi lastnosti rane in bolnika. S statističnim pristopom smo ugotovili, da ni veliko neposrednih vplivov lastnosti rane in bolnika na hitrost celjenja, ampak da ti delujejo na hitrost celjenja v medsebojni kombinaciji. Z algoritmi za strojno učenje smo vpliv teh lastnosti uredili v naslednjem vrstnem redu: površina, starost bolnika, čas od nastanka rane do začetka zdravljenja, razmerje diagonal (oblika rane), lokacija rane, način zdravljenja, čas od poškodbe hrbtenjače do nastanka rane, dnevno trajanje stimulacije, stopnja rane, diagnoza bolnika in vrsta rane.

Z algoritmi za strojno učenje smo tudi izboljšali napovedovanje hitrosti celjenja. Zgradili smo regresijsko drevo z linearnimi enačbami v listih na osnovi lastnosti ran, bolnikov in načina zdravljenja. Ugotovili smo, da hitrosti celjenja ni mogoče napovedati ob začetku zdravljenja. Šele z vključitvijo ocene hitrosti celjenja na osnovi tedenskega opazovanja poteka celjenja smo dosegli dobre rezultate napovedovanja hitrosti celjenja. Ugotovili smo, da je optimalni čas opazovanja rane, preden podamo napoved hitrosti celjenja, tri tedne. Po treh tednih je relativna napaka drevesa 0,181. Že po dveh tednih pa lahko podamo grobo oceno hitrosti celjenja s relativno napako 0,347. Znanje, ki je shranjeno v obliki regresijskega drevesa, je osnova ekspertnega sistema za napovedovanje uspešnosti zdravljenja. Zdravnik ima tako že po dveh tednih opazovanja poteka celjenja kronične rane grob podatek o uspešnosti zdravljenja in na osnovi te informacije lahko bolj zanesljivo potrdi pravilnost izbranega načina zdravljenja ali pa se odloči za zamenjavo, če je napoved neugodna.

Abstract

Clinical research of slow processes such as healing of chronic wounds is lengthy and arduous. Therefore 390 wound cases collected in a database is important long-term work of several researchers, clinicians and specialists. The quantity of available data permits employment of statistical tools and artificial intelligence methods for analysis of the healing process by itself, as well as the effects of different therapeutic modalities. In clinical studies of treatment effects in wound healing, small number of included wound cases renders analysis of wound and patient characteristics on wound healing process impossible. Now quantity of data available in our database permits extensive analysis of prognostic factors on wound healing process in which induction tree learning algorithms were employed. Knowledge extracted from wound cases collected in our database is basis of an expert system for helping clinician choosing appropriate treatment and consequently to shorten patients recovery period.

In the first part of our study we confirmed former presumptions that wound healing process has to be weekly followed because of nonlinear behaviour of wound healing dynamics. Wound healing dynamics is nonlinear irrespective to wound status definition. Therefore we propose to weekly measure wound area, which can be estimated from two mutually perpendicular diagonals of the wound. We found out that wound shape has insignificant effect on wound healing dynamics. Dynamics of wound area change in time has delayed exponential behaviour. Mathematical equation of delayed exponential curve was characterized as the most general structure of mathematical model. Parameters of model were calculated for each wound case. If parameters of mathematical model were calculated after at least four weeks of wound healing process follow-up and after performed at least five wound area measurements, dynamics description did not differ significantly from actual one. This allows us to accurately predict time to healing after at least four-week observation period.

There is no uniform measure of wound healing treatment effects assessment. Therefore we analysed frequently used measures of wound treatment assessment and introduced most general measure of wound healing rate. It is defined as advance of wound margin towards wound centre measured in millimetres per day. Such wound healing rate measure is independent on initial wound size and shape. That is very important quality in clinical trials when wound healing rates of wounds of different initial size and shapes are compared. This measure is calculated from time to complete wound closure, which can be estimated after at least four weeks of follow up.

New measure of wound healing rate was used to evaluate effect of electrical stimulation. We found that electrically stimulated wounds healed significantly faster than conventionally

treated wounds and wound with placed non-active electrodes. No significant difference in healing rate between conventionally and sham treatment was found. Wounds stimulated with biphasic electric current healed at significantly higher rate than conventionally and sham treated wounds, while difference between direct current stimulation and other treatment modalities was not significant. Wounds in direct current stimulation group differ in electrode placement. Though electrode placement affect wound healing, wounds stimulated with direct current were analysed as one group to achieve enough samples and to generalize results.

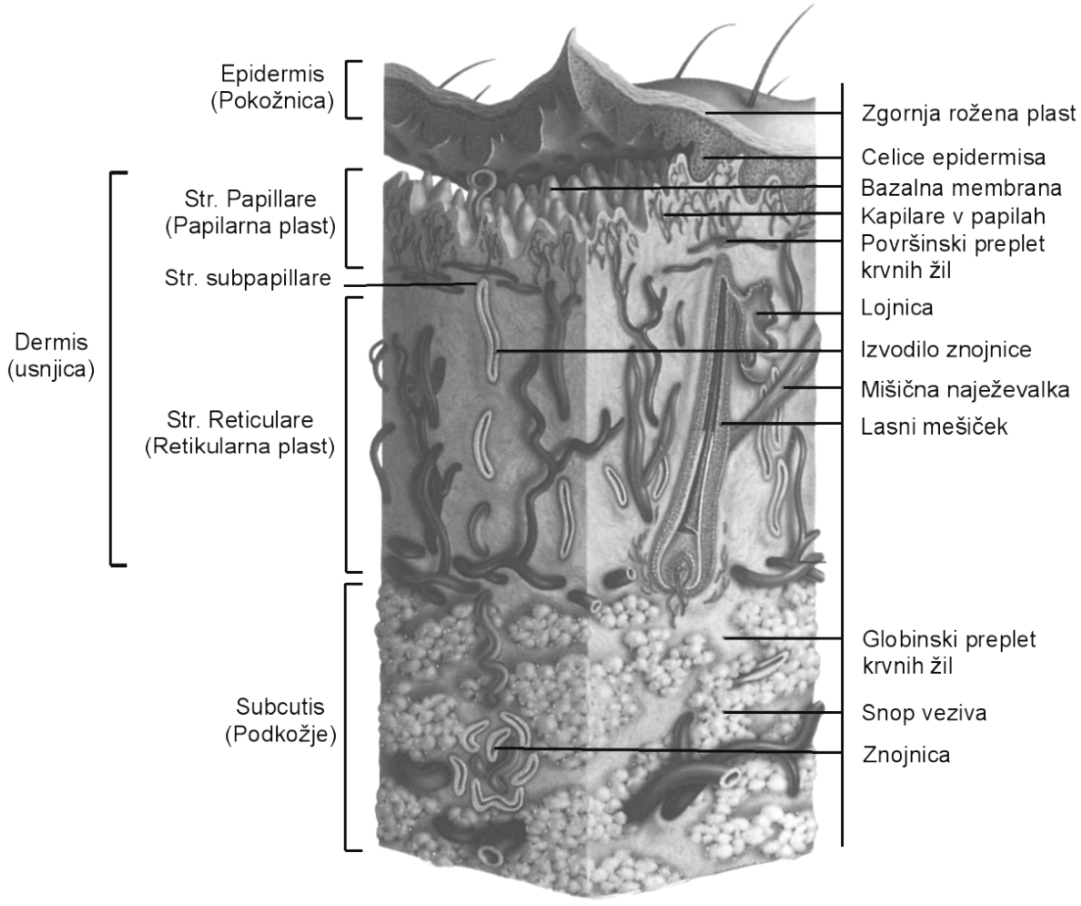
We found that wound healing rate depends on treatment characteristics. But wound healing rate also depend on wound and patient characteristics. Using statistical analysis we determined that characteristics effect wound healing rate in mutual combination. With algorithms for induction tree learning effect of parameters was determined in following order: wound area, patient age, elapsed time from wound appearance to beginning of treatment, width to length ratio (wound shape), location, type of treatment, elapsed time from spinal cord injury to wound appearance, daily duration of stimulation, wound grade, diagnosis and aetiology. It is possible that two characteristics that individually has only moderate effect on wound healing rate, has very important effect in mutual combination.

Induction tree learning algorithms are searching such mutual effects of wound, patient and tretaemnt characteristics on wound healing rate. Resulted tree can be used to predict wound healing rate of new wound cases. Best results were achieved with regression tree which had linear equations in leaves. We found that wound healing rate can not be predicted at beginning of treatment, but after few weeks of wound healing process follow up. After two weeks relative error was 0.347 and after three weeks only 0.181. That means that after two weeks of follow up, effect of wound treatment can be estimated. Regression trees are basis of an expert system for wound healing rate prediction. Expert system is useful tool to help in decisions whether treatment should be changed.

1 Uvod

1.1 Anatomija in fiziologija kože

Koža je vitalni organ, saj izguba večjega dela kože lahko ogrozi življenje posameznika. Poškodba kože je lahko akutna, kot posledica mehanske ali toplotne poškodbe, ali pa se pojavi rana v kronični obliki, kot razjeda. Poškodovana koža ne ščiti telesa pred mikroorganizmi ter pred izgubo vode in elektrolitov. Večja kožna okvara tako poruši naravni ščit posameznika, kar lahko privede do šoka zaradi pretirane izgube tekočine in elektrolitov ali do sepse, ki je rezultat zastrupitve telesa z mikrobi ali njihovimi toksini v krvi. Pogoste poškodbe zunanjega izvora so opekline. V ZDA vsako leto obravnavajo 2,15 milijona primerov. Od tega jih je 150.000 sprejetih v bolnišnično oskrbo, med katerimi jih sedem odstotkov umre [Bringham in McLoughlin, 1996].



Slika 1.1 *Pregledna slika morfologije kože (modif. po Betetto in Fettich (1993))*

Površina kože je od 1,2 m^2 do 1,8 m^2, debelina je od 2 mm do 5 mm (brez maščevja), teža pa znaša do 16% telesne teže [Betetto in Fettich, 1993]. V normalni koži ločimo tri sloje tkiva (slika 1.1).

Zunanji sloj, epidermis (vrhnjica), je samo 0,1mm debel sloj, sestavljen iz samih epitelijskih celic, ki tvorijo zgornjo roženo plast in spodnjo rodno plast, v približno štirih tednih dozorijo in ko se pomikajo iz notranjosti na površino, odmrejo. Epidermis je brez ožilja in vezivnega tkiva. Celice dobivajo kisik in hranila z difuzijo iz spodaj ležeče usnjice in zraka.

Dermis je od 2 mm do 5 mm debel sloj prekrvljenega in oživčenega vezivnega tkiva, sestavljenega iz vlaken, osnovne substance in celic. Pretežni del vlaken sestavlja preplet kolagenskih (vezivnih) vlaken, ki dajejo koži trdnost in razteznost. Med celicami so najpomembnejši fibroblasti, ki izdelujejo kolagenska in elastična vlakna ter osnovno substanco. Osnovna substanca je iz kislih mukopolisaharidov, vode, soli in beljakovin. V dermisu najdemo še lojnice, znojnice in lasne mešičke.

Med epidermisom in dermisom je približno 20 nm debela večslojna bazalna membrana.

Tretji sloj, ki leži pod dermisom, je subcutis (podkožje). Sloj vsebuje od 0,4 mm do 4 mm večinoma maščobnega tkiva. Omogoča mehanično in termično izolacijo tkiv in organov v globini.

Poleg zgoraj omenjenih vitalnih funkcij kože (organizem varuje pred izgubo vode in elektrolitov ter pred infekcijo) le-ta tudi varuje organizem pred toploto in mrazom, mehanskimi poškodbami, kemikalijami in ultravijoličnim sevanjem. To nalogo lahko opravlja predvsem zato, ker je njena površina mastna. Maščobo ji dajejo lojnice in epidermogena maščoba. Mehanično varovalo je tudi vezivo dermisa in mehka podlaga maščevja v subkutisu. Med najpomembnejše dejavnosti kože spada termoregulacija. S širjenjem in krčenjem arterij v koži in z izhlapevanjem znoja pri potenju omogoča izravnavanje temperature telesa. Koža kot največji čutni organ preko senzibilnih živčnih vlaken in tipalnih telesc v epidermisu zaznava signale iz okolice, kot so tip, dotik, pritisk, bolečina in temperatura. Nenazadnje koža prenaša tudi čustvene signale okolici, kot je rdečica in bledost obraza ter oddaja vonj (feromoni). Torej je koža veliko več kot le membrana, ki ščiti notranje organe - koža je kompleksen organ. Koža varuje telo pred raznovrstnimi škodljivostmi, je del imunskega sistema, sodeluje v termoregulaciji in prometu vode, sintetizira vitamin D, uravnava krvni tlak in je največje čutilo.

1.2 Kronične rane in načini zdravljenja

Kožna rana je vsaka prekinitev kontinuitete kože, ki nastane zaradi različnih zunanjih (mehanskih, toplotnih, kemičnih, aktiničnih) ali notranjih (žilne bolezni – venska insuficienca in ateroskleroza, infekcije, neoplazme, nevrogene motnje, hematološke bolezni) vzrokov. Ulkus (razjeda) je globoka rana, ki sega v podkožje in nastane, ko se nekrotični del tkiva demarkira in izloči navzven. Ker je intaktna koža ključnega pomena za izpolnjevanje vseh njenih funkcij, se ob nastali okvari aktivira vrsta mehanizmov, ki skušajo okvaro odpraviti.

V procesu celjenja rane ločimo več časovnih obdobij: zapolnitev nastale rane s krvnim strdkom v nevrogenem obdobju, destruktivno obdobje z razgrajevanjem odmrlega tkiva in

eventuelnih tujkov (mikrobov), produktivno obdobje z vraščanjem kapilar in zapolnitvijo ranjenega mesta z granulacijskim tkivom, epitelizacijo in kontrakcijo rane in nazadnje obdobje maturacije z nastankom zrele brazgotine [Singer in Clark, 1999].

Če je zaradi kakršnegakoli razloga zavrta katera od faz celjenja ali njen del, je celjenje rane upočasnjeno. Vzroki so lahko: okužba rane, ki podaljša destruktivno obdobje, nezadostna oksigenacija tkiva, ki slabi proliferativno obdobje, hipoproteinemija, hipovitaminoze, stres, različna zdravila (predvsem citostatiki), obsevanje z ionizirajočimi žarki, nižja temperatura okolja, pomanjkanje nekaterih mikroelementov (cink, baker, železo) in višja starost. Vrsta bolezenskih stanj na posamičen ali več zgoraj naštetih načinov zavira celjenje rane: bolezni arterij (ateroskleroza), sladkorna bolezen (diabetes mellitus), rak, jetrne bolezni itn.

Kadar kljub dlje časa trajajoči negi rane in bolnika ne zaznamo procesa celjenja ali pa je ta zelo zakasnjen, govorimo o kroničnih ranah. Te predstavljajo precejšen socialni, ekonomski in medicinski problem tako zaradi pogostnosti, izrazito kroničnega poteka kot tudi pogostih ponovitev in izrazito dolgotrajnega zdravljenja, ki večkrat zahteva tudi hospitalizacijo in včasih celo kirurški poseg. Zdravljenje kroničnih ran se pogosto zaplete zaradi infekcije. Kronične rane predstavljajo za organizem veliko energijsko breme, stalno grožnjo z zapleti, nezaželen poseg v bolnikov vsakdan, oviro za normalen potek rehabilitacije. Nenazadnje pa je njihovo zdravljenje tudi precej drago.

Zdravljenje temelji na odstranjevanju vzročnih dejavnikov in omejitvi dejavnikov, ki delujejo zaviralno na celjenje ran. V določenih primerih pride v obzir tudi kirurško zdravljenje vzročnih dejavnikov (npr.: premostitvene operacije na arterijah, operacija varikoznih ven) in presaditev kože. Ker tak način zdravljenja ni primeren za vse oblike kroničnih ran in za vse bolnike, bolnik pa je izpostavljen vsem nevarnostim, ki so povezane z operativnim zdravljenjem, raziskovalci iščejo najrazličnejše metode, s katerimi skušajo celjenje ran pospešiti.

Celjenje kroničnih ran skušajo pospešiti z:

- nepropustnimi (okluzivnimi) obvezami [Kannon in Garett, 1995; Bergemann *et al.*, 1999],
- električno stimulacijo [Vodovnik in Karba, 1992; Stefanovska *et al.*, 1993],
- obsevanjem z laserskimi žarki [Gogia, 1995a],
- ultrazvokom [Brown, 1995],
- terapijo s hiperbaričnim kisikom [Gogia, 1995b],
- dodajanjem rastnih faktorjev [Martin *et al.*, 1992; Glover *et al.*, 1997; Kunimoto, 1999] in
- umetno kožo [Singer in Clark, 1999; Brem *et al.*, 2000] ter
- njihovimi kombinacijami (okluzivne obveze v kombinaciji z električno stimulacijo [Karba *et al.*, 1995], kombinacija ultrazvoka in ultravijoličnih žarkov [Nessbaum *et al.*, 1994]).

Med naštetimi metodami je električna stimulacija najnatančneje opisna, poleg tega je njen pozitiven učinek potrjen v več študijah. Kot dodatek konzervativnemu zdravljenju preležanin in drugih vrst kroničnih ran se uporablja že preko 30 let [Wolcott *et al.*, 1969]. Z električno

stimulacijo so bile zdravljene predvsem nevrogene [Baker *et al.*, 1997] in venske razjede ter preležanine [Jerčinović *et al.*, 1994]. V literaturi lahko zasledimo naslednje pozitivne učinke električne stimulacije [Gentzkow in Miller, 1991; Kloth in McCulloch, 1996]:

- pospešena epitelizacija in celjenje,
- zacelitev višjega odstotka ran in zacelitev tudi tistih kroničnih ran, ki se niso odzvale na konzervativni način zdravljenja,
- preprečitev gangrene in antibakterijski učinek,
- izboljšana prekrvitev,
- povečana stopnja kontrakcije rane,
- večja natezna trdnost brazgotine,
- povečan odziv fibroblastov,
- zmanjšanje nevropatskih bolečin in
- zmanjšana periferna nevropatija.

Približno odstotek ljudi ima enkrat v življenju kronično razjedo na nogi, med katere sodi predvsem starejša populacija [Skene *et al.*, 1992]. V ZDA je vsako leto 1,25 milijona ljudi hudo opečenih in 6,5 milijona ljudi trpi za kroničnimi ranami, ki so posledica mehanskih vzrokov (stalen pritisk) ali nevrogenih in žilnih bolezni. Petindvajset odstotkov sladkornih bolnikov ima vsaj enkrat v življenju na spodnjih okončinah nevrogene razjede in šest odstotkov sladkornih bolnikov je vsako leto sprejetih v bolnišnično oskrbo zaradi teh razjed. Največ amputacij spodnjih okončin opravijo zaradi sladkorne bolezni in nevrogenih razjed - 50.000 primerov letno v ZDA. Število amputacij je moč zmanjšati z uspešnejšim zdravljenjem nevrogenih razjed [Glover *et al.*, 1997]. Kar enajst odstotkov (več kot dva milijona v ZDA) bolnikov je v bolnišnični oskrbi zaradi preležanin. Preležanine se pojavijo pri približno treh do petih odstotkih bolnikov, ki so v bolnišnični oskrbi zaradi drugih bolezni. Verjetnost za nastanek kronične rane je pri bolnikih z okvaro hrbtenjače kar od 25 do 85 odstotna.

Zaradi tako obsežne problematike kroničnih ran so pred desetletjem na Inštitutu Republike Slovenije za rehabilitacijo (IRSR) v sodelovanju s Fakulteto za elektrotehniko Univerze v Ljubljani pričeli izvajati obsežno študijo učinkov električne stimulacije na celjenja kroničnih ran. V manjšem obsegu se je študija izvajala tudi v drugih rehabilitacijskih centrih. To so bili Rehabilitacijski center Varaždinske toplice, Institut za rehabilitacijo v Beogradu in Splošna bolnišnica Celje, oddelek za rehabilitacijo. Rezultati študije [Stefanovska *et al.*, 1993] so pripeljali do redne klinične uporabe električne stimulacije za pospeševanje celjenja kroničnih ran na omenjenih inštitutih.

1.3 Električna stimulacija

Pri električni stimulaciji z elektrodami dovedemo v predel rane električni tok nizke jakosti. Različne raziskovalne skupine so v študijah vpliva električne stimulacije na celjenje kroničnih ran uporabile različne oblike električnega stimulacijskega signala, ga različno aplicirale in tudi zelo različno razlagale njene učinke. Objektivna primerjava prednosti in pomanjkljivosti

posameznih metod je zaradi razlik v protokolih študij in različnih meril za vrednotenje učinkov zelo težavna, na različnih etiologijah ran pa so se vse izkazale kot uspešne. Zaradi te univerzalne učinkovitosti, slabe kakovosti večine študij (neobjektivne kontrolne skupine, številčno nezadostni vzorci, neprimerno vrednotenje učinkov) in predvsem nepoznavanja osnovnih mehanizmov, preko katerih električni signali vplivajo na regenerativne procese, je optimizacija električne stimulacije kroničnih ran zelo težavna.

1.3.1 Stimulacija z enosmernim električnim tokom

V normalni koži se med vrhnjo in spodnjo plastjo epidermisa aktivno vzdržuje razlika ionskih koncentracij, ki ustvarja razliko v električnih potencialih velikosti nekaj 10mV. Po poškodbi kože, pri kateri pride do prekinitve plasti kože, se vzpostavi prevodna pot med poloma epidermalne baterije [Barker *et al.*, 1982], po kateri zaradi razlike potencialov steče ionski poškodbeni tok velikosti nekaj μA [Illingworth in Barker, 1980]. Čeprav vloga endogenih električnih pojavov pri celjenju ran ni znana, so bili prav ti pojavi povod za vrsto študij v katerih je bil uporabljen konstanten enosmerni tok. V eni izmed prvih kliničnih študij so Wolcott *et al.* (1969) namestili negativno elektrodo neposredno na rano in drugo na zdravo kožo v njeni okolici. Uporabili so enosmerni tok jakosti 0,2-1,0mA in rano stimulirali trikrat na dan po dve uri v štiriurnih presledkih. Ko so opazili napredek v celjenju, so polariteto elektrod zamenjali. Površinska uporaba šibkega enosmernega toka se je izkazala za zelo dobro (hitrejše celjenje, tvorba čvrstejše brazgotine in intenzivnejša vnetna reakcija). V nekaterih študijah se je menjavanje polaritete v različnih fazah celjenja oz. vsakič, ko je prišlo do zastoja celjenja, izkazalo za učinkovito [Kloth in McCulloch, 1996], spet drugi pa so poročali o enakih rezultatih brez menjavanja polaritete elektrod, pri čemer je bila pozitivna elektroda (anoda) nameščena v rani, druga pa na zdravi koži v okolici rane. Na ta način naj bi dosegli posnemanje endogenih električnih pojavov.

Na Inštitutu RS za rehabilitacijo je bila izvedena študija, v kateri so primerjali dve različni postavitvi elektrod. Rane so bile stimulirane z enosmernim električnim tokom amplitude 0,6mA dve uri dnevno. S postavitvijo pozitivne elektrode na rano in negativne elektrode na zdravo kožo, ki obdaja rano, so bili doseženi značilno boljši rezultati kot pri namestitvi elektrod na nepoškodovano kožo na nasprotnih straneh rane [Karba *et al.*, 1997; Šemrov *et al.*, 1997]. Pri obeh postavitvah elektrod so se električno stimulirane rane celile hitreje od ran z nameščenimi neaktivnimi elektrodami, vendar je bila razlika statistično značilna le pri postavitvi pozitivne elektrode neposredno na rano. Slabost te postavitve je nepraktično vsakdanje nameščanje stimulacijskih elektrod neposredno na rano.

1.3.2 Stimulacija z izmeničnim električnim tokom

Nekatere raziskovalne skupine so preučile tudi možnost stimulacije z izmeničnim električnim tokom. Te študije se poleg uporabe različnih parametrov stimulacije razlikujejo tudi po mestu aplikacije. Z njimi so stimulirali v predelu rane, hrbtenjačo ali akupunkturne točke [Vodovnik in Karba, 1992]. V študiji Baker *et al.* (1997) so uporabili lokalno stimulacijo preležanin s pravokotnimi bifaznimi pulzi frekvence 50Hz in amplitude, ki ni povzročila mišične kontrakcije.

Na inštitutu RS za rehabilitacijo je v redni klinični uporabi stimulacija z vlakom bifaznih pulzov. Njeni parametri izhajajo iz funkcionalne električne stimulacije, ki se pri paraliziranih bolnikih uporablja za krepitev mišic in izvajanje funkcionalnih gibov. Električni signal je sestavljen iz vlakov bifaznih, nabojsko uravnovešenih tokovnih impulzov (40Hz), ki se ritmično izmenjavajo z enako dolgimi pavzami (4s). Amplituda signala je nastavljena na vrednost, ki v stimuliranem tkivu povzoča rahlo krčenje mišic (do 35mA). Elektrodi nameščajo na nepoškodovano kožo ob robovih rane (na nasprotnih straneh rane) in stimulirajo rano dve uri dnevno, dokler se le-ta ne zaceli oz. bolnik ne zapusti bolnišnice. Izboljšana prekrvitev rane in okoliškega tkiva, ki je posledica rahlega krčenja mišic pod vplivom pulzirajočega toka, se v tem primeru zdi najbolj očitna razlaga mehanizma pospeševanja celjenja stimuliranih ran [Likar *et al.*, 1993, Renata, 1996].

1.3.3 Stimulacija z monofaznimi napetostnimi ali tokovnimi pulzi

Nekakšna kombinacija obeh oblik električnih signalov je stimulacija z monofaznimi napetostnimi pulzi, katerih amplituda je nastavljena tik pod prag vidne mišične kontrakcije [Kloth in Feedar, 1988]. Pozitivna elektroda je bila postavljena neposredno na rano. Če je bil opažen zastoj v celjenju je bila polariteta elektrod zamenjana. Zamenjava polaritete se je pokazala za uspešno, kadar je bila rana inficirana. Postavitev negativne elektrode na rano ima dezinfekcijski učinek. Amplituda napetosti je bila od 100 V do 175V, frekvenca pa 105 Hz. Stimulirali so 45 minut na dan, pet dni v tednu.

Ista raziskovalna skupina je kasneje uspešno preizkusila monofazne tokovne pulze frekvence 128 Hz in amplitude 29,2 mA [Feedar *et al.*, 1991]. Rane so stimulirali dvakrat dnevno po pol ure. Negativna elektroda je bila nameščena neposredno na rano, polariteto pa so zamenjali, ko so zaznali celjenje. Leto kasneje so Lundeberg *et al.* (1992) uporabili namestitev elektrod na nepoškodovano kožo na nasprotnih straneh rane, vendar so vseeno obračali polariteto. Najprej so dvajset minut stimulirali z eno polariteto elektrod, naslednjih dvajset minut pa z obrnjeno. Pravokotni tokovni pulzi dolžine 1 ms so se ritmično menjavali s prekinitvami 80 krat na sekundo. Amplituda toka je dosegla rahlo kontrakcijo mišičevja.

V zgoraj podanem kratkem pregledu uporabe električne stimulacije za pospeševanje celjenja kroničnih ran opazimo raznolikost parametrov električne stimulacije in raznolikost načinov njene uporabe (dnevno trajanje stimulacije, skupni čas stimulacije in postavitev elektrod). Mehanizmi, preko katerih se proces celjenja pospeši, še vedno niso pojasnjeni. Očitno gre za kombinacijo več mehanizmov, ki pozitivno vplivajo na potek celjenja [Biedebach, 1989]. Parametrov električne stimulacije brez poznavanja mehanizmov ne moremo optimizirati, lahko pa eksperimentalno iščemo najboljše. Mehanizmi učinkov električne stimulacije so lahko odvisni od toka, napetosti, polaritete, frekvence, časa trajanja pulza, oblike pulza, namestitve elektrod in režima stimulacije. Vpliv nekaterih od naštetih parametrov je bil že eksperimentalno preizkušen. Žal pa rezultati študij med seboj niso primerljivi zaradi neenotnega in velikokrat neprimernega ocenjevanja učinkov zdravljenja [Lazarus *et al.*, 1994]. Zelo malo je bilo opravljenih študij, ki so zajele več različnih parametrov električne stimulacije. Večina takšnih študij je temeljila na majhnem številu primerov, kar je vodilo k pristranskemu deljenju ran v skupine in ni omogočalo študije vplivov stopnje rane, lokacije in

drugih vplivnih lastnosti na celjenje ran. Za optimizacijo parametrov električne stimulacije je potrebna široka kontrolirana študija, ki temelji na enotnem ocenjevanju učinkov električne stimulacije. Sheffet *et al.* (2000) so pokazali, da je za študijo vpliva lastnosti rane, bolnika in zdravljenja potrebno vsaj 164 primerov kroničnih ran. Za objektivno podajanje rezultatov je nujno potrebna kvantitativna ocena učinkov zdravljenja [Bardsley *et al.*, 1995]. Pogosto so učinki električne stimulacije kvantitativno opisani s hitrostjo celjenja, ki pa ni enolično definirana. Avtorji namreč uporabljajo zelo različne opise časovnega poteka celjenja kroničnih ran [Gorin *et al.*, 1996]. Pri tem se naslanjajo predvsem na redne meritve površine rane, merjenje premera, diagonal ali obsega rane. Le poenoteno podajanje rezultatov omogoča primerjavo učinkov različnih načinov zdravljenja in s tem optimizacijo parametrov električne stimulacije. Zato mora biti predstavljena enolično definirana mera, ki bo splošno sprejeta za vrednotenje uspešnosti celjenja ran ali pa moramo poiskati relacijo med različnimi načini podajanja rezultatov, če seveda takšna relacija obstaja.

1.4 Analiza in napovedovanje hitrosti celjenja kroničnih ran

Rdeča nit dela, ki je opisano v disertaciji, je vrednotenje vpliva lastnosti ran, bolnikov in načina zdravljenja na celjenje kroničnih ran. Poznavanje vplivnih lastnosti ran, bolnikov in načinov zdravljenja na hitrost celjenja je dobra osnova za razvoj ekspertnega sistema za napovedovanje hitrosti celjenja ran. Osnova za delo so bili klinični podatki o celjenju kroničnih ran. Privoljenje za študijo je dala Republiška strokovna komisija za medicinsko etična vprašanja v Ljubljani 1990 (št.: 64/90). Delo je razdeljeno na pet med seboj tesno povezanih tematskih sklopov:

1. V prvem sklopu smo izbrali najprimernejši parameter za opis stanja rane. Parameter smo tedensko merili najmanj tri tedne. Na podlagi meritev smo poiskali strukturo matematičnega modela, ki najbolje opisuje časovni potek spreminjanja stanja rane.
2. V drugem sklopu smo s pomočjo znanega matematičnega modela procesa celjenja definirali mero uspešnosti zdravljenja ran. Kritično smo jo primerjali z merami, ki jih uporabljajo druge raziskovalne skupine in navedli njihove prednosti in slabosti.
3. V tretjem sklopu smo s pridobljenim znanjem o dinamiki celjenja kroničnih ran in definirano mero uspešnosti zdravljenja ovrednotili uspešnost zdravljenja z električno stimulacijo na obstoječi podatkovni bazi.
4. V četrtem sklopu smo ocenili vpliv lastnosti ran in bolnikov na uspešnost zdravljenja kroničnih ran.
5. V zadnjem sklopu smo na podlagi znanja pridobljenega iz prejšnjih sklopov zgradili sistem za napovedovanje uspešnosti zdravljenja ran. Določili smo minimalni potrebni čas opazovanja poteka celjenja rane, preden lahko podamo dovolj zanesljivo napoved.

2 Spremljanje poteka celjenja kroničnih ran

Lazarus *et al.* (1994) so v preglednem članku podali napotke ter načine opisovanja in spremljanja celjenja ran. V članku poudarjajo, da je vedno potrebno zajeti parametre, ki opisujejo vzrok za nastanek rane, fiziologijo bolezni in stanje rane. Najpomembnejši so parametri, ki opisujejo stanje rane.

2.1 Stanje rane

Stanje rane se v procesu celjenja dinamično spreminja, zato ga moramo ocenjevati periodično. Zaradi potrebe po pogostem ocenjevanju stanja rane morajo biti metode ocenjevanja hitre in preproste, da jo lahko izvaja tudi tehnično manj podkovano osebje, neinvazivne, da ne vplivajo na potek celjenja, in seveda s čim nižjimi stroški. Stanje rane opišemo z njeno velikostjo (dimenzijami rane) in/ali z njeno stopnjo, ki po določenem ključu uvrsti rano v odgovarjajočo kategorijo. Pri tem lahko uporabimo invazivne ali neinvazivne merilne metode (tabela 2.1).

Tabela 2.1 *Načini ocenjevanja velikosti in stopnje rane*

PARAMETER	NEINVAZIVNA METODA	INVAZIVNA METODA
površina, obseg	iz obrisa rane s planimetrijo, iz diagonal	
prostornina	stereometrija	odlitek fiziološke raztopine
	magnetna resonančno slikanje	odlitek zobotehničnega voska
	ultrazvok	
stopnja	vizualno	kirurška odstranitev nekrotičnega tkiva
	ultrazvok	biopsija
	rentgenogram	

Velikost rane ocenimo neinvazivno z meritvijo obsega, površine ali najdaljše diagonale in nanjo pravokotne najdaljše diagonale rane ali prostornine. Ker so metode spremljanja prostornine in globine rane invazivne [Covington *et al.*, 1989] ali pa tehnično zahtevne (ultrazvok, MRI, stereometrija) [Plassmann in Jones, 1992], so neprimerne za pogosta merjenja. Rane so v splošnem nepravilnih oblik in se celijo nesimetrično. Obstajajo različni načini ocenjevanja obsega in površine. Obris rane preko sterilne prozorne folije najnatančneje

opisuje površino in obseg rane, potrebno pa je uporabiti planimetrijo. Preprosteje je izračunati površino rane iz meritve med seboj pravokotnih diagonal rane. Dolžina rane je največja diagonala rane, širina pa nanjo pravokotna največja diagonala. Metoda je preprosta, hitra, ponovljiva in jo z lahkoto opravi tudi tehnično manj podkovano osebje. Še preprostejša, a nekoliko nepraktična metoda, je primerjava že vnaprej narisanih likov znanih površin in obsegov z obliko in velikostjo rane. Iz pregleda literature (Tabela 2 v dodatku C) vidimo, da je velikost rane najpogosteje opisana s površino, obsegom ali med seboj pravokotnima diagonalama, pri tem pa se največkrat rano obriše in kasneje izmeri potrebne parametre.

Stopnjo rane ocenimo iz podatkov o površini, globini rane, iz podatkov o poškodovanih kožnih slojih in o poškodbah podkožnih tkiv. Obstajajo različni sistemi točkovanja, po katerih ocenjujemo stopnjo rane, vsi pa temeljijo na predpostavki, da velikost rane ni dovolj informativna. Poleg velikosti rane vključujejo tudi opis nekroze, barvo kože v okolici rane, zapolnitev razjede s sokrvico in nastanek strdka, granulacijsko tkivo, epitelizacijo, infekcijo, sušenje, krasto in eksudate. Zaradi lažje uporabnosti sistemi uporabljajo majhno število stopenj, ki se giblje med štiri in sedem. Slabost takšnih sistemov točkovanja je njihova velika kompleksnost, pomanjkljiva zanesljivost in neobčutljivost na spremembe, ki se dogajajo v procesu celjenja. National Pressure Ulcer Advisory Panel (NPUAP) (1989) zato opozarja, da ti sistemi (še) niso primerni za spremljanje poteka celjenja in sklepanje o učinkovitosti zdravljenja. Kasneje se je pojavilo še nekaj sistemov ocenjevanja stopnje rane, ki so bolj občutljivi na spremembe, ki se dogajajo v procesu celjenja. Večina teh sistemov je še vedno v fazi testiranja, najobetavnejša sistema pa sta Sessing scale [Ferrell *et al.*, 1995] in PUSH [Bartolucci in Thomas, 1997]. Sistem točkovanja Sessisng scale na podlagi podatkov o granulaciji, infekciji, sušenju, nekrozi in krasti rane razvrsti rane na sedem stopenj. PUSH pa po točkovalnem sistemu točkuje rane v mejah od 8 do 34 na podlagi meritev površine, eksudata in časa od pojava rane pa do začetka zdravljenja.

Ker sistemi za ocenjevanje stopnje rane še niso dovolj preizkušeni, so zapleteni ali niso dovolj občutljivi na spremembe, ki se dogajajo v procesu celjenja, je še vedno za spremljanje stanja rane najprimerneje uporabiti velikost rane. Ta pa je najhitreje in najlaže ocenjena z meritvijo premera, obsega, obeh diagonal ali površine rane.

2.2 Parametri za opis rane in bolnika

Rano lahko opišemo še z vrsto parametrov, ki so vezani na nego rane pred začetkom zdravljenja ali pa jih določimo ob pregledu bolnika pred začetkom zdravljenja. V tabeli 2.2 so našteti parametri, ki smo jih zasledili v literaturi, iz katerih je razviden vzrok za nastanek rane, patofiziologija in status rane ob začetku zdravljenja [Lazarus *et al.*, 1994].

Za razumevanje vzrokov in ovrednotenje vpliva sistemskih dejavnikov na celjenje ran je nujno potreben tudi opis bolnika. Za opis bolnika potrebujemo demografske podatke, podatke o sistemskih obolenjih (diabetes, venska insuficienca, trauma, arteroskleroza, poškodba hrbtenjače itd) in o sistemskih agensih (radioaktivno obsevanje, transfuzija, citotoksični agensi, hormoni, dializa, antikoagulanti, imunosupresivi, protivnetna in antimikrobna sredstva itd), ki vplivajo na celjenje ran.

Tabela 2.2 *Parametri za opis rane in bolnika*.

PARAMETRI ZA OPIS RANE	PARAMETRI ZA OPIS BOLNIKA
lokacija rane	starost
čas od nastanka rane do začetka zdravljenja	spol
čas od nastanka primarnega vzroka do pojava rane	fizična aktivnost
nega rane pred prihodom v bolnišnico	demografski podatki
etiologija	sistemski agensi, ki vplivajo na celjenje
bolečina	spremljajoča sistemska obolenja (diagnoza)
eksudat	
barva	
vonj	
nekroza	
podkožni žepi	
prizadetost podkožnih tkiv in organov	
prekrvitev/oksigenacija	
infekcija	
edem	

2.3 Podatkovna baza kroničnih ran zdravljenih na IRSR

Za temeljito analizo procesa celjenja kroničnih ran in iskanje parametrov (lastnosti ran, bolnikov in načinov zdravljenja), ki vplivajo na celjenje kroničnih ran, potrebujemo dovolj veliko množico podatkov, t.i. učnih primerov. V desetletju uporabe električne stimulacije za pospeševanje celjenja kroničnih ran na IRSR so fizioterapevti vpisovali podatke o bolniku, rani in poteku zdravljenja v posebne obrazce. Bolnik je pred vključitvijo v študijo podal pisno izjavo, da je s študijo seznanjen in privolil v uporabo podatkov. Te podatke smo vnesli v podatkovno bazo hranjeno v Laboratoriju za biokibernetiko na Fakulteti za elektrotehniko, Univerze v Ljubljani. Sprva je bila postavljena v programsko okolje DOS in se izvajala pod programskim paketom DBase III [Krošelj *et al.*, 1990]. S prehodom večine programskih orodij na programsko okolje MS Windows 95/98/NT smo zaradi njene lažje povezljivosti z ostalimi programskimi orodji prenesli podatkovno bazo v MS Access. Pri tem je bilo na osnovi izkušenj iz prejšnje baze opravljenih nekaj sprememb. Dodali smo polje o smrti pacienta in izpustili podatkovna polja za katera se je izkazalo, da so nepotrebni ali pa jih iz drugih razlogov fizioterapevti niso vnašali. Delno smo dopolnili manjkajoče podatke. Tako smo zbrali podatke o zdravljenju 266 pacientov s 390 ranami. V tabeli 2.3 so navedeni podatki hranjeni v podatkovni bazi, ki so primerni za nadaljnjo obdelavo.

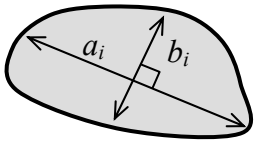
Ob sprejetju bolnika v bolnišnično oskrbo je bilo ocenjeno stanje rane na podlagi velikosti in stopnje rane. Stopnja rane je bila ocenjena po Shea-jevi lestvici [Shea, 1975]. Lestvica razvrsti rane v štiri stopnje. Prva stopnja opisuje poškodbe epidermisa, koža je rdeča in ob pritisku obledi. Druga stopnja opisuje poškodbo kože, ki sega v dermis. Tretja stopnja opisuje poškodbe kože, ki segajo do podkožja. Rane četrte stopnje pa segajo do podkožnih struktur

kot so kosti in sklepi. Velikost rane je bila ocenjena z meritvami globine, površine rane in med seboj pravokotnih diagonal rane.

Tabela 2.3 *Podatki o rani, bolniku in poteku zdravljenja zbrani v podatkovni bazi.*

RANA	BOLNIK	ZDRAVLJENJE
dolžina rane	spol	način zdravljenja
širina rane	datum rojstva	dnevno trajanje terapije
globina	skupno število ran	čas zdravljenja
stopnja	diagnoza	tedenska meritev velikosti rane
datum nastanka rane	datum poškodbe hrbtenjače	
datum začetka zdravljenja	stopnja spastičnosti	
etiologija		
lokacija		

Tedensko so bile redno merjene le med seboj pravokotne diagonale ran. Površina izračunana s planimetrijo iz obrisa rane (slika 2.1) ni bila več računana, ko so Stefanovska *et al.* (1993) pokazali statistično neznačilno razliko v površini rane izračunane iz med seboj pravokotnih diagonal (1) in izračunane s pomočjo planimetrije na vzorcu desetih tedensko spremljanih ran do zacelitve. Iz diagonal a_i in b_i lahko izračunamo tudi obseg rane (2), razmerje diagonal (3) pa nam podaja informacijo o obliki rane ob času $t=t_i$ (kjer je i zaporedna oznaka tedna, i=0,1,...,n in n število tednov opazovanja rane).



Slika 2.1 *Na rano položimo sterilno prozorno folijo in s pisalom obrišemo rano.*

$$S_i = \frac{\pi}{4} a_i \cdot b_i \tag{1}$$

$$p_i = \pi\left[\frac{3}{4}(a_i + b_i) - \frac{1}{2}\sqrt{a_i \cdot b_i}\right] \tag{2}$$

$$r_i = \frac{b_i}{a_i} \leq 1 \tag{3}$$

Pred pričetkom študije smo izbrali parametre za opis rane in pacienta, ki smo jih potem redno vnašali v podatkovno bazo. Izbira parametrov se zdi ustrezna, a v literaturi zasledimo kot parametre, ki pomembno vplivajo na hitrost celjenja tudi druge. To so barva, nekroza, granulacija, epitelizacija, infekcija in izločki rane.

Rezultate analize endogenih rastnih faktorjev prisotnih v izločkih preležanin je v doktorski disertaciji podala Karba (1996). Analiza endogenih rastnih faktorjev omogoča vpogled v proces celjenja na molekularni ravni in s tem ponuja razlago pozitivnih učinkov električne stimulacije. Ker nas v študiji ni zanimal proces celjenja na molekularni rani in ker je

zajemanje izločka rane invazivno, izločkov nismo obravnavali. Lyman *et al.* (1970) so ugotovili, da se inficirane rane celijo počasneje kot rane, ki niso obremenjene s kolonijami bakterij, vendar so metode zajemanja podatkov o infekciji invazivne in so bile zato opravljene le na majhni množici ran.

V študiji učinkov električne stimulacije na celjenje kroničnih ran so Jerčinović *et al.*, 1994, poleg lokacije, površine in globine rane shranjevali tudi podatke o njeni nekrozi in granulaciji. Granulacijsko tkivo se je pojavilo (zamenjalo nekrotično tkivo) v večjem obsegu in v krajšem času pri električno stimuliranih kot pri konzervativno zdravljenih ranah.

Podatek o barvi rane je posredno vsebovan v podatku o stopnji rane, tako da podatka o barvi nismo posebej zajemali. Podatki o epitelizaciji, nekrozi in granulaciji so bili pomanjkljivi in jih nismo uspeli naknadno dopolniti.

3 Dinamika celjenja kroničnih ran

Za definicijo mere hitrosti celjenja kroničnih ran, ki še danes ni enoumno podana, moramo dobro poznati časovni potek oz. dinamiko celjenja kroničnih ran. Cilj zdravljenja kroničnih ran je njihova zacelitev. Ko je rana zaceljena, je njena velikost enaka nič. Torej nas zanima, kako se časovno spreminja velikost rane. Če se velikost rane s časom manjša, se rana celi, drugače stagnira ali se celo povečuje. Hitrost spreminjanja velikosti rane definiramo kot hitrost celjenja rane. Velikost rane smo opisali s površino, obsegom in med seboj pravokotnima diagonalama rane. Ker za opis velikosti rane potrebujemo skalar, moramo izbrati le enega izmed naštetih parametrov ali pa njihovo kombinacijo.

Daleč najpogosteje je velikost rane ocenjena s površino [Gilman ,1990]. Ker nas pri časovnem poteku celjenja zanimajo le spremembe površine in bi radi časovne poteke celjenja ran med seboj primerjali, površino rane normiramo (4).

$$norm(S_i) = \frac{S_i}{S_0} \cdot 100 \ ; \ i=0,1,\ldots,n \tag{4}$$

S_0 je začetna površina rane, S_i površina po i tednih opazovanja in n število tednov opazovanja rane. Začetna velikost rane je tako vedno sto odstotkov, ne glede na dejansko površino rane. V naslednjem poglavju je podan postopek in rezultati iskanja strukture matematičnega modela dinamike časovnega spreminjanja normirane površine.

Gilman (1990) je predložil drugačno oceno velikosti rane izračunane iz površine in obsega (5) in jo imenoval prirastek tkiva podan v milimetrih.

$$d_i = \frac{\Delta S_i}{\bar{p}_i}, \tag{5}$$

kjer je $\bar{p}_i = \frac{p_0 + p_i}{2}$ (mm) povprečni obseg izračunan iz obsega rane ob začetku zdravljenja in obsega rane po i tednih. $\Delta S_i = S_0 - S_i$ (mm^2) je sprememba površine rane v tem času. Če je sprememba površine negativna (površina rane se poveča), je prirastek tkiva negativen. V literaturi mero redko zasledimo. Predlagana ocena velikosti rane vključuje še informacijo o obliki rane, ki je skrita v obsegu. Avtor trdi, da je mera linearna, kar pomeni, da se s časom ne spreminja (neodvisna od i) in jo zato lahko, podano na enoto časa, uporabljamo tudi kot mero hitrosti celjenja. Ker trditev ni dokazana, smo se odločili izračunati tudi dinamiko spreminjanja prirastka tkiva.

3.1 Matematični model časovnega poteka spreminjanja normirane površine

Privzeli smo, da velikost rane zadovoljivo opišemo s površino. Časovni potek spreminjanja normirane površine rane pa smo opisali z matematičnim modelom. Ker je proces celjenja izredno kompleksen in mnogi fiziološki parametri še niso pojasnjeni, je teoretičen pristop k modeliranju nemogoč. Tako smo se lotili eksperimentalnega iskanja strukture modela. S takšnim modeliranjem želimo določiti matematično strukturo modela. Ob znani strukturi modela iščemo za vsako kronično rano ocene njegovih parametrov, ki dajo optimalno prileganje odzivov sistema in modela. Iz takšnih modelov ne dobimo nobene informacije o fiziološkem ozadju problema. Dobljen model je uporaben le kot celota. Strukturo matematičnega modela smo iskali eksperimentalno, pri čemer smo se oprli na znane časovne poteke podobnih fizioloških problemov (npr. rast tumorja, kopičenje kolagena pri celjenju ran [Bardsley *et al.*, 1995]). Razvili smo devet različnih modelov, ki smo jim določili parametre za vsako od 226 v študijo vključenih kroničnih ran. Modele smo vrednotili s kriteriji in metodami, ki so predstavljene v nadaljevanju. Po testiranju in primerjavi možnih modelov smo izbrali model z najustreznejšo strukturo za matematični model časovnega poteka spreminjanja normirane površine.

3.1.1 Kriteriji vključevanja ran v študijo iskanja matematične strukture modela

Zaradi splošnosti modela se pri vključevanju ran v študijo nismo ozirali na bolnikova sistemska obolenja, niti na etiologijo ran in način zdravljenja. Postavili pa smo naslednje kriterije za vključitev ran v študijo iskanja matematične strukture modela:

- Zahtevali smo, da se način zdravljenja med študijo ni spremenil, oz. če se je spremenil, smo upoštevali le obdobje prvega načina zdravljenja.
- Zaradi nenatančnosti meritev površin manjših od enega kvadratnega centimetra, smo to vrednost postavili za mejo najmanjše začetne površine ran, ki so bile vključene v študijo.
- Pri velikih in kompleksnih ranah četrte stopnje se zdravnik največkrat odloči za plastično operacijo, pri kateri del zdravega tkiva presadijo na obolelo mesto. Rana je s tem pokrita, koža pa je na tem mestu tudi po dolgotrajnem okrevanju mnogo tanjša kot je normalno. Zato lahko na takem mestu hitro pride do ponovnega odprtja in kronične rane. Ker gre za presajeno tkivo, katerega dinamika celjenja je lahko drugačna od "zdravega", takšnih kroničnih ran nismo vključili v študijo.
- Matematični model smo iskali med dvo-, tri- in štiriparametrskimi modeli. Parametre modela smo izračunali tako, da se je model optimalno prilegal tedenskim meritvam površine rane. Za konsistentno računanje parametrov modela potrebujemo vsaj eno meritev več kot ima model prostostnih stopenj (parametrov). Štiriparametrski modeli nas tako omejujejo na najmanj pet meritev površine rane, kar pomeni, da mora biti rana spremljana vsaj štiri tedne.

Z upoštevanjem naštetih kriterijev se je število v študijo vključenih bolnikov skrčilo na 168, število ran pa na 226.

3.1.2 Predstavitev možnih matematičnih struktur modela

V literaturi najpogosteje zasledimo linearni (6) in eksponencialni model (8) [Jerčinović *et al.*, 1994] poteka celjenja rane. Oba modela sta dvodimenzionalna in preprosta, v dobro jima lahko štejemo tudi to, da imata njuna parametra biofizikalen pomen. Parametra S_{LIN} in S_{EXP} sta oceni normirane začetne površine rane, parametra θ_{LIN} in θ_{EXP} pa sta ocenjeni hitrosti celjenja rane v odstotkih na dan. Pozitivna vrednost parametra θ vedno pomeni, da se rana celi, negativna pa, da se povečuje.Velika slabost linearnega modela je ta, da ne upošteva dejstva, da površina rane ne more biti negativna.

$$\hat{S}(t) = S_{LIN} - \theta_{LIN} t \tag{6}$$

Ta problem lahko rešimo z uporabo lomljene linearne krivulje (7)

$$\hat{S}(t) = \begin{cases} 0 & ; S_{PLN} - \theta_{PLN} t \le 0 \\ S_{PLN} - \theta_{PLN} t & ; S_{PLN} - \theta_{PLN} t > 0 \end{cases} \tag{7}$$

ali pa z uporabo eksponencialnega modela.

$$\hat{S}(t) = S_{EXP} \cdot e^{-\theta_{EXP} t} \tag{8}$$

Iz pregleda časovnih potekov celjenja kroničnih ran smo ugotovili, da se precej ran prične celiti šele po določeni časovni zakasnitvi. Zakasnitev celjenja daljša od treh dni in pol je bila opažena pri 51% vključenih ran, daljša od enega tedna pri 40% ran in daljša od dveh tednov pri 26% vključenih ran. Takšen časovni potek celjenja ne moremo opisati zgolj z dvema parametroma. Če parametroma za opis eksponencialne krivulje dodamo še parameter, ki opisuje časovno zakasnitev v dneh in ga označimo s T, lahko zapišemo enačbo (9) za zakasnjen eksponencialni model. Pomen ostalih dveh parametrov je ostal tak kot pri eksponencialnem modelu, le da θ_{DEX} sedaj opisuje relativno hitrost celjenja rane po časovni zakasnitvi T_{DEX}.

$$\hat{S}(t) = \begin{cases} S_{\mathrm{DEX}} & ;\ t \le T_{DEX} \\ S_{DEX} \cdot e^{-\theta_{DEX}(t - T_{DEX})} & ;\ t > T_{DEX} \end{cases} \tag{9}$$

Tak potek celjenja je zelo podoben sigmoidi (10), ki se pogosto pojavlja kot primeren opis časovnega poteka dogajanj v bioloških procesih.

$$\hat{S}(t) = \frac{S_{SGM}}{1 + e^{\frac{t - T_{SGM}}{\theta_{SGM}}}} \tag{10}$$

V literaturi o modeliranju časovnega poteka spreminjanja volumna čvrstih tumorjev [Miklavčič *et al.*, 1995; Vaidya in Alexandro, 1981] zasledimo logistični (11) in Gompertzov model (12), ki sta lahko primerna tudi za opis dinamike celjenja kroničnih ran.

$$\hat{S}(t)=\begin{cases}\dfrac{S_{LOG}\left|\dfrac{t}{T_{LOG}}\right|^{-\theta_{LOG}}}{1+\left|\dfrac{t}{T_{LOG}}\right|^{\theta_{LOG}}} & ;\quad \theta_{LOG}\le 0\\[2ex] \dfrac{S_{LOG}}{1+\left|\dfrac{t}{T_{LOG}}\right|^{\theta_{LOG}}} & ;\quad \theta_{LOG}>0\end{cases} \tag{11}$$

Parametri sigmoide in logističnega modela so biofizikalno opisljivi, saj sta S_{SGM} in S_{LOG} oceni normirane začetne površine rane, parametra θ_{SGM} in θ_{LOG} negativni naklon tangente na krivuljo v točkah T_{SGM} oz. T_{LOG}, ki sta potrebna časa, da se površina rane zmanjša na 50% začetne vrednosti. Parametri Gompertzovega modela pa nimajo ekvivalentnega biofizikalnega opisa.

$$\hat{S}(t)=S_{GOM}\cdot e^{-e^{\left(\frac{t-\beta_{GOM}}{\alpha_{GOM}}\right)}} \tag{12}$$

Z dvojno eksponencialno krivuljo (13) lahko opišemo veliko bioloških procesov [Bardsley *et al.*, 1995]. Model je štiriparametrski, biofizikalni pomen parametrov modela pa ni enoumno določljiv.

$$\hat{S}(t)=S_{1DED}\cdot e^{-\theta_{1DED}t}+S_{2DED}\cdot e^{-\theta_{2DED}t} \tag{13}$$

Zelo fleksibilen, kar se tiče prileganja, je štiriparameterski racionalni model (14).

$$\hat{S}(t)=\frac{S_{R4P}+\alpha_{R4P}\cdot t}{1+\beta_{R4P}\cdot t+\gamma_{R4P}\cdot t^2} \tag{14}$$

V splošnem vsak dodaten parameter prinaša modelu dodatno prostostno stopnjo in s tem tudi boljše prileganje meritvam, vendar model lahko hitro postane preparametriziran in s tem doprinese manj novega znanja o sistemu kot model z manjšim številom parametrov. Štiriparametrske modele smo vključili v študijo zaradi njihove velike fleksibilnosti in ocene, koliko bi pridobili oz. izgubili pri vključitvi še enega parametra.

3.1.3 Kriteriji in mere za vrednotenje modelov

Kvalitativna kriterija za vrednotenje modelov sta bila:

- model naj ima čim manjše število parametrov,
- parametri modela naj bodo biofizikalno razumljivi.

Poleg tega smo uporabili še pet kvantitativnih mer za vrednotenje modelov [Devore, 1995]:

(1) SSE (error sum of squares), vsota kvadratov napake (15), podaja skupno napako prileganja krivulje podatkom.

$$SSE = \sum_{i=1}^{n} \left(\hat{S}_i - S_i \right)^2 \tag{15}$$

S_i je meritev površine rane v *i*-tem tednu opazovanja poteka celjenja; *i*=1,2,...,*n*; *n* je število meritev in $\hat{S}_i = \hat{S}\left(i \cdot \Delta t\right)$ je iz modela ocenjena vrednost površine v diskretnem trenutku $t = i \cdot \Delta t$ (Δt je časovni interval enega tedna).

(2) SE (standard error of estimate), standardna napaka ocene (16), je normirana mera SSE, ki omogoča primerjavo napak modelov z različnimi števili parametrov.

$$SE = \sqrt{\frac{SSE}{n-k}} \tag{16}$$

k je število prostostnih stopenj modela.

(3) r^2 (coeficient of determination), dobrota prileganja (17), opisuje, kako ustrezen je model za opis podatkov. Bliže, ko je vrednost dobrote prileganja vrednosti 1, boljše je prileganje, in obratno, manjša, ko je njena vrednost, slabše je prileganje.

$$r^2 = 1 - \frac{\sum_{i=1}^{n} \left(\hat{S}_i - S_i \right)^2}{\sum_{i=1}^{n} S_i^{\,2} - \frac{1}{n} \left(\sum_{i=1}^{n} S_i \right)^2} \tag{17}$$

Ker iščemo model, ki naj bo preprost (relativno majhno število parametrov) in se dobro prilega podatkom, uporabimo uravnano dobroto prileganja (adjusted r^2):

$$Adjusted\ r^2 = \frac{(n-1)r^2 - k + 1}{n-k} \tag{18}$$

(4) PRESS (predicted residual error sum of squares), ocena vpliva manjkajočih podatkov na model (19) ima velik pomen, saj meritve pogosto niso bile redno izvajane.

$$PRESS = \frac{\sum_{i=1}^{n-1} \left(\hat{S}_i' - S_i \right)^2}{n-1} \tag{19}$$

Izračunamo jo tako, da iz obstoječih *n* meritev vsakokrat odstranimo eno (razen prve), npr. *i*-to, in prilegamo krivuljo na preostalih *n*–1 meritev. Nato izračunamo razliko med ocenjeno vrednostjo površine $\hat{S}_i'$ in izmerjeno vrednostjo S_i.

(5) MPRESS (multiple predicted residual error sum of squares), napovedna sposobnost modela (20), ocenjuje sposobnost napovedovanja poteka celjenja na podlagi opravljenih m meritev (m–1 tednov opazovanja) površine rane.

$$MPRESS(m) = \frac{\sum_{i=m+1}^{n} \left(\hat{S}_i' - S_i\right)^2}{n-m} \qquad (20)$$

Mero lahko izračunamo le v primeru, ko pri tedenskem spremljanju površine rane ni manjkajočih podatkov. Redno je bilo tedensko merjenih 144 ran vsaj tri tedne, 92 ran štiri tedne, 70 ran pet tednov in 44 ran najmanj šest tednov. Iz tedenskih meritev izločimo m meritev, nanje prilegamo krivuljo in nato iz dobljenih parametrov modela ocenimo vrednosti površine rane $\hat{S}_i'$ v naslednjih n–m tednih ter izračunamo napako.

3.1.4 Postopek prileganja

Za vsako od devetih predlaganih struktur modela smo izračunali parametre modela tako, da se matematični model poteka celjenja kar najbolje ujema z dejanskim potekom. Ta postopek računanja parametrov modela smo imenovali prileganje modela dejanskemu poteku celjenja. Vsak model smo prilegali vsakemu od 226 znanih potekov celjenja. Razvili smo programski paket za izračun parametrov predlaganih matematičnih struktur modelov ter izračun opisanih petih mer vrednotenja modela. Parametre modela smo izračunali po Marquardt-Levenbergovem algoritmu [Press *et al.*, 1992]. Algoritem potrebuje prve parcialne odvode matematičnih struktur modelov in v iteracijskem postopku išče minimum kriterijske funkcije SSE (najmanjšo vsoto kvadratov napake). Podatke o časovnih meritvah površine rane programski paket črpa neposredno iz podatkovne baze, kamor tudi shranjuje rezultate, t.j. parametre modela in mere vrednotenja modela. Rezultati so bili obdelani s komercialnimi statističnimi programskimi orodji [SPSS Inc., 1997]. Ker smo ugotovili, da so za našo učno množico primerov mere vrednotenja modelov neparametrično porazdeljene in te porazdelitve ni bilo mogoče prevesti v normalno, smo uporabili neparametrične statistične metode. Pri vrednotenju modelov smo za določitev statistične značilnosti razlik uporabili Mann-Whitney-jev neparametrični test.

3.1.5 Izbira najsplošnejše strukture modela

Vsota kvadratov napake (SSE) je statistično značilno največja v primeru linearnega modela. Sledita mu ostala dvoparametrska modela, ki pa sta se izkazala za enakovredna. Statistično pomembno manjšo vsoto kvadratov napake naredimo, če izberemo triparametrski model. Med seboj pa se triparameterski modeli statistično značilno niso razlikovali. Statistično pomembno najmanjšo vsoto kvadratov napake smo dosegli, kot smo tudi pričakovali, z uporabo štiriparametrskih modelov.

Meri kakovosti prileganja, uravnana dobrota prileganja (Adjusted r^2) in standardna napaka ocene (SE), upoštevata tako število opravljenih meritev kot tudi število parametrov modela. Statistično obdelani rezultati obeh mer so popolnoma identični. Zopet se je kot statistično značilno najslabši izkazal linearni model, ki ima najmanjšo uravnano dobroto prileganja in največjo standardno napako ocene. Kot statistično značilno boljša, a enakovredna mu sledita

ostala dvoparametrska modela. Statistično značilno najboljši so triparametrski modeli, med katerimi ni statistično pomembnih razlik. Štiriparametrska modela sta se izkazala za enakovredna triparametrskim modelom.

Statistično značilno največjo napako ocene manjkajočih podatkov smo naredili z linearnim modelom. Sledita mu lomljen linearni model in eksponencialni model, med katerima nismo našli statistično značilne razlike. Prav tako nismo našli statistično pomembne razlike med sigmoidnim, logističnim, Gompertzovim in eksponencialnim modelom. Le zakasnjen eksponencialni in štiriparametrski dvojni eksponencialni model sta v primerjavi z dvoparamterskimi modeli dosegla statistično značilno manjšo napako ocene manjkajočih podatkov, oba pa se med seboj in v razmerju do ostalih tri in štiriparametrskih modelov nista statistično pomembno razlikovala.

Napovedna sposobnost modela je bila izračunana na podlagi izvedenih meritev v prvih 3, 4, 5 in 6 tednih opazovanja rane. Statistično značilno največjo napako napovedovanja bodočega poteka celjenja rane smo dosegli z uporabo linearnega in štiriparametrskih modelov. Ostali modeli so bili statistično značilno boljši od omenjenih, med njimi pa ni bilo statistično značilnih razlik.

Na osnovi zgoraj podanih rezultatov primerjanja mer za vrednotenje modelov smo zaključili, da je najustreznejše število parametrov modela za opis dinamike celjenja kroničnih ran tri. Pomembna slabost logističnega modela je nezmožnost realnega opisovanja naraščajočih potekov spreminjanja površine rane, saj naraščajoč potek vedno prične v koordinatnem izhodišču. Kvalitativni kriterij biofizikalnega pomena parametrov ni izpolnjen pri Gompertzovem modelu. Biofizikalen pomen parametra ocene začetne površine rane pri sigmoidi pa je vprašljiv, saj je njena srednja vrednost v primerih, ko ni časovne zakasnitve celjenja, kar 4374±7451%. Na osnovi mere PRESS sicer ni statistično pomembnih razlik med triparametrskimi modeli, vseeno pa se je zakasnjen eksponencialni model izkazal za statistično značilno boljšega od dvoparametrskega eksponencialnega modela, medtem ko se ostali niso. Prednost zakasnjenega eksponencialnega modela je tudi smiselna biofizikalna opisljivost parametrov modela v primeru, ko ni časovne zakasnitve poteka celjenja rane. V teh primerih je zakasnjen eksponencialni model identičen že pogosto uporabljanemu eksponencialnemu modelu.

Zaključimo lahko, da je najustreznejša uporaba zakasnjenega eksponencialnega modela, ki se je izkazal za najsplošnejši model časovnega poteka celjenja kroničnih ran. Pomen njegovih parametrov je sledeč. Parameter S_{DEX} [*%*] je ocena začetne spremembe velikosti rane, parameter θ_{DEX} [dan^{-1}] določa časovno konstanto eksponencialne funkcije in T_{DEX} [*dan*] opisuje časovno zakasnitev začetka procesa celjenja.

3.2 Matematični model časovnega poteka prirastka tkiva

V zgornjem poglavju smo eksperimentalno poiskali strukturo matematičnega modela časovnega spreminjanja normirane površine. Strukturo matematičnega modela poteka prirastka tkiva skozi čas pa smo izpeljali iz dobljenega zakasnjenega eksponencialnega modela (9).

Struktura modela časovnega poteka spreminjanja velikosti rane ima tri stopnje prostosti. To pomeni, da ima model tri parametre. Za iskanje parametrov modela potrebujemo vsaj štiri periodične meritve velikosti rane. Za študijo iskanja strukture modela spreminjanja normirane površine skozi čas smo zahtevali vsaj pet periodičnih meritev površine rane. Torej smo lahko kriterij za vključevanje ran v študijo omilili. Število ran vključenih v študijo se je tako povečalo iz 226 na 300.

Primerjali smo začetna razmerja diagonal ran s povprečjem razmerja diagonal v času opazovanja za vsako rano. Z analizo parnih podatkov s testom *t* nismo mogli zavrniti domneve, da se začetno razmerje razlikuje od povprečnega (p=0,260). Povprečje vseh izmerjenih razmerij diagonal (n=2481) je bilo 0,653±0,229. Sklepali smo, da se med procesom celjenja oblika rane zanemarljivo spreminja in smo to v matematičnem modelu časovnega poteka prirastka tkiva tudi upoštevali.

Podroben postopek izpeljave je naveden v dodatku C (Appendix 1). Struktura matematičnega modela je podana v enačbi 21

$$\hat{d}(t)=\begin{cases} 2\dfrac{S_0}{p_0}\left(1-\sqrt{\dfrac{S_{ERM}}{100}}\right) & ;\quad 0\le t<T_{ERM} \\ 2\dfrac{S_0}{p_0}\left(1-\sqrt{\dfrac{S_{ERM}}{100}}e^{-\frac{\theta_{ERM}}{2}(t-T_{ERM})}\right) & ;\quad t\ge T_{ERM} \end{cases}, \tag{21}$$

kjer sta S_0 začetna površina in p_0 obseg rane. Izraz $2S_0/p_0$ je ocena največjega prirastka tkiva, ki je v primeru rane v obliki kroga enak polmeru kroga podanega v milimetrih. Biofizikalen pomen parametrov modela je sledeč: parameter S_{ERM} [*%*] je ocena začetnega prirastka tkiva, parameter θ_{ERM} [dan^{-1}] določa časovno konstanto eksponentno naraščajoče funkcije do maksimalne vrednosti prirastka tkiva in parameter T_{ERM} [*dan*] opisuje časovno zakasnitev začetka procesa celjenja. Če se rana povečuje, prirastek tkiva in časovna konstanta zavzameta negativne vrednosti.

Izrazito nelinearni potek prirastka tkiva skozi čas nam dokazuje, da njegova uporaba kot mera hitrosti celjenja, vsaj v takšni obliki kot jo podaja Gilman (1990), ni upravičena.

3.3 Primerjava matematičnega modela časovnega poteka spreminjanja normirane površine in matematičnega modela časovnega poteka prirastka tkiva

Matematični model časovnega poteka prirastka tkiva upošteva obliko rane, za katero smo predpostavili, da se s časom zanemarljivo spreminja in je opisana z začetnim razmerjem diagonal. Matematični model časovnega poteka spreminjanja normirane površine pa ne vsebuje niti informacije o začetni obliki rane. V izpeljavi matematičnega modela poteka prirastka tkiva smo obliko rane aproksimirali z elipso. Če aproksimiramo obliko rane s krogom, izgubimo vso informacijo o obliki rane. Krog je le poseben primer elipse, ko sta diagonali enakih dolžin. Tako lahko obseg kroga izračunamo neposredno iz površine po enačbi 22.

$$p_0 = 2\sqrt{\pi S_0} \tag{22}$$

Če vstavimo enačbo 22 v enačbo 21 dobimo matematično strukturo modela poteka prirastka tkiva pri neupoštevanju oblike rane.

$$\hat{d}(t) = \begin{cases} \sqrt{\frac{S_0}{\pi}}\left(1 - \sqrt{\frac{S_{ERM}}{100}}\right) & ; \quad 0 \le t < T_{ERM} \\ \sqrt{\frac{S_0}{\pi}}\left(1 - \sqrt{\frac{S_{ERM}}{100}} e^{-\frac{\theta_{ERM}}{2}(t - T_{ERM})}\right) & ; \quad t \ge T_{ERM} \end{cases} \tag{23}$$

Vidimo lahko, da se parametri modela S_{ERM}, θ_{ERM} in T_{ERM} niso spremenili. Iz tega smo zaključili, da oblika rane ne vpliva na opis dinamike celjenja kroničnih ran, kar pa še ne pomeni, da ne vpliva na mero hitrosti celjenja. Modela se razlikujeta le v oceni največjega prirastka tkiva S_0/p_0, ki je v primeru neupoštevanja oblike rane precenjen. Napaka je večja pri bolj podolgovatih ranah. Relativno napako smo izračunali po enačbi 24.

$$e_0 = \frac{3}{2}\left[\frac{1}{2}\left(\sqrt{\frac{1}{r_0}} + \sqrt{r_0}\right) - 1\right] \cdot 100 \quad [\%] \tag{24}$$

Relativna napaka je funkcija razmerja diagonal. Povprečno začetno razmerje diagonal je 0,672±0,216 (n=300). Pri takšnem razmerju diagonal, ki se s časom ne spreminja, naredimo pri poenostavitvi oblike rane s krogom 2,97% napake v oceni največjega prirastka tkiva. Napaka je zanemarljiva.

Domneva o nespremenjenem modelu dinamike celjenja kroničnih ran pri neupoštevanju oblike rane je bila preizkušena na kliničnih podatkih. Za vsako od 300 v študijo vključenih ran smo izračunali prirastek tkiva iz izmerjenih diagonal v času opazovanja rane (5) na dva načina. Najprej pa so bili izračunane vrednosti prirastka tkiva iz dejanskih vrednosti diagonal rane. Prilegali smo model (21) izračunanim vrednostim prirastka tkiva. Nato so bile diagonale rane preračunane tako, da je površina ostala nespremenjena, razmerje diagonal pa je bilo enako ena. Iz preračunanih diagonal smo izračunali vrednosti prirastka tkiva. S tem smo obliko rane aproksimirali s krogom. Prilegali smo model (23) izračunanim vrednostim prirastka tkiva. Prav tako smo prilegali zakasnjen eksponencialni model (9) normiranim površinam v študijo vključenih ran. Primerjali smo parametre vseh treh modelov za vsako rano posebej. Uporabili smo analizo parnih podatkov s testom *t* in ugotovili, da se vrednosti parametrov modelov med seboj ne razlikujejo značilno. Zaradi zanemarljivega vpliva oblike rane na opis dinamike celjenja kroničnih ran, smo zaradi enostavnejšega merjenja površine rane, uporabili za opis dinamike zakasnjen eksponencialni model.

Neobčutljivost časovnega poteka celjenja od oblike rane še ne pomeni, da oblike rane ni potrebno upoštevati v definiciji mere hitrosti celjenja kroničnih ran.

4 Mere hitrosti celjenja kroničnih ran

Lundeberg *et al.* (1992) so uporabili za mero hitrosti celjenja čas celjenja rane. Sheffet *et al.* (2000) tudi priporočajo uporabo "časa celjenja" za vrednotenje uspešnosti zdravljenja. Takšna definicija hitrosti celjenja se zdi najustreznejša, saj je zacelitev rane naš končni cilj. Njena velika pomanjkljivost pa je, da ne omogoča primerjanja hitrosti celjenja ran različnih začetnih velikosti, kar pa je najpomembnejša lastnost, ki jo mora mera imeti. Pri tem lahko logično sklepamo, da se velika rana pri enaki hitrosti celjenja zaceli pozneje kot manjša rana. Vendar to ni edina pomanjkljivost te mere hitrosti celjenja. Večina študij je finančno in s tem časovno omejenih, kronične rane pa se, vsaj v kontrolni skupini, celijo izredno počasi. Zato potrebujemo definicijo mere hitrosti celjenja na osnovi omejenega časa opazovanja.

Lyman *et al.* (1970) so iz meritev med seboj pravokotnih diagonal ocenili površino rane (1). Meritev so opravili ob začetku in ob zaključku opazovanja celjenja rane. Čas zdravljenja se je med ranami razlikoval, rane pa niso bile vedno zaceljene v tem času. Spremembo površine v času opazovanja so delili z začetno površino in s tem površino normirali. Normirano razliko so delili s časom opazovanja in pomnožili s sto. Tako so lahko podali hitrost celjenja v odstotkih na dan (25).

$$hitrost\ celjenja = \frac{\pi/4 \cdot a_0 b_0 - \pi/4 \cdot a_m b_m}{(t_m - t_0) \cdot \pi/4 \cdot a_0 b_0} \cdot 100\ \left(\%/dan\right) \tag{25}$$

V enačbi (25) do (28) se indeks (0 ali *m*) nanaša na dan v katerem je bila opravljena meritev. Čas t_0=0 je dan začetka zdravljenja rane. Čas t_m je čas opravljanja naslednje meritve in je merjen v dnevih od začetka opazovanja. Čas je diskretiziran, zato smo zanj uporabili oznako *t* z indeksom, ki označuje zaporedno številko opravljene meritve. Hitrost celjenja zaradi normiranja omogoča primerljivost ran z zelo različnimi začetnimi površinami. Slabost metode je, da predpostavlja linearen potek celjenja rane in torej ne upošteva nelinearnega poteka celjenja, pri katerem je izredno pomemben časovni interval med meritvama.

Feedar *et al.* (1991) so površino rane ocenili kot produkt med seboj pravokotnih diagonal rane. Hitrost celjenja rane so definirali kot normirano spremembo površine v štirih tednih (*m*=28) (26). Tudi ta mera predpostavlja linearen potek celjenja rane.

$$hitrost\ celjenja = \frac{a_0 b_0 - a_m b_m}{4 \cdot a_0 b_0} \cdot 100\ \left(\%/teden\right) \tag{26}$$

Johnson (1997) je podal zelo podobno mero prav tako temelječo na konstantnem časovnem intervalu (štiri tedne) opazovanja rane ($m \approx 28$). Pri tem je omogočal rahlo odstopanje od tega intervala, vendar je zato v mero hitrosti celjenja vgradil popravek (27).

$$hitrost\ celjenja = \frac{S_0 - S_m}{S_0} \frac{28}{t_m - t_0} \cdot 100\ \left(\%/štiri\ tedne\right) \tag{27}$$

Gorin *et al.* (1996) so ob vključitvi bolnika v študijo in po dveh tednih opazovanja izmerili površino in obseg rane. Hitrost celjenja rane so definirali kot prirastek tkiva v dveh tednih (m=14) (28).

$$hitrost\ celjenja = \frac{S_0 - S_m}{\frac{1}{2}\left(p_0 + p_m\right)\left(t_m - t_0\right)}\ \left(mm/dan\right) \tag{28}$$

Definicije hitrosti celjenja s točno določenim časovnim intervalom med dvema meritvama so gotovo primernejše od definicij s poljubnim časovnim intervalom. Še vedno pa takšne definicije ne upoštevajo nelinearne dinamike celjenja kroničnih ran, kaj šele časovne zakasnitve celjenja.

Lundeberg *et al.* (1992) so se problemu izognili tako, da so podali le normirane spremembe površine ran v dvotedenskih časovnih intervalih. Rane so primerjali med seboj tako, da so primerjali odstotek zmanjšanja površine po dvanajstih tednih.

Boljšo in bolj praktično rešitev so predstavili Baker *et al.* (1997), ki so tedensko spremljali površino rane in izračunali povprečno spreminjanje normirane površine med posameznimi meritvami (29) (n je število meritev in i zaporedna številka meritve).

$$hitrost\ celjenja = \frac{1}{n-1} \sum_{i=1}^{n-1} \frac{\frac{S_{i-1} - S_i}{S_{i-1}}}{t_{i-1} - t_i} \cdot 7 \cdot 100\ \left(\%/teden\right) \tag{29}$$

Jerčinović *et al.* (1994) so tedensko spremljali površino rane, kolikor dolgo je bilo mogoče. Nato so uporabili nelinearno regresijo in normiranim meritvam površine prilegali eksponencialno krivuljo. Obratno vrednost časovne konstante so definirali kot hitrost celjenja ran.

Nobena od zgoraj podanih definicij mere hitrosti celjenja ne upošteva zakasnitve celjenja in s tem zakasnjenega nelinearnega poteka celjenja. Prav tako iz zgornjih definicij ne moremo iz hitrosti celjenja sklepati na čas celjenja rane. Zato smo definirali mero hitrosti celjenja, ki upošteva nelinearni potek celjenja in vsebuje informacijo o času celjenja rane.

4.1 Čas celjenja rane

Definicija hitrosti celjenja naj vsebuje informacijo o času celjenja rane. Ker od 300 v študijo vključenih ran 126 ni bilo opazovanih do zacelitve rane, je zelo pomembno, da znamo čas celjenja napovedati. Napovedovanje nadaljnjega poteka celjenja in s tem časa do zacelitve

nam je omogočil zakasnjen eksponentni model. Rano smo opazovali nekaj tednov in pri tem vsaj tedensko merili površino rane. Nato smo izračunali parametre zakasnjenega eksponencialnega modela s prileganjem modela normiranim vrednostim površine. Iz modela smo potem izračunali oceno časa celjenja. Ker ima model eksponencialen potek, je težko določiti, kdaj je rana zaceljena. Pogoj, da je rana zaceljena, ko je njena površina enaka nič, ni matematično ustrezen. Eksponencialni potek namreč doseže asimptoto šele v neskončnosti. Torej model ne opisuje dobro poteka spreminjanja normirane površine v limiti, to je, ko se površina rane bliža vrednosti nič. Zato smo rano obravnavali kot zaceljeno, ko je dosegla pet odstotkov začetne velikosti (30). Odločitev je izhajala iz dejstva, da pet odstotkov začetne vrednosti dosežemo po treh časovnih konstantah. Ker pa lahko pri velikih ranah pet odstotkov začetne površine predstavlja več, kot je začetna velikost najmanjših v študijo vključenih ran, smo vključili dodaten pogoj, ki pravi, da mora biti površina rane po treh časovnih konstantah manjša od kvadratnega centimetra (31). Tako rano obravnavamo kot zaceljeno šele, ko je njena velikost po vsaj treh časovnih konstantah manjša od kvadratnega centimetra (32).

$$T_{5\%} = T_{DEX} + \ln\frac{S_{DEX}}{5}\frac{1}{\theta_{DEX}} \ [dan] \tag{30}$$

$$T_{1cm^2} = T_{DEX} + \ln\left(\frac{S_0 S_{DEX}}{10^4}\right)\frac{1}{\theta_{DEX}} \ [dan] \tag{31}$$

$$T = \begin{cases} T_{5\%} & ; \quad \text{če } |T_{5\%}| \geq |T_{1cm^2}| \\ T_{1cm^2} & ; \quad \text{drugače} \end{cases} \tag{32}$$

Tezo smo preizkusili na učni množici 174 ran, ki so bile opazovane do zacelitve. Za vsako od teh ran smo s prileganjem zakasnjenega eksponencialnega modela normiranim vrednostim površine rane izračunali parametre modela. Parametre smo nato uporabili v enačbah (30, 31 in 32) za izračun časa celjenja. Primerjali smo dejanske čase celjenja z ocenjenimi časi iz modela. Z naravnim logaritmiranjem časa celjenja smo dosegli normalno porazdelitev. V parametričnih testih smo zato uporabljali transformiran čas. S *t* testom parnih podatkov smo dokazali popolno ujemanje časov (p=0,958). Rezultat potrjuje ustreznost predlaganega kriterija po katerem smo določili, kdaj je rana zaceljena.

V naslednjem koraku smo na učni množici 174 ran preizkusili še zanesljivost napovedovanja časa celjenja iz modela, ko rana ni bila opazovana do zacelitve. Najprej smo učno množico skrčili le na primere, ki so bili redno tedensko spremljani vsaj štiri tedne. Nato smo izločili vse meritve površine ran po treh tednih opazovanja. S prileganjem zakasnjenega eksponencialnega modela normiranim izmerjenim vrednostim v prvih treh tednih smo določili parametre modela. Iz parametrov modela smo izračunali čase celjenja ran in jih primerjali z dejanskimi časi celjenja. Z naravnim logaritmom časa celjenja smo zopet dosegli normalno porazdelitev in s tem možnost uporabe parametričnih testov. Rezultat analize parnih podatkov s testom *t* je podan v tabeli 4.1. Postopek smo ponovili še za rane, ki so bile redno tedensko spremljane najmanj pet (šest in sedem) tednov. Zopet smo izločili vse meritve površine ran po štirih (petih in šestih) tednih opazovanja. S prileganjem smo določili parametre modela, iz njih pa izračunali čase celjenja. Rezultati so podani v tabeli 4.1.

Tabela 4.1 *Rezultati testiranja domneve, da ni razlike med dejanskim časom celjenja rane in časom celjenja ocenjenim iz časa opazovanja rane, ki je vsaj teden dni krajši od dejanskega časa celjenja*.

ocenjen čas celjenja	dejanski čas celjenja	število ran
po treh tednih opazovanja	p<0,001	88
po štirih tednih opazovanja	p=0,062	56
po petih tednih opazovanja	p=0,484	40
po šestih tednih opazovanja	p=0,900	26

Iz rezultatov smo sklepali, da je za napovedovanje časa celjenja potrebno rano opazovati in tedensko meriti njeno površino vsaj štiri tedne.

4.2 Definicija mere hitrosti celjenja

Čas celjenja rane pa ni primeren kot definicija mere hitrosti celjenja v primerih, ko se rane ne celijo. Čas celjenja izračunan iz modela je v takem primeru neskončen. Ker se neceleče rane različno hitro večajo, nekatere pa samo stagnirajo, smo izračunali čas do podvojitve površine rane, ki smo mu pridali negativen predznak. Tak pristop pa ne reši vseh težav. Za rane, ki stagnirajo, je čas celjenja ali čas podvojitve površine še vedno neskončen. Zato smo v naslednjem koraku izračunali inverzno vrednost časa celjenja. Odpravili smo problem velikih števil, saj imajo rane, ki stagnirajo, hitrost celjenja nič. Rane, ki se jim velikost veča imajo hitrost celjenja negativno in rane, ki se celijo imajo hitrost celjenja pozitivno. Večja vrednost hitrosti celjena pomeni hitrejše manjšanje oz. pri negativnih vrednostih večanje površine rane.

Ker nas zanima, za koliko se bo velikost rane zmanjšala na dan, pomnožimo inverzno vrednost časa celjenja z začetno površino rane. Tako definirana mera hitrosti celjenja podaja absoluten delež površine zmanjšane ali povečane na dan (33).

$$\Theta_{abs} = \frac{S_0}{T}\left[mm^2/dan\right] \tag{33}$$

Od mere hitrosti celjenja smo zahtevali še zmožnost primerjanja hitrosti celjenja ran različnih začetnih velikosti. Veliko se v ta namen uporablja normirana površina rane, ki ob vključitvi bolnika v študijo znaša sto odstotkov. Zato smo pomnožili inverzno vrednost časa celjenja s sto odstotki in dobili mero hitrosti celjenja (34), ki je podana v odstotkih zaceljene površine rane na dan.

$$\Theta_{norm} = \frac{100}{T}\left[\%/dan\right] \tag{34}$$

Prav tako pa uporaba prirastka tkiva "obljublja" neodvisnost od začetne velikosti rane. Zato smo mero hitrosti celjenja definirali še kot največji prirastek tkiva pomnožen z inverzno vrednostjo časa celjenja (35). Tako definirana mera hitrosti celjenja podaja prirastek tkiva v milimetrih na dan.

$$\Theta_{prirastek} = 2\frac{S_0}{p_0 T}\left[mm/dan\right] \tag{35}$$

Primerjave predlaganih mer smo se lotili na 300 ranah iz učne množice. Za rane, katere niso bile opazovane do zacelitve, smo ocenili čas celjenja po enačbah (30, 31 in 32). Za vse rane smo izračunali mere hitrosti celjenja. Mediana začetne velikosti ran iz učne množice je bila 633 mm^2. Mediana je razdelila primere v dve skupini, v skupino manjših in v skupino večjih ran. Testirali smo domnevo, da ni razlike v hitrosti celjenja malih in velikih ran. Pri merah hitrosti celjenja, ki temeljijo na normiranju površine ali absolutni površini, smo domnevo zavrgli z verjetnostjo napake p<0,001. Ko pa smo uporabili mero hitrosti celjenja, ki temelji na prirastku tkiva, domneve nismo mogli zavreči (p=0,338).

S korelacijskim testom smo preizkusili linearno odvisnost mer hitrosti celjenja od začetne površine, obsega ali oblike (razmerje diagonal) rane. Da smo dosegli normalno porazdelitev spremenljivk, smo morali izračunati naravni logaritem površine, obsega in mer hitrosti celjenja (vključene so le celeče se rane, n=275). V tabeli 4.2 so podani Pearsonovi korelacijski koeficienti (*rs*) in verjetnosti domnev (*p*), da ni linearnih medsebojnih odvisnosti med testiranimi spremenljivkami.

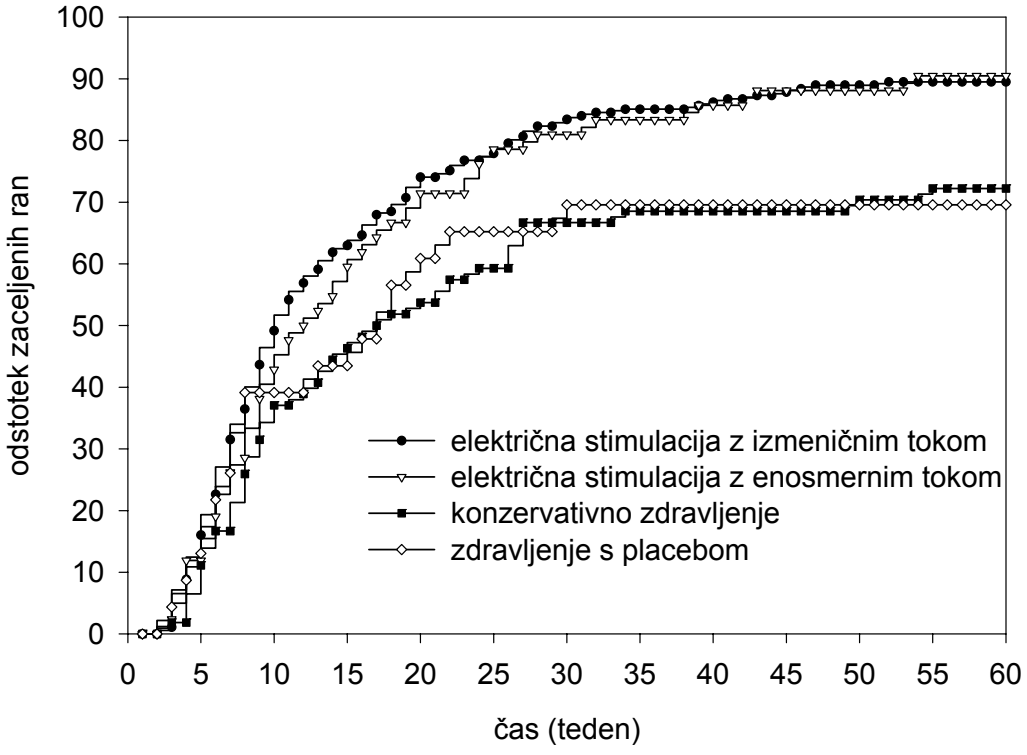
Tabela 4.2 *Pearsonovi korelacijski koeficienti in verjetnosti linearnih povezav med merami hitrosti celjenja in parametri za opis velikosti rane (n=275)*.

	prirastek tkiva		**normirana površina**		**absolutna površina**	
	rs	*p*	*rs*	*p*	*rs*	*p*
površina	0,146	0,091	-0,431	<0,001	0,580	<0,001
obseg	0,121	0,266	-0,413	<0,001	0,571	<0,001
razmerje diagonal	0,105	0,493	-0,153	0,067	0,132	0,170

Le mera hitrosti celjenja osnovana na oceni prirastka tkiva je bila neodvisna od začetne velikosti rane. Če smo uporabili normirano površino, je bila hitrost celjenja majhnih ran precenjena, pri absolutni vrednosti površine pa je bila hitrost celjenja velikih ran podcenjena. Ugotovitve so se skladale z domnevami, ki jih je podal Gilman (1990). V nadaljnjih analizah smo zato uporabljali mero hitrosti celjenja, ki temelji na oceni prirastka tkiva (35).

5 Ovrednotenje učinkov električne stimulacije

Prav tako kot so imeli avtorji v drugih študijah učinkov električne stimulacije težave s pridobitvijo kontrolne skupine bolnikov, je tudi v naši študiji primanjkovalo bolnikov v kontrolni skupini. Od 300 ran je bilo v kontrolno skupino konzervativno zdravljenih ran vključenih 54 ran, v skupino študije učinka placeba pa 23 ran. V kontrolno skupino so bili vključeni le bolniki z okvaro hrbtenjače in preležaninami. Rane drugih etiologij niso bile vključene v to skupino. V nadaljnji obravnavi smo analizirali vse rane ne glede na etiologijo. Učna množica je bila tako velika, da imajo rezultati statističnih testov precejšnjo težo. Zaradi nenormalnih porazdelitev smo uporabili neparametrične statistične metode. S Kruskal-Wallisovim testom smo ugotovili, da ni statistično značilnih razlik v velikosti ran vključenih v različne načine zdravljenja. Tako lahko že s primerjavo časov celjenja ovrednotimo učinkovitost različnih načinov zdravljenja.



Slika 5.1 *Odstotek zaceljenih kroničnih ran skozi čas, prikazan ločeno za vse štiri načine zdravljenja*.

Iz slike 5.1 je razvidno, da se električno stimulirane rane celijo hitreje in v večjem obsegu kot ostale rane. V šestdesetih tednih se je zacelilo 90,6% ran stimuliranih z izmeničnim električnim tokom in 90,5% ran stimuliranih z enosmernim električnim tokom. Občutno manjši odstotek ran se je zacelil v kontrolni skupini 72,2% ran zdravljenih konzervativno in 69,6% ran z nameščenimi neaktivnimi elektrodami. Iz značilno eksponencialnega poteka krivulj celjenja ran podanega na sliki 5.1 je razvidno, da tudi po daljšem času opazovanja odstotki ne bi bili bistveno višji. V skupini ran zdravljenih z izmeničnim električnim tokom so združeni primeri, ki so bili dnevno stimulirani od pol ure pa do dveh ur. Učinkovitost 30 minutne dnevne stimulacije je zelo slaba, vendar smo želeli vključiti v primerjavo vse primere, čeprav to nekoliko zmanjša učinkovitost električne stimulacije. Enako smo naredili tudi s skupino ran zdravljeno z enosmernim električnim tokom. V tej skupini so bile rane stimulirane dve uri dnevno, elektrode pa so bile v polovici primerov nameščene ob rani in v drugi polovici primerov s pozitivno elektrodo na rani in negativni ob njej. Karba *et al.* (1997) so ugotovili statistično hitrejše celjenje ran z nameščeno pozitivno elektrodo neposredno na rano. Zaradi primerljivosti rezultatov z ostalimi skupinami in zaradi zagotovitve dovolj velikega števila primerov ran stimuliranih z enosmernim električnim tokom, smo skupini združili. S tem je učinkovitost stimulacije z enosmernim tokom navidezno zmanjšana.

Tabela 5.1 *Primerjava hitrosti celjenja ran zdravljenih na štiri načine. Domnevo o enaki hitrosti celjenja pri različnih načinih zdravljenja smo testirali z neparametričnim testom Kolmogorov-Smirnov. V tabeli so podani rezultati testa (verjetnosti p). Domnevo smo ovrgli pri statistični značilnosti p<0,05. Hitrost celjenja je podana v obliki mediane (25%–75% območje)*.

	hitrost celjenja (*mm/dan*)	**n**	**AC**	**DC**	**CO**	**SH**
AC	0,190 (0,114–0,328)	181	1,000			
DC	0,168 (0,089–0,434)	42	0,365	1,000		
CO	0,145 (0,026–0,261)	54	0,031	0,085	1,000	
SH	0,162 (-0,046–0,205)	23	0,008	0,056	0,607	1,000

Primerjali smo tudi hitrosti celjenja ran razdeljenih v štiri skupine glede na način zdravljenja (tabela 5.1). Najhitreje so se celile električno stimulirane rane. Rane stimulirane z izmeničnim tokom so se celile značilno hitreje kot konzervativno zdravljene rane ali rane z nameščenimi neaktivnimi elektrodami. Razlika v hitrosti celjenja med ranami stimuliranimi z izmeničnim in ranami stimuliranimi z enosmernim tokom ni bila značilna. Prav tako nismo našli značilne razlike v hitrosti celjenja konzervativno zdravljenih ran in ran z nameščenimi neaktivnimi elektrodami. Rane stimulirane z enosmernim tokom so se celile hitreje od ran iz kontrolne skupine, vendar razlika ni bila značilna. Če bi se omejili na rane z nameščeno pozitivno elektrodo neposredno na rani, bi bila razlika v hitrosti celjenja večja.

6 Vpliv lastnosti rane, bolnika in načina zdravljenja na hitrost celjenja kroničnih ran

Hitrost celjenja prav gotovo ni odvisna le od načina zdravljenja, ampak nanjo vplivajo tudi karakteristične lastnosti rane in bolnika. V literaturi lahko najdemo le malo poskusov določitve vpliva teh lastnosti na hitrost celjenja ran. Skene *et al.* (1992) so določili prognostični koeficient na primeru venskih razjed na nogi. Ugotovili so, da je celjenje majhnih razjed hitrejše. Pomembno pa je tudi čim hitreje pričeti z zdravljenjem razjede, ki je bolj uspešno pri mladih bolnikih z vensko insuficienco povrhnjih žil (ugotovljeno s fotopletizmografijo). Zaključili so, da ima površina rane največjo napovedno moč celjenja razjed. Birke *et al.* (1992) so ugotovili, da je čas celjenja močno odvisen od globine in premera rane. Johnson (1997) našteva štiri vplivne parametre na celjenje venskih razjed. To so ABpI (razmerje tlakov merjenih na gležnju in laketi), liposkleroza, edem in površina razjede. Lyman *et al.* (1970) so našli statistično značilno povezavo med hitrostjo celjenja in bakterijsko obremenitvijo rane.

V literaturi smo torej zasledili vplivne lastnosti ran in bolnikov na hitrost celjenja ran, ki jih nismo merili ali vnašali v našo podatkovno bazo kroničnih ran. Vse naštete študije obravnavajo le venske razjede, nismo pa zasledili študije, ki bi iskala vpliv lastnosti rane in bolnika na ostale etiologije ran. Naša baza vsebuje največ podatkov o preležaninah, katerih hitrost celjenja do sedaj še ni bila podrobneje analizirana. Prav tako nismo zasledili študije, ki bi vključevala električno stimulacijo kot način zdravljenja.

Omejili smo se na lastnosti ran, bolnikov in načinov zdravljenja, ki so bile zajete v naši podatkovni bazi (tabela 2.3), in poiskali njihove medsebojne odnose in vpliv na hitrost celjenja kroničnih ran. Za iskanje linearnih zvez med parametri smo uporabili Spearmanov neparametrični korelacijski test. Rezultate podajamo s Spearmanovim korelacijskim koeficientom (*rs*), tveganjem domneve, da sta parametra medsebojno odvisna, (*p*) in številom ran za katere je parameter znan. Za močno medsebojno odvisne parametre smo označili tiste, ki imajo korelacijski koeficient večji od 0,500 in tveganje domneve, da sta parametra linearno povezana, manjše od pet odstotkov. Rahlo medsebojno odvisni parametri so tisti s korelacijskim koeficientom med 0,300 in 0,500 in tveganjem manjšim od pet odstotkov. Če je bil korelacijski koeficient manjši od 0,300 pri tveganju manjšim od pet odstotkov, smo linearno povezavo parametrov sicer komentirali, vendar je odvisnost parametrov skoraj zanemarljiva. Diskretne oz. kvalitativne parametre smo med seboj primerjali s hi-kvadrat testom.

6.1 Parametri za opis rane

Najmočnejšo medsebojno odvisnost smo našli med površino rane in obsegom rane (tabela 6.1). Iz te povezave lahko sklepamo, da se rane po obliki niso močno razlikovale. Pričakovana je bila močna linearna povezava med začetno stopnjo rane in začetno globino rane. Z večjo stopnjo smo namreč označili globlje in večje rane. Zato je stopnja rane rahlo odvisna tudi od površine in obsega rane. Rahlo linearno povezavo najdemo tudi med globino rane in površino ter globino in obsegom rane. Ker je bil obseg rane tako močno odvisen od površine, ga v nadaljnjih analizah nismo več upoštevali. Globina rane je bila močno odvisna od stopnje rane. Ker je bila globina rane izmerjena le v 43% primerov, stopnja rane pa je znana v 94% primerov, globine rane v nadaljnjih analizah nismo več upoštevali.

Tabela 6.1 *Medsebojna odvisnost med hitrostjo celjenja in parametri za opis velikosti rane. Podani so Spearmanovi korelacijski koeficienti in tveganje pri zaključku, da sta parametra medsebojno odvisna.*

		površina	obseg	globina	stopnja	razmerje diagonal	čas celjenja	hitrost celjenja
površina	*rs*	1,000						
	p	<0,001						
	n	300						
obseg	*rs*	0,969	1,000					
	p	<0,001	<0,001					
	n	300	300					
globina	*rs*	0,364	0,327	1,000				
	p	<0,001	<0,001	<0,001				
	n	132	132	132				
stopnja	*rs*	0,343	0,355	0,639	1,000			
	p	<0,001	<0,001	<0,001	<0,001			
	n	281	281	128	281			
razmerje diagonal	*rs*	0,260	0,106	0,214	0,053	1,000		
	p	<0,001	0,068	0,014	0,379	<0,001		
	n	300	300	132	281	300		
čas celjenja	*rs*	0,357	0,348	0,347	0,226	0,122	1,000	
	p	<0,001	<0,001	<0,001	<0,001	0,035	<0,001	
	n	300	300	132	281	300	300	
hitrost celjenja	*rs*	0,105	0,062	-0,185	-0,237	0,106	-0,385	1,000
	p	0,068	0,284	0,035	<0,001	0,066	<0,001	<0,001
	n	300	300	132	281	300	300	300

Čas celjenja je po pričakovanju odvisen od velikosti rane. Večje rane se dlje celijo. Izbrana mera hitrosti celjenja (35) pa je neodvisna od velikosti rane (površina in obseg). Iz rahle medsebojne odvisnosti stopnje rane in hitrosti celjenja je razvidno, da se rane z višjo stopnjo celijo počasneje. Našli smo tudi statistično značilno linearno povezavo med velikostjo rane (površina, obseg, globina in stopnja) in časom celjenja. Večje rane se dalj časa celijo. Ker pa se rane, ki se dalj časa celijo, celijo tudi značilno počasneje, smo našli posredno povezavo med velikostjo rane in hitrostjo celjenja. Čeprav neposredne medsebojne odvisnosti površine in hitrosti celjenja ni, nam povezava med površino in časom celjenja govori o tem, da so se večje rane verjetno počasneje celile.

Ostali parametri za opis rane, ki jih najdemo v podatkovni bazi, so vrsta rane in lokacija, ki sta kvalitativna parametra, ter čas od poškodbe hrbtenjače do nastanka rane in čas od nastanka rane do začetka zdravljenja, ki sta kvantitativna parametra.

V tabeli 6.2 smo podali medsebojno odvisnost časa od poškodbe hrbtenjače do nastanka rane (podan le za bolnike s poškodbo hrbtenjače), časa od nastanka rane do začetka zdravljenja, parametrov za opis velikosti rane in mere hitrosti celjenja. Med parametri nismo našli močnih medsebojnih odvisnosti, najbolj zanimiva in smiselna pa je povezava med hitrostjo celjenja in časom od nastanka rane do začetka zdravljenja. Povezava sledi iz medsebojne odvisnosti stopnje rane in časa od nastanka rane do začetka zdravljenja. Dalj časa, ko rana ni bila ustrezno negovana, globlja (višje stopnje) je bila. Rane višje stopnje pa se počasneje celijo. Zato je tudi povezava med hitrostjo celjenja in časom od nastanka do začetka zdravljenja rane negativna, kar naj bi pomenilo, da dalj časa, ko rane ne bomo začeli ustrezno zdraviti, počasneje se bo celila.

Tabela 6.2 *Medsebojna odvisnost časovnih intervalov in parametrov, ki opisujejo velikost rane ter hitrostjo celjenja. Podani so Spearmanovi korelacijski koeficienti (rs) in tveganje (p) pri zaključku, da sta parametra medsebojno odvisna*.

		čas od poškodbe hrbtenjače do nastanka rane	čas od nastanka rane do začetka zdravljenja
čas od poškodbe hrbtenjače do nastanka rane	*rs*	1,000	
	p	<0,001	
	n	178	
čas od nastanka rane do začetka zdravljenja	*rs*	-0,099	1,000
	p	0,188	<0,001
	n	178	243
površina	*rs*	-0,261	0,087
	p	<0,001	0,176
	n	178	243
stopnja	*rs*	-0,121	0,181
	p	0,108	0,005
	n	177	242
razmerje diagonal	*rs*	0,032	0,078
	p	0,673	0,223
	n	178	243
čas celjenja	*rs*	0,053	0,132
	p	0,479	0,039
	n	178	243
hitrost celjenja	*rs*	-0,086	-0,215
	p	0,254	<0,001
	n	178	243

Dlje časa, ko je minilo od poškodbe hrbtenjače do nastanka rane, manjša je ta bila ob začetku zdravljenja. Nastanek rane je definiran kot dan, ko je bolnik ali njegov negovalec rano opazil. Bolnik je ta podatek podal v pristopni izjavi k študiji, pri tem pa se zavedamo, da je rana lahko nastala že prej in da je podatek v nekaterih primerih le približno točen. Vzrok za omenjeno povezavo je morda v večji izurjenosti bolnika po daljšem času od poškodbe pri negi in opazovanju telesa. Zato so verjetno ti bolniki preležanino tudi prej opazili, ko je bila rana še majhna.

Za določitev razlik v porazdelitvi parametrov ran glede na določen kvalitativni parameter smo uporabili Kruskal-Wallisov enosmerni test variance. Če smo našli razlike v porazdelitvah

glede na kvalitativni parameter, smo uporabili Kolmogorov-Smirnov test s katerim smo primerjali porazdelitve pri posameznih vrednostih kvalitativnega parametra. Za razlikovanje testov smo rezultate tega testa podali na dve decimalni mesti natančno, rezultate Kruskal-Wallisovega testa pa na tri. Za testiranje medsebojnih odvisnosti kvalitativnih parametrov smo uporabili test hi-kvadrat. Parametra smo obravnavali kot statistično značilno medsebojno odvisna, pri $p<0,05$.

Tabela 6.3 *Statistična analiza parametrov glede na lokacijo rane*.

	skupaj n=300 (100,0)	zadnjica n=32 (8,0)	križnica n=93 (31,0)	trohanter n=58 (19,3)	ostalo[a] n=110 (36,7)	p
starost* (*leto*)	n=296 41 (28–59)	n=32 57 (39–82)	n=92 37 (28–49)	n=57 35 (23–49)	n=108 51 (30–61)	<0,001
čas od poškodbe hrbtenjače do nastanka rane* (*mesec*)	n=178 5 (2–38)	n=22 4 (2–197)	n=63 4 (2–11)	n=37 11 (4–69)	n=56 5 (1–60)	0,167
čas od nastanka rane do začetka zdravljenja* (*teden*)	n=243 8 (3–18)	n=30 4 (2–13)	n=72 9 (3–16)	n=42 11 (4–29)	n=99 8 (4–18)	0,066
površina* (mm^2)	n=300 634 (308–1871)	n=32 684 (370–1249)	n=93 1012 (518–2714)	n=58 1018 (382–2721)	n=110 393 (231–678)	<0,001
razmerje diagonal*	n=300 0,71 (0,55–0,83)	n=32 0,74 (0,65–0,87)	n=93 0,71 (0,53–0,86)	n=58 0,72 (0,61–0,86)	n=110 0,67 (0,46–0,80)	0,093
število ran*	2 (1–3)	1 (1–2)	1 (1–2)	2 (2–3)	2 (1–3)	<0,001
stopnja[#] (*n*(%))						0,236
I	24 (8,0)	3 (9,4)	5 (5,4)	4 (6,9)	12 (10,1)	
II	138 (46,0)	17 (53,1)	34 (36,6)	31 (53,4)	56 (10,9)	
II	87 (29,0)	8 (25,0)	36 (38,7)	14 (24,1)	29 (26,4)	
IV	32 (10,7)	4 (12,5)	14 (15,1)	5 (8,6)	9 (8,2)	
vrsta rane[¤] (*n*(%))						---
preležanina	248 (82,7)	30 (93,8)	93 (100,0)	58 (100,0)	60 (54,5)	
arterijska razjeda	3 (1,0)	1 (3,1)	0 (0,0)	0 (0,0)	2 (1,8)	
venska razjeda	11 (3,7)	0 (0,0)	0 (0,0)	0 (0,0)	11 (10,0)	
nevrogena razjeda	19 (6,4)	0 (0,0)	0 (0,0)	0 (0,0)	19 (17,3)	
travmatska razjeda	18 (6,0)	1 (3,1)	0 (0,0)	0 (0,0)	17 (15,4)	
diagnoza[¤] (*n*(%))						---
poškodba hrbtenjače	215 (71,7)	15 (46,9)	86 (92,5)	53 (91,4)	54 (49,1)	
starostna oslabelost	10 (3,3)	5 (15,6)	1 (1,1)	0 (0,0)	4 (3,6)	
multipla skleroza	9 (3,0)	2 (6,3)	3 (3,2)	3 (5,2)	1 (0,9)	
sladkorna bolezen	22 (7,3)	0 (0,0)	0 (0,0)	1 (1,7)	21 (19,1)	
venska insuficienca	9 (3,0)	1 (3,1)	1 (1,1)	0 (0,0)	7 (6,4)	
poškodba	34 (11,3)	9 (28,1)	2 (2,1)	1 (1,7)	22 (20,0)	
čas dnevne stimulacije[#] (0, 30, 60, 120 *minut*)	n=300 120 (30–120)	n=23 90 (30–120)	n=93 120 (30–120)	n=58 120 (30–120)	n=110 120 (30–120)	0,929
čas celjenja* (*dan*)	n=276 63 (37–137)	n=32 54 (36–105)	n=93 84 (36–157)	n=58 109 (45–279)	n=110 54 (34–92)	0,003
hitrost celjenja* (*mm*/*dan*)	n=300 0,176 (0,090–0,315)	n=32 0,234 (0,111–0,423)	n=93 0,223 (0,131–0,372)	n=58 0,115 (0,024–0,259)	n=110 0,175 (0,097–0,302)	0,004

[a] stopalo (15), peta (25), koleno (7), noga (19), gleženj (2), rama (5), amputacijski krn (34), in sednica (3).
Vrednosti parametrov so podane v obliki *n* (*%*) ali mediana (25%–75% področje). Odstotki so izračunani glede na število vseh ran vključenih v študijo (300).
Vrste parametrov: *zvezni (kvantitativni), [#]ordinalni in [¤]nominalni (kvalitativni).
Hi-kvadrat test v primeru vrste rane in diagnoze ni bil izvedljiv.

V tabeli 6.3 so podani rezultati primerjave parametrov ran, bolnika in zdravljenja glede na lokacijo rane. Rane so se glede na lokacijo celile z značilno različno hitrostjo (p=0,004). Rane

na trohanterju so se celile značilno (p<0,03) počasneje od ran na ostalih lokacijah. Med ostalimi lokacijami nismo našli značilnih razlik v hitrosti celjenja (p>0,06). Rane na lokacijah trohanter, zadnjica in križnica so značilno večje (p<0,001) od ran na ostalih lokacijah.

Rane na lokacijah trohanter, zadnjica in križnica so bile vse po etiologiji preležanine. Druge vrste ran se v podatkovni bazi pojavljajo redkeje (tabela 6.4). Hitrost celjenja ran je neodvisna od vrste ran (p=0,236). Venske razjede so bile značilno kasneje vključene v študijo kot ostale rane. Preležanine so imele v povprečju večjo površino kot druge rane, čeprav je razlika značilna le pri travmatskih in nevrogenih razjedah. Sklepali smo, da bi se venske in arterijske razjede prav tako značilno razlikovale po velikosti od preležanin, če bi imeli več primerov teh ran. Nevrogene razjede se zaradi anatomskih okoliščin, kjer se pojavljajo pogosteje podolgovate oblike. Ker so bile nevrogene razjede v povprečju zgodaj ugotovljene in zaradi lokacij na katerih se pojavljajo ne morejo biti velike, so bile ob začetku zdravljenja manjših velikosti, kar je razlog za navidez nepričakovano medsebojno odvisnost velikosti rane in njene oblike.

Tabela 6.4 *Statistična analiza parametrov glede na vrsto rane*.

	preležanina n=248 (82,8)	arterijska razjeda n=3 (1,0)	venska razjeda n=11 (3,7)	nevrogena razjeda n=19 (6,4)	travmatska razjeda n=18 (6,0)	p
starost* (*leto*)	n=245 38 (27–53)	n=3 41 (27–59)	n=11 72 (57–73)	n=19 64 (58–71)	n=18 31 (23–41)	<0,001
čas od poškodbe hrbtenjače do nastanka rane* (*mesec*)	n=178 5 (2–38)	---	---	---	---	---
čas od nastanka rane do začetka zdravljenja* (*teden*)	n=193 8 (3–18)	n=2 1 (0–2)	n=11 52 (9–601)	n=19 5 (4–11)	n=18 7 (5–10)	0,014
površina* (mm^2)	n=248 687 (362–2160)	n=3 393 (245–480)	n=11 534 (224–714)	n=19 371 (251–603)	n=18 346 (264–643)	0,003
razmerje diagonal*	n=248 0,72 (0,58–0,86)	n=3 0,50 (0,43–0,73)	n=11 0,70 (0,63–0,75)	n=19 0,27 (0,20–0,69)	n=18 0,57 (0,31–0,78)	<0,001
število ran*	n=206 2 (1–3)	n=3 1 (1–1)	n=10 2 (1–2)	n=19 1 (1–2)	n=17 2 (1–2)	0,096
stopnja# (*n*(%))						0,117
I	23 (9,3)	1 (33,3)	0 (0,0)	0 (0,0)	0 (0,0)	
II	109 (44,0)	1 (33,3)	3 (27,3)	11 (57,9)	14 (77,8)	
II	69 (27,8)	1 (33,3)	6 (54,5)	7 (36,8)	4 (22,2)	
IV	29 (11,7)	0 (0,0)	2 (18,2)	1 (5,3)	0 (0,0)	
diagnoza¤ (*n*(%))						<0,001
poškodba hrbtenjače	212 (85,5)	2 (66,7)	0 (0,0)	0 (0,0)	1 (5,6)	
starostna oslabelost	8 (3,2)	0 (0,0)	2 (18,2)	0 (0,0)	0 (0,0)	
multipla skleroza	9 (3,6)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	
sladkorna bolezen	1 (0,0)	0 (0,0)	2 (18,2)	19 (100,0)	0 (0,0)	
venska insuficienca	2 (0,0)	0 (0,0)	7 (63,6)	0 (0,0)	0 (0,0)	
poškodba	16 (6,5)	1 (33,3)	0 (0,0)	0 (0,0)	17 (94,4)	
čas dnevne stimulacije# (0, 30, 60, 120 *minut*)	n=248 120 (30–120)	n=3 30 (30–98)	n=11 120 (30–120)	n=19 120 (75–120)	n=18 60 (30–120)	0,319
čas celjenja* (*dan*)	n=226 74 (38–149)	n=3 31 (19–57)	n=10 59 (25–173)	n=18 59 (37–111)	n=18 45 (25–173)	0,111
hitrost celjenja* (*mm*/*dan*)	n=248 0,180 (0,090–0,319)	n=3 0,216 (0,180–0,668)	n=11 0,158 (0,097–0,313)	n=19 0,100 (0,087–0,186)	n=18 0,204 (0,150–0,348)	0,236

Vrednosti parametrov so podane v obliki *n* (*%*) ali mediana (25%–75% področje). Odstotki so izračunani glede na število vseh ran vključenih v študijo (300).
Vrste parametrov: *zvezni (kvantitativni), #ordinalni in ¤nominalni (kvalitativni).

6.2 Parametri za opis bolnika

Parametri za opis bolnikov zbrani v podatkovni bazi so starost, število ran, diagnoza in stopnja spastičnosti, če gre za bolnika z okvaro hrbtenjače. V številu ran bolnika so zajete vse rane, ki jih je bolnik imel pred vključitvijo v študijo. Bolniki z ranami na lokacijah križnica in trohanter so bili značilno ($p<0,01$) mlajši od bolnikov z ranami na ostalih lokacijah. Vzrok je v neenakomerni porazdelitvi lokacij glede na vrsto rane. Na trohanterju in križnici so se pojavile le preležanine. Bolniki s preležaninami so večinoma bolniki s poškodbo hrbtenjače, ti pa so v povprečju mladi. Zato smo našli razliko tudi med starostjo bolnikov in lokacijami ran (tabela 6.5). Skupno število ran, ne glede na lokacijo, ki jih je imel bolnik z rano na trohanterju, je značilno večje ($p<0,02$) kot pri bolnikih z rano na drugih mestih. Ugotovili smo, da število ran ne vpliva na hitrost celjenja, zato se zaradi večjega števila ran, ki jih ima bolnik, rane na trohanterju ne celijo počasneje. Stopnja spastičnosti ni linearno odvisna od hitrosti celjenja ran, obstaja pa šibka linearna odvisnost med stopnjo spastičnosti in časom od poškodbe hrbtenjače do nastanka rane. Spastičnost nastopi nekaj tednov po poškodbi hrbtenjače. V obdobju spastičnosti je zaradi prizadetosti avtonomnega živčevja koža slabo prekrvljena, suha, hitro lahko nastopijo trofične spremembe in hitro lahko nastanejo preležanine.

Tabela 6.5 *Primerjava starosti, števila ran in spastičnosti bolnika s parametri, ki opisujejo velikost rane in hitrost celjenja. Podani so Spearmanovi korelacijski koeficienti in tveganje pri zaključku, da sta parametra medsebojno odvisna*.

		starost	število ran	stopnja spastičnosti
starost	*rs*	1,000		
	p	<0,001		
	n	296		
število ran	*rs*	-0,021	1,000	
	p	0,736	<0,001	
	n	255	255	
stopnja spastičnosti	*rs*	-0,152	0,010	1,000
	p	0,012	0,873	<0,001
	n	273	250	273
čas od poškodbe hrbtenjače do nastanka rane	*rs*	-0,034	0,081	0,320
	p	0,657	0,300	<0,001
	n	178	164	171
čas od nastanka rane do začetka zdravljenja	*rs*	-0,030	0,102	0,098
	p	0,640	0,127	0,136
	n	243	224	234
površina	*rs*	-0,067	0,057	0,127
	p	0,252	0,362	0,036
	n	296	255	273
stopnja	*rs*	-0,072	-0,097	0,054
	p	0,232	0,131	0,384
	n	278	246	260
razmerje diagonal	*rs*	-0,095	0,101	0,076
	p	0,102	0,109	0,209
	n	296	255	273
čas celjenja	*rs*	-0,006	0,067	0,196
	p	0,925	0,310	0,002
	n	272	233	250
hitrost celjenja	*rs*	-0,001	-0,078	-0,090
	p	0,982	0,215	0,138
	n	296	255	273

Bolniki z diagnozo starostna oslabelost (77 (72–88) let), sladkorna bolezen (68 (60–77) let) in venska insuficienca (63 (54–72) let) so bili značilno ($p<0,001$) starejši od bolnikov z diagnozami: poškodba hrbtenjače (36 (26–51) let), multipla skleroza (41 (33–52) let) in poškodba (43 (25–74) let). Bolniki z venskimi razjedami in nevrogenimi razjedami so bili značilno ($p<0,01$) starejši od bolnikov z drugimi vrstami kroničnih ran, kar se sklada z ugotovitvami diagnoze. Venske razjede so bile odkrite značilno pozneje od drugih vrst kroničnih ran. Verjetno je razlog v tem, da so to stari bolniki, ki tudi zaradi mesta rane, niso takoj poiskali ustrezne pomoči, ali pa niso bili takoj sprejeti v bolnišnično oskrbo. Rane starostno oslabelih bolnikov (0,271 mm/dan) in bolnikov, katerih rana je posledica mehanske poškodbe ali amputacije uda (0,224 mm/dan), so se celile značilno ($p=0,005$) hitreje kot rane bolnikov z drugačno diagnozo: poškodba hrbtenjače (0,173 mm/dan), venska insuficienca (0,171 mm/dan) in sladkorna bolezen (0,102 mm/dan). Vzrok je lahko v tem, da ran bolnikov z diagnozo starostna oslabelost in poškodba skoraj ne najdemo na trohanterju, kjer smo ugotovili, da se rane celijo najpočasneje. Prav tako pa ti bolniki nimajo motenega krvnega obtoka, kar je lahko zopet vzrok za hitrejše celjenje. Najpogostejša diagnoza bolnikov je bila poškodba hrbtenjače (71,7%), sledi poškodba v 11,3% primerov in sladkorna bolezen v 7,3% primerov. Diagnoze starostna oslabelost (3,3%), multipla skleroza (3%) in venska insuficienca so bile statistično zanemarljivo zastopane v podatkovni bazi. Zaradi tako nehomogene učne množice, iskanje medsebojnih odvisnosti diagnoze bolnika in ostalih parametrov, ki opisujejo rano in bolnika, hitro zavede v napačne zaključke. Ker je bila medsebojna odvisnost diagnoze in vrste rane statistično značilna ($p<0,001$), smo diagnozo iz nadaljnje analize izpustili.

6.3 Parametri za opis zdravljenja

Zdravljenje je v podatkovni bazi opisano z načinom zdravljenja in s trajanjem dnevne stimulacije. Načini zdravljenja so že opisani: AC – stimulacija z izmeničnim električnim tokom, DC – stimulacija z enosmernim električnim tokom, CO – konzervativni način zdravljenja, SH – rane z nameščenimi neaktivnimi elektrodami za študijo placeba. V tabeli 6.6 so predstavljene porazdelitve parametrov ran, bolnika in hitrosti celjenja za naštete načine zdravljenja.

Skupina ran stimulirana z enosmernim električnim tokom ni bila homogena. Elektrode so bile postavljene ali s pozitivno neposredno na rani in negativno na zdravi koži ob rani ali pa sta bili obe elektrodi postavljeni na zdravo kožo ob rani. V študiji primerjave vpliva postavitve elektrod na hitrost celjenja preležanin so ugotovili [Karba *et al.*, 1997], da je celjenje ran s postavitvijo pozitivne elektrode neposredno na rano hitrejše, ker bolje vzpostavlja endogene razmere na robu rane. Ker so druge skupine [Barker *et al.*, 1982] poročale o pozitivnih učinkih električne stimulacije tudi v primerih, ko sta elektrodi postavljeni na zdravi koži ob robu rane ali pri menjavanju polaritete elektrode nameščene neposredno na rani [Wolcott *et al.*, 1969], in ker je bilo število ran stimuliranih z enosmernim električnim tokom majhno, smo skupini ran združili in tako zagotovili dovolj veliko množico in splošnost podatkov.

Tabela 6.6 *Statistična analiza parametrov glede na način zdravljenja*.

	skupaj n=300	AC n=181	DC n=42	CO n=54	SH n=23	p
starost* (*leto*)	n=296 41 (28–59)	n=178 43 (30–62)	n=42 43 (25–59)	n=54 39 (23–51)	n=23 37 (23–57)	0,053
čas od poškodbe hrbtenjače do nastanka rane* (*mesec*)	n=178 5 (2–38)	n=94 11 (3–69)	n=27 3 (1–4)	n=42 3 (1–10)	n=15 6 (4–24)	<0,001
čas od nastanka rane do začetka zdravljenja* (*teden*)	n=243 8 (3–18)	n=150 7 (3–17)	n=33 6 (4–12)	n=44 13 (4–22)	n=16 8 (2–14)	0,247
površina* (mm^2)	n=300 634 (308–1871)	n=181 566 (283–1539)	n=42 660 (346–2108)	n=54 797 (432–2160)	n=23 661 (289–1180)	0,359
razmerje diagonal*	n=300 0,71 (0,55–0,83)	n=181 0,71 (0,54–0,81)	n=42 0,71 (0,50–0,90)	n=54 0,69 (0,57–0,86)	n=23 0,70 (0,52–0,82)	0,983
število ran*	2 (1–3)	2 (1–2)	1 (1–2)	2 (1–3)	2 (1–2)	0,071
stopnja spastičnosti# (*n*(%))						0,628
0	207 (69,0)	126 (69,6)	27 (64,3)	37 (68,5)	17 (73,9)	
1	29 (9,7)	13 (7,2)	6 (14,3)	7 (13,0)	3 (13,0)	
2	21 (7,0)	12 (6,6)	4 (9,5)	3 (5,6)	2 (8,7)	
3	16 (5,3)	13 (7,2)	1 (2,4)	2 (3,7)	0 (0,0)	
stopnja# (*n*(%))						0,254
I	24 (8,0)	10 (5,5)	3 (7,1)	9 (16,7)	2 (8,7)	
II	138 (46,0)	92 (50,8)	13 (31,0)	23 (42,6)	10 (43,5)	
II	87 (29,0)	52 (28,7)	17 (40,5)	11 (20,4)	7 (30,4)	
IV	32 (10,7)	19 (10,5)	4 (9,5)	6 (11,1)	3 (13,0)	
lokacija¤ (*n*(%))						0,012
zadnjica	32 (10,7)	21 (11,6)	7 (16,7)	3 (5,5)	1 (4,3)	
križnica	93 (31,0)	44 (24,3)	19 (45,2)	22 (40,7)	8 (34,8)	
trohanter	58 (19,3)	34 (18,8)	5 (11,9)	13 (24,1)	6 (26,1)	
ostalo[a]	110 (36,7)	80 (44,2)	11 (26,2)	11 (20,4)	8 (34,8)	
vrsta rane¤ (*n*(%))						---
preležanina	248 (82,7)	136 (75,1)	35 (83,3)	54 (100,0)	23 (100,0)	
arterijska razjeda	3 (1,0)	3 (1,7)	0 (0,0)	0 (0,0)	0 (0,0)	
venska razjeda	11 (3,7)	11 (6,1)	0 (0,0)	0 (0,0)	0 (0,0)	
nevrogena razjeda	19 (6,4)	16 (8,8)	3 (7,1)	0 (0,0)	0 (0,0)	
travmatska razjeda	18 (6,0)	15 (8,3)	3 (7,1)	0 (0,0)	0 (0,0)	
diagnoza¤ (*n*(%))						---
poškodba hrbtenjače	215 (71,7)	111 (61,3)	28 (66,7)	54 (100,0)	22 (95,7)	
starostna oslabelost	10 (3,3)	10 (5,5)	0 (0,0)	0 (0,0)	0 (0,0)	
multipla skleroza	9 (3,0)	5 (2,8)	4 (9,5)	0 (0,0)	0 (0,0)	
sladkorna bolezen	22 (7,3)	18 (9,9)	3 (7,1)	0 (0,0)	1 (4,3)	
venska insuficienca	9 (3,0)	9 (5,0)	0 (0,0)	0 (0,0)	0 (0,0)	
poškodba	34 (11,3)	28 (15,5)	6 (14,3)	0 (0,0)	0 (0,0)	
čas dnevne stimulacije#						<0,001
0 (*minut*)	54 (18,0)	0 (0,0)	0 (0,0)	54 (100,0)	0 (0,0)	
30	53 (17,7)	51 (28,2)	2 (4,8)	0 (0,0)	0 (0,0)	
60	18 (6,0)	13 (7,2)	5 (11,9)	0 (0,0)	0 (0,0)	
120	175 (57,3)	117 (64,6)	35 (83,3)	0 (0,0)	23 (100,0)	
čas celjenja* (*dan*)	n=276 63 (37–137)	n=178 63 (36–132)	n=40 64 (37–132)	n=42 83 (45–177)	n=16 64 (36–123)	0,631
hitrost celjenja* (*mm/dan*)	n=300 0,176 (0,090–0,315)	n=181 0,190 (0,114–0,328)	n=42 0,168 (0,089–0,434)	n=54 0,145 (0,026–0,261)	n=23 0,162 (-0,046–0,205)	0,007

[a] stopalo (15), peta (25), koleno (7), noga (19), gleženj (2), rama (5), amputacijski krn (34), in sednica (3). Vrednosti parametrov so podane v obliki *n* (*%*) ali mediana (25%–75% področje). Odstotki so izračunani glede na število vseh ran vključenih v študijo (300).
Vrste parametrov: *zvezni (kvantitativni), #ordinalni in ¤nominalni (kvalitativni).
Hi-kvadrat test v primeru vrste rane in diagnoze ni bil izvedljiv.

Čas od poškodbe hrbtenjače do nastanka rane je statistično značilno ($p<0,001$) krajši v kontrolni skupini ran in skupini stimuliranih ran z enosmernim električnim tokom. Čas je koreliran le s stopnjo spastičnosti in z nobenim drugim parametrom ali mero hitrosti celjenja. Zato nenaključna delitev ran v štiri skupine zdravljenja, glede na čas od poškodbe hrbtenjače do nastanka rane, ne vpliva na zaključke o učinkovitosti različnih načinov zdravljenja.

Rane na križnici in trohanterju so bile statistično značilno ($p=0,03$) pogosteje vključene v konzervativno zdravljeno skupino ali skupino ran zdravljenih s placebom kot rane iz drugih lokacij. Primerjali smo hitrosti celjenja ran na trohanterju glede na različne načine zdravljenja. Rane stimulirane z izmeničnim električnim tokom ($n=34$) so se celile statistično značilno ($p=0,05$) hitreje kot rane zdravljene konzervativno ($n=13$) in tudi značilno ($p=0,03$) hitreje od ran zdravljenih s placebom (n=6). Zdravljenje z enosmernim električnim tokom se ni značilno razlikovalo od ostalih. Rane na križnici so se značilno ($p=0,04$) hitreje celile, če so bile stimulirane z izmeničnim električnim tokom ($n=44$) kot v primeru konzervativnega zdravljenja ($n=22$). Drugih razlik v hitrosti celjenja nismo našli. Verjetno tudi zato, ker je bila skupina zdravljena s placebom maloštevilna ($n=8$). Ker se električno stimulirane rane celijo hitreje od nestimuliranih, nam to razloži nepojasnjeno dejstvo, da so se rane na trohanterju in križnici celile značilno počasneje kot rane na drugih lokacijah. V kontrolno skupino in skupino študije placeba so bile vključene le preležanine. Preležanine so edina vrsta ran, ki je znatno prisotna v vseh skupinah. Vse vrste ran so prisotne le v skupini ran stimuliranih z izmeničnim električnim tokom. Po primerjanju hitrosti celjenja različnih vrst ran v tej skupini smo ugotovili, da se hitrosti celjenja ne razlikujejo značilno ($p=0,13$). Zaključili smo, da hitrost celjenja ni odvisna od vrste rane.

Čas zacelitve ran se ne razlikuje značilno pri naštetih načinih zdravljenja. Vzrok temu je, da v tej primerjavi niso upoštevane rane, ki se niso celile. Takšnih je bilo v CO skupini 22%, v SH skupini 30%, v DC 5% in v AC skupini le 2%. Že te številke govorijo o uspešnosti električne stimulacije. Neceleče rane so vključene v izračun mere hitrosti celjenja, rezultate pa smo že podali v tabeli 5.1.

Če obravnavamo le rane, ki so imele nameščene elektrode dve uri dnevno, so se rane stimulirane z izmeničnim električnim tokom celile značilno ($p=0,02$) hitreje (0,166 mm/dan (0,097–0,328)) od ran z nameščenimi neaktivnimi elektrodami (0,162 mm/dan (-0,046–0,205)) in enako hitro ($p=0,17$) kot rane stimulirane z enosmernim električnim tokom (0,217 mm/dan (0,098–0,450)). Rane stimulirane z enosmernim električnim tokom so se celile hitreje, vendar ne značilno ($p=0,09$), od ran z nameščenimi neaktivnimi elektrodami.

Le eno uro z enosmernim tokom stimulirane rane so se celile ($p=0,07$) počasneje (0,090 mm/dan (0,089–0,120)) kot dve uri stimulirane in značilno počasneje ($p<0,01$) kot eno uro stimulirane rane z izmeničnim električnim tokom (0,260 mm/dan (0,190–0,460)). Eno uro dnevno stimulirane rane z izmeničnim električnim tokom so se celile značilno ($p=0,02$) hitreje kot dve uri stimulirane in hitreje ($p=0,36$) kot pol ure stimulirane rane z izmeničnim električnim tokom (0,207 mm/dan (0,152–0,309)). Pol ure z izmeničnim tokom stimulirane rane so se celile enako hitro ($p=0,06$) kot dve uri stimulirane rane. Zaradi majhnega števila primerov ran stimuliranih eno uro dnevno (n=13) ne moremo zaključiti, da je enourna stimulacija optimalna. Prav tako bi tudi za optimizacijo časa dnevne stimulacije z enosmernim električnim tokom potrebovali večjo homogeno skupino ran vključenih v študijo.

6.4 Določitev vpliva parametrov na hitrost celjenja z metodami strojnega učenja

Iz zgoraj podanih analiz medsebojnih odvisnosti in porazdelitev parametrov, ki opisujejo rane in pacienta ob začetku zdravljenja, je razvidno, da našteti parametri niso linearno in neposredno povezani z mero hitrosti celjenja kroničnih ran. Med parametri pa lahko obstajajo nelinearne povezave, ki jih s klasičnimi statističnimi pristopi ne moremo najti. Z avtomatsko gradnjo baze znanja z algoritmi za induktivno učenje lahko najdemo povezave, ki sicer niso očitne.

Tabela 6.7 *Vplivnost parametrov za opis rane in bolnika na hitrost celjenja. Vplivnost parametra je večja, če je njegov delež pri razlagi koncepta večji.*

	delež razloženega koncepta v tednu						
parameter	0	1	2	3	4	5	6
površina (mm^2)	0,135	0,168	0,171	0,161	0,127	0,123	0,122
starost (leto)	0,123	0,114	0,094	0,095	0,096	0,092	0,094
nastanek do zdravljenje (teden)	0,119	0,121	0,104	0,131	0,121	0,114	0,115
razmerje diagonal	0,096	0,098	0,099	0,095	0,103	0,108	0,113
lokacija	0,085	0,084	0,085	0,081	0,081	0,081	0,081
način zdravljenja	0,066	0,058	0,051	0,052	0,050	0,051	0,051
poškodba do nastanek (mesec)	0,062	0,065	0,044	0,050	0,035	0,040	0,039
čas stimuliranja (minuta)	0,046	0,039	0,031	0,035	0,025	0,025	0,026
stopnja	0,046	0,039	0,057	0,048	0,048	0,047	0,043
diagnoza	0,039	0,039	0,038	0,038	0,038	0,038	0,037
vrsta rane	0,027	0,025	0,026	0,024	0,024	0,0239	0,024
ocena hitrosti celjenja iz modela	0,000	0,399	0,602	0,626	0,663	0,659	0,670

poškodba do nastanek: čas od poškodbe hrbtenjače do nastanka rane (*mesec*)
nastanek do zdravljenje: čas od nastanka rane do začetka zdravljenja (*teden*)

Z algoritmom RReliefF [Robnik-Šikonja in Kononenko, 1997] smo ocenili vplivnost parametrov na hitrost celjenja ran. Algoritem RReliefF oceni parametrovo moč deljenja preiskovanega prostora glede na to, kako dobro vrednosti parametra razlikujejo podobne primere iz učne množice. RReliefF temelji na dejstvu, da je posebej težko razlikovati primere, ki so si podobni, torej blizu skupaj. Če sta si primera blizu, vendar spadata v različen razred, posebej cenimo parametre, ki imajo v takšnih primerih različne vrednosti. Takšni parametri nam pomagajo, da ju bomo, kljub njuni bližini, razlikovali. Po drugi strani ne želimo, da imajo parametri različne vrednosti pri primerih iz istega razreda; če jih imajo, jim to štejemo v slabost. Parameter razloži večji delež koncepta, če loči podobne primere ran iz učne množice z različnimi hitrostmi celjenja in če ne loči podobnih primerov ran z enakimi hitrostmi celjenja. Uporabili smo 5 diskretnih in 6 zveznih parametrov. Ti so našteti v tabeli 6.7, stolpec teden nič, kjer so našteti po vrsti glede na njihovo vplivnost. Večji, ko je razloženi delež koncepta, večji vpliv ima parameter na hitrost celjenja rane. Če je delež razloženega koncepta negativen, parameter nima vpliva na hitrost celjenja. Na prvem mestu je površina rane. Sledi starost bolnika in čas od nastanka rane do začetka zdravljenja. Oblika rane in lokacija imata že manjši vpliv. Sledi pa način zdravljenja, ki po pričakovanju ni na prvem mestu.

7 Napovedovanje hitrosti celjenja ran

Celjenje kroničnih ran je običajno dolgotrajen proces. Zdravnik pa bi rad že vnaprej vedel, kako uspešen bo kateri od možnih načinov zdravljenja. Napovedovanje procesa celjenja je smiselno že ob samem začetku zdravljenja ali vsaj v zgodnji fazi zdravljenja. Ob negativnih pokazateljih uspešnosti celjenja je morda potreben bolj radikalen, na primer kirurški poseg. Vendar kirurško zdravljenje zahteva strogo postoperativno nego, ki traja tudi po več mesecev in pogosto zahteva strogo ležanje. V nekaterih primerih pa celo ni izvedljivo zaradi bolnikovega splošnega zdravja.

Tabela 7.1 *Primerjava napovedane hitrosti celjenja po i tednih opazovanja procesa celjenja in dejanske hitrosti celjenja (p vrednosti Wilcox-ovega neparametričnega testa)*.

	Θ
$\Theta_{1\ teden}$	<0,001
$\Theta_{2\ tedna}$	<0,001
$\Theta_{3\ tedni}$	0,028
$\Theta_{4\ tedni}$	0,199
$\Theta_{5\ tednov}$	0,405
$\Theta_{6\ tednov}$	0,508

Θ - dejanska hitrost celjenja rane
Θ_i - ocena hitrosti celjenja rane na osnovi i tedenskega opazovanja

Mero hitrosti celjenja ran smo definirali kot prirastek tkiva v milimetrih na dan. Izračunali smo jo iz zmnožka največjega prirastka tkiva in inverzne vrednosti časa celjenja. Če hočemo napovedati hitrost celjenja rane, še preden se ta zaceli, moramo najprej napovedati čas celjenja. V tabeli 4.1 smo podali rezultate napovedovanja časa celjenja rane na podlagi meritev površine rane v prvih treh do šestih tednih opazovanja procesa celjenja. Ugotovili smo, da je z zadostno natančnostjo možno čas celjenja napovedati že po štiri tedenskem opazovanju rane. Analizo smo ponovili z mero hitrosti celjenja, tokrat tudi za krajša obdobja opazovanja. Oceno hitrosti celjenja smo izračunali na osnovi eno do šest tedenskega opazovanja procesa celjenja. Upoštevali smo tedensko merjene diagonale rane in izračunali površino in obseg, iz njiju pa največji prirastek tkiva. Po prvem tednu opazovanja smo imeli opravljeni dve meritvi diagonal rane. V študiji dinamike celjenja kroničnih ran smo ugotovili, da je ta, po časovni zakasnitvi, ekponencialne narave. Zakasnjen eksponencialni model celjenja je tri parametričen in za izračun parametrov modela potrebujemo vsaj štiri tedenske

meritve površine rane oz. moramo proces celjenja opazovati vsaj tri tedne. Ugotovili smo že, da ima polovica v študijo vključenih ran zakasnitev celjenja manjšo od polovice tedna. Zato smo privzeli, da je za oceno hitrosti celjenja v krajšem času najboljši približek eksponencialni model brez zakasnitve. Za lažje računanje parametrov eksponencialnega modela smo logaritmirali izmerjene vrednosti površine in s prileganjem linearnega modela (36) izračunali parametre eksponencialnega modela.

$$\ln \hat{S}(t) = \ln S_{EXP} - \theta_{EXP} t \tag{36}$$

V enačbe (30, 31 in 32) smo vnesli vrednosti parametrov $S_{DEX}=S_{EXP}$, $\theta_{DEX}=\theta_{EXP}$ in $T_{DEX}=0$ in izračunali oceno časa do zacelitve rane. Iz enačbe (35) smo nato izračunali oceno hitrosti celjenja. Postopek smo ponovili za vseh tristo v študijo vključenih ran. Na tak način smo izračunali ocene hitrosti celjenja na podlagi enega in dveh tednov opazovanja procesa celjenja. Ocene hitrosti celjenja na podlagi treh, štirih, petih in šestih tednov opazovanja pa smo določili iz prileganja zakasnjenega eksponencialnega modela opravljenim meritvam površine. Pri tem smo si prav tako pomagali z logaritmiranjem površine in s tem problem prileganja prevedli na lomljen linearni problem (37).

$$\ln \hat{S}(t) = \begin{cases} \ln S_{DEX} - \theta_{DEX}\left(t - T_{DEX}\right) & ; \quad t \geq T_{DEX} \\ \ln S_{DEX} & ; \quad t < T_{DEX} \end{cases} \tag{37}$$

POGOJ: $T \geq 0$

Oceno hitrosti celjenja smo primerjali z dejansko hitrostjo celjenja, izračunano iz znanih časov celjenja (tabela 7.1). Za primerjavo smo uporabili neparametrični Wilcox-ov test. Ugotovili smo, da se ocena hitrosti celjenja rane statistično značilno ne razlikuje od dejanske po vsaj štiri tedenskem opazovanju procesa celjenja (t.j. po petih zaporednih tedenskih meritvah površine rane).

7.1 Uporaba metod strojnega učenja

Hitrost celjenja pa bi radi napovedali v krajšem času od štirih tednov. Za klinično uporabo bi bilo idealno napovedati hitrost celjenja že ob začetku zdravljenja ali pa vsaj v prvih tednih. Pri tem smo si pomagali z induktivnim strojnim učenjem. Algoritmi za strojno učenje se učijo povezav na rešenih primerih, ki obstajajo arhivirani v podatkovni bazi. Množico rešenih primerov imenujemo učna množica

$$\mathcal{L}=\{(x_1, \Theta_1),..., (x_N, \Theta_N)\},$$

kjer je (x_n, Θ_n) vektorski zapis primera rane (n = 1,...,N), x_n je vektor lastnosti rane, bolnika in načina zdravljenja, Θ_n je dejanska hitrost celjenja te rane in N je število primerov ran v učni množici (N=300).

Rezultat učenja iz učne množice primerov so pravila $d(x)$, ki jih lahko uporabimo za reševanje novih problemov z ekspertnim sistemom. Pravila lahko zapišemo v ljudem prijazni obliki drevesa. Zgradili smo odločitvena in regresijska drevesa z mediano v listih in regresijska

drevesa z linearnimi enačbami v listih za napovedovanje hitrosti celjenja kroničnih ran. Za gradnjo odločitvenih dreves smo uporabili algoritem ReliefF [Kononenko *et al.*, 1997b] in za gradnjo regresijskih dreves algoritem RReliefF [Robnik-Šikonja in Kononenko, 1997]. Drevesa smo gradili na osnovi lastnosti ran, bolnikov in načinov zdravljenja shranjenih v podatkovni bazi. Na podlagi opravljene analize vplivnosti teh lastnosti na hitrost celjenja ne pričakujemo velikih zanesljivosti dreves pri napovedovanju hitrosti celjenja že ob začetku zdravljenja. Zato smo skušali določiti minimalni čas opazovanja rane po katerem lahko zanesljivo napovemo čas do zacelitve rane. Petim diskretnim in šestim zveznim lastnostim ran, bolnikov in načina zdravljenja smo dodali še ocene hitrosti celjenja ran izračunane na podlagi enega, dveh, treh, štirih, petih ali šestih tednov opazovanja procesov celjenj. Zgradili smo drevesa brez in z upoštevanjem ocene hitrosti celjenja. Število primerov v listih dreves smo omejili na najmanj pet, drevesa pa smo z algoritmi rezanja še zmanjšali. Pri tem nismo izgubili na natančnosti razvrščanja, ampak le pridobili na razumljivosti.

7.1.1 Vrednotenje odločitvenih in regresijskih dreves

Znanje, ki smo ga tako pridobili, pa je bilo potrebno še preveriti in ovrednotiti. Zanesljivost razvrščanja odločitvenega drevesa smo določili z ocenjevanjem deleža pravilnih odgovorov na novih primerih, ki niso bili na voljo med učenjem. Interpretiramo jo lahko kot verjetnost, da bo naključno izbran primer pravilno razvrščen. Če bi imeli na voljo vse možne primere problema na danem področju (N), bi lahko izračunali točno napako razvrščanja $R^*(d)$. Ker pa je testna množica veliko manjša ($N << N^{ts}$), je izračunana klasifikacijska točnost le ocena $R^{ts}(d)$. Če je N^{ts} število vseh testnih primerov in $N^{ts(p)}$ število pravilno razvrščenih primerov, je ocena klasifikacijske točnosti (38).

$$R^{ts}(d) = \frac{N^{ts(p)}}{N^{ts}} \cdot 100\% \tag{38}$$

Pri regresijskih problemih zanesljivosti razvrščanja ne moremo uporabiti, ker imamo opravka z zveznimi funkcijami. Uporabili smo relativno srednjo kvadratno napako ali krajše kar relativno napako. Relativna napaka (RE) je mera točnosti regresijskega drevesa, izračunali pa smo jo na primerih iz testne množice $\mathcal{L}_{ts}$ [Breiman *et al.*, 1984]. Definirana je kot razmerje (42) srednje kvadratne napake (39) in povprečnega kvadrata razlike med dejansko hitrostjo celjenja in povprečno hitrostjo celjenja vseh primerov (41). Srednja kvadratna napaka je definirana kot povprečni kvadrat razlike med napovedano vrednostjo $d(x_i)$ in dejansko hitrostjo celjenja na testni množici primerov. Regresijsko drevo $d(x_i)$, s katerim napovedujemo hitrost celjenja, je ocena idealnega regresijskega drevesa.

$$R^{ts}\left(d\right) = \frac{1}{N_{ts}} \sum_{(x_i,\Theta_i)\in\mathcal{L}_{ts}} \left(\Theta_i - d\left(x_i\right)\right)^2 \tag{39}$$

$$\overline{\Theta} = \frac{1}{N}\sum_{i=1}^{N}\Theta_i \tag{40}$$

$$R\left(\overline{\Theta}\right) = \frac{1}{N}\sum_{i=1}^{N}\left(\Theta_i - \overline{\Theta}\right)^2 \tag{41}$$

$$RE^{ts}(d) = \frac{R^{ts}(d)}{R(\bar{\Theta})} \tag{42}$$

Relativna napaka je nenegativna in za sprejemljive hipoteze manjša od ena. Vrednost ena zavzame v trivialnem primeru, ko je regresijsko drevo za napovedovanje hitrosti celjenja kar enako povprečni vrednosti vseh primerov. Če je za neko regresijsko drevo $RE(d) > 1$, je le-to popolnoma neuporabno. Želimo čim manjšo relativno napako napovedovanja. Pomembno je tudi vedeti, da pravo vrednost relativne napake dobimo šele na neskončno veliki testni množici. Na končno veliki testni množici je izračunana relativna napaka le ocena. Nekateri avtorji podajajo vrednost $1 - RE^{ts}(d)$ in jo imenujejo delež razložene variance, čeprav $R(d)$ ni varianca. Čeprav je nesmiselno podajati delež razložene variance, smo jo poleg relativne napake navajali za lažjo primerjavo naših rezultatov z rezultati podobnih študij.

7.1.2 Prečno preverjanje

Za vrednotenje zgrajenega drevesa potrebujemo testno množico, ki predstavlja vsaj 30% velikosti učne množice za oceno. Pri takšni delitvi množice primerov bi v učni množici ostalo "le" 210 ran.

Množica do sedaj spremljanih procesov celjenja ran (množica primerov) $\mathcal{L}$ je premajhna (300 primerov), da bi jo enostavno razpolovili na učno $\mathcal{L}^{tr}$ in testno $\mathcal{L}^{ts}$ množico. Ocena napake drevesa $R^{*}(d)$ bo točnejša, če bo testna množica velika, vendar bo zato drevo zgrajeno na manjši učni množici slabše zaobjelo znanje skrito v množici vseh primerov.

V primeru majhnih učnih množic (kot je naša) je priporočljivo uporabiti metodo prečnega preverjanja [Kononenko, 1997a]. Množico primerov smo naključno razdelili na 10 delov enake velikosti.

$$\mathcal{L} \#\Rightarrow \#\mathcal{L}_1, \mathcal{L}_2, \ldots \mathcal{L}_{10}$$

Za vsak v, v=1,...,10, smo zgradili odločitveno drevo $d^v(x)$ iz učne množice vzorcev $\mathcal{L}-\mathcal{L}_v$. Izločene primere $\mathcal{L}_v$ smo uporabili za izračun ocene $R(d^v)$. Postopek smo ponovili za preostale $\mathcal{L}_v$. Končna ocena napake razvrščanja $R^{cv}(d)$ je povprečje vseh desetih ocen (43).

$$R^{cv}(d) = \frac{1}{10}\sum_{v=1}^{10} R(d^v) \tag{43}$$

Končno drevo je bilo zgrajeno na celotni učni množici, njegova zanesljivost pa je podana s povprečjem in standardnim odklonom zanesljivosti desetih prečnih ponovitev.

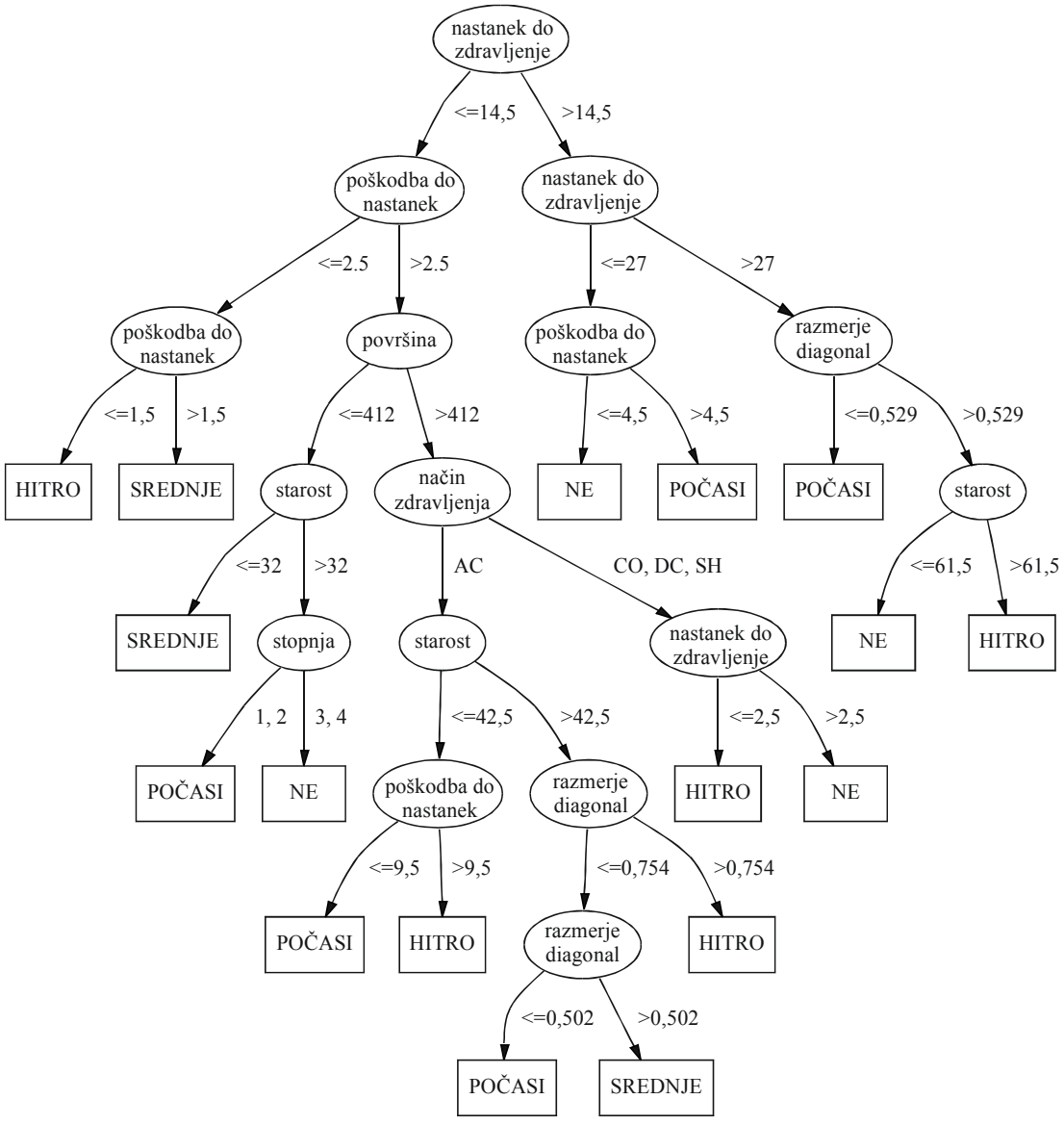
7.2 Odločitveno drevo

Učno množico primerov smo razdelili v štiri razrede glede na hitrost celjenja ran. V tabeli 7.2 so predstavljene oznake razredov, način razdelitve učne množice v štiri razrede, število učnih primerov v razredih in a priori verjetnosti razredov. Razred z največjim številom primerov in zato tudi razred z največjo a priori verjetnostjo je razred hitro celečih se ran. Če nov primer vedno razvrstimo v ta razred, je verjetnost, da se ta rana tudi v resnici hitro celi, 26,3%.

Tabela 7.2 *Razdelitev primerov iz učne množice v štiri razrede glede na njihovo hitrost celjenja*.

razred	pogoj	število primerov	a priori verjetnost
NECELEČE RANE	$\Theta \leq 0{,}095$ mm/dan	77	0,257
POČASI CELEČE RANE	$0{,}095 \text{ mm/dan} < \Theta \leq 0{,}180$ mm/dan	77	0,257
SREDNJE CELEČE RANE	$0{,}180 \text{ mm/dan} < \Theta \leq 0{,}300$ mm/dan	67	0,223
HITRO CELEČE RANE	$0{,}300 \text{ mm/dan} < \Theta$	79	0,263

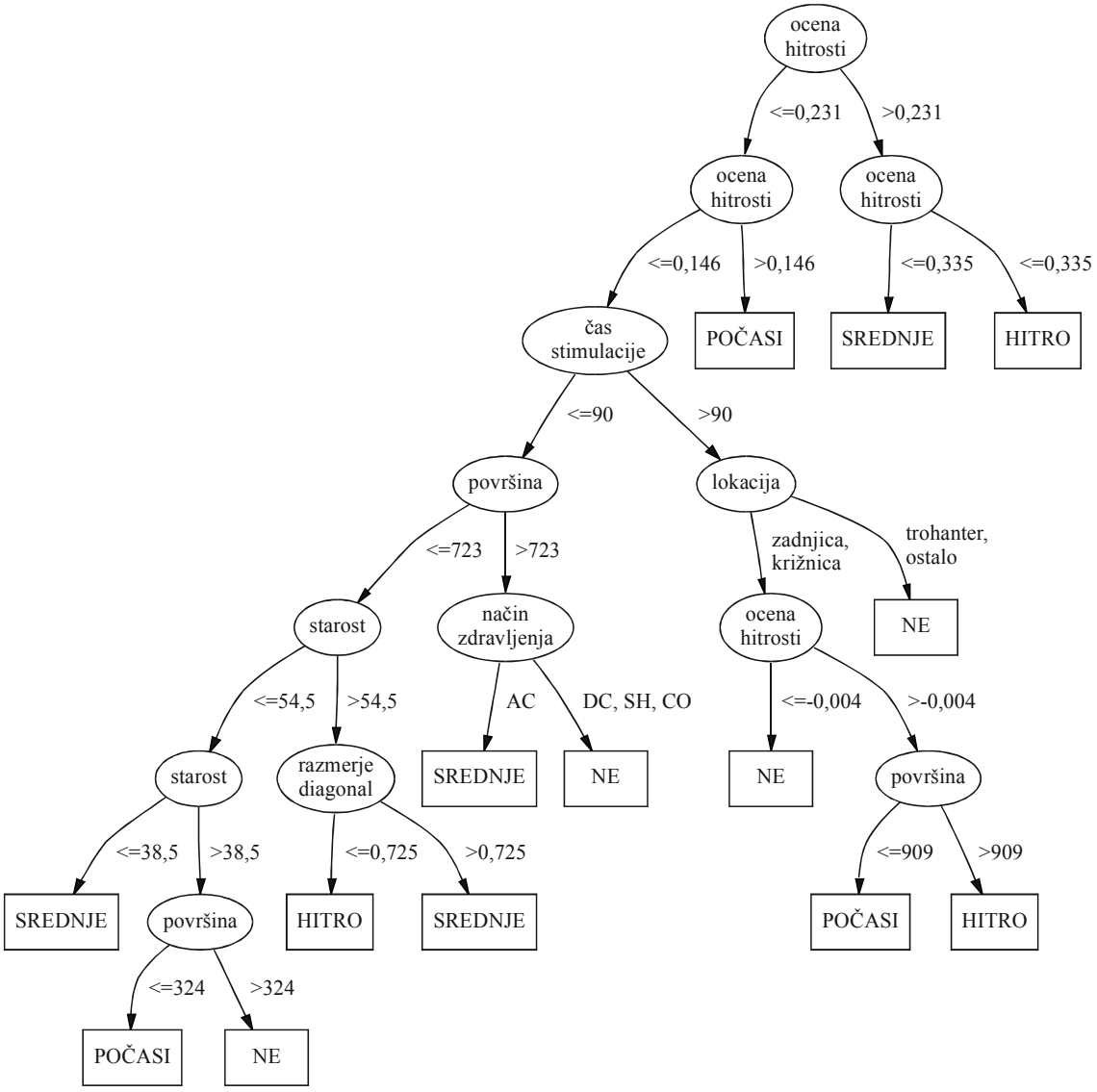
Θ – hitrost celjenja ran



Slika 7.1 *Odločitveno drevo za napovedovanje hitrosti celjenja iz vrednosti parametrov znanih ob začetku zdravljenja. NE – neceleče rane, POČASI – počasi celeče rane, SREDNJE – srednje celeče rane in HITRO – hitro celeče rane*.

Na sliki 7.1 je predstavljeno odločitveno drevo zgrajeno z algoritmom ReliefF na podlagi začetnih lastnosti rane, bolnika in načina zdravljenja. V listih je oznaka večinskega razreda,

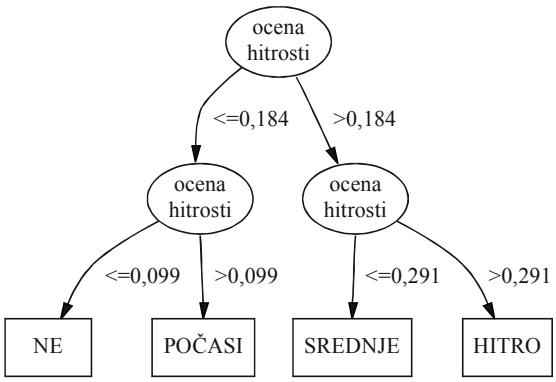
uporabili smo močnejše rezanje. Verjetnost napačnega razvrščanja smo določili z metodo prečnega preverjanja. Dosegli smo 29,7% zanesljivost razvrščanja. Na hitrost celjenja ima predvsem vpliv kombinacija začetne površine, stopnje in oblike rane (razmerje diagonal), starosti bolnika, načina zdravljenja, časa od poškodbe hrbtenjače do nastanka rane in časa od nastanka rane do začetka zdravljenja. Napredek od a priori verjetnosti 26,3% na verjetnost 29,7% je zanemarljivo majhen. Torej so parametri, ki opisujejo rano in bolnika ob začetku zdravljenja premalo informativni, da bi lahko napovedali uspešnost zdravljenja.



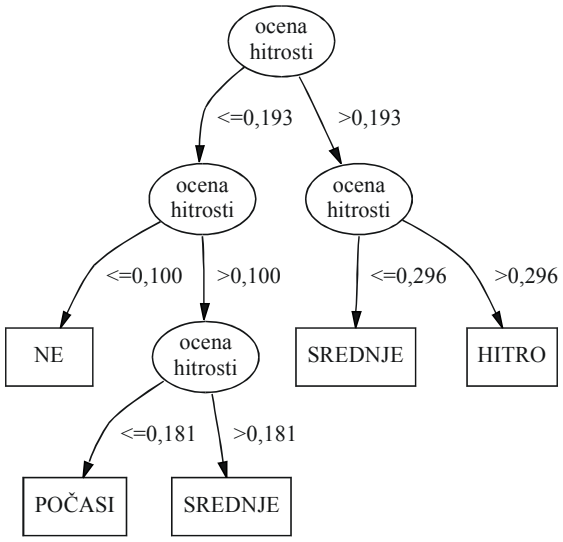
Slika 7.2 *Odločitveno drevo za napovedovanje hitrosti celjenja po enem tednu opazovanja procesa celjenja rane. Ocena hitrosti je izračunana iz prileganja eksponencialnega modela meritvama površine v prvem tednu opazovanja procesa celjenja rane*.

Na slikah 7.2, 7.3, 7.4, 7.5, 7.6 in 7.7 so predstavljena odločitvena drevesa zgrajena na podlagi lastnosti rane, bolnika, načina zdravljenja in ocene hitrosti celjenja po enem, dveh, treh, štirih, petih in šestih tednih opazovanja poteka celjenja. Po prvem tednu zdravljenja rane lahko z odločitvenim drevesom prikazanim na sliki 7.2 napovemo hitrost celjenja na podlagi ocene hitrosti celjenja po enem tednu opazovanja poteka celjenja rane, začetne površine,

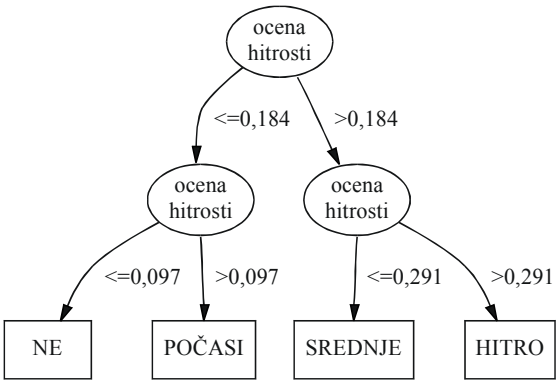
trajanja dnevne stimulacije, lokacije rane, načina zdravljenja in oblike rane (razmerje diagonal). Že po dveh tednih opazovanja poteka celjenja rane je za napovedovanje hitrosti celjenja rane zadostna že ocena hitrosti celjenja rane.



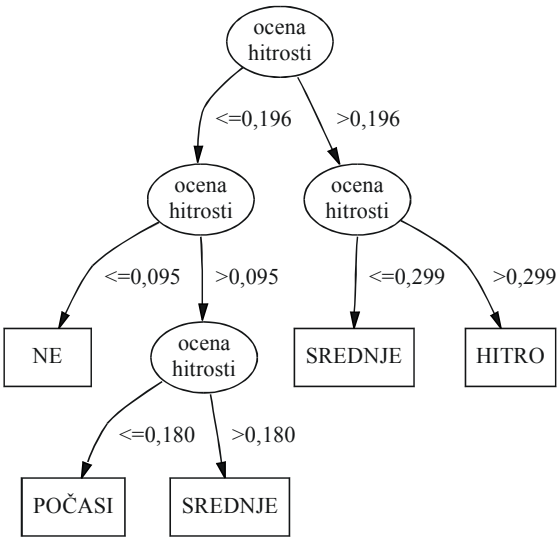
Slika 7.3 *Odločitveno drevo za napovedovanje hitrosti celjenja po dveh tednih opazovanja procesa celjenja rane*.



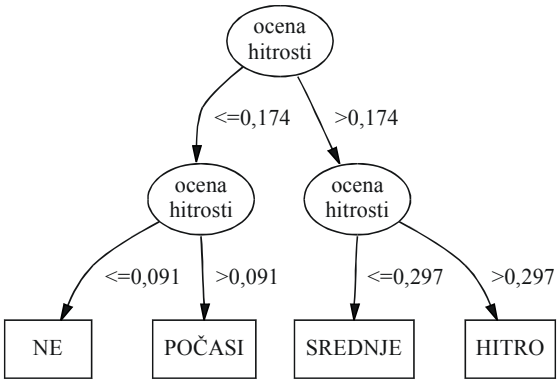
Slika 7.4 *Odločitveno drevo za napovedovanje hitrosti celjenja po treh tednih opazovanja procesa celjenja rane*.



Slika 7.5 *Odločitveno drevo za napovedovanje hitrosti celjenja po štirih tednih opazovanja poteka celjenja*.



Slika 7.6 *Odločitveno drevo za napovedovanje hitrosti celjenja po petih tednih opazovanja procesa celjenja rane*.



Slika 7.7 *Odločitveno drevo za napovedovanje hitrosti celjenja po šestih tednih opazovanja procesa celjenja rane.*

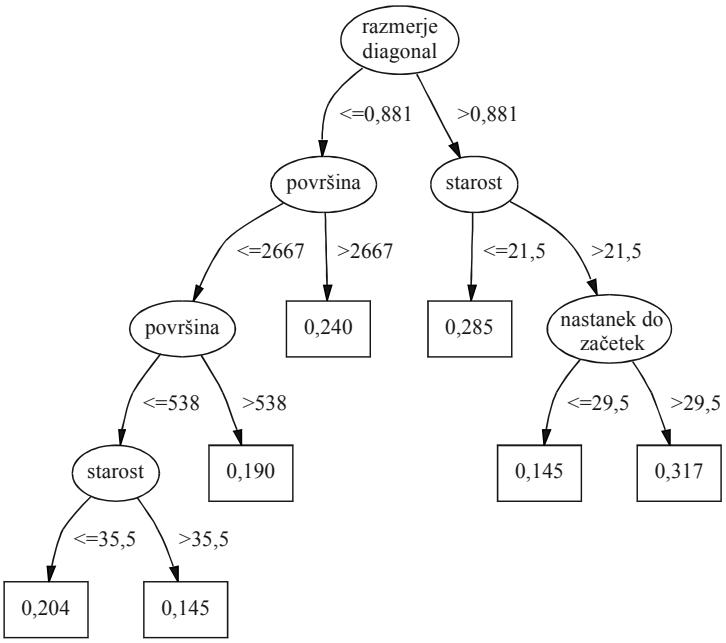
V tabeli 7.3 je so podane zanesljivosti razvrščanja novih primerov zgrajenih dreves. Po dveh tednih opazovanja poteka celjenja lahko napovemo hitrost celjenja rane z 61,7% zanesljivostjo, po treh tednih pa zanesljivost že prekorači 80%.

Tabela 7.3 *Zanesljivost razvrščanja novih primerov z odločitvenim drevesom ob začetku zdravljenja in po enem do šestih tednih opazovanja procesa celjenja*.

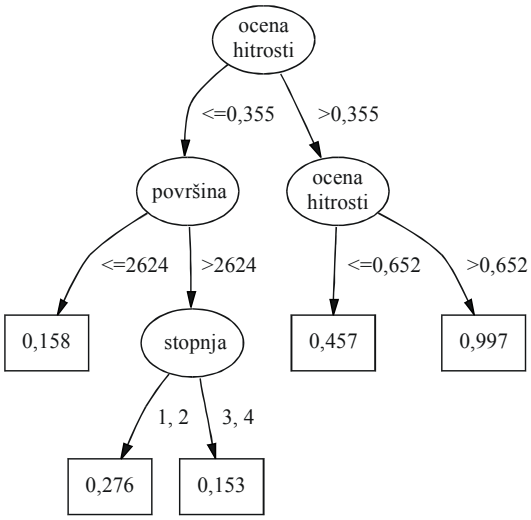
št. tednov opazovanja	povprečna zanesljivost razvrščanja	standardni odklon
0	29,7	0,106
1	41,0	0,245
2	61,7	0,201
3	80,0	0,185
4	83,7	0,178
5	89,0	0,186
6	89,0	0,182

7.3 Regresijsko drevo – mediana

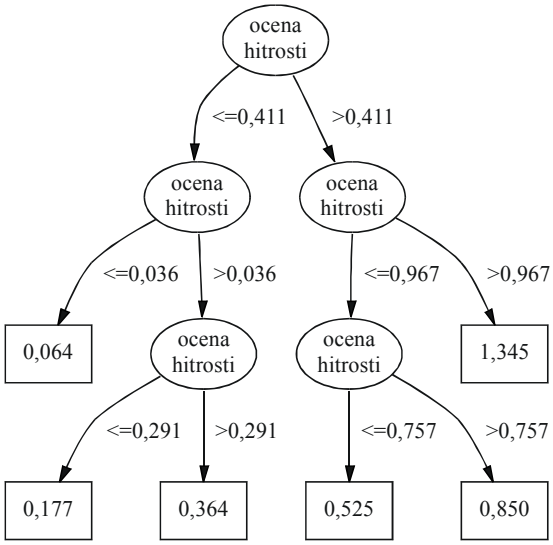
Regresijsko drevo za razliko od odločitvenega drevesa napoveduje zvezen parameter, ki je v našem primeru hitrost celjenja ran. Na sliki 7.8 je predstavljeno regresijsko drevo za napovedovanje hitrosti celjenja iz lastnosti rane, bolnika in načina zdravljenja ob začetku zdravljenja. Ob začetku zdravljenja na hitrost celjenja rane najbolj vpliva kombinacija oblike (razmerje diagonal) in površine rane, starosti bolnika in časa od nastanka rane do začetka zdravljenja. Vendar je relativna napaka (1,058) napovedovanja hitrosti celjenja s tem drevesom več od ena, kar pomeni, da bi naredili manjšo napako, če bi predpostavili, da se je rana celila kar z mediano hitrosti celjenja učne množice.



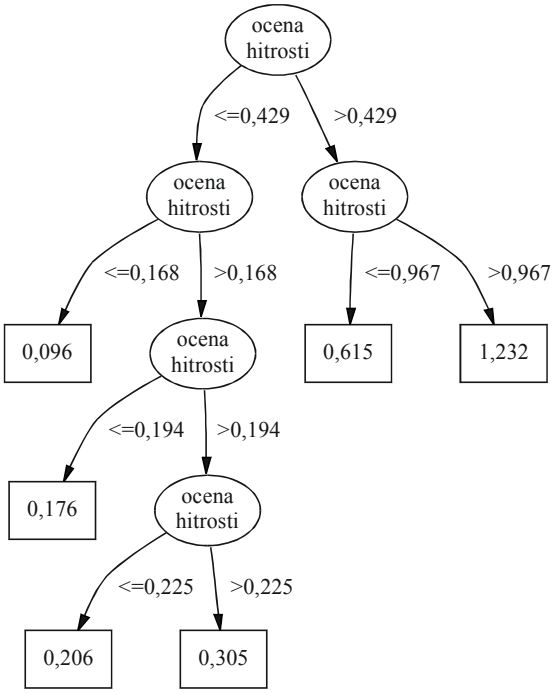
Slika 7.8 *Regresijsko drevo za napovedovanje hitrosti celjenja kroničnih ran ob začetku zdravljenja. V listih so podane mediane primerov razvrščenih v ta list.*



Slika 7.9 *Regresijsko drevo z mediano v listih za napovedovanje hitrosti celjenja po enem tednu opazovanja poteka celjenja.*

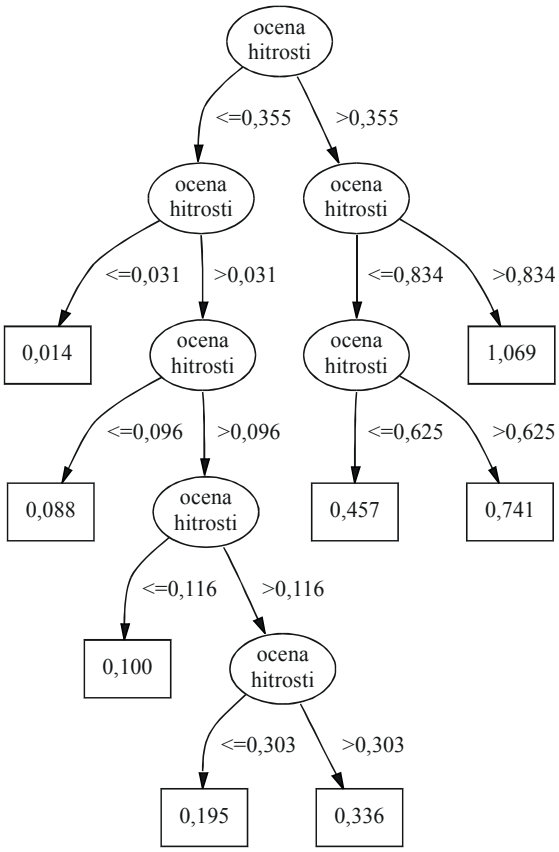


Slika 7.10 *Regresijsko drevo z mediano v listih za napovedovanje hitrosti celjenja po dveh tednih opazovanja poteka celjenja.*

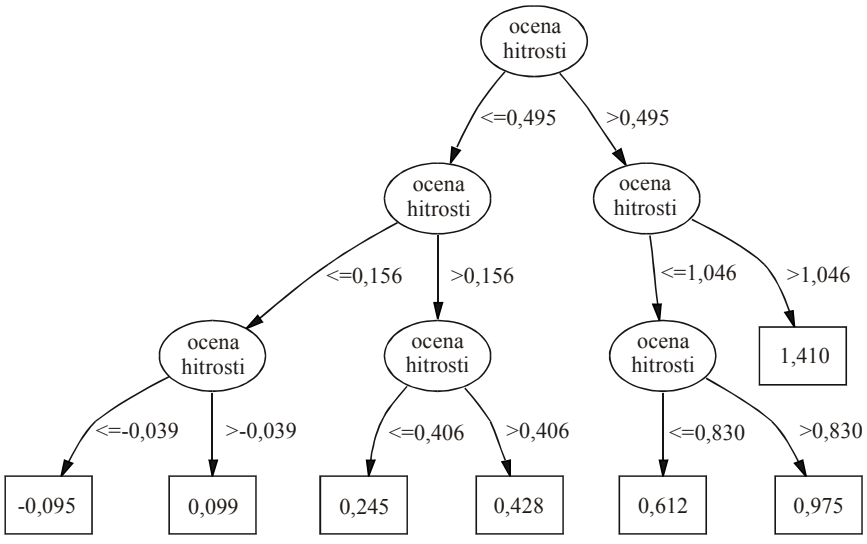


Slika 7.11 *Regresijsko drevo z mediano v listih za napovedovanje hitrosti celjenja po treh tednih opazovanja poteka celjenja.*

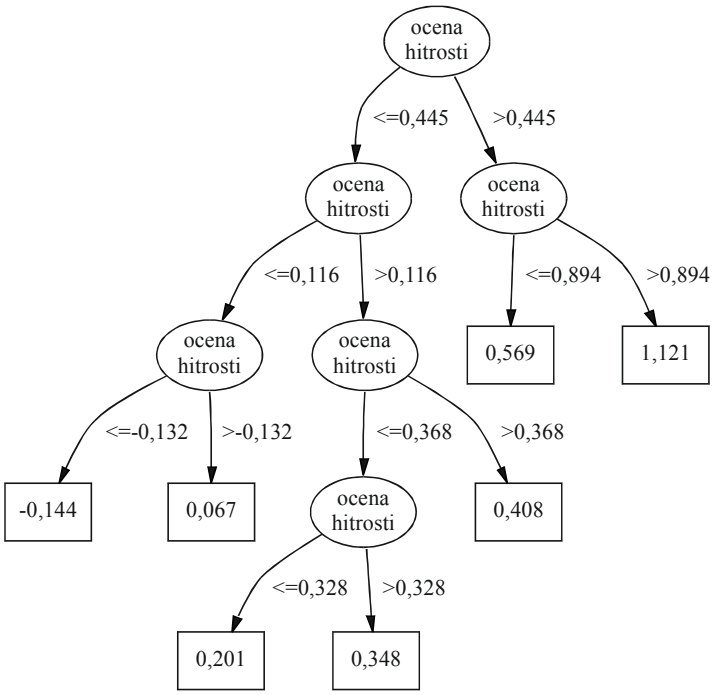
Takšen rezultat nakazuje, da so parametri, ki opisujejo rano in bolnika ob začetku zdravljenja premalo informativni, da bi jih lahko uporabili za napovedovanje hitrosti celjenja. Tem parametrom smo zato dodali še oceno hitrosti celjenja določeno iz od enega do šestih tednov opazovanja procesa celjenja rane.



Slika 7.12 *Regresijsko drevo z mediano v listih za napovedovanje hitrosti celjenja po štirih tednih opazovanja poteka celjenja.*



Slika 7.13 *Regresijsko drevo z mediano v listih za napovedovanje hitrosti celjenja po petih tednih opazovanja poteka celjenja.*



Slika 7.14 *Regresijsko drevo z mediano v listih za napovedovanje hitrosti celjenja po šestih tednih opazovanja poteka celjenja.*

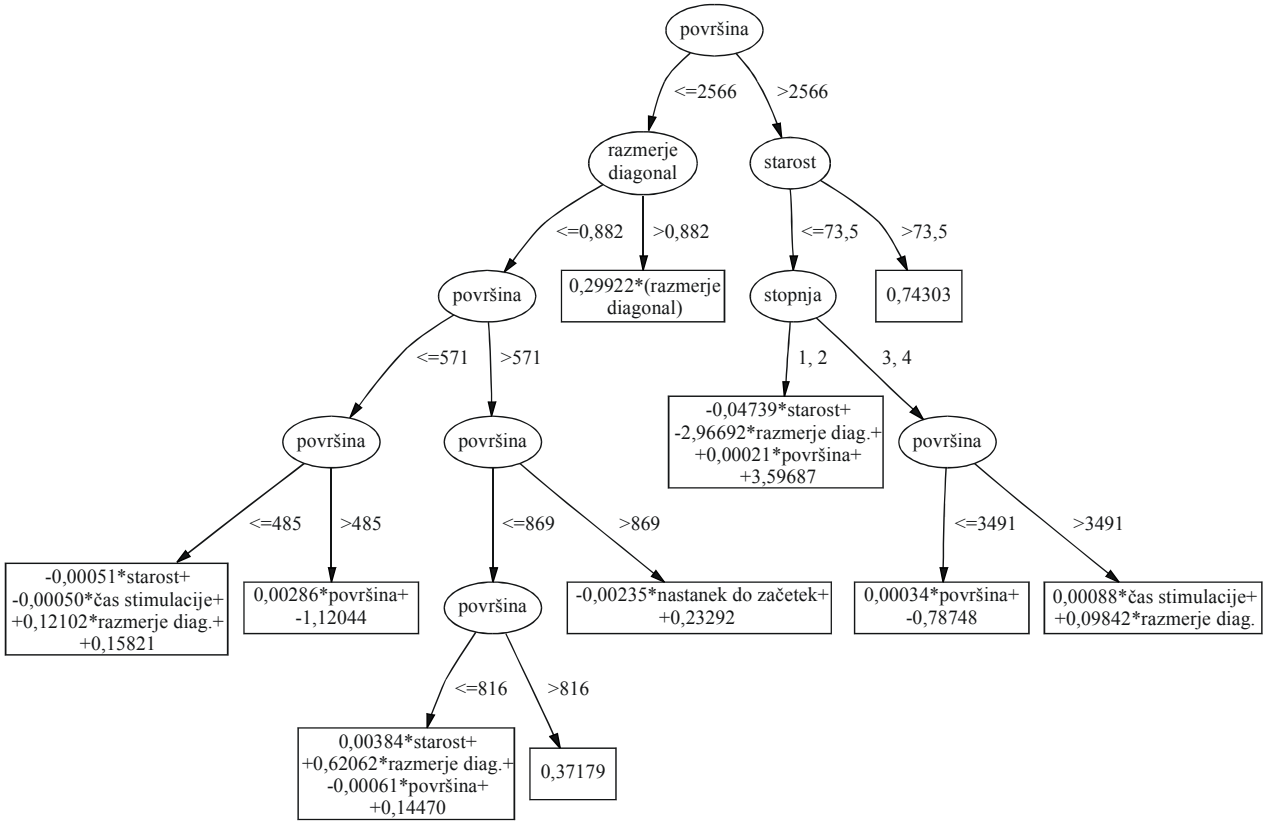
Tabela 7.4 *Relativna napaka regresijskega drevesa ob začetku zdravljenja in po enem do šestih tednih opazovanja poteka celjenja. Izračunana je po metodi 10-kratnega prečnega preverjanja.*

št. tednov opazovanja	povprečna relativna napaka	standardni odklon
0	1,058	0,106
1	0,699	0,245
2	0,347	0,201
3	0,308	0,185
4	0,228	0,178
5	0,206	0,186
6	0,187	0,182

Na slikah 7.9, 7.10, 7.11, 7.12, 7.13 in 7.14 so podana regresijska drevesa zgrajena na podlagi lastnosti rane, bolnika, načina zdravljenja in ocene hitrosti celjenja po enem, dveh, treh, štirih, petih in šestih tednih opazovanja poteka celjenja. Že po enem tednu opazovanja poteka celjenja je množina informacije ocene hitrosti celjenja mnogo večja od množine informacije lastnosti rane, bolnika in načina zdravljenja, tako da se v listih dreves pojavlja le ocena hitrosti celjenja rane. Učenje smo ponovili desetkrat z vsakokrat drugače razdeljeno množico primerov na učno in testno množico. V tabeli 7.4 so podane povprečne relativne napake s standardnimi odkloni napovedovanja hitrosti celjenja za zgrajena drevesa.

7.4 Regresijsko drevo – linearne enačbe

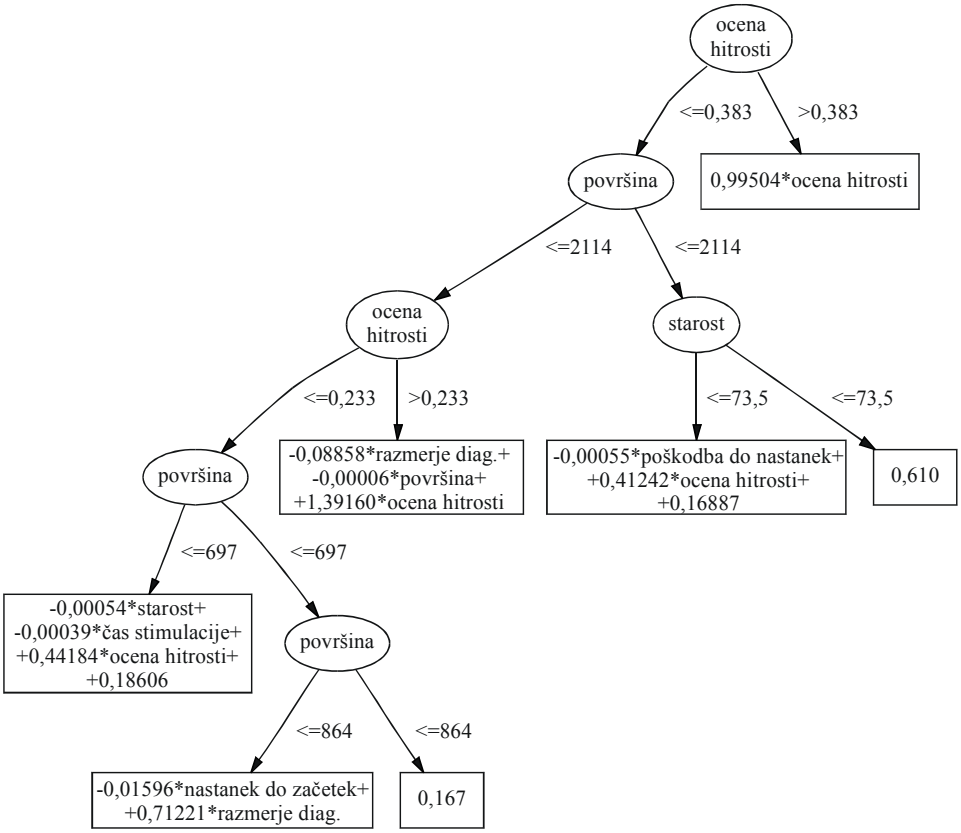
Na podlagi začetnih lastnosti rane, bolnika in načina zdravljenja smo zgradili še regresijsko drevo, ki je imelo v listih linearne enačbe (slika 7.15). Drevesa z linearnimi enačbami v listih niso primerna za kvalitativno podajanje znanja, a so običajno pri regresijskih problemih zelo učinkovita. Povprečna relativna napaka (10-kratno prečno preverjanje) napovedovanja hitrosti celjenja je 1,342. Ker je relativna napaka več od ena, iz vrednosti parametrov ob začetku zdravljenja ni mogoče sklepati na hitrost celjenja.



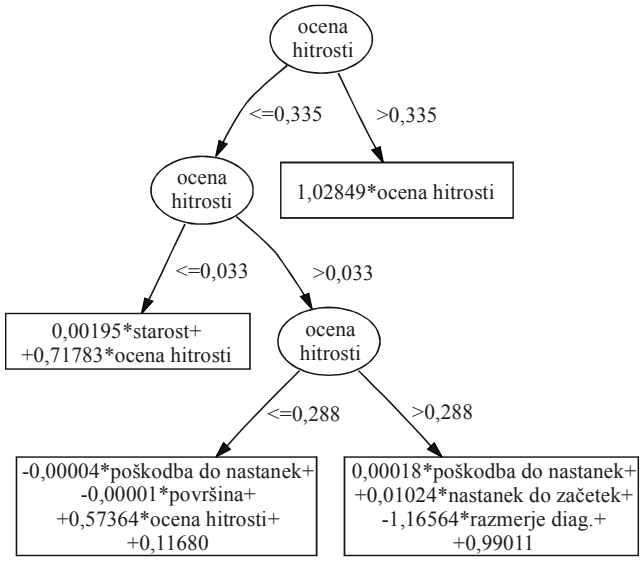
Slika 7.15 *Regresijsko drevo za napovedovanje hitrosti celjenja kroničnih ran iz parametrov znanih ob začetku zdravljenja z linearnimi enačbami v listih drevesa*.

Začetnim lastnostim rane, bolnika in načina zdravljenja smo dodali oceno hitrosti celjenja izračunano iz modela na podlagi opazovanja površine rane skozi določeno časovno obdobje. Na sliki 7.16 je prikazano regresijsko drevo za napovedovanje hitrosti celjenja z oceno hitrosti celjenja izračunano po enem tednu opazovanja poteka celjenja. Povprečna relativna napaka drevesa, podana v tabeli 7.5, je občutno nižja (0,640) kot pri drevesu iz slike 7.15. Na slikah 7.17, 7.18, 7.19, 7.20 in 7.21 so podana regresijska drevesa zgrajena na podlagi lastnosti rane, bolnika, načina zdravljenja in ocene hitrosti celjenja po dveh, treh, štirih, petih in šestih tednih opazovanja poteka celjenja. V tabeli 7.5 so podane povprečne relativne kvadratne napake s standardnimi odkloni napovedovanja hitrosti celjenja za našteta drevesa. Ocene hitrosti celjenja po petih ali šestih tednih opazovanja poteka celjenja ni mogoče izboljšati z upoštevanjem začetnih lastnosti rane, bolnika in načina zdravljenja. Napoved hitrosti celjenja po štirih tednih ali manj opazovanja poteka celjenja pa je poleg ocene hitrosti celjenja možno izboljšati z upoštevanjem lastnosti rane, bolnika in načina zdravljenja. Način zdravljenja se v

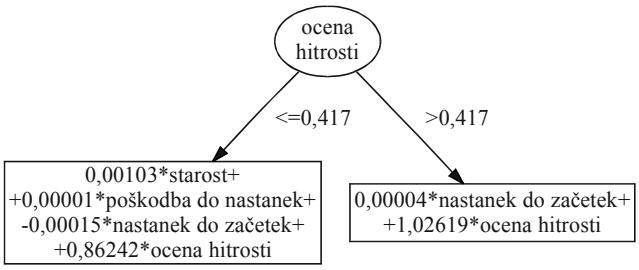
drevesih ne pojavlja neposredno. Pojavi se kot dnevno trajanje stimulacije, ki je nič pri konzervativno zdravljenih in več od nič pri ostalih načinih zdravljenja. Na hitrost celjenja predvsem vpliva medsebojna kombinacija lastnosti: začetna površina, stopnja in oblika rane (razmerje diagonal), starost bolnika, čas od poškodbe hrbtenjače do nastanka rane in čas od nastanka rane do začetka zdravljenja.



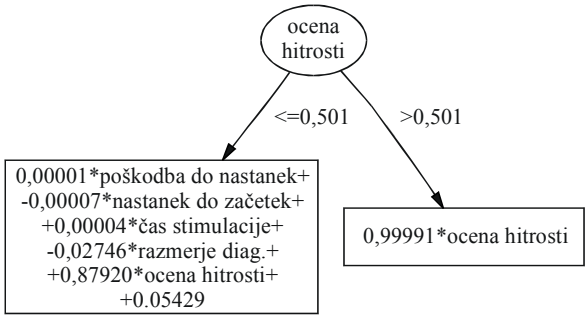
Slika 7.16 *Regresijsko drevo z linearnimi enačbami v listih za napovedovanje hitrosti celjenja po enem tednu opazovanja poteka celjenja*.



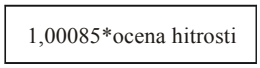
Slika 7.17 *Regresijsko drevo z linearnimi enačbami v listih za napovedovanje hitrosti celjenja po dveh tednih opazovanja poteka celjenja*.



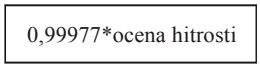
Slika 7.18 *Regresijsko drevo z linearnimi enačbami v listih za napovedovanje hitrosti celjenja po treh tednih opazovanja poteka celjenja*.



Slika 7.19 *Regresijsko drevo z linearnimi enačbami v listih za napovedovanje hitrosti celjenja po štirih tednih opazovanja poteka celjenja*.



Slika 7.20 *Regresijsko drevo (list) z linearno enačbo v listu za napovedovanje hitrosti celjenja po petih tednih opazovanja poteka celjenja*.



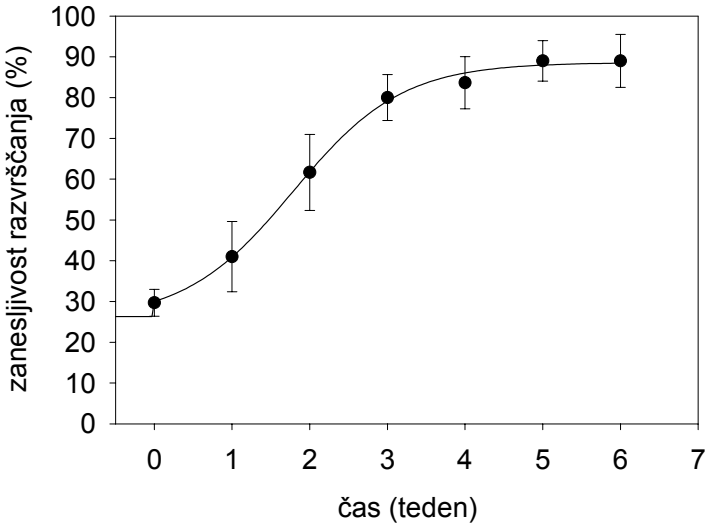
Slika 7.21 *Regresijsko drevo (list) z linearno enačbo v listu za napovedovanje hitrosti celjenja po šestih tednih opazovanja poteka celjenja*.

Tabela 7.5 *Relativna napaka regresijskega drevesa z linearnimi enačbami v listih ob začetku zdravljenja in po enem do šestih tednih opazovanja poteka celjenja. Izračunana je po metodi prečnega preverjanja*.

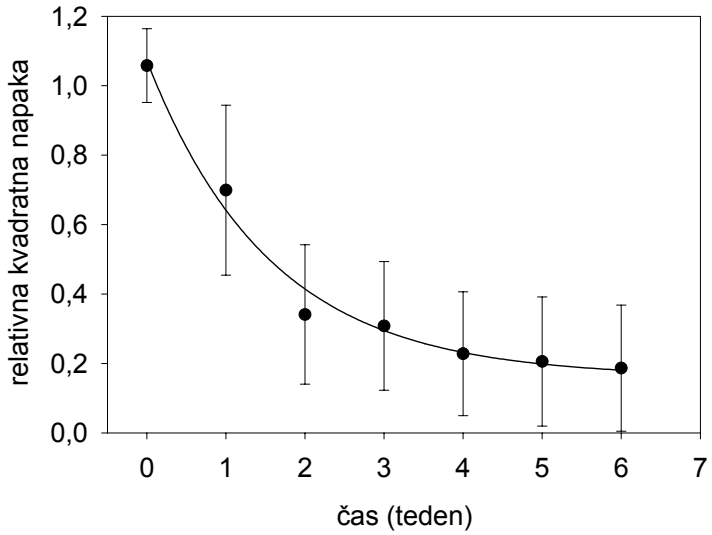
št. tednov opazovanja	povprečna relativna napaka	standardni odklon
0	1,342	0,341
1	0,640	0,216
2	0,347	0,250
3	0,181	0,161
4	0,088	0,115
5	0,070	0,120
6	0,059	0,123

7.5 Sistem za napovedovanje hitrosti celjenja kroničnih ran

Na slikah 7.22, 7.23, in 7.24, so prikazane zanesljivosti razvrščanja oz relativne kvadratne napake kot funkcije časa opazovanja rane. Iz slik je razvidno, da je zanesljivost razvrščanja oz. relativna kvadratna napaka na podlagi le začetnih lastnosti rane in bolnika izredno nizka oz. velika. Razvrščanje je na nivoju ugibanja z znanjem o a priori velikosti razredov iz učne množice, zato napovedovanje hitrosti celjenja ran ob začetku zdravljenja bolnika ni smiselno. Šele, ko smo dodali informacijo o poteku celjenja kronične rane v prvih tednih, smo izboljšali zanesljivost razvrščanja oz. zmanjšali relativno kvadratno napako napovedovanja hitrosti celjenja.



Slika 7.22 *Zanesljivost razvrščanja odločitvenega drevesa za napovedovanje hitrosti celjenja kot funkcija časa opazovanja celjenja rane. Drevo razvršča primere v štiri razrede: NECELEČE, POČASI CELEČE, SREDNJE CELEČE in HITRO CELEČE rane*.

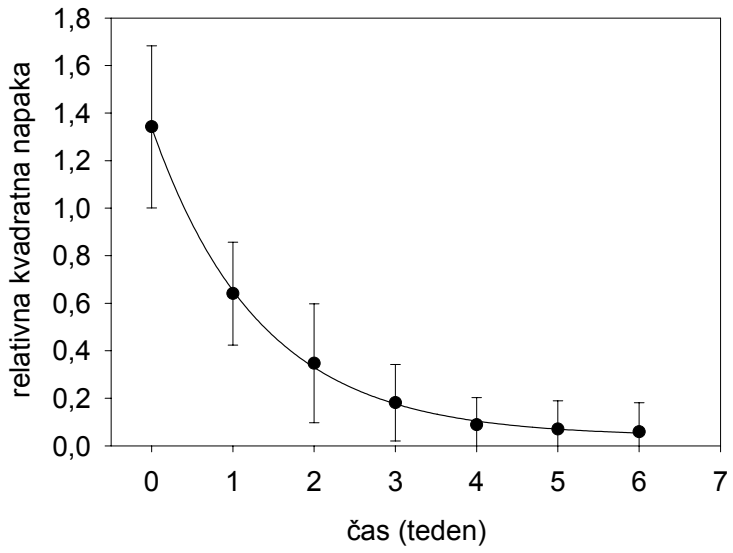


Slika 7.23 *Relativna napaka regresijskega drevesa za napovedovanje hitrosti celjenja kot funkcija časa opazovanja celjenja rane. V listih regresijskega drevesa so mediane*.

Ugotovili smo, da za napovedovanje hitrosti celjenja iz časovnega opazovanja poteka celjenja potrebujemo vsaj štiri tedne, da je se ocena hitrosti celjenja ne razlikuje statistično značilno od dejanske. Z drevesi, ki združujejo oceno hitrosti celjenja in lastnosti bolnika, rane in načina zdravljenja, smo potreben čas za napoved hitrosti celjenja skrajšali iz štirih tednov na tri tedne, grobo oceno hitrosti celjenja pa smo dobili že po dveh tednih (tri meritve površine rane) opazovanja poteka celjenja.

Odločitveno drevo že po treh tednih opazovanja poteka celjenja rane napove uspešnost celjenja z 80% zanesljivostjo. Zanesljivost razvrščanja po dveh tednih opazovanja je precej manjša (61,7%), a še vedno 2,3 krat večja kot je a priori verjetnost največjega razreda. Po štirih tednih ni bistvenega izboljšanja napovedi.

Z regresijskimi drevesi smo dobili že po dveh tednih zadovoljivo oceno hitrosti celjenja. Najboljše rezultate smo dosegli z regresijskim drevesom, ki je imel v listih linearne enačbe. Ta je že po enem tednu opazovanja razložil 36% variance, po dveh tednih 65,3% variance in po treh tednih opazovanja kar 81,9% variance. Po štirih tednih opazovanja je ocenjena hitrost iz modela že enaka dejanski hitrosti celjenja rane. Poleg tega pa ta drevesa napovedujejo zvezno spremenljivko, ki ni diskretizirana kot pri odločitvenih drevesih in delno tudi pri regresijskih drevesih z mediano v listih. Ta drevesa predstavljajo osnovo ekspertnega sistema za pomoč strokovnjaku pri napovedovanju celjenja kroničnih ran.



Slika 7.24 *Relativna napaka regresijskega drevesa za napovedovanje hitrosti celjenja kot funkcija časa opazovanja celjenja rane. V listih regresijskega drevesa so linearne enačbe.*

Primerjali smo rezultate naše študije z rezultati podobnih študij. Študije vpliva lastnosti ran in bolnika na hitrost celjenja ran so zelo redke, še manj je študij, ki iz teh lastnosti napovedujejo uspešnost celjenja ran. Nekatere temeljijo le na napovedovanju uspešnosti celjenja na podlagi znanih začetnih lastnosti rane in bolnika, nekatere pa vključujejo tudi nekaj tedensko opazovanje poteka celjenja. Poudariti pa je potrebno, da nobena od naštetih študij ne vključuje električne stimulacije.

Skene *et al.* (1992) so 200 venskih razjed na spodnjih ektremitetah opazovali največ štiri mesece in merili čas celjenja. Celjenje je bilo hitrejše v primerih ran z manjšo površino, s

krajšim časom od nastanka rane do začetka zdravljenja, pri mlajših bolnikih in površinski venski insuficienci. Starost bolnika lahko vpliva neodvisno od bolezni perifernega obtoka, ker so venske razjede bolj pogoste pri starejših ljudeh. Ugotovili so, da bakterijska obremenitev rane nima vpliva na hitrost celjenja. Iz teh prognostičnih lastnosti rane in bolnika so sestavili točkovalni sistem za napovedovanje celjenja. Glede na vrednost točk so lahko ocenili verjetnost zacelitve rane v določenem času (40, 80 ali 120 dneh). Sistem je bil preizkušen le na učni množici primerov, zato avtorji opozarjajo, da lahko pri razvrščanju novih primerov odpove.

Birke *et al.* (1992) so na 80 primerih nevrogenih razjed razvili regresijski model, ki je vključeval globino, premer rane in starost sladkornega bolnika za napovedovanje časa celjenja. Globoke rane so se celile počasneje, ker so bile pri tem prizadete tudi podkožne strukture (kite, sklepi in kosti). Ugotovili so tudi, da večina nervrogenih ran nastane zaradi zmanjšane izgube občutka za dotik in mehanske obremenitve. Model je razložil 36% variance na učni množici. Točno tolikšen del variance nam je uspelo razložiti po tednu dni opazovanja poteka celjenja rane na neodvisni testni množici, kar predstavlja veliko večji uspeh.

Johnson (1997) je uporabila hierarhično rojenje 156 venskih razjed na podlagi naslednjih lastnosti ran in bolnika: eksudati, edem, liposkleroza, razmerje gleženjskega in laketnega pritiska ter površina. Rezultat rojenja so bili trije enako močni roji. Med njimi je bila razlika v hitrosti celjenja, čeprav ne statistično značilna. Hitrost celjenja je merila kot spremembo površine rane v štirih tednih opazovanja. Roje je označila s hitro, počasi in necelečimi ranami.

Kantor in Margolis (2000) sta na podlagi odstotka spremembe površine v prvih štirih tednih napovedala ali bo rana v štiriindvajset tednih zaceljena ali ne. Zanesljivost razvrščanja v dva razreda, zaceljene in nezaceljene po 24 tednih, je bila 68,2% oz. 74,7%. Veliko bolj kompleksen problem, ki smo ga rešili z odločitvenim drevesom, ima po štirih tednih opazovanja kar 83,7% zanesljivost razvrščanja.

8 Zaključek

Disertacija obravnava dinamiko celjenja kroničnih ran, načine vrednotenja učinkov zdravljenja, vpliv lastnosti ran in bolnikov na potek celjenja kroničnih ran ter gradnjo ekspertnega sistema za napovedovanje hitrosti celjenja. Delo temelji na 300 kliničnih primerih spremljanja poteka celjenja kroničnih ran.

Za spremljanje poteka celjenja kroničnih ran se je izkazalo najpomembnejše tedensko merjenje velikosti rane. Velikost rane se ne glede na način merjenja s časom spreminja nelinearno. Ali merimo le površino ali pa tudi obseg rane, dinamika celjenja ostaja nespremenjena. Zaradi enostavnosti meritve smo se odločili za tedensko merjenje površine rane, ki smo jo ocenili iz med seboj pravokotnih diagonal rane. Časovni potek spreminjanja površine rane najbolje opisuje zakasnjen eksponencialni model. Ugotovili smo, da se izračunani parametri modela ne razlikujejo značilno od dejanskih, če jih izračunamo iz vsaj petih meritev površine izvedenih v vsaj štirih tednih. Na podlagi te lastnosti modela lahko že napovedujemo nadaljnji potek celjenja po štirih tednih opazovanja poteka celjenja.

Na področju kroničnih ran je vrednotenje učinkov zdravljenja neusklajeno. Zato je bil namen našega dela analizirati dosedanje načine vrednotenja učinkov zdravljenja na hitrost celjenja ran in predlagati najustreznejšega. Za primerjavo učinkov celjenja smo na osnovi modela dinamike celjenja kroničnih ran definirali mero, ki podaja prirastek tkiva od roba rane proti središču v milimetrih na dan. Tako definirana hitrost celjenja je neodvisna od začetne velikosti rane (površine in oblike), kar nam omogoča primerjavo hitrosti celjenja ran različnih začetnih velikosti.

S tako definirano mero hitrosti celjenja smo na kliničnih podatkih statistično dokazali hitrejše celjenje kroničnih ran stimuliranih z izmeničnim električnim tokom od ran zdravljenih konzervativno ali z nameščenimi neaktivnimi elektrodami. Med skupinama konzervativno zdravljenih ran in ran zdravljenimi s placebom nismo našli značilnih razlik. Uspešnost stimulacije z enosmernim električnim tokom je bila primerljiva uspešnosti izmenične električne stimulacije in boljša od uspešnosti konzervativnega zdravljenja ali zdravljenja s placebom. Skupina ran stimulirana z enosmernim električnim tokom je majhna in združuje dve vrsti postavitve elektrod. V literaturi omenjajo obe postavitvi za uspešni pri pospeševanju celjenja kroničnih ran, vendar se je po medsebojni primerjavi izkazalo nameščanje pozitivne elektrode neposredno na rano uspešnejše od nameščanja obeh elektrod na zdravo kožo ob rani. Morda ravno zaradi združevanja različnih postavitev elektrod razlika v hitrosti celjenja ran stimuliranih z enosmernim električnim tokom in ran zdravljenih konzervativno ali s placebom ni značilna.

Način zdravljenja pa ni edini niti ne najvplivnejši parameter, ki vpliva na hitrost celjenja kroničnih ran. Na hitrost celjenja vplivajo tudi lastnosti rane in bolnika. S statističnim pristopom smo ugotovili, da ni veliko neposrednih vplivov lastnosti rane in bolnika na hitrost celjenja, ampak da ti delujejo na hitrost celjenja v medsebojni kombinaciji. Z algoritmom RReliefF za strojno učenje smo vpliv teh lastnosti uredili v naslednjem vrstnem redu: površina, starost bolnika, čas od nastanka rane do začetka zdravljenja, razmerje diagonal (oblika rane), lokacija rane, način zdravljenja, čas od poškodbe hrbtenjače do nastanka rane, dnevno trajanje stimulacije, stopnja rane, diagnoza bolnika in vrsta rane.

Iz začetnih lastnosti rane, bolnika in načina zdravljenja, ki smo jih zajeli v našo podatkovno bazo, ni bilo mogoče dovolj zanesljivo napovedati hitrosti celjenja. Z upoštevanjem modela procesa celjenja kroničnih ran in regresijskim drevesom z linearnimi enačbami v listih smo razložili 36% variance pri napovedovanju hitrosti celjenja po enem tednu opazovanja, 65% variance po dveh tednih in 82% po treh tednih opazovanja. Hitrost celjenja lahko grobo ocenimo že po dveh tednih, po treh tednih opazovanja pa je ocena že zelo dobra. Znanje, ki je shranjeno v obliki regresijskega drevesa je osnova ekspertnega sistema. Z drevesom predstavljeno znanje je človeku prijetna oblika predstavitve pravil, ki jih je zgradil algoritem induktivnega strojnega učenja za razvrščanje novih primerov. Zdravnik ima tako že po dveh tednih opazovanja zdravljenja kronične rane grob podatek o nadaljnji hitrosti celjenja oz. času do zacelitve rane. Na osnovi te informacije lahko bolj zanesljivo potrdi pravilnost izbranega načina zdravljenja ali pa se odloči za zamenjavo, če je napoved neugodna.

9 Literatura

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Izvirni prispevki k znanosti

Na osnovi dela, predstavljenega v doktorski disertaciji, prosim za priznanje naslednjih izvirnih prispevkov k znanosti in razumevanju ožjega znanstvenega področja:

Dinamični model celjenja kroničnih ran s sposobnostjo napovedovanja poteka celjenja

Na osnovi tedenskih meritev velikosti rane smo razvili dinamični model celjenja kroničnih ran. Pri izbiri modela smo bili še posebno pozorni na njegovo občutljivost na manjkajoče meritve velikosti rane in sposobnost napovedovanja poteka celjenja. Zapis modela je odvisen od načina merjenja velikosti rane, vendar smo ugotovili, da so modeli med seboj prevedljivi. Tedensko spremljanje površine rane je povsem zadovoljivo za oceno dinamike celjenja, meritev pa lahko celo poenostavimo na merjenje med seboj pravokotnih diagonal rane.

Analiza možnih mer uspešnosti celjenja kroničnih ran

Oblika rane nima pomembne vloge pri dinamiki celjenja kroničnih ran, kar pa še ne pomeni, da nima pomembne vloge pri hitrosti celjenja. Ker ima celjenje rane nelinearni potek, ni dovolj definirati mero hitrosti celjenja na osnovi dveh meritev velikosti rane, kakor jo najpogosteje najdemo definirano v literaturi. Tako definirana mera namreč ne upošteva nelinearnega poteka in je zato odvisna od časovnega intervala med meritvama. Definirali smo mero, ki upošteva nelinearni potek celjenja in je neodvisna od začetne velikosti in oblike rane. Ker mora mera hitrosti celjenja v prvi vrsti podajati čas do zacelitve rane, smo jo definirali kot produkt inverzne vrednosti časa do zacelitve in povprečnega polmera rane. Imenujemo jo prirastek tkiva v milimetrih na dan.

Ovrednotenje učinkov električne stimulacije z uporabo definirane mere uspešnosti celjenja kroničnih ran na obsežni bazi kliničnih podatkov

Na 300 primerih kroničnih ran stimuliranih z izmeničnim električnim tokom, enosmernim električnim tokom, konzervativno zdravljenih in zdravljenih s placebom smo ugotovili hitrejše celjenje stimuliranih ran. Z izmeničnim električnim tokom stimulirane rane so se celile značilno hitreje od konzervativno in s placebom zdravljenih ran. Hitrost konzervativno in s placebom zdravljenih ran se ni razlikovala. Z enosmernim električnim tokom stimulirane rane so se celile hitreje od konzervativno in s placebom zdravljenih ran, a razlika ni bila značilna.

Določitev vplivnih sistemskih in lokalnih parametrov na uspešnost celjenja kroničnih ran na osnovi kliničnih podatkov

Preverili smo vplivnost lokalnih in sistemskih parametrov na uspešnost celjenja kroničnih ran. Iskanja vplivnih parametrov na celjenje kroničnih ran smo se v prvem koraku lotili na osnovi analitičnih statističnih pristopov. Ker pri uporabi teh metod predpostavimo statistično neodvisnost parametrov in iščemo le linearne povezave, po pričakovanjih nismo našli veliko značilnih povezav. Zato smo v naslednjem koraku uporabili metode induktivnega strojnega učenja (odločitvena in regresijska drevesa) in z njimi ovrednotili vplivnost posameznih parametrov na hitrost celjenja in znanje predstavili v obliki dreves.

Sistem za napovedovanje uspešnosti zdravljenja kroničnih ran

Znanje predstavljeno v obliki dreves in dinamičnega modela celjenja kroničnih ran je osnova ekspertnega sistema za napovedovanje hitrosti celjenja. Iz vrednosti parametrov, ki so znani ob sprejemu bolnika v bolnišnično oskrbo ni mogoče napovedati hitrosti celjenja rane. Po štirih tednih opazovanja rane se ocenjena hitrost iz dinamičnega modela ne razlikuje značilno od dejanskega. Z vključitvijo znanja predstavljenega v obliki dreves pa se ta čas še skrajša. Po dveh tednih opazovanja poteka celjenja rane lahko že ocenimo hitrost celjenja in s tem tudi čas do zacelitve rane. Ekspertni sistem je zdravniku v pomoč pri odločitvah, ali je izbrani način zdravljenja uspešen ali pa ga je potrebno spremeniti.

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Izjavljam, da sem avtor te disertacije, ki je nastala pod mentorstvom izr. prof. dr. Damijana Miklavčiča. Delo drugih sodelavcev je razvidno iz člankov v dodatkih A, B, C in D ter iz zahvale.

V Ljubljani, 19. junij 2000.

David Cukjati

Dodatek A

Mathematical modeling of chronic wound healing

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Mathematical modeling of chronic wound healing

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Abstract – The wound-healing process has previously been modeled either with exponential or with linear curves. In the present study, we proposed a new model, called delayed exponential model, and compared all three models. Assessment of the models was based on healing data of two large groups of pressure ulcers in spinal-cord-injured (SCI) patients. The first group consisted of conventionally treated wounds and the second group of wounds additionally treated with biphasic electric-current-pulse stimulation, which was applied locally to the wound. Linear, exponential, and delayed exponential curves were fitted to experimental data (weekly measurements of the wound surface area). Numerical criteria, in the form of the least sum of squares of errors and goodness-of-fit, were calculated for each wound and model. Both numerical criteria showed that delayed exponential model offers the best fit of the three models tested.

Keywords – electric stimulation, pressure ulcers, curve fitting

1 Introduction

A majority of the reports in the literature that deal with mathematical description of the wound-healing process assume the healing process to be linear, and accordingly calculate the percentage change over time in the wound surface area or the wound volume [KLOTH AND FEEDAR, 1988, GAULT AND GATENS, 1976]. Other authors claim that for most chronic wounds, fitting errors are reduced when exponential fitting is applied, i.e., that the healing process, once triggered, exhibits exponential behavior [STEFANOVSKA *ET AL.*, 1993, KARBA *ET AL.*, 1991]. Observing a large group of pressure ulcers, treated either conventionally or with electrical stimulation in a previous study that we had done [JERČINOVIĆ *ET AL.*, 1994], we found the healing process to be delayed for a period from few days to a few weeks in 50% of wounds after beginning of the particular treatment. We thus suggested a new model, called delayed exponential model, which encompasses this feature of "delayed" healing.

Wounds of different etiologies, such as vascular wounds, amputational wounds, and pressure ulcers, heal with different dynamics. We therefore assessed the models described above with pressure ulcers in uniform population of spinal-cord-injured (SCI) patients, treated either conventionally (control group) or additionally with biphasic electric-current-pulse stimulation applied locally to the wound (electric stimulation group).

2 Materials and Methods

In our study, the wound-healing process was evaluated through weekly measurements of wound surface area. Criteria for inclusion of wound cases in the assessment of healing models were a minimal number of wound-area measurements (at least 3) and minimum initial wound area (1 cm^2). Wounds that had previously been treated surgically were excluded from analyses. With the foregoing inclusion criteria, the control (CO) group consisted of 40 patients with 59 wounds, and the electric-stimulation (ES) group consisted of 74 patients with 106 wounds.

Patients from CO group received conventional treatment of their wounds for 1 month. If within this month some healing was observed, the patient remained in this group and data were collected until complete closure of the wound. If within the first month of conventional treatment no healing occurred, or if the wound increased in size, the patient was assigned to the ES group [JERČINOVIĆ *ET AL.*, 1994]. This was done for obvious ethical reasons. No significant difference was obtained between exponential and linear models for the CO group, because most of the wounds in the CO group were followed for only about 1 month (35 ± 18 days), whereas the mean observation period for wounds in the ES group was 63 ± 45 days. For short observation times, such as 1 month, exponential and linear fits were of very similar quality.

Linear, exponential and delayed exponential curves, described by Equations 1, 2, and 3, respectively, were fitted to experimental data, i.e., measurements of wound area.

$$\hat{S}_l = \Theta_l t + S_0 \quad (1)$$

$$\hat{S}_e = S_0 e^{-\Theta_e t} \quad (2)$$

$$\hat{S}_d = S_0 e^{-\Theta_d (t-T)} \quad (3)$$

where $\hat{S}_l$, $\hat{S}_e$, and $\hat{S}_d$ represent estimated values of wound surface area at time *t*, when the time course of the surface area is fitted linearly, exponentially, and delayed-exponentially, respectively; S_0 represents the fitted initial value of the wound surface area (fitted area of the wound surface at the beginning of the particular treatment); Θ_l is the linear healing rate; Θ_e is the exponential healing rate; and Θ_d is the delayed exponential healing rate; and *t* is time expressed in days.

Fig. 1 illustrates the linear, exponential, and delayed exponential fitting for a typical wound case in the ES group.

Two numerical criteria were used for assessing linear, exponential, and delayed-exponential models. The first criterion was the least sum of squares of errors (LSSE) (eqn 4) and the second one goodness-of-fit (r^2) (eqn 5):

$$LSSE = \sum_{i=1}^{n} \left(\hat{S}_i - S_i \right)^2 \quad (4)$$

$$1 - r^2 = \frac{\sum_{i=1}^{n} \left(\hat{S}_i - S_i \right)^2}{\sum_{i=1}^{n} S_i^{\,2} - \frac{1}{n} \left(\sum_{i=1}^{n} S_i \right)^2} \quad (5)$$

where S_i represents the *i*th measured value of the wound surface area (experimental data); $\hat{S}_i$ represents the ith estimated value of the area of the wound surface; and *n* represents the number of ulcers.

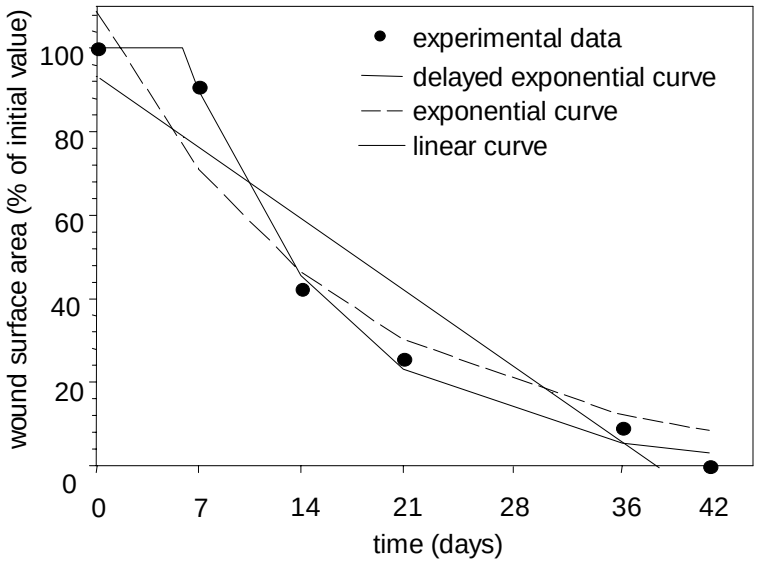

Fig. 1 *Data fitting with linear, exponential, and delayed exponential curves for a typical wound case from the electric stimulation (ES) group.*

Table 1 *The mean value of the least sum of squared errors for linear, exponential, and delayed exponential fit.*

	CO group	ES group	Both groups
Number of ulcers	59	106	165
Mean $LSSE_l \pm SE$	885,2 ± 172,7	1808,9 ± 274,5	1478,6 ± 189,7
Mean $LSSE_e \pm SE$	956,4 ± 209,9	1264,2 ± 312,4	1154,2 ± 214,1
Mean $LSSE_d \pm SE$	589,0 ± 158,6	783,6 ± 190,3	714,0 ± 134,6

CO = control; ES = electric stimulation; $LSSE_l$ = least sum of squared errors for linear model; $LSSE_e$ = least sum of squared errors for exponential model; $LSSE_d$ = least sum of squared errors for delayed-exponential model; SE = standard error.

Table 2 *Mean value of goodness-of-fit for linear, exponential and delayed-exponential fit.*

	CO group	ES group	Both groups
Number of ulcers	59	106	165
Mean $r_l^2 \pm$ SE	0,7327 ± 0,0366	0,7720 ± 0,0223	0,7581 ± 0,0193
Mean $r_e^2 \pm$ SE	0,7301 ± 0,0368	0,8444 ± 0,0224	0,8040 ± 0,0199
Mean $r_d^2 \pm$ SE	0,8064 ± 0,0363	0,8856 ± 0,0204	0,8576 ± 0,0186

CO = control; ES = electric stimulation; r_l = goodness-of-fit for linear model; r_e = goodness-of-fit for exponential model; r_d = goodness of fit for delayed-exponential model; SE = standard error.

3 Results

After fitting the healing of all wounds with three models, we calculated mean values and standard errors of LSSE and r^2. The mean values of the least sum of squared errors for linear ($LSSE_l$), exponential ($LSSE_e$) and delayed-exponential ($LSSE_d$) fit of ulcer healing in the study are given in Table 1.

The mean value of goodness-of-fit for linear (r_l^2), exponential (r_e^2), and delayed-exponential (r_d^2) fit of healing of ulcers included in the study are given in Table 2.

For our sample of 165 ulcers, the LSSE of the delayed-exponential model was 38.1% and 51.7% smaller than LSSEs for exponential and linear models, respectively. Goodness-of-fit of the delayed-exponential model was 6.7% and 13.1% greater than goodness-of-fit for the exponential and linear models, respectively.

For the CO group of wounds, the LSSE of the delayed-exponential model was 38.4% and 33.5% smaller than the LSSEs for the exponential and linear models, respectively. Goodness-of-fit of the delayed-exponential model in this group of wounds was 10.5% and 10.1% greater than goodness-of-fit for the exponential and linear models, respectively.

For the ES group of wounds, the LSSE of the delayed-exponential model was 38% and 56.7% smaller than the LSSEs for the exponential and linear models, respectively. The delayed-exponential model for the ES group of wounds was characterized by a 4.9% and 14.72% better goodness-of-fit than with the exponential and linear models, respectively.

Both numerical criteria show that delayed-exponential model offers the best fit of the three models tested.

Because of non-normal distribution of data, the nonparametric Wilcoxon's signed rank test was used to determine whether there was a significant difference between the mean values of LSSE and goodness-of-fit for the wound-healing models tested. For our sample of 165 ulcers, the hypothesis for equality of mean LSSE and goodness-of-fit for the linear, exponential, and delayed-exponential models could be rejected at a significance level of $p = .005$ when comparing the fit with the delayed-exponential with that of the exponential, as well as that of the linear model.

For the CO group of wounds, the hypothesis for equality of LSSE and goodness-of-fit could be rejected at a significance level of $p \leq .001$ when comparing the fit with the delayed exponential with the fit with exponential model, and at a significance level of $p = .002$ when comparing the fit with the delayed-exponential with the fit with the linear model.

For the ES group, the foregoing hypothesis could be rejected at a significance level of $p \leq .001$ when comparing fit with the delayed-exponential and exponential models, as well as when comparing fit with the delayed-exponential and linear models. The obtained results demonstrate that a delayed-exponential curve fits the healing process significantly better than do exponential or linear curves in both the CO and ES groups.

The difference between exponential and linear models was found to be non-significant for the CO group ($p = .210$), whereas the exponential model was significantly better in the ES group ($p \leq .001$). This result was obtained by observing both assessment criteria: LSSE and goodness-of-fit.

4 Conclusions

The delayed-exponential model was found to offer a better description of the wound-healing process for pressure ulcers in SCI patients than were the exponential and linear models. However, it also has several drawbacks. It introduces an additional parameter “delay” (T), the meaning of which is not easily identifiable in physiological terms. Application of the model with more parameters also requests greater number of experimental data to be trustworthy, which necessarily means longer observation periods. Moreover, and not least, the delayed-exponential model is relatively mathematically complicated, which makes its wider acceptance by other groups questionable. The latter certainly presents an important drawback, making general comparison of wound-treatment efficacies more difficult.

Additionally, it should be pointed out that the wound-healing process is not merely a surface phenomenon. It can be described by wound surface area, but is also dependent on other parameters, such as wound duration before the beginning of a particular

treatment, wound depth, the patient's age, duration of patient's disability, and the patient's general health status. The progress of healing also strongly depends on the location of the wound [JERČINOVIĆ *et al.*, 1994]. Basing the healing rate, Θ only on changes in wound area therefore does not provide a complete description of the healing process; the healing rate should additionally contain at least information about the wound depth. However, owning to problems with measurement of wound depth, as well its incorporation into the mathematical description of the healing processes, wound area as the only parameter seems to be a reasonably accurate compromise solution.

Our further studies will be devoted to improving the understanding of model parameters (delay, *T*, and wound healing rate, Θ) and their correlation with other parameters of the wound-healing process. The model parameters will be used in combination with other parameters of the wound-healing process in a prediction study in which we will try to build a classifier for prediction, after treatment is applied for a definite time, of wound healing rate.

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Dodatek B

Modelling of chronic wound healing dynamics

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Abstract – Following chronic wound area over time can give us a general overview of wound healing dynamics. Decrease or increase in wound area over time has been modeled either with exponential or linear models, which are two-parameter mathematical models. In many cases of chronic wound healing, a delay of healing process was noticed. Such dynamics cannot be described solely with two parameters. The reported study deals with two-, three-, and four-parameter models. Assessment of the models was based on weekly measurements of 226 chronic wounds of various aetiologies.

Several quantitative fitting criteria, i.e. goodness of fit, handling missing data and prediction capability, and qualitative criteria, i.e. number of parameters and their biophysical meaning were considered. The median of goodness of fit of three- and four-parameter models was between 0.937 and 0.958, and the median of two-parameter models was 0.821 to 0.883. Two-parameter models fitted wound area over time significantly ($p = .010$) worse than three- and four-parameter models. The criterion handling missing data provided similar results, with no significant difference between three- and four-parameter models. Median prediction error of two-parameter models was between 111 and 746, three-parameter models resulted in error of 64 to 128, and finally four-parameter models resulted in significantly highest prediction error of 407 and 238.

Based on the values of quantitative fitting criteria obtained, three parameters were chosen as the most appropriate. Based on qualitative criteria, the delayed exponential model was selected as the most general three-parameter model. It was found to have good prediction capability and in this capacity it could be used to help physicians choose the most appropriate treatment for patients with chronic wounds after an initial three-week observation period, when median error increase of fitting is 74%.

Keywords – mathematical modelling, wound healing, chronic wounds

1 Introduction

CHRONIC WOUNDS are slow- or non-healing wounds [WALDORF and FEWKES, 1995; YARKONY, 1994] that can last for weeks, months or even years despite adequate and appropriate care. Such wounds are difficult and frustrating to manage. Typical chronic wounds are pressure ulcers in spinal cord injured patients, ischemic ulcers in lower extremities of patients with peripheral vascular disease, ulcers in geriatric patients and wounds after limb amputations [DAGHER, 1985]. Patients are subjected to discomfort, stress, and the cost of the long-term conventional treatment required to heal such ulceration is high. Therefore extensive efforts have been made to find a treatment that would accelerate the wound healing process. One therapeutic modality is electrical stimulation, which has been proved to accelerate wound healing by number of research groups [GENTZKOW and MILLER, 1991; VODOVNIK and KARBA, 1992] and is regularly used for more than a decade at the Institute of the Republic of Slovenia for Rehabilitation. At the Faculty of Electrical Engineering in Ljubljana a database of all treated patients is maintained.

Despite different research groups having proved that electrical stimulation can accelerate wound healing, it is still not widely used. One of the reasons could be a non-unified method of wound healing dynamics quantification. Most researchers use weakly measurements of wound area, depth and/or volume [STEFANOVSKA *et al.*, 1993]. These data allow quantitative determination of wound healing dynamics; however, use of different mathematical models to estimate wound healing rate renders published reports difficult to compare. The wound healing rate is estimated as the difference between the wound area in week 4 and the initial wound area normalized to the initial wound area [JOHNSON, 1997]; as the average of the sequentially computed weekly healing rates (normalized difference between two sequential measurements) [BAKER *et al.*, 1997]; as a percentage of the initial wound size at 12 weeks [LUNDEBERG *et al.*, 1992]; as the time needed to complete wound closure [BIRKE *et al*., 1992]; as the average percentage reduction in wound size each week over a four-week observation period [FEEDAR *et al*., 1991]; as the average linear healing of the wound edge toward the center of the wound [GORIN *et al.*, 1996], and using a two-parameter exponential wound

healing model by JERČINOVIĆ *et al.* (1994). Wound healing process models in the above reports are generally based on a two-parameter wound healing rate estimate and an estimate of the initial wound area. In addition to wound healing modeling, different classification systems for monitoring the dynamic process of chronic wound healing have been introduced [CUDDIGAN, 1997]. In these systems scaling of wound status is determined by one or several indicators of wound healing such as the wound area, wound exudate and surface appearance [BARTOLUCCI and THOMAS, 1997].

Two-parameter wound healing models exclude the possibility of considering an initial delay to healing following the start of observation and/or specific therapy, which is currently noticed in chronic wounds. Such wound healing dynamics cannot be described solely with two-parameters. In our study three- and four-parameter models were considered in order to find the most general mathematical model of chronic wound healing dynamics. An optimal mathematical model for wound healing should satisfy the following criteria:

- it should have a minimum number of parameters;
- variables described in the model should be measurable so that collection of experimental data is possible (e.g. wound area);
- it should give a good fit to the experimental data, irrespective of wound aetiology, location and type of treatment;
- it should be capable of predicting the wound healing process with reasonable accuracy;
- it should have a biophysical basis;
- it should improve the general understanding of wound healing.

Chronic wound treatment results of different research groups can only be compared if standardized parameters of wound healing are used.

Present study of chronic wound healing dynamics modeling was performed in the following four steps:

- definition of criteria for inclusion of wound cases in the assessment of mathematical models;
- selection of possible two-, three- and four-parameter models;
- selection of criteria for fitting quality determination; and
- comparison of models and selection of the best model.

2 Criteria for inclusion of wound cases

Wound healing dynamics can be described using weekly measurements of wound area, depth and/or volume. Because measurements of wound depth and volume involve invasive methods, which could interfere with healing, these measurements are generally avoided. Planimetric measurements of wound area are not invasive and can be performed quickly and easily. In the present study, healing process modelling was performed based on wound area measurements, although an error is automatically introduced when using a two-dimensional curve for the description of a three-dimensional wound cavity. Wounds were considered to be healed at closure of the epithelium (i.e. the wound no longer open). Wound area was recorded at weekly intervals. During the course of the clinical study dealing with the effects of electrical stimulation on the healing of chronic wounds, information on 390 wounds of different aetiologies in 266 patients was collected. Patients were examined by a physician for an initial assessment of their wound status and relevant factors. The experimental procedure was explained to them and all patients agreed to participate in the study by signing an informed consent form [JERČINOVIĆ *et al*, 1994].

The first criterion for inclusion of wound cases in the assessment of mathematical models of chronic wound healing comprised a minimum of five consecutive wound area measurements over time since at least one more measurement is needed than there are model parameters. The second criterion was a minimal initial wound area of 100 mm^2, smaller areas being difficult to measure accurately. The last criterion demands no plastic surgery at the wound site before or during the study. Altogether 226 chronic wounds met these inclusion criteria. This group involved wounds of various aetiologies (e.g. vascular (arterial or venous) ulcerations, amputation wounds, pressure ulcers, neuropathic ulcerations (diabetic ulcers), etc.), and locations on patients with various diagnoses (e.g. spinal cord injury (SCI), diabetes mellitus, sclerosis multiplex, vascular diseases, etc.). The distribution of wounds included in the study with respect to aetiology and diagnosis is presented in Table 1. Wounds were treated either solely conventionally or with biphasic [JERČINOVIĆ *et al.*, 1994] or direct current electrical stimulation [KARBA *et al.*, 1997] or with sham treatment which involved placement of inactive electrodes. The distribution of the included wound cases with respect to the different treatments is presented in Table 2.

Table 2 *Treatment of wounds, which were included in the study.*

Type of treatment	Number of wounds
Biphasic electric current	135
Direct electric current	41
Conventional treatment only	30
Inactive electrodes (sham)	20

Table 1 *Distribution of wounds included in the study with respect to etiology and diagnosis. For one included patient diagnosis and etiology is unknown. Altogether 226 wounds have been included in analysis.*

		Diagnosis						
	Number of patients / Number of wounds	Spinal cord injury	Geriatrics	Sclerosis multiplex	Diabetes mellitus	Trauma	Vascular insufficiency	Total
Aetiology	Pressure ulcer	116/166	3/4	5/8	1/1	11/12	1/1	137/192
	Arterial ulceration	1/1						1/1
	Vascular ulceration		1/2		1/2		5/5	7/9
	Neurotrophic ulceration				15/15			15/15
	Traumatic ulceration, amputation wounds					7/8		7/8
	Total	117/167	4/6	5/8	17/18	18/20	6/6	167/225

3 Mathematical models of wound healing dynamics

A wound healing model is mathematical expression describing change of wound size (i.e. wound area) with respect to time. When wounds are included in the study at the start of observation they can be extremely heterogeneous in term of size. By normalizing measured wound areas to initial values, these differences are eliminated and data analysis facilitated. Researchers generally use linear (1) and exponential (2) two-parameter models to represent the wound healing process.

$$\hat{S}(t) = S_{LIN} - \theta_{LIN} t \tag{1}$$

$$\hat{S}(t) = S_{EXP} \cdot e^{-\theta_{EXP} t} \tag{2}$$

where S_{LIN} and S_{EXP} are the estimated initial wound areas expressed as a percentage of the initial wound area, and parameters θ_{LIN} and θ_{EXP} are wound healing rates in % per day. Positive values of wound healing rate θ indicate wound area decreasing with time (wound is healing) and negative values indicate increasing wound area (non-healing wound). Both models are distinguished by a small number of parameters, which have biophysical meaning. However, neither of models has an adequate physiological basis. Most prominent disadvantage of the linear model is that it sets no limit to wound area (Fig. 1*a*). Knowing that wound area cannot be negative, a limitation should be introduced to the linear model to limit wound area to a minimum of 0%. The modified linear model is termed by piecewise linear model (3) (Fig 1*b*).

$$\hat{S}(t) = \begin{cases} S_{PLN} - \theta_{PLN} t ; S_{PLN} - \theta_{PLN} t \geq 0 \\ 0 \qquad\quad ; S_{PLN} - \theta_{PLN} t < 0 \end{cases} \tag{3}$$

The advantage of the exponential model (2) (Fig 1*c*) over the linear model is that it assumes wound healing rate to be proportional to wound area at time *t*. It also assumes wound area to be greater than zero. The exponential model allows the introduction of concept of halving time, the time required for wound area $S(t)$ to halve $t_{½}$ (4).

$$t_{½} = \frac{ln2}{\theta_{EXP}} \tag{4}$$

A Survey of analyzed normalized wound area time plots revealed that 51% of wounds which fulfilled the inclusion criteria have an exponential wound healing process with an initial delay longer than 3.5 days (half a week); in 40% of wounds the delay was more than seven days and in 26% of wounds the delay was more then 14 days. Fig. 2 shows the distribution of time delay as a histogram plot. Such wound healing dynamics cannot be described with a two-parameter model, which led to the introduction of the parameter *T* to describe the time delay between the start of observation and the onset of healing, expressed in days. This modified exponential model was termed the delayed exponential model (5) (Fig 1*d*):

$$\hat{S}(t) = \begin{cases} S_{\mathrm{DEX}} & ; t \leq T_{DEX} \\ S_{DEX} \cdot e^{-\theta_{DEX}(t - T_{DEX})} & ; t > T_{DEX} \end{cases} \tag{5}$$

where S_{DEX} is the estimated initial wound area expressed as a percentage of the initial wound area, θ_{DEX} is the wound healing rate in $\%day^{-1}$ and T_{DEX} is the time delay in days. The delayed exponential model and the piecewise linear model have non-continuous first partial derivatives of model parameters.

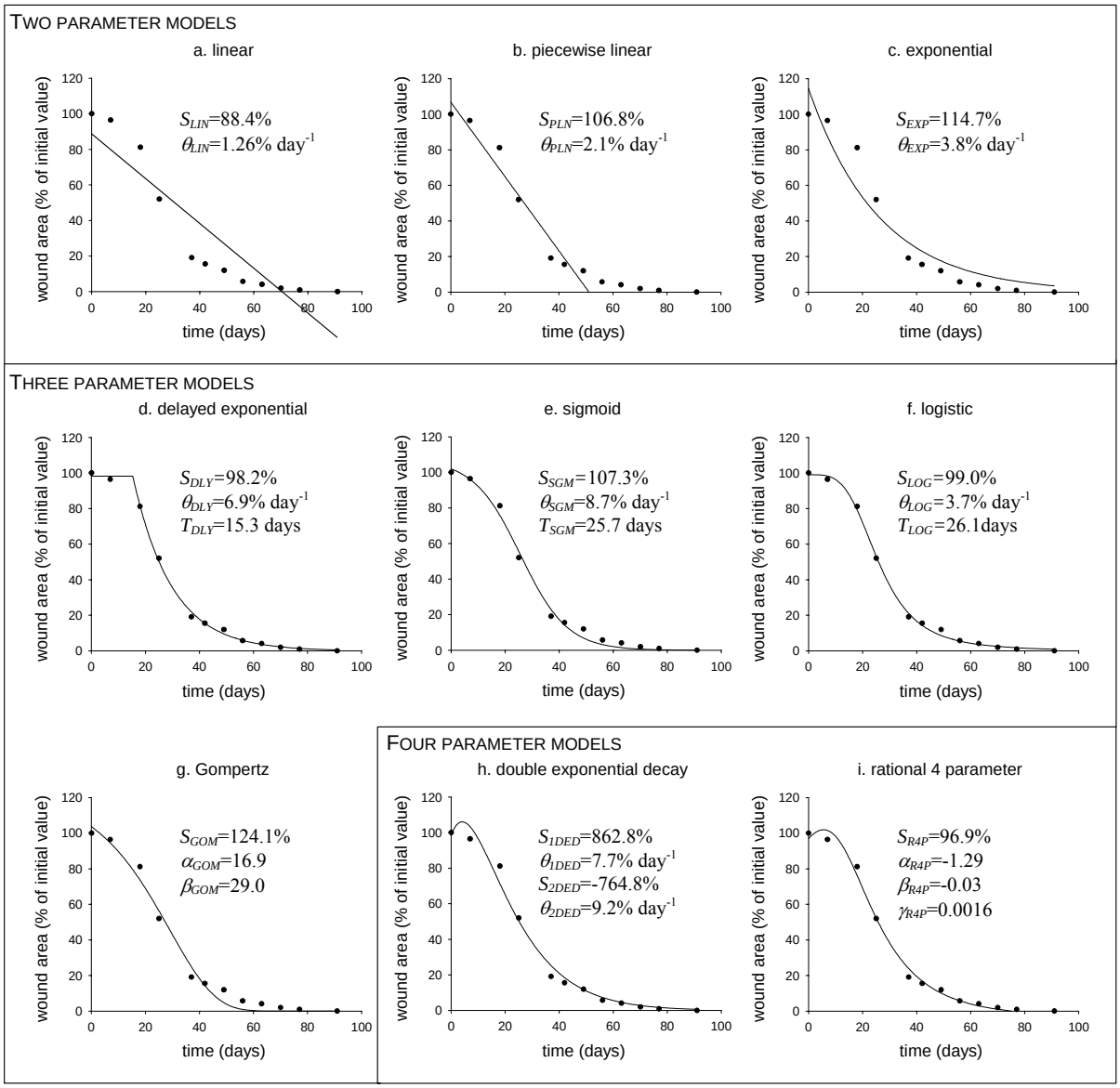

Fig. 1 *Graphical presentation of investigated mathematical models based on follow-up measurements of 36 old male spinal cord injured patient. Initial pressure ulcer area was 1315mm^2 and after 92 days of treatment with biphasic electrical stimulation it has been closed.*

Many biological processes can be described by three-parameter sigmoid model (6) shown in Fig. 1*e*.

$$\hat{S}(t) = \frac{S_{SGM}}{1 + e^{\frac{t - T_{SGM}}{\theta_{SGM}}}} \tag{6}$$

In the literature describing tumor volume modelling [VAIDYA and ALEXANDRO, 1982; MIKLAVČIČ *et al.*, 1995], the logistic model (7) and the Gompertz model (8) are often considered. These three-parameter models could also be used to describe dynamics of the wound healing process. They are presented in Fig. 1*f* and 1*g*.

$$\hat{S}(t) = \begin{cases} \dfrac{S_{LOG}}{1 + \left| \dfrac{t}{T_{LOG}} \right|^{\theta_{LOG}}}; & \theta_{LOG} > 0 \\ \dfrac{S_{LOG} \cdot \left| \dfrac{t}{T_{LOG}} \right|^{-\theta_{LOG}}}{1 + \left| \dfrac{t}{T_{LOG}} \right|^{-\theta_{LOG}}}; & \theta_{LOG} \le 0 \end{cases} \tag{7}$$

$$\hat{S}(t) = S_{GOM} \cdot e^{-e^{\left(\frac{t - \beta_{GOM}}{\alpha_{GOM}} \right)}} \tag{8}$$

The parameters of the sigmoid and logistic model can be described in a similar fashion. S_{SGM} and S_{LOG} are estimated initial wound areas expressed as a percentage of the initial wound area, parameters θ_{SGM} and θ_{LOG} in %day^{-1} describe negative slope of the tangent to the curve at time points T_{SGM} and T_{LOG}, while T_{SGM} and T_{LOG} are the times needed for the wound area to decrease to 50% of the initial wound area, expressed in days. The parameters of the logistic and sigmoid models are thus biophysically explainable. The logistic model suffers from convergence problems when t approaches zero and/or when parameter T_{LOG} approaches zero.

The major drawback of the Gompertz model is that the equation describing it is not derived on any biophysical basis. In spite of the inability to find any biophysical meaning for the Gompertz model parameters it was still compared with other models.

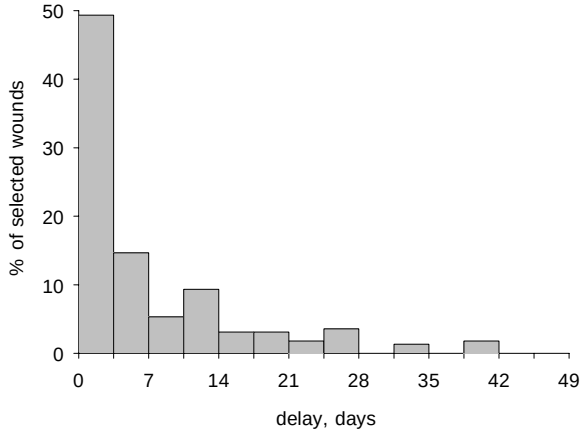

Fig. 2 *Histogram of wound distribution due to delay of healing process. Presented delay is delayed exponential model parameter T_{DLY}.*

Sums of exponential curves can be made to fit almost any time-dependent biologic data set by simply increasing the number of exponential components [BARDSLEY *et al.*, 1995]. We confined ourselves to two exponential components because with more exponentials, parameter estimates become imprecise and with two exponents the parameters have no unequivocal meaning.

$$\hat{S}(t) = S_{1DED} \cdot e^{-\theta_{1DED} t} + S_{2DED} \cdot e^{-\theta_{2DED} t} \qquad (9)$$

Double exponential decay model (9) is a four-parameter model and is shown in Fig. 1*h*. In general each added parameter adds one level of freedom and that means that model can better fit data. But such a model can be over-determined, consequently its parameters have no biophysical meaning (i.e. the model is ill-conditioned). In that case adding parameters cannot improve the general understanding of wound healing. It was also difficult to find good starting values when fitting the double exponential model to wound area measurements. One often has to try different sets of starting values to achieve convergence.

The rational four-parameter model (10) was also used because this model is highly flexible and fits to almost any data. It is shown in Fig. 1*i*. Its parameters, however, have no biophysical meaning.

$$\hat{S}(t) = \frac{S_{R4P} + \alpha_{R4P} \cdot t}{1 + \beta_{R4P} \cdot t + \gamma_{R4P} \cdot t^2} \qquad (10)$$

4 Model fitting

A computer program was developed to perform curve fitting and calculating five different fitting quality criteria. To fit an n-parameter nonlinear equation to wound area measurements, Marquardt-Levenberg algorithm [PRESS *et al.*, 1992] was used. This nonlinear regression algorithm seeks the values of parameters that minimize the sum of squared differences between the values of the observed and predicted values of the wound area. This process is iterative. It starts with initial parameter estimates, checks to see how well the equation fits, then continues to make better estimates until the differences between the residual sums of squares no longer decrease significantly (algorithm converges). The algorithm also needs first partial derivative of the fitted equation for each parameter. Weekly wound area measurement data were derived directly from a chronic wound database and results (model parameters and fitting quality criteria) were saved to the same database. A commercial statistical package was used to perform statistical analysis [SPSS INC., 1997].

5 Criteria for model assessment

Criteria for model assessment can be divided in quantitative and qualitative criteria.

5.1 Quantitative criteria

(a) The sum of squares of errors (SSE) can be interpreted as a measure of how much variation in S (wound area) is left unexplained by the model. It is defined as

$$SSE = \sum_{i=1}^{n} \left(\hat{S}_i - S_i\right)^2 \qquad (11)$$

where S_i is the ith wound area measured at discrete time t_i, i=1,2,...,n, $\hat{S}_i$ is the ith estimated value of wound area and n is the number of wound area measurements over time. SSE is minimized in the Marquardt-Levenberg optimization algorithm. When minimized it is called the least sum of squares of errors.

(b) Standard error of the estimate (SE) is the normalized SSE resulting from the elimination of the effects of a number of experimental points (n) and a number of model parameters (k). In eqn 12, denominator $n - k$ is used because k degrees of freedom (number of parameters or independent variables) are lost in estimating the model parameters. SE enables comparison of models with different numbers of parameters.

$$SE = \sqrt{\frac{SSE}{n-k}} = \sqrt{\frac{\sum_{i=1}^{n}\left(\hat{S}_i - S_i\right)^2}{n-k}} \qquad (12)$$

(c) The coefficient of determination or goodness-of-fit (r^2) is the portion of observed variation of the parameter S explained by the model (13). Good fit is characterized by the values of the criterion r^2 close to 1, while decreasing values of r^2 indicate worsening fit.

$$1 - r^2 = \frac{\sum_{i=1}^{n}\left(\hat{S}_i - S_i\right)^2}{\sum_{i=1}^{n} S_i^{\,2} - \frac{1}{n}\left(\sum_{i=1}^{n} S_i\right)^2} = \frac{SSE}{SST} \qquad (13)$$

Total sum of squares (SST) gives a quantitative measure of the total amount of variation in observed values of the parameter S. The objective of regression analysis is to find a model that is both simple (relatively few parameters) and provides a good fit to data. To balance the cost of using more parameters against the gain in r^2, many statisticians use the adjusted coefficient of multiple determination (adjusted r^2):

$$Adjusted\ r^2 = 1 - \frac{n-1}{n-k}\frac{SSE}{SST} = \frac{(n-1)r^2 - k + 1}{n-k} \qquad (14)$$

where k is the number of parameters and n the number of experimental points.

(d) Predicted residual error sum of squares (PRESS) is a measure of how well a regression model predicts missing data. Smaller values of PRESS indicate better capability of handling missing data. The PRESS (15) is computed by summing the squares of the prediction errors (the differences between predicted and observed values) for each observation (except the initial one), with that point deleted from the computation of the regression equation. In a case of n wound area measurements over time, test was performed $n - 1$ times and the average calculated:

$$PRESS = \frac{\sum_{i=1}^{n-1}\left(\hat{S}_i' - S_i\right)^2}{n-1} \qquad (15)$$

where $\hat{S}_i'$ is the estimated value of S_i, when the model was obtained without the ith observation, and n is the number of experimental points.

Because wound area was not always regularly measured, there is a lot of missing data in the chronic wound database and therefore the capability of the model in handling missing data is very important.

(e) Multiple predicted residual sum error of squares (MPRESS) measures the capability of the model to predict the dynamics of the wound healing process after a certain observation period. In contrast to PRESS, which removes only one measurement from a set of experimental data, MPRESS (16) removes the last $n - m$ measurements. The model is fitted to the first m measured experimental points (m=4,5,6 or 7) and then from calculated model parameters the error between wound area estimates and measured values in the remaining $n - m$ points is calculated. MPRESS can be calculated only for wounds followed regularly every week (with no missing data). There were 144 wounds weekly followed with no missing data, at least during the first three weeks (four measurements), 92 wounds were followed for at least the first four weeks, 70 wounds were followed for at least the first five weeks and 44 wounds were followed weekly with no missing data for at least six weeks. We seek the model with the highest prediction capability (lowest MPRESS). MPRESS was calculated for observation periods of three to six weeks.

$$MPRESS(m) = \frac{\sum_{i=m+1}^{n}\left(\hat{S}_i' - S_i\right)^2}{n-m} \qquad (16)$$

5.2 Qualitative criteria

In addition to above quantitative criteria, two qualitative criteria were used:

- The model should have a minimum number of parameters. Problems associated with ill-conditioned regression resulting from the use of over-determined models should be avoided.
- Model parameters should have biophysical meaning and the model should improve the general understanding of wound healing.

6 Results

All five listed quantitative criteria are unimodal and of non-parametric distribution for wound healing data when considering the above described models. Therefore, we compared their medians using non-parametric statistical methods. Mann-Whitney Rank Sum Test [DEVORE, 1995] was used to test the hypothesis of equality of models, which was rejected at selected significance level p=0.01. The data set of criteria is ordered from smallest to largest and the lower and upper quarter calculated. The lower (upper) quarter is the median of the smallest (largest) half of the data.

6.1 The sum of squares of errors

Medians of SSE for the nine models are presented on the left-hand side of Table 3. The hypothesis concerning the equality of SSEs of different models was tested and the resulting *p* values are presented on the right-hand side of Table 3. It can be seen that three-parameter models fit wound area measurements over time significantly better than two-parameter models. Two-parameter models resulted in values of SSE double (or more) those of three-parameter models. Furthermore, three-parameter models resulted in values of SSE roughly double those of four-parameter models. There are also differences among two-parameter models. The piecewise linear model and the exponential model are statistically significantly better than the linear model but there is no significant difference between the first two. There is also no significant difference between three-parameter models. It seems that all three-parameter models fit wound healing dynamics similarly. The fit of four-parameter models is significantly closer to experimental points than any two- or three-parameter model, while there is no difference among the selected four-parameter models.

6.2 Standard error of the estimate

From Table 4 it can be seen that the more parameters model has, the closer the fit to wound area measurements. Results of testing the hypothesis concerning equality of SEs of different models are very similar to results gained with SSE. The only difference is that there is no significant difference between the four-parameter double exponential decay model and three-parameter models.

6.3 Adjusted Coefficient of Determination

The higher the value of adjusted coefficient of determination the better model fits data. The value range is between 0 and 1. From Table 5 it can be seen that the results of hypothesis testing are the same as the results obtained with the measure SE. Measure definitions of SE and adjusted r^2 are similar and consequently their results are also similar. Both measures show that in contrast to results gained with SSE there is no significant difference between the four-parameter double exponential decay model and three-parameter models.

Table 3 *Medians of SSE for 226 analysed wounds and values of p.*

	SSE			*p*								
Model	Median	25%	75%	LIN	PLN	EXP	DEX	SGM	LOG	GMP	DED	R4P
LIN	931	418	2369	1.000	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PLN	610	257	1370		1.000	0.687	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
EXP	567	227	1340			1.000	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
DEX	277	98	772				1.000	0.957	0.965	0.890	**0.004**	**<0.001**
SGM	284	107	769					1.000	0.937	0.824	**0.005**	**<0.001**
LOG	292	80	776						1.000	0.920	**0.005**	**<0.001**
GMP	282	111	760							1.000	**0.002**	**<0.001**
DED	169	58	604								1.000	0.176
R4P	145	31	549									1.000

LIN – linear, PLN – piecewise linear, EXP – exponential, DEX – delay exponential, SGM – sigmoid, LOG – logistic, GMP – Gompertz, DED – double exponential decay and R4P – rational four parameter model. Values of p equal or less than significance level 0.01 are printed in bold.

Table 4 *Medians of SE for 226 analysed wounds and values of p.*

	SE			*p*								
Model	Median	25%	75%	LIN	PLN	EXP	DEX	SGM	LOG	GMP	DED	R4P
LIN	13.2	8.9	17.6	1.000	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PLN	9.4	6.9	14.3		1.000	0.694	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
EXP	10.0	5.8	15.4			1.000	**<0.001**	**<0.001**	**<0.001**	**0.001**	**<0.001**	**<0.001**
DEX	7.5	4.5	11.7				1.000	0.963	0.902	0.834	0.279	**0.004**
SGM	7.2	4.7	12.4					1.000	0.984	0.784	0.339	**0.004**
LOG	7.5	4.3	11.7						1.000	0.761	0.347	**0.007**
GMP	6.9	4.9	12.4							1.000	0.220	**0.002**
DED	6.8	4.3	11.8								1.000	0.055
R4P	5.7	3.3	10.7									1.000

Table 5 *Medians of Adjusted r^2 for 226 analysed wounds and values of p.*

	Adjusted r^2			*p*								
Model	Median	25%	75%	LIN	PLN	EXP	DEX	SGM	LOG	GMP	DED	R4P
LIN	0.821	0.658	0.907	1.000	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PLN	0.885	0.757	0.951		1.000	0.714	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
EXP	0.883	0.731	0.957			1.000	**<0.001**	**0.001**	**0.001**	**0.002**	**<0.001**	**<0.001**
DEX	0.941	0.822	0.977				1.000	0.964	0.962	0.881	0.425	**0.007**
SGM	0.946	0.792	0.978					1.000	0.985	0.815	0.454	**0.010**
LOG	0.937	0.812	0.982						1.000	0.837	0.482	**0.008**
GMP	0.946	0.789	0.975							1.000	0.344	**0.005**
DED	0.943	0.838	0.981								1.000	0.045
R4P	0.958	0.846	0.988									1.000

Table 6 *Medians of PRESS and values of p.*

	PRESS			*p*								
Model	Median	25%	75%	LIN	PLN	EXP	DEX	SGM	LOG	GMP	DED	R4P
LIN	226	26.7	9.4	61.3	1	**0.007**	**0.002**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PLN	222	19.2	6.1	41.9		1	0.524	**0.002**	**0.006**	0.020	**0.006**	**0.002**
EXP	225	15.3	5.2	52.2			1	0.041	0.086	0.190	0.083	0.030
DEX	217	11.5	4.0	27.3				1	0.750	0.427	0.770	0.651
SGM	224	11.7	3.8	35.9					1	0.643	0.968	0.516
LOG	206	13.2	4.3	32.4						1	0.633	0.275
GMP	225	10.7	3.3	37.5							1	0.531
DED	217	8.6	3.0	43.5								1
R4P	223	15.6	4.1	68.0								

Table 7 *Medians of MPRESS (m=5) for 92 wounds and values of p.*

	MRESS (m = 5)			*p*								
Model	Median	25%	75%	LIN	PLN	EXP	DEX	SGM	LOG	GMP	DED	R4P
LIN	746	199	2589	1	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.100	**<0.001**
PLN	134	35	429		1	0.852	0.057	0.337	0.764	0.396	**0.003**	0.012
EXP	111	29	607			1	0.067	0.316	0.841	0.317	**0.003**	0.021
DEX	74	18	179				1	0.488	0.019	0.532	**<0.001**	**<0.001**
SGM	74	22	413					1	0.171	0.928	**<0.001**	**<0.001**
LOG	128	28	405						1	0.171	**0.005**	0.022
GMP	64	14	461							1	**<0.001**	**<0.001**
DED	407	43	3034								1	0.337
R4P	238	66	844									1

6.4 Predicted residual error sum of squares

The PRESS measures ability of a model to handle missing data. Using the Levenberg-Marquardt algorithm, problems with convergence were encountered in some cases. The numbers of successfully converged cases are shown in the second column of Table 6. It can be concluded from results shown in Table 6 that a larger number of model parameters does not automatically mean significantly lower PRESS. That can be seen in the case of the rational four-parameter model, which handles missing data very badly, although it has four parameters. However the highest PRESS was found in the two-parameter linear model which has also significantly higher error than the other two-parameter models, piecewise linear and exponential. Also, the two-parameter piecewise linear model is, in terms of PRESS, significantly worse than the delay exponential, sigmoid, Gompertz and double exponential model, while the two-parameter exponential model does not differ significantly from

the three- and four-parameter models. There is no statistically significant difference between three-parameter and four-parameter models. The lowest value of PRESS was obtained for the four-parameter double exponential model; however, the hypothesis regarding equality with other models could be rejected only for two-parameter models LIN and PLN.

6.5 Model prediction capability (MPRESS for m=4,5,6 and 7)

The MPRESS measures prediction capability of the model. Low values of MPRESS results in higher model prediction capability. The results shown in Table 7 are for prediction based on model fitting to the first five measurements: 92 wounds out of 226 analyzed wounds were followed regularly once per week for at least the first four weeks. The greatest prediction error was obtained using the linear model and the four-parameter double exponential model. Between these two models there is no significant difference. Other two- and three-parameter models are significantly better than the linear and double exponential model, but there is no significant difference between them. Predictability of the four-parameter rational model is significantly better than that of the linear model but equal to the piecewise linear, exponential and logistic model and has a significantly worse prediction capability than the delay exponential, sigmoid and Gompertz model. There is no significant difference between four-parameter models. From Table 7 it can be seen that the lowest error was produced with three-parameter models. Among three-parameter models there is no differences. Four-parameter models are significantly worse than three-parameter models, except in the case of the logistic model. The four-parameter double exponential decay model error is significantly greater than the error of piecewise linear and exponential models. The prediction capability of the four-parameter double exponential decay model is as bad as that of the worst model, the linear model. A characteristic of models with higher numbers of parameters is their flexibility, which, on one hand assures a good fit to experimental data, while on the other, decreases the prediction capability of models. Comparison of the prediction capability of models, illustrated by MPRESS, revealed the same relations for m=4, m=6 and m=7.

7 Discussion

Based on the results using quantitative criteria it can be concluded that the two-parameter linear model has the worst fit to experimental data. Other two-parameter models, piecewise linear and exponential, have a better fit but still significantly worse than three- and four-parameter models. Because the exponential model handles missing data significantly better than the piecewise linear model, the exponential model was found to be the best of the two-parameter models.

Three-parameter models have a good fit to wound area measurements, they can handle missing data well and have good prediction capability. Four-parameter models have even better fit, their handling missing data is comparable to three-parameter models but their prediction capability can only be compared to the prediction capability of two-parameter models. It can be concluded that optimal number of model parameters is three.

Between three-parameter models there are no statistically significant differences, but we can see that the logistic model produced at least 50% greater error when handling missing data than the other three-parameter models. The logistic model also cannot describe increasing wound area dynamics, because in the case of a negative wound healing rate the estimated initial wound area S_{LOG} is zero.

Qualitative criteria relating to biophysical meaning of model parameters were not fulfilled in the case of the Gompertz model. The delayed exponential model may be considered unreal because of its break point at time T_{DEX}. Biological systems works more like a sigmoid with smooth changes. If all wounds started to heal after a delay, then sigmoid would be the choice, but 49% of wounds started to heal with no delay (less than a half of week) and 6% of wounds did not heal at all. Such healing processes can still be represented with a sigmoid, but the meaning of its parameters cannot be determined. In cases when wounds started to heal with no delay, the sigmoid model estimated the initial wound area mean value to be 4374 ± 7451%. Such estimation has no biophysical explanation. The delayed exponential model is very similar to the exponential model in such cases. We conclude that the delayed exponential model is the most general model for wound healing dynamics over time.

Quantitative criteria for model prediction capability MPRESS can be used only for model comparison; it does not give an overview of the absolute prediction capability of the model. To achieve such a measure, the delayed exponential model prediction capability was further investigated. The relative prediction error measures the level of error increase if model is fitted only to the first m wound area measurements instead to all n measurements. It is calculated by dividing difference between the SSE of fit to all experimental data points and the SSE of fit to the first m experimental points calculated for all experimental points and the SSE of fit to all experimental points. Percentages are presented in Table 8. The level of error increase is 73% in the case of fitting after three weeks observation, 35% increase after four weeks observation, 34% increase after five weeks and 17% increase after six weeks. The goal of model prediction is to predict healing dynamics as accurately as possible and to make such prediction as soon as

possible. Optimal follow-up duration before predicting healing dynamics is four weeks, based on the mentioned two contradictory criteria.

Table 8 *Relative prediction error (RP) for delay exponential model.*

prediction based on	*No*	*median*	*25%*	*75%*
3 weeks	144	74	9	346
4 weeks	92	35	3	127
5 weeks	70	34	1	160
6 weeks	44	17	5	100

RP is calculated as difference between error sum of squares of fit to all measurements and error sum of squares of fit to first m measurements calculated for all measurements divided by error sum of squares of fit to all measurements. RP gives us a percentage estimate of error increase when delayed exponential model is fitted to less number of wound area measurements.

The exponential model is very close to three-parameter models in handling missing data. Although it has a greater prediction error than three-parameter models, the difference was not significant. The advantage of the exponential model is that it has only two-parameters.

As S_{DEX} describes estimated the initial wound area, which after normalization is always around 100% and can be eliminated from the wound healing rate description, parameters θ_{DEX} and T_{DEX} describe the wound healing process. In the exponential model only one parameter, θ_{EXP}, describes wound healing dynamics. That is very convenient when using different statistical methods as well as induction tree learning algorithms. Using a three-parameter model in such cases requires a new parameter to describe the wound healing rate determined from the parameter combination T_{DEX} and θ_{DEX} or even better from all three-parameters. If the goal is to compare wound healing rates, the exponential model should be used. Considering that almost half of all wounds started to heal with a delay less than half a week, the error due to fewer model parameters should not be increased too much. Three-parameter models allows one to separately study the delay of healing process and wound healing rate after delay.

8 Conclusion

In our study all wounds were pooled irrespective of wound aetiology, location and type of treatment because we were looking for the most general model of chronic wound healing dynamics. After considering a number of two-, three- and four-parameter models, the delayed exponential model was found to offer better fit and handling of missing wound area data over time than two- or four-parameter models and better describes the wound healing process than other three-parameter models. According to the two-parameter models, application of a model with more parameters requires more experimental data, which means longer observation periods, but it can still be fitted easily to four or more wound area measurements.

Delayed exponential model was proved to accurately describe the wound healing process and to have good prediction capability. This means that, based on wound area follow-ups in the first few weeks (three weeks minimum is recommended) healing process dynamics in the next weeks can be predicted. However, such prediction based on fitting wound area measurements to the model of wound healing dynamics described would be rather rough. Since the wound healing process is not merely a surface phenomena, other parameters should also be considered to increase prediction accuracy, such as patient and wound parameters. Patient parameters are patient identifiers, such as age, diagnosis and if he/she is a spinal cord injury patient, date of injury and degree of spasticity. Wound parameters could be duration of the wound from its appearance at start of treatment, wound type, wound grade, location and size. Also other parameters can be included, however they are rarely measured and we do not plan to use them in future: examples include bacteriological analyses, measurements of wound potentials, oximetry and NMR imaging. Finally we should not forget the type of treatment as a parameter that has very important effect on wound healing dynamics.

A future goal is to build a classifier for wound healing prediction where model parameters would be used in combination with patient and wound parameters. The resulting classifier for wound healing prediction could be realized as a computer application, which would not demand any modelling knowledge. Of course, use of a personal computer cannot be avoided. The clinician would enter the required wound and patient data and the application would return as an output a probability that the wound is going to heal with a certain healing rate using a specific type of treatment. Such application would be particularly useful as an aid to decision making on wound treatment (conventional treatment, plastic surgery, electric stimulation, etc.).

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Dodatek C

Digression on chronic wound healing rate

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MEDICAL & BIOLOGICAL ENGINEERING & COMPUTING (SUBMITTED)

Digression on chronic wound healing rate

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Abstract – Several wound healing rate measures have been introduced with the main goal to enable quantification of effects of various therapeutic modalities on healing of skin wounds. Different definitions of wound healing rate render comparison of clinical results difficult. The goal of our study was to examine effect of wound shape on wound healing dynamics and to propose a measure of wound healing rate that is independent on initial wound size.
Since wound area does not comprise information about wound shape, in contrary to advance of wound margin towards wound centre, we compared wound area dynamics, described by delayed exponential model, and advance of wound margin towards wound centre dynamics, described by delayed exponential rise to maximum model. Analysis was performed on 300 wound cases, whose surface was approximated with an ellipse or a circle. Parameters of delayed exponential rise to maximum model calculated for circular and elliptical wound approximations were compared with parameters of delayed exponential model. No significant differences between model parameters and descriptions were found. We concluded that incorporating wound perimeter (shape) does not improve wound healing dynamics description.
Due to its nonlinear nature, the healing process cannot be easily described with a single parameter - healing rate. Definition of wound healing rate should incorporate time needed to complete wound closure. Not all wounds were healed in observation time. If time to complete wound closure was predicted from delayed exponential model, whose parameters were obtained from weekly measurements of wound area for at least four weeks, no significant difference between actual and predicted time to complete wound closure was found. We compared wound healing rate defined as absolute area healed per day, percentage of initial area healed per day and advance of wound margin towards wound centre per day. Disadvantage of wound healing measures absolute area healed per day and percentage of initial area healed per day is their very limited use for comparison of healing rates of wounds with differing initial areas. This disadvantage was overcome by incorporating wound perimeter; thus obtaining the measure of advance of wound margin towards wound centre. We propose definition of healing rate expressed as the greatest advance of wound margin towards wound centre divided by time to complete wound closure.

Keywords – chronic wounds, wound healing rate, wound healing dynamics

1 Introduction

Cutaneous wound is any loss of skin integrity due to injury or illness. Since intact skin is of vital importance to protect organism against environment, regenerative mechanisms are activated to restore defect. The primary goal of healing is to restore preinjuried form and function of derma. Cutaneous wound healing is a dynamic biological process that begins after tissue injury and is divided into three overlapping phases: inflammatory, proliferative phase and maturation [WALDORF AND FEWKES, 1995]. If any of these phases or its part is suppressed, wound healing is prolonged or even prevented. Reasons for slower or retarded healing can be local, such as bacterial infection, which prolongs inflammatory phase, lower oxygen tension, which prolongs proliferative phase; or systemic, such as injuries of the nervous system, metabolic and ageing problems, which affect one or more phases of wound healing. When conservative methods of wound care cannot enable wound healing, wound is considered to be chronic. Such chronic wounds can last for months or even years, hinder normal course of rehabilitation and represent a major social, medical and economic problem.

This resulted in many treatment modalities which were tested and reported to facilitate chronic wound healing, including wound dressings [KANNON AND GARETT, 1995], low energy laser [GOGIA, 1995A], ultrasound [BROWN, 1995], ultrasound/ultraviolet treatment [NESSBAUM *ET AL.*, 1994], hyperbaric oxygen [GOGIA, 1995B], skin substitutes [SINGER AND CLARK, 1999; BREM *ET AL.*, 2000], use of growth factors [MARTIN *ET AL.*, 1992; KUNIMOTO, 1999] and electrical stimulation [VODOVNIK AND KARBA, 1992].

One of the treatment modalities, which is well documented and enables and facilitates chronic wound healing, is electrical stimulation. Since WOLCOTT *ET AL.* (1969) published promising results of extensive clinical study of electrical stimulation treatment, many reports confirmed positive effects of electrical stimulation, though different stimulation protocols were used. A review of literature reporting the use of electrical stimulation (Table 1) reveals little uniformity with respect to electrical signal properties, placement of stimulation electrodes and treatment regime. Practically all reports are rather exclusive regarding their specific treatment techniques and even quantification of treatment results (Table 2). Due to different quantification methods used it is impossible to make a quantitative analysis of the comparative advantages and disadvantages of different treatment modalities. In order to enable quantification and comparison of treatment efficacy, uniform measure of wound healing needs to be generally accepted, which ideally would fulfil the following criteria: simple calculation, suitable for statistical handling, transparency – evident physiological meaning, employability for different wound types, sizes, shapes and healing/non-healing courses. Comparable and uniform quantification method is important when optimal treatment regime is sought for. In spite of evident need for uniform measure of wound healing, several measures have been employed in literature to date. The aim of this paper is to examine and compare different measures, which were used by various authors, and to propose uniform measure of wound healing or so called wound healing rate. Evaluation of different measures was based on the data of 300 chronic wounds, which were primarily collected for the purpose of studying the effects of electrical wound treatment [STEFANOVSKA *ET AL.*, 1993, JERČINOVIĆ *ET AL.*, 1994 and KARBA *ET AL.*, 1997]. It involves wounds of various aetiologies (e.g. vascular ulcerations, amputation wounds, pressure ulcers, neuropathic ulcerations), locations and different treatment in patients with different diagnoses (e.g. spinal cord injury, diabetes mellitus, sclerosis multiplex, vascular diseases). The wound healing rate measure should describe healing irrespective of wound aetiology, location and treatment.

Table 1 *Diversity of electrical stimulation modalities for chronic wound healing.*

Stimulation type	Application time	Electrode polarity & placement	Wounds	Reference
Direct current, 0.2 – 1mA	2 hours of stimulation, 4 hours pause, three times a day.	Negative electrode over ulcer, change of polarity as wound progressed.	ischemic ulcers	WOLCOTT *ET AL.*, 1969
High voltage pulses, 100V - 175V, frequency of 105Hz	45 minutes per day, 5 days a week	Positive electrode over ulcer, switched if wound healing plateau is reached.	decubitus ulcers	KLOTH AND FEEDAR, 1988
Monophasic pulsed current (frequency of 128pps, peak amplitude of 29.2mA)	30 minutes, twice daily.	Negative electrode over ulcer, change of polarity as wound progressed.	pressure, vascular ulcers, trauma or surgery wounds	FEEDAR *ET AL.*, 1991
Alternating constant current square-wave pulses (80pps, pulse width 1ms, intensity-evoking paresthesias)	20 minutes twice daily for 12 weeks	Electrodes placed outside the ulcer surface area, polarity was changed after each treatment.	diabetic ulcers	LUNDEBERG *ET AL.*, 1992
Asymetric biphasic pulses (40pps, amplitude up to 35mA) in trains lasting 4s, followed by 4s pause.	30,60 or 120 min per day	Electrodes placed on the intact skin symmetrically on opposite sides of the wound.	pressure ulcers	JERČINOVIĆ *ET AL.*, 1994
Direct current, 0.6mA	2 hours per day	Positive electrode overlaid the ulcer.	pressure ulcers	KARBA *ET AL.*, 1997
Asymmetric and symmetric biphasic square-wave pulses, frequency of 50pps, amplitude below contraction	90 minutes per day	Electrodes placed on the intact skin symmetrically on opposite sides of the wound.	ischemic ulcers	BAKER *ET AL.*, 1997

Table 2 *A review of wound healing rate definitions.*

Measured values	Wound healing rate definition	Units	Frequency of measurements	Reference
width, *length*	$\frac{\pi/4 \times length_0 \times width_0 - \pi/4 \times length_n \times width_n}{(day_n - day_0) \times \pi/4 \times length_0 \times width_0} \times 100$	%/day	initial and at end of treatment	LYMAN *ET AL.*, 1970
width, *length*	$\frac{length_0 \times width_0 - length_4 \times width_4}{4 \times length_0 \times width_0} \times 100$	%/week	five in four weeks	FEEDAR *ET AL.*, 1991
area	$\frac{area_0 - area_i}{area_0} \times 100$; $i = 0,2,4,6,8,12.$	%	initial and after 2, 4, 6, 8 and 12 weeks.	LUNDEBERG *ET AL.*, 1992
area	Time needed to complete wound closure.	days	initial and final	BIRKE *ET AL.*, 1992
area	Fitting $S_0 \exp(-\theta t)$ or $S_0 + (-A \cdot t)$ to $\frac{area_i}{area_0} \times 100;\ \ i = 1,2,\ldots,n$ Parameters θ or A were defined as wound healing rate.	%/day	2<n≤5 in four weeks	JERČINOVIĆ *ET AL.*, 1994
granulation, *infection*, *drainage*, *necrosis*, *eschar*	Average change in Sessing scale (7 stage classification system) between two consecutive scorings.	scaling	twice per week	FERRELL *ET AL.*, 1995
area, *perimeter*	$\frac{area_0 - area_i}{\frac{1}{2}\left(perimeter_0 + perimeter_i\right)\left(day_i - day_0\right)}$	mm/day	initial and after two weeks	GORIN *ET AL.*, 1996
area	$\frac{area_0 - area_4}{area_0} \frac{28}{day_4 - day_0} \times 100$	%/four weeks	initial and after four weeks	JOHNSON, 1997
area	$\frac{1}{n-1} \sum_{i=1}^{n-1} \frac{\frac{area_{i-1} - area_i}{area_{i-1}}}{day_{i-1} - day_i} \times 7 \times 100$	%/week	weekly	BAKER *ET AL.*, 1997
area, *exudate*, *appearance*	Linear regression to PUSH (Pressure Ulcer Scale for Healing) values in week 0, 2, 4, 6 and 8.	scaling	initial and after 2, 4, 6 and 8 weeks	CUDDIGAN, 1997 BARTOLUCCI AND THOMAS, 1997

$Area_0$, $perimeter_0$, $length_0$ and $width_0$ are initial area, perimeter, length and width, respectively, and $area_i$, $perimeter_i$, $length_i$ and $width_i$ are wound area, perimeter, length and width after i weeks, respectively. Day_0 is initial assessment date and day_i is assessment date after i weeks. n is number of sequential wound area measurements.

2 Wound status assessment

Assessment of wound status is essential in clinical trials and practise for monitoring treatment efficacy. LAZARUS *ET AL.* (1994), proposed guidelines for assessment of wounds. They listed attributes that are clues to the cause, pathophysiology and status of the wound. Assessment of wound status should begin with the extent of the wound. Because the extent of the wound changes with time, it requires periodic assessment. There are several techniques that are employed to assess wound extent. To be clinically acceptable, the assessment of chronic wounds healing should be practical enough to be regularly used by nursing stuff, noninvasive and inexpensive. As presented in Table 2 most often wound area, wound perimeter or mutually perpendicular diameters (largest diameter of the wound and diameter taken at right angle to the largest one) are assessed. Wound volume and depth assessment techniques are invasive (dental moulds) [COVINGTON *ET AL.*, 1989] or require expensive equipment (stereoscopy, MRI) [PLASSMANN AND JONES, 1992] and are rarely periodically used. Since wounds are often irregular in shape and heal asymmetrically, different estimates of wound area are used. Acetate tracings can provide the

most accurate description of wound area and perimeter but require manual or computer planimetry ones the tracings are completed. Estimates of wound area can be derived from product of two mutually perpendicular perimeters, or by calculation of the area of a circle or ellipse from measured diameters. Surface area can also be estimated by simply comparing ulcers to pre-drawn circles or ellipses of known area. STEFANOVSKA *ET AL.* (1993) have established that the approximation of the wound area by the area of the ellipse, calculated from two diameters, does not significantly differ from the area obtained by planimetry. The measurement of two diameters is simple, reproducible, and easy to perform at the bedside.

Another wound status assessment possibility are scaling systems. They base on an assumption that wound extent is not sufficiently descriptive. Beside wound extent they also incorporate description of necrosis, surrounding skin colour, peripheral tissue edema and induration, granulation tissue, epithelialization, infection, drainage, eschar and exudates. Drawbacks of such scaling systems are their reliability and complexity. The most widely used pressure ulcer scaling system is the four stage system developed by the National Pressure Ulcer Advisory Panel (NPUAP) [NATIONAL PRESSURE ULCER ADVISORY PANEL (NPUAP), 1989]. NPUAP also warns that staging should not be used to determine progress towards wound healing. For this reason several tools have been proposed, which are responsive to changes during wound healing. These systems are still in various stages of testing, but most promising seems to be a seven point categorical Sessing scale [FERRELL *ET AL.*, 1995] and PUSH [BARTOLUCCI AND THOMAS, 1997] which is based on area, exudates and wound appearance. Scaling systems are widely used as a wound assessment alternative, as they are practical for daily monitoring. However it is still not clear if it is appropriate to use them for the follow-up of changes in wound healing. Small number of stages makes them easy to use and at the same time makes them not sensitive enough for wound healing progress description. Based on above considerations wound extent should be used for monitoring wound status when progress towards chronic wound healing has to be determined.

3 Wound healing process dynamics

If wound extent assessment is one-dimensional quantitative value (a scalar) and it is periodically assessed, linear or nonlinear regression can reveal wound healing dynamics over time. In our paper we consider wound extent assessed with perimeter, area or two mutually perpendicular diameters of the wound. One-dimensional wound extent can be achieved by using one of them or any of their combinations.

GILMAN (1990) defined a measure of wound extent that incorporates wound area and perimeter. It was termed advance of wound margin towards wound centre (eq. 1):

$$d_i = \frac{\Delta S_i}{\overline{p}_i} \tag{1}$$

where $\overline{p}_i = \frac{p_0 + p_i}{2}$ is mean perimeter measured in millimetres and calculated from initial perimeter and wound perimeter at time $t_i > t_0$ and $\Delta S_0 = S_0 - S_i$ is absolute change in wound area in mm^2. This measure is rarely used. According to authors, its advantages are independence on initial wound area and exact wound shape consideration.

Majority of other researchers use measures of wound extent, which are based on wound area measurements over time. They are defined as absolute or normalized wound area calculated from two diagonals or using planimetry.

Before defining wound healing rates based on presented one-dimensional wound extent measures, we have to examine their dynamics over time. Dynamics of absolute and normalized wound area over time is similar, therefore we concentrated on normalized wound area, where wound area was divided by initial wound area and multiplied by 100. We assumed that wound can be estimated with an ellipse and wound area S_i calculated from mutually perpendicular wound diameters a_i and b_i measured at time t_i (eq. 2) accordingly to STEFANOVSKA *ET AL.* (1993):

$$S_i = \frac{\pi}{4} a_i \cdot b_i \;;\; i = 0,1,\ldots,n-1 \tag{2}$$

where index i is describing wound extent assessment at time t_i, $t_0 = 0$ is time of initial wound assessment and n number of periodic assessments. Diameters a_i and b_i define width to length ratio r_i (eq. 3), which describes wound shape ($r_i \leq 1$).

$$r_i = \frac{b_i}{a_i} \tag{3}$$

Perimeter of wound estimated with the ellipse at time t_i was calculated according to eq. 4.

$$p_i = \pi \left[\frac{3}{4}\left(a_i + b_i\right) - \frac{1}{2}\sqrt{a_i \cdot b_i} \right] \tag{4}$$

Following normalized wound area or advance of wound margin towards wound centre over time can give us a general overview of wound healing dynamics. In following section both measures are considered.

In our recent study [CUKJATI *ET AL.*, 2000] we established that decrease (or increase) in normalized wound area over time is best described by a delayed exponential model. An example of such wound healing dynamics is presented in Fig. 1. Mathematical

description of delayed exponential model is given by eq. 5.

$$\hat{S}_i = \begin{cases} S_{DEX} & ;0 \le t_i < T_{DEX} \\ S_{DEX} e^{-\theta_{DEX}(t_i - T_{DEX})} & ; \quad t_i \ge T_{DEX} \end{cases} \tag{5}$$

where $\hat{S}_i$ is estimated wound area in percent of initial wound area and three parameters S_{DEX}, θ_{DEX} and T_{DEX} are describing wound healing dynamics. Parameter S_{DEX} [%] estimates initial wound area change, parameter θ_{DEX} [day^{-1}] defines time constant of exponent function and time delay of healing process initiation is defined by parameter T_{DEX} [*day*]. The choice and assessment of this mathematical model was based on periodic weekly measurements of 226 chronic wounds of various aetiologies and different treatments. We showed that model has good prediction capability and in this capacity it could be used to predict time needed to wound closure. This can be very useful in clinical trials, where not all wounds included in the study are healed within the observation period.

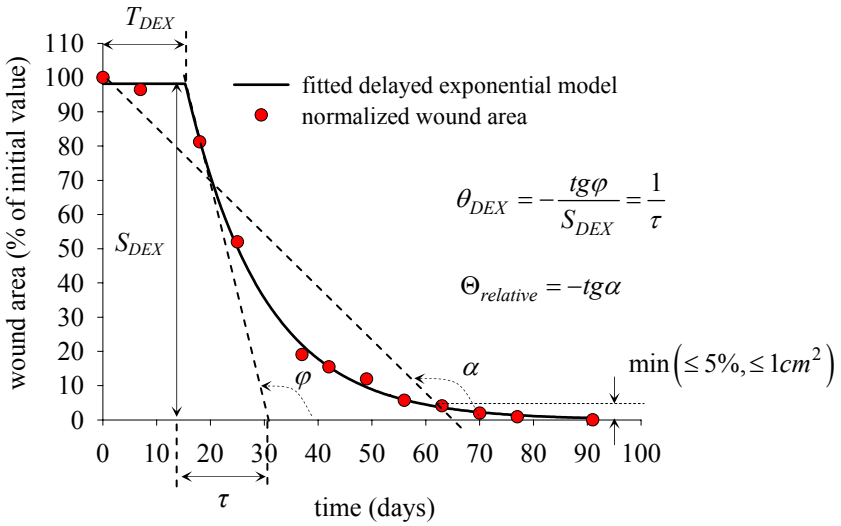

Fig. 1 *Example of following wound area and fitting delayed exponential model to normalized data. S_{DEX}, θ_{DEX}, T_{DEX} are calculated parameters of delayed exponential model and $\Theta_{relative}$ a measure of wound healing rate.*

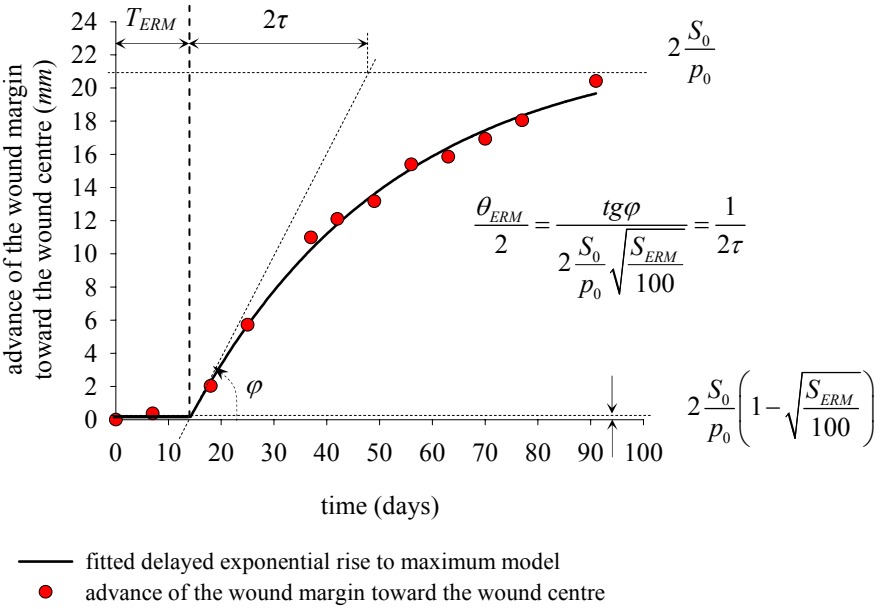

Fig. 2 *Example of following wound area and perimeter over time, calculating advance of wound margin towards wound centre and fitting delayed exponential rise to maximum model to calculated data. S_{ERM}, θ_{ERM} and T_{ERM} are calculated parameters of fitting delayed exponential rise to maximum model.*

We derived mathematical model of advance of wound margin towards wound centre dynamics on the basis of delayed exponential behaviour of wound area over time. Detailed procedure is explained in Appendix 1. Resulting three-parameter mathematical model is given by eq. 6

$$\hat{d}_i = \begin{cases} 2\dfrac{S_0}{p_0}\left(1-\sqrt{\dfrac{S_{ERM}}{100}}\right) & ; \quad 0 \le t_i < T_{ERM} \\ 2\dfrac{S_0}{p_0}\left(1-\sqrt{\dfrac{S_{ERM}}{100}}e^{-\frac{\theta_{ERM}}{2}(t_i-T_{ERM})}\right) & ; \quad t_i \ge T_{ERM} \end{cases} \tag{6}$$

where S_0 is initial wound area, p_0 is initial perimeter, index $i = 0,1,\ldots,n-1$ and $2\dfrac{S_0}{p_0}$ is maximum advance of wound margin towards wound centre, which is, in case of circular wound shape, equal to circle radius in *mm*. Parameter S_{ERM} [*%*] estimates initial advance of wound margin towards wound centre. Parameter θ_{ERM} [day^{-1}] defines time constant of the exponent function. Positive values relate to healing wounds and negative values to nonhealing wounds. Time delay of healing process initiation is defined by parameter T_{ERM} [*day*]. Example of advance of wound margin towards wound centre dynamics is presented in Fig. 2 for the same wound as dynamics of wound area in Fig. 1.

As collagen is accumulating wound is shrinking from initial wound margin towards wound centre. Therefore it is not surprisingly that fitting to collagen accumulation has the same curve trend [BARDSLEY *ET AL.*, 1995] as advance of wound margin towards wound centre.

Wound can also be approximated with a circle. However in that case all information about wound shape is lost. Circular approximation of wound shape is just a special case of elliptical approximation, when width to length ratio is one and it is not changing within time. Considering

$$p_0 = 2\sqrt{\pi S_0}$$

in eq. 6 results in eq. 7.

$$\hat{d}_i = \begin{cases} \sqrt{\dfrac{S_0}{\pi}}\left(1-\sqrt{\dfrac{S_{ERM}}{100}}\right) & ; \quad 0 \le t_i < T_{ERM} \\ \sqrt{\dfrac{S_0}{\pi}}\left(1-\sqrt{\dfrac{S_{ERM}}{100}}e^{-\frac{\theta_{ERM}}{2}(t_i-T_{ERM})}\right) & ; \quad t_i \ge T_{ERM} \end{cases} \tag{7}$$

After comparing dynamics of d_i obtained from elliptical (eq. 6) and circular (eq. 7) approximation we concluded that values of parameters S_{ERM}, θ_{ERM} and T_{ERM} are the same for both models. But in case of circular approximation of wounds with $r_0 < 1$ maximum advance of wound margin towards wound centre S_0/p_0 is overestimated, because circle has the least perimeter at given area. Relative difference between circular and exponential approximation (eq. 8) is calculated by subtracting eq. 6 from eq. 7 and divided by eq. 6.

$$e_0 = \frac{\sqrt{\dfrac{S_0}{\pi}} - 2\dfrac{S_0}{p_0}}{2\dfrac{S_0}{p_0}} \cdot 100 = \left[\frac{p_0}{2\sqrt{\pi S_0}} - 1\right] \cdot 100 \tag{8}$$

Relative difference expressed as function of width to length ratio is presented in eq. 9.

$$e_0 = \frac{3}{2}\left[\frac{1}{2}\left(\sqrt{\frac{1}{r_0}} + \sqrt{r_0}\right) - 1\right] \cdot 100 \quad [\%] \tag{9}$$

4 Wound healing rate definition

In a recent study involving 226 chronic wounds [CUKJATI *ET AL.*, 2000] we concluded that normalized wound area over time is best described by a delayed exponential model, thus wound healing dynamics is a nonlinear process. In previous chapter we proved that healing dynamics is nonlinear irrespective of how wound extent is measured. Since wound healing initiation can be delayed, function can not be linearised. The majority of authors has adopted that measure of wound extent has linear behaviour over time. This assumption is misleading and definitions of wound healing rate based only on two wound extent measurements performed in observation period were reported.

Final goal of wound care is a complete wound closure i.e. healing. Therefore wound healing rate should describe time needed to wound closure, directly or indirectly. Because clinical trials are financially and time limited, not all wounds are followed regularly or until complete wound closure. In these cases we have to be able to predict time of wound closure. Prediction based on wound healing rate calculated from initial wound extent measurement and one measurement obtained during wound healing is inaccurate. We have to take into account that wound healing dynamics is nonlinear. Wound extent has to be periodically followed and the data obtained fitted to a known model of healing dynamics. From calculated values of model parameters time needed to complete wound closure can be defined. Exponential behaviour of wound healing renders impossible determination of time needed to complete wound closure, because exponential function reaches its asymptote at infinite time. Therefore we considered wound to be healed when its area is estimated to be smaller than five percent of initial value and at the same time smaller than $100mm^2$. In Appendix 2 mathematical expression for prediction of time needed to complete wound closure T (eq. 26) is defined according to these two requirements.

We compared wound healing rates defined as absolute area healed per day (eq. 10), as percentage of

initial area healed per day (eq. 11) and as advance of wound margin towards wound centre per day (eq. 12).

$$\Theta_{absolute} = \frac{S_0}{T}\left[mm^2/day\right] \tag{10}$$

$$\Theta_{relative} = \frac{100}{T}\left[\%/day\right] \tag{11}$$

$$\Theta_{edge} = 2\frac{S_0}{p_0 T}\left[mm/day\right] \tag{12}$$

Wound healing rate should not be affected by wound size, when wounds of differing size are compared. To examine effect of wound area, perimeter and width to length ratio on these three wound healing rates, correlation analysis was performed on clinical data.

5 Testing on clinical data

Evaluation of wound healing dynamics and wound healing rate was based on the data of 300 chronic wounds collected in a study of electrical wound healing treatment effects [STEFANOVSKA *ET AL.*, 1993; JERČINOVIĆ *ET AL.*, 1994 and KARBA *ET AL.*, 1997].

Two mutually perpendicular diameters of the wound were measured periodically every week. In total 2481 measurements were performed. Wound area and perimeter were calculated according to eq. 2 and eq. 4, respectively. Because wound area is function of width to length ratio and wound perimeter is function of square root of ratio, wound perimeter was squared. Squared perimeter was then compared to surface and ratio. Initial wound area S_0 was strongly correlated (r=0.990, n=300) (r = Pearson correlation coefficient, n = number of cases) to squared initial wound perimeter p_0, while initial width to length ratio r_0 was mildly correlated to initial wound area (r=0.201, n=300), and not correlated to squared initial perimeter (r=0.116, n=300). Considering all wound extent measurements we found that wound area was strongly correlated (r=0.985, n=2481) to squared wound perimeter, while width to length ratio was modestly correlated to wound area (r=0.211, n=2481), and not to squared perimeter (r=0.147, n=2481). It seems that wound area is more linearly dependent on wound shape than perimeter, though both correlations are negligible. Strong positive correlation between perimeter and area was suspected.

Average, minimal and maximal width to length ratio r_i over observation time for each of 300 wound cases was calculated. Mean of average values with std. dev. is 0.663 ± 0.170 (n=300), mean of minimal values with std. dev. is 0.476 ± 0.206 (n=300), and mean of maximal values with std. dev. is 0.899 ± 0.167 (n=300). Maximal values are close to one, since healed wound (last measurement) was considered to have width to length ratio equal to one. Mean initial width to length ratio with std. dev. is 0.672 ± 0.216 (n=300). Comparing initial and average width to length ratio with paired t-test showed no significant difference (P=0.260). Therefore we concluded that width to length ratio is not changing significantly during the healing process. Mean width to length ratio of all measurements performed in the study with std. dev. was 0.653 ± 0.229 (n=2481). GORIN *ET AL.* (1996) reported mean initial width to length ratio 0.58 ± 0.20 (n=49), which is lower, but still close to our findings (P=0.027).

Relative overestimation of maximum advance of wound margin towards wound centre of circular approximation (eq. 9) is function of width to length ratio. Assuming that ratio is not changing over time, overestimation at mean initial width to length ratio 0.672 is only 3.0%.

5.1 Wound healing dynamics

Additional analysis on clinical data was performed to evaluate if there is any difference in parameters S_{ERM}, θ_{ERM} and T_{ERM} of wound healing dynamics model between elliptical and circular approximation. In case of elliptical approximation for each wound case advance of wound margin towards wound centre values d_i, i=0,1,...,n–1, were calculated from measured wound diameters. In case of circular approximation wound shape was not considered and width to length ratio was recalculated to one without changing wound area. Values of d_i, i=0,1,...,n–1, were calculated from recalculated diameters. Calculated values of d_i, i=0,1,...,n–1, were fitted to the corresponding model (eq. 6 or eq. 7).

Table 3 *Paired samples t-tests performed on each parameter calculated from advance of wound margin towards wound centre model (elliptical and circular approximation) and wound area dynamics model. Calculating natural logarithm normalized nonnormal distribution of parameter θ. Bonferroni adjustment probability was used.*

	$S_{DER\ ellipse}$	$S_{DER\ circle}$	S_{DEX}
$S_{DER\ ellipse}$	1.000	1.000	0.026
$S_{DER\ circle}$		1.000	0.083
S_{DEX}			1.000
	$\theta_{DER\ ellipse}$	$\theta_{DER\ circle}$	θ_{DEX}
$\theta_{DER\ ellipse}$	1.000	0.275	0.052
$\theta_{DER\ circle}$		1.000	0.236
θ_{DEX}			1.000
	$T_{DER\ ellipse}$	$T_{DER\ circle}$	T_{DEX}
$T_{DER\ ellipse}$	1.000	0.128	0.159
$T_{DER\ circle}$		1.000	0.371
T_{DEX}			1.000

We compared parameters of delayed exponential rise to maximum model in case of elliptical and circular wound shape approximation and parameters of delayed exponential model. From the results presented in Table 3, it is evident that wound shape does not significantly affect model parameters. Advance of wound margin towards wound centre is dependent on wound shape, but effect of wound shape on wound healing dynamics description is not significant. Since it is easier to follow-up wound area, we presume that wound healing dynamics is accurately estimated from regular wound area measurements (eq. 5). In Table 4 mean parameter values of delayed exponential model for 300 wound cases are presented. Out of 300 wound cases only 174 wound cases were healed in observation period. For this group time needed to complete wound closure calculated from model can be compared to time needed to complete wound closure obtained within observation period. By logging time needed to complete wound closure normal distribution was achieved. Paired samples t-test on time needed to complete wound closure obtained from model vs. time needed to complete wound closure obtained in observation period of 174 wound cases resulted in probability 0.958. Difference is insignificant, which means that model describes wound healing dynamics accurately.

Table 4 *Mean values with std. dev. of parameters describing healing dynamics of 300 wound cases and their median values with interquartile range.*

	S_{DEX}	θ_{DEX}	T_{DEX}
Mean	98.1	0.068	8.8
Std. Dev.	11.9	0.079	14.4
Median	99.8	0.049	3.6
Interquartile range	95.9–100.0	0.020–0.091	0.0–11.1

From 174 wound cases, which were healed in observation period, we selected wound cases that were weekly assessed with no missing measurements. Delayed exponential model was fitted to wound area measurements assessed in first three to six weeks. Time needed to complete wound closure was predicted from parameters of delayed exponential model. Predicted times were compared to actual times wounds needed to heal. Because of nonnormal distribution of time needed to complete wound closure, data were transformed using natural logarithm to achieve normal distribution. Results of paired t-test are presented in Table 5. There is significant difference between actual time needed to complete wound closure and the predicted one from measurements of wound area in first three weeks of wound observation (four measurements). If wound area is followed four or more weeks, there is no statistically significant difference between predicted and actual time to complete wound closure. Therefore wound has to be observed at least four weeks before time to complete wound closure can be reliably predicted.

Table 5 *Results (p values) of paired t-test between actual time needed to complete wound closure and predicted time needed to complete wound closure after three to six weeks of observation period. 174 wounds, which healed in observation period were examined. Wounds were healed in 8.4±5.6 (mean±SD) weeks, minimum 3 and maximum 34 weeks, with median (interquartile range) 6 (5–11) weeks. Before analysis was performed, values were transformed using normal logarithm.*

Predicted healing time	Actual time
After 3 weeks	$p < 0.001$
After 4 weeks	$p = 0.062$
After 5 weeks	$p = 0.484$
After 6 weeks	$p = 0.900$

5.2 Wound healing rate

Pearson correlation analysis (r = Pearson correlation coefficient, p = probability of being wrong in concluding that there is a true association between the variables) was used to examine the effect of wound area, perimeter and with to length ratio on the calculated wound healing rates according to eq. 10, eq. 11 and eq. 12. Logging successfully normalized nonnormal area and perimeter distributions of 300 wound cases. When healing rate was calculated as absolute area healed per day, healing rates correlated with the initial wound area (r=0.580, p<0.001), perimeter (r=0.571, p<0.001) but not with width to length ratio (r=0.132, p=0.170). When healing rate was expressed as percentage of initial area healed per day, healing rates moderately correlated with initial wound area (r=–0.431, p<0.001) and perimeter (r=–0.413, p<0.001) but not with width to length ratio (r=–0.153, p=0.067). When healing rate was expressed as advance of wound margin towards wound centre per day, no correlation with initial wound area (r=0.146, p=0.091), perimeter (r=0.121, p=0.266), or width to length ratio (r=0.105, p=0.493) was found. Wound healing rate expressed as absolute area healed per day tends to exaggerate the healing rates of larger wounds and healing rate expressed as percentage of initial area healed per day tends to exaggerate the healing rates of smaller wounds. Only wound healing rate expressed as advance of wound margin towards wound centre per day is not influenced by initial wound size.

Median initial wound area of 300 wound cases was $633mm^2$. If all wound cases were divided into a group of smaller (S_0<$633mm^2$) and a group of larger wounds (S_0>$633mm^2$) we found that there is no significant difference (p=0.338) between advance of wound margin towards wound centre per day mean values of both groups using two-sample t test, while significant (p<0.001) differences testing other two healing rate measures were found. Therefore we propose using wound healing rate expressed as advance of wound margin towards wound centre per day when healing rates of wounds with different initial areas are compared.

6 Conclusion

One of the most important principles of chronic wound management is periodic assessment of wound healing. It is important to document healing progress, and assess the effectiveness of treatment in order to maximize healing rates through treatment optimisation. A variety of measures of wound healing rate have been proposed and used. None of them is firmly established for either clinical or research purposes. Different wound status assessment techniques and different wound healing rate definitions render published reports (Table 2) difficult to compare. In our paper different techniques of wound healing rate evaluation were compared and we proposed that wound healing rate should be defined as the advance of wound margin towards wound centre per day. Many trial studies are financially and time restricted and thus observation time is limited. If wound is not healed within the observation period we have to predict time needed to complete wound closure. Since wound healing process is nonlinear and can not be linearised by any transformation, only nonlinear model can be used to describe wound healing process. Linear estimation of healing process is incorrect and can lead to deceptive results. We showed on 300 wound cases that wound healing dynamics is not influenced by wound shape, which indicates that wound area measurements are sufficient for its adequate description. Wound area measurements are normalized to percent of initial wound area and fitted to delayed exponential model. In this capacity wound area should be periodically followed at least four weeks and minimal five wound area or mutually perpendicular diameters measurements should be performed over this time. Time needed to complete wound closure is calculated from delayed exponential model parameters.

Proposed measure of wound healing rate is simple to use if wounds are healed within observation period. When fitting is required, method requires use of a computer with appropriate software. This is the most adequate estimation of wound healing rate though its complexity can represent a drawback. Only generally accepted uniform wound healing rate definition would enable comparison of treatment efficacy from different research groups.

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Appendix 1

In this appendix we discuss time dependence of the advance of wound margin towards wound centre (d_i). Advance of wound margin towards wound centre is defined as absolute change of wound area (ΔS_i) divided by mean wound perimeter ($\overline{p}_i$) in time interval t_0 to t_i (eq. 13). Wound shape can be approximated with an ellipse and wound area (S_i) simply calculated from two mutually perpendicular diameters (a_i and b_i) of the wound taken at time t_i (eq. 2). Those two diameters define width to length ratio r_i (eq. 3). As ratio r_i and wound area S_i are changing over time, also perimeter p_i (eq. 4) is changing over time. Mean wound perimeter (eq. 13) was calculated for each follow-up $i = 0,1,\ldots,n-1$.

$$\overline{p}_i = \frac{p_0 + p_i}{2} = \\ = \frac{\pi}{4}\left[\frac{3}{2}\left(a_0 + b_0 + a_i + b_i\right) - \sqrt{a_0 b_0} - \sqrt{a_i b_i}\right] \quad (13)$$

Wound area has delayed exponential behaviour over time (eq. 14) [CUKJATI *ET AL.*, 2000]

$$\hat{S}_{DEXi} = \begin{cases} S_{DEX} & ;0 \le t_i < T_{DEX} \\ S_{DEX} e^{-\theta_{DEX}(t_i - T_{DEX})} & ;\ t_i \ge T_{DEX} \end{cases} \ (\%) \quad (14)$$

where $T_{DEX} \ge 0$. Nonlinear regression of eq. 14 to n normalized wound area values measured over time results in parameters S_{DEX}, θ_{DEX} and T_{DEX}, which are describing wound healing process for the specific wound case. $\hat{S}_{DEXi}$ is estimated wound area at time t_i in percent of initial wound area. It was multiplied by absolute initial wound area S_0 in mm^2 and divided by 100 to achieve absolute value of wound area $\hat{S}_i$ (eq. 15).

$$\hat{S}_i = S_0 \frac{\hat{S}_{DEXi}}{100} = \\ = \begin{cases} S_0 \dfrac{S_{DEX}}{100} & ;0 \le t_i < T_{DEX} \\ S_0 \dfrac{S_{DEX}}{100} e^{-\theta_{DEX}(t_i - T_{DEX})} & ;\ t_i \ge T_{DEX} \end{cases} \ (mm^2) \quad (15)$$

where $S_0 S_{DEX}/100$ is estimated initial wound area in mm^2.

Considering eq. 15 absolute change in wound area at time t_i was calculated according to eq. 16.

$$\Delta\hat{S}_i = S_0 - \hat{S}_i = \\ = \begin{cases} S_0 - S_0 \dfrac{S_{DEX}}{100} e^{-\theta_{DEX}(t_i - T_{DEX})} & ;\ t_i \ge T_{DEX} \\ S_0\left(1 - \dfrac{S_{DEX}}{100}\right) & ;0 \le t_i < T_{DEX} \end{cases} \quad (16)$$

Determination of healing dynamics was performed in two steps. In the first step we presented mean wound perimeter $\overline{p}_i$ as function of ratio r_i and estimated wound area $\hat{S}_{DEXi}$. In the second step we obtained advance of wound margin towards wound centre as function of time.

Considering eq. 2 and eq. 3 we can express ellipse axes a_i and b_i as function of ratio r_i and estimated wound area S_i (eq. 17 and eq. 18).

$$\left.\begin{aligned} a_i &= \frac{4}{\pi}\frac{S_i}{b_i} \\ b_i &= r_i \cdot a_i \end{aligned}\right\} \Rightarrow a_i = \sqrt{\frac{4}{\pi} S_i \frac{1}{r_i}} \quad (17)$$

$$\left.\begin{aligned} b_i &= \frac{4}{\pi}\frac{S_i}{a_i} \\ a_i &= \frac{1}{r_i} \cdot b_i \end{aligned}\right\} \Rightarrow b_i = \sqrt{\frac{4}{\pi} S_i \cdot r_i} \quad (18)$$

After inserting eq. 17 and eq. 18 in eq. 13 mean perimeter is expressed as function of ratio r_i and wound area S_i (eq. 19).

$$\overline{p}_i = \frac{\pi}{4}\left[\frac{3}{2}\left(\sqrt{\frac{4}{\pi} S_0 \frac{1}{r_0}} + \sqrt{\frac{4}{\pi} S_0 r_0} + \right.\right. \\ \left.\left. + \sqrt{\frac{4}{\pi} S_i \frac{1}{r_i}} + \sqrt{\frac{4}{\pi} S_i r_i}\right) - \sqrt{\frac{4}{\pi} S_0} - \sqrt{\frac{4}{\pi} S_i}\right]$$

$$\overline{p}_i = k_0 \sqrt{S_0} + k_i \sqrt{S_i}\,, \quad (19)$$

where

$$k_i = \sqrt{\frac{\pi}{4}}\left[\frac{3}{2}\left(\sqrt{\frac{1}{r_i}} + \sqrt{r_i}\right) - 1\right].$$

Replacing wound area S_i in eq. 19 with estimated wound area $\hat{S}_i$ (eq. 15) results in estimated mean wound perimeter $\hat{\overline{p}}_i$ (eq. 20).

$$\hat{\overline{p}}_i = k_0 \sqrt{S_0} + k_i \sqrt{\hat{S}_i}$$

$$\hat{\overline{p}}_i = \begin{cases} \sqrt{S_0}\left(k_0 + k_i \sqrt{\dfrac{S_{DEX}}{100}}\right) & ;\ 0 \le t_i < T_{DEX} \\ \sqrt{S_0}\left(k_0 + k_i \sqrt{\dfrac{S_{DEX}}{100}} e^{-\frac{\theta_{DEX}}{2}(t_i - T_{DEX})}\right) & ;\ t_i \ge T_{DEX} \end{cases} \quad (20)$$

By dividing eq. 16 and eq. 20 we obtain a function of time (eq. 21), which is describing dynamics of advance of wound margin towards wound centre.

$$\hat{d}_i = \frac{\Delta\hat{S}_i}{\hat{\bar{p}}_i} = \begin{cases} \sqrt{S_0}\dfrac{1-\dfrac{S_{DEX}}{100}}{k_0 + k_i\sqrt{\dfrac{S_{DEX}}{100}}} & ; \quad 0 \le t_i < T_{DEX} \\ \sqrt{S_0}\dfrac{1-\dfrac{S_{DEX}}{100}e^{-\theta_{DEX}(t_i - T_{DEX})}}{k_0 + \sqrt{\dfrac{S_{DEX}}{100}}k_i e^{-\frac{\theta_{DEX}}{2}(t_i - T_{DEX})}} & ; \quad t_i \ge T_{DEX} \end{cases} \tag{21}$$

If we assume that width to length ratio r_i is not changed during wound healing process, $k_i = k_0$, i=0,1,…,n, then eq. 21 is reduced to eq. 22.

$$\hat{d}_i = \begin{cases} \dfrac{\sqrt{S_0}}{k_0}\dfrac{1-\dfrac{S_{DEX}}{100}}{1+\sqrt{\dfrac{S_{DEX}}{100}}} & ; \quad 0 \le t_i < T_{DEX} \\ \dfrac{\sqrt{S_0}}{k_0}\dfrac{1-\dfrac{S_{DEX}}{100}e^{-\theta_{DEX}(t_i - T_{DEX})}}{1+\sqrt{\dfrac{S_{DEX}}{100}}e^{-\frac{\theta_{DEX}}{2}(t_i - T_{DEX})}} & ; \quad t_i \ge T_{DEX} \end{cases} \tag{22}$$

After considering

$$(1-x)\Big/\left(1+\sqrt{x}\right) = 1-\sqrt{x}\,,$$

$$\frac{\sqrt{S_0}}{k_0} = 2\frac{S_0}{p_0}$$

and reindexing parameters final eq. 23 is reached.

$$\hat{d}_i = \begin{cases} 2\dfrac{S_0}{p_0}\left(1-\sqrt{\dfrac{S_{ERM}}{100}}\right) & ; \quad 0 \le t_i < T_{ERM} \\ 2\dfrac{S_0}{p_0}\left(1-\sqrt{\dfrac{S_{ERM}}{100}}e^{-\frac{\theta_{ERM}}{2}(t_i - T_{ERM})}\right) & ; \quad t_i \ge T_{ERM} \end{cases} \tag{23}$$

It can be shown that $\hat{d}_i$ is following delayed exponential rise to maximum behaviour, which can be mathematically expressed as a function of three parameters S_{ERM}, θ_{ERM} and T_{ERM}, where $T_{ERM} \ge 0$.

Appendix 2

As final goal of wound treatment is its closure wound healing rate should contain information about time needed to complete wound closure. This time can be obtained from delayed exponential model parameters. Because exponential curve approaches asymptote in infinity, criteria, when wound is considered to be healed, has to be defined. We assumed that wound is healed if its area is less then five percent of initial area and simultaneously less then one square centimetre.

Wound area reaches five percent of initial area after x time constants (τ) (Fig. 2). Exact value of x is calculated below.

$$S_{DEX}e^{-\theta_{DEX}(t-T_{DEX})} = 5 \;\Big|\ln$$

$$-\theta_{DEX}\underbrace{\left(t-T_{DEX}\right)}_{\frac{x}{\theta_{DEX}}} = \ln\frac{5}{S_{DEX}} = -x \;\Rightarrow\; x = \ln\frac{S_{DEX}}{5} \doteq 3\tau$$

Time needed that wound area reaches five percent of initial area is $T_{DEX} + x\tau$. According to this, time needed to complete wound closure $T_{5\%}$ is defined (eq. 24).

$$T_{5\%} = T_{DEX} + x\tau = T_{DEX} + \ln\frac{S_{DEX}}{5}\frac{1}{\theta_{DEX}}\ \left[day\right] \tag{24}$$

Wound area reaches absolute wound area $100mm^2$ after y time constants (τ). Value of y is calculated below.

$$\frac{S_{DEX}}{100}S_0 e^{-\theta_{DEX}(t-T_{DEX})} = 100 \;\Big|\ln$$

$$-\theta_{DEX}\underbrace{\left(t-T_{DEX}\right)}_{\frac{y}{\theta_{DEX}}} = \ln\left(\frac{100}{S_0}\frac{100}{S_{DEX}}\right) = -y \;\Rightarrow$$

$$\Rightarrow y = \ln\left(\frac{S_0 S_{DEX}}{10^4}\right)$$

Time needed that wound area reaches $100mm^2$ is $T_{DEX} + y\tau$. According to this, time needed to complete wound closure T_{100} is defined (eq. 25).

$$T_{100} = T_{DEX} + y\tau = T_{DEX} + \ln\left(\frac{S_0 S_{DEX}}{10^4}\right)\frac{1}{\theta_{DEX}}\ \left[day\right] \tag{25}$$

Time needed to complete wound closure T is greater of $T_{5\%}$ and T_{100} (eq. 26). If wound is not healing, time needed to complete wound closure is negative.

$$T = \begin{cases} T_{5\%} & ; \quad \text{if } \left|T_{5\%}\right| \ge \left|T_{100}\right| \\ T_{100} & ; \quad \text{otherwise} \end{cases} \tag{26}$$

Dodatek D

Prognostic factors, prediction of chronic wound healing and electrical stimulation

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MEDICAL & BIOLOGICAL ENGINEERING & COMPUTING (SUBMITTED)

Prognostic factors, prediction of chronic wound healing and electrical stimulation

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Abstract – The aim of the study was to determine effects of wound, patient and treatment parameters on wound healing rate and to propose a system for wound healing prediction. Predicting the wound healing rate from initial wound, patient and treatment data collected in our database of 300 chronic wounds was not possible. After considering weekly follow-ups, we determined that the best prognostic factors were weekly follow-ups of wound healing process, which alone were found to accurately predict the wound healing rate after follow-up period of four weeks (at least five measurements of wound area). After combining them with wound, patient and treatment attributes this period was reduced to at least two weeks (at least three measurements of wound area). After minimal follow-up period of two weeks, we were able to predict the wound healing rate of undependent test set of chronic wounds with relative squared error 0.347 and after three weeks with relative squared error 0.181 (using regression trees with linear equations in its leaves). Results show that the type of treatment is one of many prognostic factors. Arranged by their prediction capability, prognostics factors are: wound size, patient's age, elapsed time from wound appearance to the beginning of the treatment, width to length ratio, location and type of treatment.

The data collected up to now strongly support our former findings that the biphasic and direct current stimulation contributes to faster healing of chronic wounds.

Presented regression trees in combination with the mathematical model of the wound healing process dynamics represent a basis of an expert system for the chronic wound healing rate prediction. If the wound healing rate is known, then the provided information can help to formulate appropriate treatment decisions and orient resources to those individuals with poor prognosis.

Keywords – electric stimulation, inductive learning, predictors of wound healing

1 Introduction

Skin is a vital organ, in the sense that the loss of substantial fraction of its mass immediately threatens the life of the individual. Such a loss can result suddenly, either from fire or mechanical accident. The loss of skin can also occur in a chronic manner, as in skin ulcers.

In more than a decade lasting clinical use of electrical stimulation to accelerate chronic wound healing at the Institute of the Republic of Slovenia for Rehabilitation in Ljubljana each patient and wound were registered and wound healing process was weekly followed. Up to now, 266 patients with 390 chronic wounds participated in the controlled study involving conventional conservative treatment, sham treatment, biphasic pulsed current and direct current electrical stimulation. Since first reports [JERČINOVIĆ *ET AL.*, 1994] confirmed positive effects of electrical stimulation, it has been in regular use at the Institute of the Republic of Slovenia for Rehabilitation in Ljubljana. Since then more than two hundred fifty chronic wounds of different aetiologies were treated by electrical stimulation. However, dynamics of the wound healing process does not depend only on the type of the treatment, but depends also on wound and patient attributes. The aims of our study were to determine effects of wound, patient and treatment attributes on wound healing process and to propose a system for prediction of the wound healing rate. Only a limited number of groups have investigated wound and patient attributes which affect chronic wound healing. SKENE *ET AL.* (1992) found that the presence of graduated compression healing occurred more rapidly in patients with a smaller initial ulcer area, shorter duration of ulceration, younger age and when no deep vein involvement was detected on photoplethysmography. The measurement of ulcer

area was found to be the strongest predictor of ulcer healing. BIRKE *ET AL.* (1992) found that the time to healing is related to wound depth and wound diameter. JOHNSON (1997) found four factors influencing vascular ulcer healing: ABpI (ankle/brachial pressure index), liposclerosis, edema, wound status and ulcer area. LYMAN *ET AL.* (1970) found significant relationship between wound healing rate and bacterial load. None of listed studies included treatment attributes.

Presently, the quantity of available data permits employment of statistical tools and artificial intelligence methods for analyses of the healing process itself, as well as of the effects of different therapeutic modalities. In the first step of our analysis we determined which wound and patient attributes play a predominant role in the wound healing process. Then we discussed the possibility to predict wound healing rate at the beginning of treatment based on initial wound, patient and treatment attributes. Finally we discussed the possibility to enhance the wound healing rate prediction accuracy by predicting it after a few weeks of wound healing follow-up.

2 Wound, patient and treatment data

During more than a decade lasting clinical use of electrical stimulation, data concerning patients, wounds, and their treatment were collected. All together 266 patients with 390 wounds were recorded in our computer database up to date. Unfortunately many patient and wound data are missing and not all wounds were followed regularly or until the complete wound closure which is relatively common problem of clinical trials. Wound case inclusion criteria (initial wound area larger than $1cm^2$ and at least four weeks or until the complete wound closure followed wound healing process) were fulfilled in 300 wound cases (214 patients). Wounds were randomly assigned into four treatment groups: conservative treatment, sham treatment, biphasic current stimulation and direct current stimulation. Wounds were treated daily till complete wound closure. If the wound did not completely heal within the observation (inpatient) period, the patient continued his treatment at home, but follow-ups were discontinued because the reliability of the home treatment was questionable. Among 300 wound cases, observation periods were in 174 cases until the complete wound closure and shorter in the rest 126 cases. In these cases the time to healing was estimated from the wound area measurements obtained during the observation period [CUKJATI *ET AL.*, 2000A, CUKJATI ET AL., 2000B]. No significant difference between actual time to healing and estimated one (from four or more weeks of wound healing observation) was observed.

Wound extent was described with wound length, width, depth and grade. Because the time to healing was highly dependent on initial wound extent, a measure of the wound healing rate was defined as an average advance of the wound margin towards the wound centre and it was calculated as the average wound radius (initial wound area divided by initial perimeter and multiplied by 2) divided by the time to healing. Distribution of the wound healing rate was not normal and could not be transformed to normal distribution; non-parametric statistical analysis was therefore employed. In Table 1 wound, patient and treatment data collected in our computer database are listed. These data were selected to be attributes of chronic wound description. All listed attributes except wound extent were collected at the beginning of wound treatment. In addition wound extent was weekly followed during the observation period or until the complete wound closure. In further analysis we divided listed attributes into wound, patient and treatment attributes.

Table 1 *Wound, patient and treatment data collected in a database during more than a decade of using electrical stimulation at the Institute of the Republic of Slovenia for Rehabilitation.*

Wound data
Length of the wound
Width of the wound
Depth
Grade
Date of wound appearance
Date of treatment beginning
Aetiology
Location
Patient data
Sex
Date of birth
Number of wounds
Diagnosis
Date of spinal cord injury
Degree of spasticity
Treatment data
Type of treatment
Daily duration of treatment
Duration of treatment

2.1 Wound attributes

For the evaluation of the efficacy of particular treatment modality or for the evaluation of the influence of wound and patient attributes on wound healing it is necessary to periodically follow wound healing process.

It was demonstrated [CUKJATI ET AL., 2000B] that following wound area is sufficient to determine wound healing process dynamics. Further it was showed that wound shape can be approximated with an ellipse and it is thus enough to periodically follow mutually perpendicular diameters (largest wound diameter and diameter perpendicular to it) of the

wound. From measured diameters wound area, perimeter and width to length ratio were calculated. Therefore, to measure wound extent it is sufficient to take a measure of mutually perpendicular diameters, which are the easiest and the quickest measurements that can be performed at bedside [STEFANOVSKA *ET AL.*, 1993].

Wound depth measurement is invasive, because we have to enter our measuring device into the wound. Beside disturbance of the wound, the measurement can be diminished because of invisible edge at the bottom of the wound and degenerative tissue, which fills up the wound. As alternative measure of wound extent, grading systems were presented. We used four stage Shea grading system [SHEA, 1975]. Wound depth and grade were collected only at the beginning of treatment.

Wound depth was measured only in 43% of cases and wound grade determined in 94%. Positive correlation coefficient (rs=0.568, n=128) calculated in Spearman Correlation test and p value less than 0.001 shows that wound grade tends to increase with increasing wound depth and also tends to increase with increasing initial wound perimeter (rs=0.348, p<0.001, n=281) and area (rs=0.292, p<0.001, n=281) (rs = Spearman correlation coefficient, p = probability of being wrong in concluding that there is a true association between the variables and n = number of cases). As wound grade, wound depth is also correlated to perimeter (rs=0.356, p<0.001, n=132) and area (rs=0.306, p=0.004, n=132). Since wound depth was strongly correlated to wound grade and wound depth values were often missing, depth was omitted from further analysis. Also due to strong correlation between initial wound area and perimeter (rs=0.969, p<0.001, n=300), perimeter was omitted from further analysis. No other correlations between wound extent attributes were found. The time to healing is correlated to wound extent attributes, area (rs=0.428, p<0.001) and grade (rs=0.388, p<0.001). The wound healing rate is not correlated to initial area, perimeter or width to length ratio, but is moderately correlated to wound grade (rs=-0.237, p<0.001, n=281). Wounds of higher grade were healing slower.

Other collected wound attributes were wound type, location, elapsed time from spinal cord injury to wound appearance (InjuryAppear) and elapsed time from wound appearance to the beginning of treatment (AppearStart). The latter was modestly correlated to wound grade (rs=0.181, p=0.005, n=243), which can indicate that wounds should be treated as soon as they appear. Therefore it was also expected that the wound not appropriately treated for long period would heal slowlier (negative correlation coefficient when comparing AppearStart with the wound healing rate) (rs=-0.215, p<0.001, n=243). Small initial wound area (rs=-0.261, p<0.001, n=178) of wounds, which appeared a long time after spinal cord injury, is probably a result of better patients self care.

Wounds on trochanter healed at medium healing rate 0.115mm/day (0.024–0.259) (median (interquartile range)), on sacrum at medium healing rate 0.223mm/day (0.131–0.372), on gluteus at medium healing rate 0.234mm/day (0.111–0.423) and at medium rate 0.176mm/day (0.097–0.302) on other locations. Wounds on trochanter healed significantly slower (p<0.030) than wounds on other locations, between which no significant differences were found (p>0.060). Locations did not differ with respect to grade (p=0.236) but they differ with respect to area (p<0.001), revealing significantly greater wounds on locations trochanter (1018mm^2 (382–2721)) and sacrum (1012mm^2 (511–2753)) than on gluteus (684mm^2 (370–1249)) or other (393mm^2 (231–648)) locations. Wounds on trochanter, gluteus and sacrum were all pressure ulcers.

Major wound aetiology was pressure ulceration (82.7%). Other aetiologies were arterial ulceration (1.0%), neurotrophic ulceration (6.3%), traumatic ulceration (6.0%) and vascular ulceration (3.7%). The wound healing rate does not significantly (p=0.236) differ for listed aetiologies though they were not randomly assigned into four treatment groups (p=0.001).

2.2 Patient attributes

Recorded patient attributes were age, sex, total number of wounds, diagnosis and, in case of spinal cord injured patient, degree of spasticity. Median age of patients with wounds located on sacrum and trochanter was 37 (28–49, n=92) and 35 (23–49, n=57), respectively. Median age of patients with wounds located on gluteus and other locations was 57 (39–82, n=32) and 51 (30–61, n=108), respectively. Patients with wounds on sacrum or trochanter were significantly younger (p<0.010) than patients with wounds on gluteus or other locations. No significant difference in age was found between locations trochanter and sacrum (p=0.513). Since age was not correlated to the wound healing rate (p=0.541), slow wound healing of trochanter wounds can not be result of patients age.

Most frequent diagnosis was spinal cord injury (71.7%). Trauma appeared in 11.3% of cases, diabetes mellitus in 7.3%, geriatrics in 3.3%, multiple sclerosis in 3.0% and venous diseases in 3.0% of wound cases. Wounds of geriatric (healing rate=0.271mm/day) and traumatic (0.224mm/day) patients were healing significantly faster (p=0.005) than wounds of patients with other diagnosis: spinal cord injury (0.173mm/day), vascular insufficiency (0.171mm/day), diabetes mellitus (0.102mm/day) and multiple sclerosis (0.138mm/day). There were almost no geriatric or traumatic patients with wounds on trochanter, which were found to heal slow. That can at least partly explain why wounds of geriatric and traumatic patients were healing faster than wounds of patients with other diagnosis. Geriatric (age=77

(72–88), *n*=77), diabetes mellitus (68 (60–77), *n*=22) and patients with venous diseases (63 (54–72), *n*=9) were significantly (p<0.001) older than spinal cord injury (36 (26–51), *n*=215), multiple sclerosis (41 (33–52), *n*=9) or traumatic (43 (25–74), *n*=34) patients. Diagnosis was found to be strongly related to wound aetiology (p<0.001).

2.3 Treatment attributes

Wounds were randomly assigned into four treatment groups. The 54 (18.0%) wounds received conservative treatment of their chronic wounds [FEEDAR AND KLOTH, 1990]. The conservative treatment included initial selective debridement, the application of a new standard dressing to the chronic wound two or more times per day, as needed, and a broad spectrum antibiotics in cases of infection, which were rather rare. In addition to the conservative treatment, 23 (7.7%) wounds received sham treatment, where electrodes were applied to the intact skin on both sides of the wound for two hours daily and connected to stimulators, in which, however, the power source was disconnected and they delivered no current. Two different modes of electrical stimulation were used: direct and biphasic current. The 42 (14.0%) wounds stimulated with direct current were treated for half an hour, an hour or two hours daily. Positive stimulation electrode overlaid the wound surface and negative electrode was attached to the intact skin around the wound or both electrodes were places on the healthy skin at the wound edge across the wound, one of them being positive and the other negative. We have pooled different electrode placements in direct current stimulation group in spite of the difference in effectiveness of direct current stimulation [KARBA *ET AL.*, 1997]. We did this for two reasons: in literature both electrode placements were shown to accelerate chronic wound healing; and in this way we kept otherwise small direct current stimulation group of wounds at the size that allowed us statistical analysis. The 181 (60.3%) wounds were treated with biphasic current pulses [KARBA *ET AL.*, 1991] for half an hour, an hour or two hours daily with electrodes placed on both sides of the wound.

Treatment attributes were type of treatment and daily duration of electrical stimulation. Plotting percentage of healed wounds against the time (Fig. 1) revealed differences between the four treatment groups.

Electrically stimulated wounds healed at higher rate and extent then other wounds. Over 90% of electrically stimulated wounds healed within 60 weeks and only 70% of sham treated wounds and 72% of conservative treated wounds healed within the same period. The wound healing rate revealed significant difference between four treatment groups. Results of Kolmogorov-Smirnov Two Sample non-parametric test comparing treatment modalities (*p*–values) are presented in Table 2. It was found that wounds treated with biphasic current stimulation healed significantly faster than conservative or sham treated wounds. No significant difference was found in healing rates between wounds treated with direct current and wounds treated with biphasic current pulses. Difference in healing rates between direct current and conservative or sham treatment was considerable, in favour of direct current, although it was not significant. Conservative or sham treated wounds healed at the same rate.

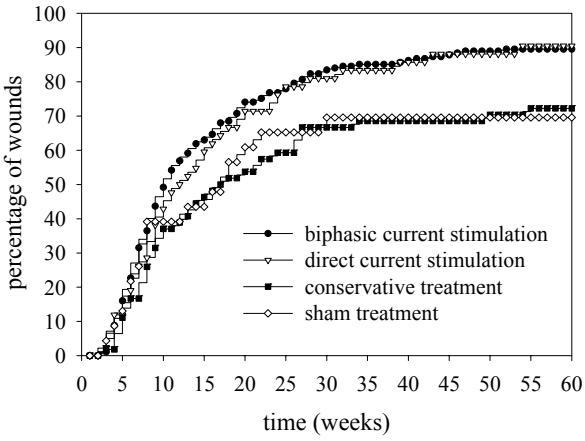

Fig. 1 *The percentage of healed wounds against time for four treatment modalities.*

Table 2 *Effects of four treatment modalities on the wound healing rate (p values of Kolmogorov-Smirnov two sample test).*

	AC	DC	CO	SH
AC	1.000			
DC	0.365	1.000		
CO	0.031	0.085	1.000	
SH	0.008	0.056	0.607	1.000

(AC = biphasic current stimulation, DC = direct current stimulation, CO = conservative treatment and SH = sham treatment)

Though wounds were randomly assigned into four listed treatment groups, some differences in attribute distributions between groups were found. In Table 3 results of attribute comparisons between treatment groups are presented. Kruskal-Wallis One Way Analysis of Variance on Ranks test or chi-square method was used as appropriate. There was no statistically significant difference (*p*=0.631) in the time to healing (when nonhealing wounds are not considered) between treatment modalities. Time elapsed from spinal cord injury to wound appearance was significantly shorter (*p*<0.001) in conservative treated and direct current stimulated group of patients than in sham treated and biphasic current stimulated group of patients. It is not correlated to the wound healing rate or any other attribute.

Table 3 *Baseline wound and patient attributes for each treatment group. Distributions of acquired attributes presented for each treatment group were compared and p values calculated.*

	Total n=300	AC n=181	DC n=42	CO n=54	SH n=23	*p*
Age*	n=296	n=178	n=42	n=54	n=23	0.053
(*years*)	41 (28–59)	43 (30–62)	43 (25–59)	39 (23–51)	37 (23–57)	
InjuryAppear*	n=178	n=94	n=27	n=42	n=15	<0.001
(*months*)	5 (2–38)	11 (3–69)	3 (1–4)	3 (1–10)	6 (4–24)	
AppearStart*	n=243	n=150	n=33	n=44	n=16	0.247
(*weeks*)	8 (3–18)	7 (3–17)	6 (4–12)	13 (4–22)	8 (2–14)	
Area*	n=300	n=181	n=42	n=54	n=23	0.359
(mm^2)	634 (308–1871)	566 (283–1539)	660 (346–2108)	797 (432–2160)	661 (289–1180)	
Perimeter*	n=300	n=181	n=42	n=54	n=23	0.296
(*mm*)	95 (68–161)	92 (64–160)	104 (73–165)	108 (77–166)	91 (64–127)	
Ratio*	n=300	n=181	n=42	n=54	n=23	0.983
	0.71 (0.55–0.83)	0.71 (0.54–0.81)	0.71 (0.50–0.90)	0.69 (0.57–0.86)	0.70 (0.52–0.82)	
Depth*	n=132	n=79	n=17	n=28	n=8	0.251
(*mm*)	4.5 (2–15)	4 (2–10)	15 (4–20)	4 (1–16)	5 (3–9)	
Number of wounds*	2 (1–3)	2 (1–2)	1 (1–2)	2 (1–3)	2 (1–2)	0.071
Grade# (*n*(%))						0.254
I	24 (8.0)	10 (5.5)	3 (7.1)	9 (16.7)	2 (8.7)	
II	138 (46.0)	92 (50.8)	13 (31.0)	23 (42.6)	10 (43.5)	
II	87 (29.0)	52 (28.7)	17 (40.5)	11 (20.4)	7 (30.4)	
IV	32 (10.7)	19 (10.5)	4 (9.5)	6 (11.1)	3 (13.0)	
Location¤ (*n*(%))						0.012
Gluteus	32 (10.7)	21 (11.6)	7 (16.7)	3 (5.5)	1 (4.3)	
Other[a]	110 (36.7)	80 (44.2)	11 (26.2)	11 (20.4)	8 (34.8)	
Sacrum	93 (31.0)	44 (24.3)	19 (45.2)	22 (40.7)	8 (34.8)	
Trochanter	58 (19.3)	34 (18.8)	5 (11.9)	13 (24.1)	6 (26.1)	
Aetiology ¤ (*n*(%))						0.001
Pressure ulcer	248 (82.7)	136 (75.1)	35 (83.3)	54 (100.0)	23 (100.0)	
Arterial ulceration	3 (1.0)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Vascular ulceration	11 (3.7)	11 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Neurotrophic ulceration	19 (6.4)	16 (8.8)	3 (7.1)	0 (0.0)	0 (0.0)	
Traumatic ulceration	18 (6.0)	15 (8.3)	3 (7.1)	0 (0.0)	0 (0.0)	
Diagnosis¤ (*n*(%))						0.010
Spinal cord injury	215 (71.7)	111 (61.3)	28 (66.7)	54 (100.0)	22 (95.7)	
Geriatrics	10 (3.3)	10 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Multiple sclerosis	9 (3.0)	5 (2.8)	4 (9.5)	0 (0.0)	0 (0.0)	
Diabetes mellitus	22 (7.3)	18 (9.9)	3 (7.1)	0 (0.0)	1 (4.3)	
Vascular insufficiency	9 (3.0)	9 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Trauma	34 (11.3)	28 (15.5)	6 (14.3)	0 (0.0)	0 (0.0)	
Daily duration of treatment#						<0.001
0 (*minutes*)	54 (18.0)	0 (0.0)	0 (0.0)	54 (100.0)	0 (0.0)	
30	53 (17.7)	51 (28.2)	2 (4.8)	0 (0.0)	0 (0.0)	
60	18 (6.0)	13 (7.2)	5 (11.9)	0 (0.0)	0 (0.0)	
120	175 (57.3)	117 (64.6)	35 (83.3)	0 (0.0)	23 (100.0)	
Healing time*	n=276	n=178	n=40	n=42	n=16	0.631
(*days*)	63 (37–137)	63 (36–132)	64 (37–132)	83 (45–177)	64 (36–123)	
Healing rate*	n=300	n=181	n=42	n=54	n=23	0.007
(*mm*/*day*)	0.176 (0.090–0.315)	0.190 (0.114–0.328)	0.168 (0.089–0.434)	0.145 (0.026–0.261)	0.162 (-0.046–0.205)	

[a] Pes (15), calcaneus (25), genu (7), lower extremities (19), malleolus (2), humerus (5), stump (34), and ischium (3).
Data are *n*(%) or median (interquartile range). Percentages are calculated using all recorded data (*n*=300).
Attribute types: * continuous, #ordinal and ¤nominal attribute.
InjuryAppear = elapsed time from spinal cord injury to wound appearance,
AppearStart = elapsed time from wound appearance to the beginning of treatment.
AC = biphasic current stimulation, DC = direct current stimulation, CO = only conservative treatment and SH = sham treatment

Wounds were also not randomly assigned to treatment groups regarding location, aetiology and diagnosis. Wounds on sacrum (32%) and trochanter (33%) were significantly (p=0.026) more often included in conservative or sham treated group than wounds on gluteus (13%) and other locations (17%). Wounds on trochanter and sacrum were healing significantly (p=0.048) faster when treated with biphasic current pulses. Since electrically stimulated wounds healed faster than conservative or sham treated wounds, that can reveal why wounds on trochanter and sacrum healed slower than wounds on other locations. Only pressure ulcers were conservative (n=54) or sham treated (n=23). 35 pressure ulcers, 3 neurotrophic ulcers and 3 traumatic ulcers were treated with direct current and 136 pressure ulcers, 16 neurotrophic ulcers, 15 traumatic ulcers, 11 vascular ulcers and 3 arterial ulcers were treated with biphasic current pulses. Since more than one fifth of data describing aetiology and diagnosis are missing, results of significant tests are only suspects. The wound healing rates of wounds treated

with biphasic electric current with respect to wound aetiology did not differ significantly (p=0.129). We concluded that the wound healing rate is not dependent on wound aetiology.

When considering healing rates obtained with two hour daily wound treatment, biphasic current stimulated wounds healed significantly (p=0.018) faster (0.166 mm/day (0.097–0.328)) than sham treated wounds (0.162 mm/day (-0.046–0.205)) and at the same rate (p=0.170) as direct current stimulated wounds (0.217 mm/day (0.098–0.450)). Direct current stimulated wounds healed faster, but not significantly (p=0.085), than sham treated wounds.

An hour direct current stimulated wounds, healed (p=0.067) slower (0.090 mm/day (0.089–0.120)) than two hour direct current stimulated wounds and significantly (p=0.001) slower than an hour biphasic current stimulated wounds (0.260 mm/day (0.190–0.460)). An hour daily biphasic stimulated wounds healed significantly (p=0.017) faster than two hour daily stimulated wounds and also faster than (p=0.357) half an hour daily biphasic current stimulated wounds (0.207 mm/day (0.152–0.309)). Two hours daily biphasic current stimulated wounds healed at the same healing rate (p=0.060) as a half an hour daily biphasic current stimulated wounds. Lack of wound cases, which were stimulated for an hour daily (n=13), renders this result statistically unreliable. Further study should be performed to optimise daily duration of electrical stimulation.

3 Prediction of the wound healing rate

We defined the wound healing rate as the advance of wound margin towards the wound centre (eq. 1) [CUKJATI ET AL., 2000B].

$$\Theta = 2\frac{S_0}{p_0}\frac{1}{T}\left[mm/day\right] \qquad (1)$$

where S_0 is initial wound area, p_0 is initial perimeter and T is the time to healing. To be appropriately calculated we have to follow the wound healing process till the complete wound closure. Because clinical trials are financially and time limited the time to healing has to be predicted from performed measurements in observation period, which may be much shorter than time to the complete wound closure. Another reason for the prediction of the time to healing is to help clinicians in making decision whether to change the treatment or not. We decided rather to predict the wound healing rate than the time to healing, because the wound healing rate is easier to handle in cases when wound is not healing. In these cases the time to healing is infinite and the wound healing rate zero or negative. Negative value of the wound healing rate is the estimate of wound growth velocity towards its double initial area. From the wound healing rate the time to healing can easily be calculated.

3.1 Estimating the wound healing rate from the wound healing model

We determined that dynamics of wound area changing over time has a delayed exponential behaviour. Delayed exponential equation is thus the structure of mathematical model of the wound healing process and by fitting this model to a particular chronic wound case, parameters of this model are calculated. We need at least four measurements (performed in at least three weeks) of wound area before parameters of mathematical model can be estimated. From parameters of mathematical model the time to healing was estimated [CUKJATI ET AL., 2000B]. Because exponential function reaches the asymptote at infinite time, we estimated that the wound is healed when its estimated area is smaller than five percent of initial value and simultaneously smaller than 1cm^2. According to Eq. 1 the estimated wound healing rate was calculated. To estimate the wound healing rate even earlier, the model with less parameters has to be introduced. Because a half of wounds had the delay of wound healing process initiation less than a half of week, we used the two parameter exponential model. To evaluate parameters of this model we performed the linear regression to logged measurements of wound area. We estimated the time to healing and calculated the wound healing rate for 300 wound cases as before, considering delay of wound healing process initiation to be zero.

The estimated wound healing rates for all wound cases were then compared to actual one calculated from observed times to the complete wound closure. We found that the estimated wound healing rate after at least four weeks of wound follow-up did not differ significantly from the actual one (Table 4). If wound was followed only three weeks or less the difference was found to be significant.

Table 4 *Comparison of the estimated the wound healing rate with the actual one. Wilcox on rank sum test was used.*

no. of measurements		Θ
2	$\Theta_{1\ week}$	$p < 0.001$
3	$\Theta_{2\ weeks}$	$p < 0.001$
4	$\Theta_{3\ weeks}$	$p = 0.028$
5	$\Theta_{4\ weeks}$	$p = 0.199$
6	$\Theta_{5\ weeks}$	$p = 0.405$
7	$\Theta_{6\ weeks}$	$p = 0.508$

Θ is the wound healing rate calculated from all collected data throughout the follow-up, and
Θ_i is the wound healing rate calculated from wound size measurements performed in the first i-weeks of follow-up.

From the known structure of mathematical model the wound healing rate can be predicted after at least four weeks of follow-up (non significant difference p=0.199 between predicted and actual wound healing rate). In clinical trials four weeks is a short period.

But in clinical practice a shorter time for treatment outcome prediction may be necessary.

3.2 Prediction of the wound healing rate from wound, patient and treatment data

From results of statistical analysis reported above, it is obvious that the wound healing rate is directly dependent on wound treatment and wound grade, while interactions of other wound and patient attributes on the wound healing rate are not easy to determine. We employed tree learning algorithms to build regression and classification trees to predict the wound healing rate based on initial wound, patient and treatment data. We also considered the estimated wound healing rate based on mathematical model and built trees for prediction of the wound healing rate after one, two, three, four, five and six weeks of follow-up. We tested several algorithms for attribute selection among which RReliefF [ROBNIK-ŠIKONJA AND KONONENKO, 1997] for regression tree generation and ReliefF [KONONENKO *ET AL.*, 1997] for classification tree generation were found to be the most effective. For models in leaves of the tree the most appropriate were linear equations for regression trees and median values for classification trees. A stopping rule of minimal five wound cases in a leaf was used. Since the sample size (n=300) was quite moderate, the 10-fold cross-validation was used as the error estimation method.

The accuracy of classification trees was measured as classification accuracy (% of correctly classified test samples).

The accuracy of regression trees was measured as relative squared error (relative error) [BREIMAN *ET AL.*, 1984]. The relative error is always nonnegative and usually less than 1. Trees with relative error close to 0 produce good prediction of the wound healing rate and trees with the relative error around 1 or even greater than 1 produce poor prediction.

Some authors are using a measure of the proportion of the variance explained by the regression tree. It is calculated as (1 – relative error). We also used this measure to compare results, though this terminology is not quite appropriate [BREIMAN *ET AL.*, 1984].

To obtain the right sized tree and to get more accurate estimates of the true probability of misclassification, the trees were pruned.

Table 5 *The wound healing rate prediction capabilities of wound, patient and treatment attributes assigned by RReliefF.*

	Partitioning power of attributes after observation period of						
Attribute	0 weeks	1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks
Area (mm^2)	0.135	0.168	0.171	0.161	0.127	0.123	0.122
Age (year)	0.123	0.114	0.094	0.095	0.096	0.092	0.094
AppearStart (week)	0.119	0.121	0.104	0.131	0.121	0.114	0.115
Width to length ratio	0.096	0.098	0.099	0.095	0.103	0.108	0.113
Location	0.085	0.084	0.085	0.081	0.081	0.081	0.081
Treatment	0.066	0.058	0.051	0.052	0.050	0.051	0.051
InjuryAppear (month)	0.062	0.065	0.044	0.050	0.035	0.040	0.039
Daily duration of treatment (minute)	0.046	0.039	0.031	0.035	0.025	0.025	0.026
Grade	0.046	0.039	0.057	0.048	0.048	0.047	0.043
Diagnosis	0.039	0.039	0.038	0.038	0.038	0.038	0.037
Aetiology	0.027	0.025	0.026	0.024	0.024	0.0239	0.024
Model estimation	0.000	0.399	0.602	0.626	0.663	0.659	0.670

InjuryAppear = elapsed time from spinal cord injury to wound appearance (month),
AppearStart = elapsed time from wound appearance to the beginning of treatment (week),
Model estimation = from model of wound healing dynamics estimated wound healing rate.

Table 6 *Dividing 300 wound cases into four classes according to their wound healing rate.*

Class	Condition	No. of cases	Apriori
NONHEALING WOUNDS	$\Theta \leq 0{,}095$ mm/day	77	0.257
SLOW HEALING WOUNDS	0,095 mm/day $< \Theta \leq$ 0,180 mm/day	77	0.257
MEDIUM HEALING WOUNDS	0,180 mm/day $< \Theta \leq$ 0,300 mm/day	67	0.223
FAST HEALING WOUNDS	$\Theta >$ 0,300 mm/day	79	0.263

Θ – the wound healing rate

The idea of the RReliefF and ReliefF algorithms is to evaluate the partitioning power of attributes according to how well their values distinguish between similar observations. An attribute is given a high score if it separates similar observations with different prediction values and does not separate similar observations with similar prediction values. RReliefF and ReliefF sample the space of observations, compute the differences between the predictions and the values of the attributes and form a kind of statistical measure for the proximity of the probability densities of the attribute and the predicted value. Attributes partitioning powers (Table 5) calculated using RReliefF revealed that initial wound area, followed by patients' age and time from wound appearance to treatment beginning are the most prognostic attributes. Important prognostic attributes are also wound shape (width to length ratio), location and type of treatment.

3.2.1 Classification trees

Domain of wound cases was divided into four classes according to Table 6. At the beginning of wound treatment, only initial wound, patient and treatment data are available. We built classification trees with ReliefF. The resulting classification tree accuracy at the beginning of treatment was 30%, which is not much above apriori probability of the most probable class (26%). Adding model estimate of the wound healing rate after one week of follow-up improved classification accuracy to 41%. With data available for two weeks the classification accuracy was 62% and with three weeks 80%. Afterwards it is slowly approaching 90% with six weeks of follow-up. In trees built after two weeks of follow-up only the model estimate of the wound healing rate can be found in tree nodes.

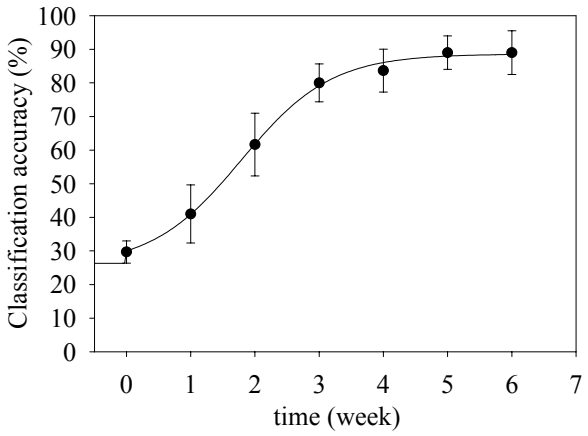

Fig. 2 *Classification accuracy of classification trees for the wound healing rate prediction as a function of observation time. Cases are classified in four domains: NONHEALING, SLOW, MEDIUM and FAST HEALING wounds.*

We found out that accurate prediction of the wound healing rate is possible with data available for at least three weeks of follow-up. Therefore, with classification trees we managed to shorten the time of follow-up for one week. Only rough estimate of the wound healing rate is possible after two weeks (Fig. 2).

3.2.2 Regression trees

Generated regression trees with linear equations in leaves for the wound healing rate prediction at the beginning of treatment had relative squared error greater than one, which means that resulting regression trees are not usable. Adding the model estimate of the wound healing rate after one week of follow-up reduced the relative squared error to 0.64, which means that 36% of variance was explained by the tree. After two weeks 65% and after three weeks 82% of variance was explained. Afterwards it was slowly approaching 94% of explained variance in six weeks of follow-up (Fig. 3).

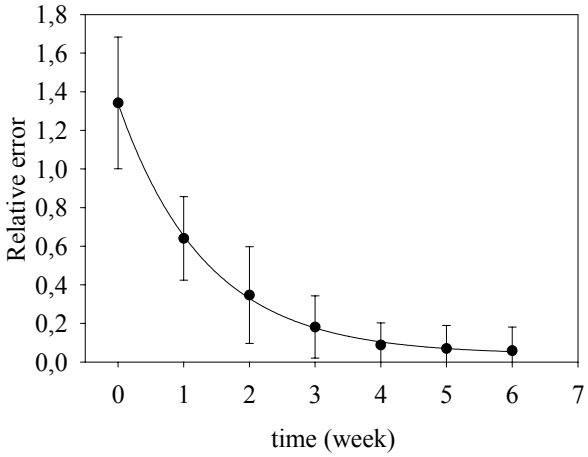

Fig. 3 *Relative error of regression trees for the wound healing rate prediction as a function of observation time. In leaves are linear equations.*

Regression trees are more useful than classification trees because the wound healing rate was estimated as continuous variable. The minimal follow-up period is two weeks. After five weeks the predicted wound healing rate is equal to the healing rate estimated by the model. The predicted wound healing rate in shorter period in addition depends on wound, patient and treatment attributes. Regression trees built after two, three and four weeks of follow-up are presented in Fig. 4, Fig. 5 and Fig. 6, respectively. Type of the treatment is indirectly included in regression trees as daily duration of treatment, which was zero in case of conservative treated wounds. Important prognostic attributes seems to be wound area, grade, shape (width to length ratio), patients age, elapsed time from spinal cord injury to wound appearance and elapsed time from wound appearance to the beginning of treatment.

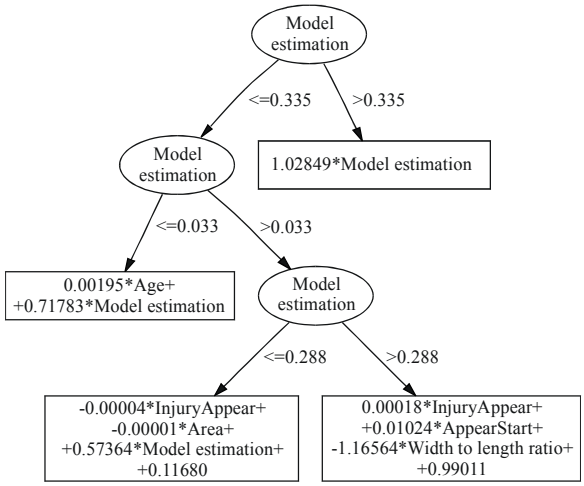

Fig. 4 *Regression tree with linear equations in leaves for prediction of wound healing rate after two weeks of treatment.*

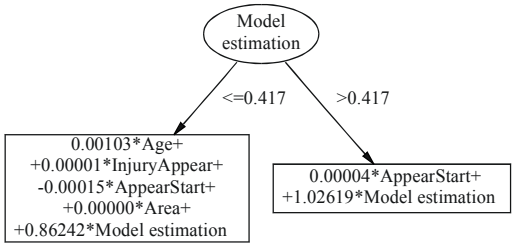

Fig. 5 *Regression tree with linear equations in leaves for prediction of wound healing rate after three weeks of treatment.*

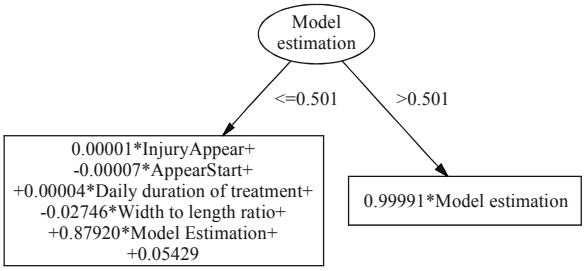

Fig. 6 *Regression tree with linear equations in leaves for prediction of wound healing rate after four weeks of treatment.*

4 Conclusion

Electrically stimulated wounds healed faster and at greater percentage than conservative or sham treated wounds. These results strongly support former findings that biphasic current stimulation contributes to faster healing of chronic wounds [JERČINOVIĆ *ET AL.*, 1994]. We noticed slightly slower healing of wounds treated with direct current than wounds treated with biphasic current, but it still seems that both treatment modalities are effective. In future it would be interesting to consider the effect of daily wound stimulation duration on wound healing rate.

Dynamics of wound healing can be accurately predicted after at least four weeks of the wound healing process follow-up. Therefore for accurate wound healing rate estimation, wounds should be followed at least four weeks. In clinical practice the wound healing rate or the time to healing should be estimated as soon as possible to select a proper treatment and thus improve patient care.

Predicting the wound healing rate from initial wound, patient and treatment data collected in our database was not possible. The best prognostic factor are weekly follow-up measurements of wound area. We determined that the minimal follow-up period is two weeks. After three weeks we were able to predict the wound healing rate at classification accuracy of 80% when using classification trees, and explain 82% of the variance with regression trees. Best results were obtained using regression trees with linear equations in leaves. In literature also other wound and patient attributes were reported to have a prognostic value. If we would also consider exudate, necrosis, granulation, epitelization and deep vein involvement our prediction might be more accurate.

Analyses of prognostic factors on wound healing are rarely found in literature. None of them incorporates electrical stimulation as the chronic wound treatment modality. They mostly base on initial wound and patient attributes. SKENE *ET AL.* (1992) observed 200 venous leg ulcerations and predict the time to healing of the ulcer. They found wound area, duration of ulceration, patients' age and depth of vein involvement as most important prognostic factors. Simple scoring system was presented for estimating the probability of ulcer healing in 40, 80 and 120 days at the beginning of treatment. The system was not tested on independent set of wound cases therefore it may miss the prediction of new cases. BIRKE *ET AL.* (1992) found wound depth and diameter significantly related to ulcer healing time. In 80 neurotrophic ulcers a regression model including depth, diameter and age explained 36% of the variation in healing time on learning set of wound cases. We managed to explain 36% of the variation in healing rate after a week of wound healing process follow-up on independent set of wound cases. KANTOR AND MARGOLIS (2000) presented a prognostic indicator of healing or non-healing at 24 weeks after following 104 venous leg ulcer area over the first few weeks. Percentage change in area from baseline to week 4 provided the best combination of positive and negative predictive values (68.2%, 74.7%). In our study after four weeks of follow-up the classification tree has 84% classification accuracy.

Presented regression trees in combination with mathematical model of wound healing process dynamics possibly present a core of the expert system for chronic wound healing rate prediction. If the wound healing rate is known, then the provided information can help to formulate appropriate

management decisions, reduce the cost and orient resources to those individuals with poor prognosis.

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