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MATHEMATICAL MODELING OF CHRONIC WOUND HEALING

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ABSTRACT

The wound-healing process has previously been modeled with exponential or with linear curves. In the present study, we proposed a new model called the delayed exponential model, and compared all three models. Assessment of the models was based on healing data for 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 the delayed exponential model offers the best fit of the three models tested.

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 (1,2). 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 (3,4). Observing a large group of pressure ulcers, treated either conventionally or with electrical stimulation in a previous study that we had done

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(5), we found the healing process to be delayed for a period from a few days to a few weeks in 50% of wounds after beginning of the particular treatment. We thus suggested a new model, called the delayed exponential model, which encompasses this feature of "delayed" healing.

Wounds of different etiologies, such as vascular wounds, amputation wounds, and pressure ulcers, heal with different dynamics. We therefore assessed the models described above with pressure ulcers in a 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).

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 minimum number of wound-area measurements (at least 3) and a minimum initial wound area (1 cm^2). Wounds that had previously been treated surgically were excluded from analysis. 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 in the 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 (5). 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.

$$\hat{S}_l = S_0 - \Theta_l t \tag{1}$$

$$\hat{S}_e = S_0 e^{-\Theta_e t} \tag{2}$$

$$\hat{S}_d = \begin{cases} S_0; t \le T \\ S_0 e^{-\Theta_d (t-T)}; t > T \end{cases} \tag{3}$$

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.

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

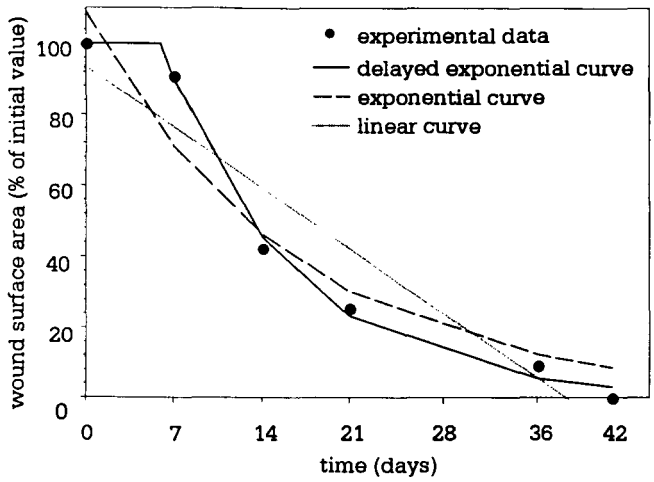

FIGURE 1. Data fitting with linear, exponential, and delayed exponential curves for a typical wound case from the electric stimulation (ES) group.

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) (4), and the second criterion was goodness of fit (r^2) (5):

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

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

where S_i represents the ith 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.

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 values 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.

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 models; r_d = goodness of fit for delayed exponential model; SE = standard error.

For our sample of 165 ulcers, the LSSE of the delayed-exponential model was 38.1% and 51.7% smaller than the LSSEs for the 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 the 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 the 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.

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 requires a 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 the patient's disability, and the patient's general health status. The progress of healing also strongly depends on the location of the wound (5). 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, owing to problems with the measurement of wound depth, as well as its incorporation into the mathematical description of the healing process, 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 defined time, of the wound-healing rate.

REFERENCES

1. Koth, L.C., and Feedar, J.A.: Acceleration of wound healing with high voltage, monophasic, pulsed current, Phys. Ther. *68*, 503–508, 1988.
2. Gault, W.R., and Gatens, P.F.: Use of low intensity direct current in management of ischemic skin ulcers, Phys. Ther. *56*, 265–269, 1976.
3. Stefanovska, A., Vodovnik, L., Benko, H., and Turk, R.: Treatment of chronic wounds by means of electric and electromagnetic fields, Part 2, Med. Biol. Eng. Comput. *31*, 213–220, 1993.
4. Karba, R., Vodovnik, L., Preseren-Strukelj, M., and Klesnik, M.: Promoted healing of chronic wounds due to electrical stimulation, Wounds *3*, 16–23, 1991.
5. Jercinovic, A., Karba, R., Vodovnik, L., Stefanovska, A., Kroselj, P., Turk, R., Dzidic, I., Benko, H., and Savrin, R.: Low frequency pulsed current and pressure ulcer healing, IEEE Trans. Rehab. Eng. *2*, 225–233, 1994.