Modelling of chronic wound healing dynamics

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Abstract—*Following chronic wound area over time can give a general overview of wound healing dynamics. Decrease or increase in wound area over time has been modelled using either 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 ($p = 0.01$) 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 an error of 64 to 128, and finally four-parameter models resulted in the 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 the median error increase of fitting is 74%.*

Keywords—*Mathematical modelling, Wound healing, Chronic wounds*

Med. Biol. Eng. Comput., 2000, **38**, 339–347

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 and 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 a 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.

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First received 14 October 1999 and in final form 1 February 2000

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 normalised to the initial wound area (JOHNSON, 1997); as the average of the sequentially computed weekly healing rates (normalised 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 towards the centre of the wound (GORIN *et al.*, 1996), and using a two-parameter exponential wound healing model by JERČINOVIČ *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 modelling, different classification systems for monitoring the dynamic process of chronic wound

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

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 standardised parameters of wound healing are used.

The present study of chronic wound healing dynamics modelling 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 (JERČINOVIČ *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), ulceration, amputation wounds, pressure ulcers, neuropathic ulceration (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 etiology and diagnosis is presented in Table 1. Wounds were treated either solely conventionally or with biphasic (JERČINOVIČ *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.

3 Mathematical models of wound healing dynamics

A wound healing model is a 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 terms of size. By normalising measured wound areas to initial values, these differences are eliminated and data analysis

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

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 the parameters θ_{LIN} and θ_{EXP} are the 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 model has an adequate physiological basis. The 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 (eqn 3) (Fig. 1*b*).

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

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

$$t_{1/2} = \frac{\ln 2}{\theta_{EXP}} \tag{4}$$

A survey of analysed normalised 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

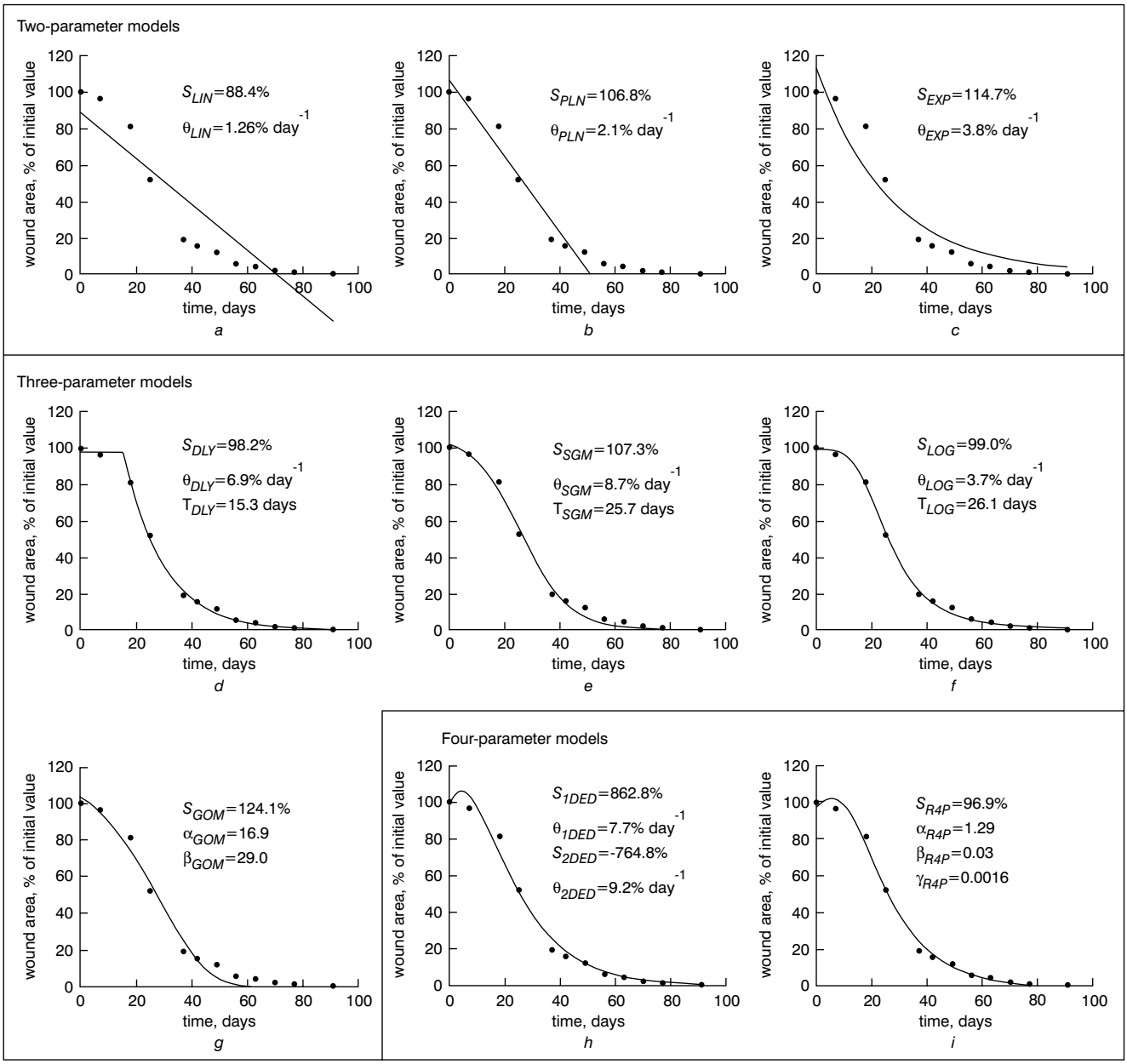

Fig. 1 *Graphical presentation of investigated mathematical models based on follow-up measurements of 36-year-old male spinal cord injured patient. Initial pressure ulcer area was 1315 mm^2 and after 92 days of treatment with biphasic electrical stimulation it has been closed. Model type: (a) linear, (b) piecewise linear, (c) exponential, (d) delayed exponential, (e) sigmoid, (f) logistic, (g) Gompertz, (h) double exponential decay, (i) rational 4-parameter*

more than seven days and in 26% of wounds the delay was more than 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 (Fig. 1*d*):

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

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.

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

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

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

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

$$\hat{S}(t) = S_{GOM} \cdot e^{-e(t-\beta_{GOM}/\alpha_{GOM})} \quad (8)$$

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 the 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 the other models.

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 even with two exponents the parameters have no unequivocal meaning:

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

The double exponential decay model (eqn 9) is a four-parameter model and is shown in Fig. 1*h*. In general each added parameter adds one level of freedom so that the model can better fit the 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 (eqn 10) was also used because this model is highly flexible and fits almost any data. It is shown in Fig. 1*i*. Its parameters, however, have no biophysical meaning.

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

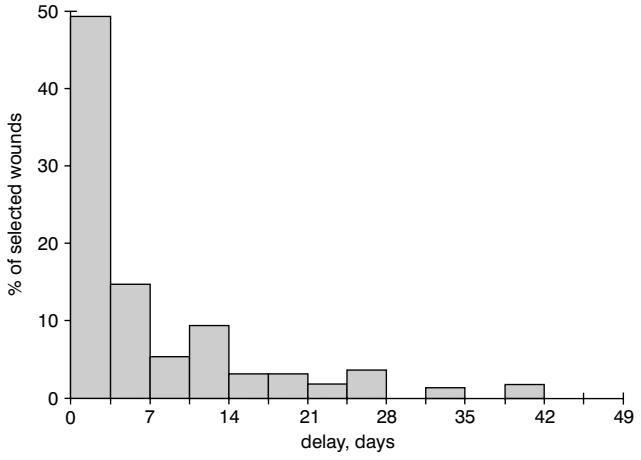

Fig. 2 *Histogram of wound distribution due to delay of healing process. The delay used is delayed exponential model parameter T_{DLY}*

4 Model fitting

A computer program was developed to perform curve fitting and to calculate five different fitting quality criteria. To fit an n-parameter nonlinear equation to wound area measurements, the Marquardt–Levenberg algorithm (PRESS *et al.*, 1992) was used. This nonlinear regression algorithm seeks the values of parameters that minimise 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 into 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

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

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

(*b*) Standard error of the estimate (SE) is the normalised 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.

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

(*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 (eqn 13). Good fit is characterised by values of the criterion r^2 close to 1, while decreasing values of r^2 indicate worsening fit.

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

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):

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

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. Small values of PRESS indicate better capability of handling missing data. The PRESS (eqn 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 the case of n wound area measurements over time, the test was performed $n - 1$ times and the average calculated:

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

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 (eqn 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 followed weekly 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.

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

5.2 *Qualitative criteria*

In addition to the 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. The Mann–Whitney Rank Sum Test (DEVORE, 1995) was used to test the hypothesis of equality of models, which was rejected at a 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

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	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PLN	610	257	1370		1	0.687	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
EXP	567	227	1340			1	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
DEX	277	98	772				1	0.957	0.965	0.890	**0.004**	**<0.001**
SGM	284	107	769					1	0.937	0.824	**0.005**	**<0.001**
LOG	292	80	776						1	0.920	**0.005**	**<0.001**
GMP	282	111	760							1	**0.002**	**<0.001**
DED	169	58	604								1	0.176
R4P	145	31	549									1

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.

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 a 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 the model fits the 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.

6.4 *Predicted residual error sum of squares*

PRESS measures the 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 the results shown in Table 6

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	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PLN	9.4	6.9	14.3		1	0.694	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
EXP	10.0	5.8	15.4			1	**<0.001**	**<0.001**	**<0.001**	**0.001**	**<0.001**	**<0.001**
DEX	7.5	4.5	11.7				1	0.963	0.902	0.834	0.279	**0.004**
SGM	7.2	4.7	12.4					1	0.984	0.784	0.339	**0.004**
LOG	7.5	4.3	11.7						1	0.761	0.347	**0.007**
GMP	6.9	4.9	12.4							1	0.220	**0.002**
DED	6.8	4.3	11.8								1	0.055
R4P	5.7	3.3	10.7									1

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	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PLN	0.885	0.757	0.951		1	0.714	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
EXP	0.883	0.731	0.957			1	**<0.001**	**0.001**	**0.001**	**0.002**	**<0.001**	**<0.001**
DEX	0.941	0.822	0.977				1	0.964	0.962	0.881	0.425	**0.007**
SGM	0.946	0.792	0.978					1	0.985	0.815	0.454	**0.010**
LOG	0.937	0.812	0.982						1	0.837	0.482	**0.008**
GMP	0.946	0.789	0.975							1	0.344	**0.005**
DED	0.943	0.838	0.981								1	**0.045**
R4P	0.958	0.846	0.988									1

Table 6 Medians of PRESS and values of p

	PRESS				p								
Model	No	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**	**0.009**
PLN	222	19.2	6.1	41.9		1	0.524	**0.002**	**0.006**	0.020	**0.006**	**0.002**	0.493
EXP	225	15.3	5.2	52.2			1	0.041	0.086	0.190	0.083	0.030	0.837
DEX	217	11.5	4.0	27.3				1	0.750	0.427	0.770	0.651	0.042
SGM	224	11.7	3.8	35.9					1	0.643	0.968	0.516	0.083
LOG	206	13.2	4.3	32.4						1	0.633	0.275	0.188
GMP	225	10.7	3.3	37.5							1	0.531	0.074
DED	217	8.6	3.0	43.5								1	0.028
R4P	223	15.6	4.1	68.0									1

that a larger number of model parameters does not automatically mean significantly lower PRESS. This 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)*

MPRESS measures the prediction capability of a model. Low values of MPRESS result in high 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 analysed 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 are 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 of 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 the optimal number of model parameters is three.

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

	MPRESS (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

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 the 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 work 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 $4374 \pm 7451\%$. 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 the 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.

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 normalisation 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. This 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 in healing processes and wound healing rate after delay.

Table 8 Relative prediction error for delay exponential model. It 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

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

8 Conclusion

In our study all wounds were pooled irrespective of wound etiology, 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.

The 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 phenomenon, 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 the 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 a 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 realised 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.).

Acknowledgment—This research was supported by the Ministry of Science and Technology of the Republic of Slovenia. The authors would like to thank the Institute of the Republic of Slovenia for Rehabilitation, especially H. Benko for collecting the data and R. Turk and R. Šavrin for making them available for the study.

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