The Impact of the Wound Shape on Wound Healing Dynamics: Is it Time to Revisit Wound Healing Measures?

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Abstract: Introduction: Wound healing is a multifaceted process, which can be impacted by many endogenous (e.g., compromised immune system, limited blood supply) or exogenous (e.g., dressing, presence of infection) factors. An essential step in wound management is to track wound healing progress. It typically includes tracking the wound size (length, width, and area). The wound area is the most often used indicator in wound management. In particular, wound closure is the single parameter used by the FDA to measure wound therapeutics' efficiency. Here, we present some arguments on why the wound area alone is insufficient to predict wound healing progress. Methods: We have developed an analytical approach to characterize an epithelization process based on the wound's area and perimeter. Results: We have obtained the explicit results for wound healing trajectory for several wound shapes: round (2D), elongated cut (1D), and rectangular. The results can be extended to complex shapes. Conclusions: From geometrical considerations, the wound healing time is determined by the shortest dimension (the width) of the wound. However, within that time, the wound healing trajectory can be different. Our calculations show that the shape of the wound may have significant implications on a wound healing trajectory. For example, in the middle of the wound healing process (t/T=0.5), the 1D wound model predicts 50% closure, while the 2D model predicts 75% closure (25% remaining). These considerations can be helpful while analyzing clinical data or designing clinical or pre-clinical experiments.

1 INTRODUCTION

Wound healing is a multifaceted process, which can be impacted by many endogenous (e.g., compromised immune system, limited blood supply) or exogenous (e.g., dressing, presence of infection) factors.

Successful acute wound healing depends on orderly progression through four phases: hemostasis, inflammation, proliferation, and remodeling or maturation. During hemostasis and the early inflammatory phase, platelets and inflammatory cells migrate into the wound bed. During the inflammatory phase, neutrophils enter the wound (Diegelmann, 2004), followed by macrophages that are responsible for neutrophil and damaged matrix removal (Meszaros, 2000). During the proliferative phase, the migration of fibroblasts and keratinocytes into the wound occurs. Keratinocytes cause re-epithelization of the wound. Fibroblasts produce collagen and other extracellular matrix (ECM) proteins necessary for granulation tissue formation. During the final phase of wound remodeling (which takes months and years), collagen deposition continues, and collagen III is gradually replaced with collagen I (Xue, 2015).

The emphasis of the current work is the proliferation phase. The sign of the successful proliferation is the re-epithelization of the tissue, which occurs due to keratinocytes' migration.

An important aspect of wound management is to track wound healing progress. Geometrical wound measurements (length, width, and depth) are essential tools in wound care armamentarium. In particular, wound closure is the single parameter used by the FDA to measure wound therapeutics' efficiency.

The geometrical wound measurements typically are being performed manually, using a ruler. There are two primary methods used for wound measurements (Swezey, 2014):

- "Greatest length and width method: In this method, the greatest length and the greatest width of the wound are measured across the wound's diameter, from wound edge to the opposite wound edge.

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- Clock method: In this method, the face of a clock is used to guide measurement. The 12:00 reference position is towards the head of the body, and measurements are obtained from 12:00 to 6:00 (length) and from 9:00 to 3:00 (width).” Notice that the width can be larger than the length in this case.

However, only the length, L, and width, W, can be determined using these methods. The surface area of the wound, S in this case, can be estimated as $S=LxW$, which is a very rough approximation that does not take into account the shape of the wound. This type of calculation has been shown to overestimate the wound area by 10% to 44% (Goldman, 2002), with accuracy decreasing as wound size increases (Majeske, 1992). Thus, tracking the wound healing progress in time manually will be relatively imprecise. The accuracy of wound measurements can be increased with digital photography. In this case, the precise wound area can be calculated in addition to the more accurate length and width measurements. Note that it can also be done with wound tracing on a sterile sheet or film (Langemo, 1998). However, it is a very labor-intensive process. In particular, digital technology may lead to a 10x increase in the accuracy of wound measurements. However, the initial implementation of such techniques using DSL cameras got limited clinical traction, primarily due to the significant extra time required to take pictures using specialized equipment. Thus, this process did not fit well in a busy clinical workflow. With the advent of smartphones, wound management was revolutionized. The ability to capture an image and annotate the wound using the same tool significantly improved the overall wound management workflow.

Many wound healing measures are proposed (a brief overview can be found in (Cukjati, 2001)). However, most commonly, a measure of the change in wound area is used and is expressed either as a raw number (cm^2) or as a percentage of the initial wound area. The wound area, S, is an important clinical indicator of the wound status and can be used to predict wound healing progress and clinical outcomes. In particular, S is a part of several wound indices (e.g., PUSH score for pressure injuries).

However, it is known that the wound healing rate expressed as absolute area healed per day tends to exaggerate larger wounds' healing rates. Similarly, the healing rate expressed as a percentage of initial area healed per day tends to exaggerate smaller wounds' healing rates (Cukjati, 2001). Thus, more objective methods need to be adopted into clinical use.

Here we present some arguments why wound area alone is not sufficient to predict wound healing progress. The shape of the wound (e.g., round, complex, or elongated) also play an essential role in wound healing dynamics. In particular, we argue that wound healing for quasi-2D (round shape) wounds will have significantly different dynamics from quasi-1D wounds (e.g., cuts). Thus, objective wound healing measures need to account for the wound shape.

2 METHODS

Let's consider a wound with an arbitrary shape. It can be characterized by the area S and the perimeter P. If the epithelization starts from the wound margin, and keratinocytes propagate on the distance dx, then in the first approximation, we can write

$$dS = -Pdx \quad (1)$$

Now, let's consider this process in more detail. In particular, we will be interested in how the shape of the wound affects wound healing dynamics.

2.1 Lattice Model

To elucidate the details, we will consider a lattice model of the wound. The epithelized tissue bounds the wound. During each time interval Δt, the wound wall propagates inwards by $\Delta x=v\Delta t$, where v is the wound closure speed. For practical reasons, the time interval Δt can be set to one day.

If we consider the wound of an arbitrary shape, then the wall propagation dynamics will be different in different parts of the curve. For the square lattice, there are three cases to consider: a convex angle (Figure 1), a concave (or reflex) angle (Figure 2), and a flat segment (Figure 3).

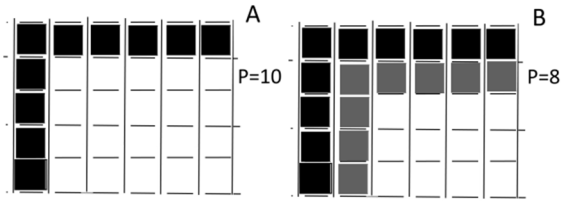

Figure 1: Healing dynamics in the case of a convex segment.

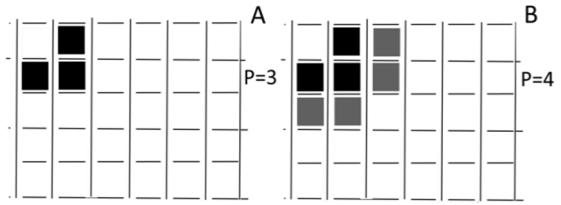

Figure 2: Healing dynamics in the case of a concave segment.

Suppose we calculate the perimeter at each step of the wall propagation. In that case, one can see that the perimeter (and according to Eq.1, the rate of wound closure) increases at reflex segments (Figure 2), decreases at convex segments (Figure 1), and stays constant for the flat segments (Figure 3).

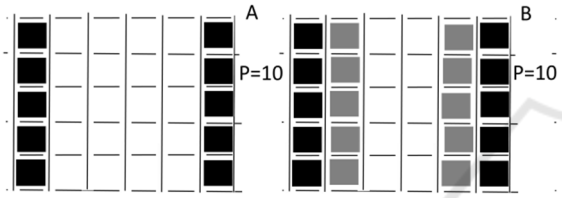

Figure 3: Healing dynamics in the case of two parallel walls.

Thus, intuitively, the wound healing rate behaves very differently at various points of the closed curve (wound margin).

2.2 Wound Closure Rate

Let's discuss what the wound closure speed, v is. The naïve idea would be to link this speed with the migration rate of keratinocytes. According to Tao et al. (Tao, 2007), the keratinocytes migration rate is 10-20 μm/h *in vitro*. However, to have a viable epithelial layer, it needs to be supplied with oxygen and nutrients. In particular, to have adequate oxygen supply, the oxygen diffusion length should not exceed 200μm. Thus, the tissue underneath a new epithelium needs to be vascularized, which may include angiogenesis and collagen matrix deposition by fibroblasts. Without an appropriate collagen scaffold, the vascular network will collapse.

Consequently, we can consider the re-epithelization process as three processes run in parallel: 1) keratinocytes migration, 2) revascularization via angiogenesis beneath a newly epithelized surface, and 3) fibroblast migration and collagen deposition. Based on this model, we can estimate the wound closing speed, v. Based on the maximal oxygen diffusion length (L_d=200μm), we can expect that the epithelial layer cannot overtake the new vasculature by much more than L_d. Thus, we can expect that the wound closing rate, v, will be equal to the smallest of three values: keratinocytes migration rate, angiogenesis rate, and fibroblast migration rate.

Epithelization happens through two primary mechanisms: crawling of cells on the substratum and constriction of a supracellular actomyosin cable at the edge of the gap in a purse-string-like mechanism (Klarlund, 2012). In the presence of ECM, crawling is a predominant mechanism. However, in the general case, wound closure is an interplay of these two mechanisms (Ravasio, 2015). In (Ravasio, 2015), it was also found that the shape of the wound affects the epithelization rate. These two mechanisms act in the same direction near a convex surface; thus, the closure rate is higher (up to 75 μm/h for MDCK (Madin-Darby canine kidney) cells). Near a concave surface, these two mechanisms act in opposite directions. Thus the closure speed is lower (close to 0 μm/h for MDCK cells).

Angiogenesis is a multistage process by itself. According to Felmeden et al. (Felmeden, 2003), angiogenesis consists of 7 distinct phases (endothelial cell and pericyte activation, degradation of the basement membrane, migration of endothelial cells (e.g., sprouting), proliferation of endothelial cells, differentiation of endothelial cells, and reconstitution of basement membrane). The primary factors, which drive the angiogenesis and the morphology of the newly developed vascular network are proliferation rate (PR) and migration rate (MR) of endothelial cells. The overall growth of vasculature is a result of both proliferation and migration. They were researched intensively in (Norton, 2016) numerically, where the authors found that to get normally vascularized tissue, these parameters must be close to PR=0.025 1/h and MR=10-16 μm/h. These values agree with experimental observations that doubling times for microvascular endothelial cells range from about 12 hours to 4 days (Anagnostou, 1990). Based on these values, we can conclude that assuming a sufficient supply of endothelial cells, the endothelial cell migration rate will limit the vascularization rate. Subsequently, the wound healing rate, v, will be limited by a smaller value (vascularisation rate in this case), which is 10-16 μm/h=240-380 μm/d. Note that it is hard to expect that the vascularization rate will be affected by the wound curvature.

This estimation is very close to experimental data on humans and animal models. For example, the wound closure rate can be estimated as 0.25mm/d in the rat model (Rong, 2019).

3 RESULTS

3.1 2D Case

Let's consider the 2D case: a round wound with the radius *r*. In this case, the perimeter $P = 2\pi r = 2\pi^{1/2}S^{1/2}$. If we substitute this expression in Eq.1 and notice that *dx=vdt,* we can write

$$dS = -2\pi^{1/2}S^{1/2}vdt \quad (2)$$

We can divide both sides of the equation by $2S^{1/2}$ and integrate them

$$\sqrt{S_0} - \sqrt{S} = \pi^{1/2}vt \quad (3)$$

Here, S_0 is the wound area at the moment *t=0*. From Eq.3, we can find the explicit expression for the wound area, S

$$S = (\sqrt{S_0} - \sqrt{\pi}vt)^2 \quad (4)$$

The wound healing time will be $T = \sqrt{S_0/\pi}/2v = W/2v$

3.2 1D Case

Let's consider the 1D case: a long rectangular cut, where the length of the cut *L* is much bigger than its width, *W*. In this case, the perimeter *P=2L+2W≅2L*. The wound area is *S=LW*. From this expression, one may deduce that *P=2S/W*. However, *W* is not constant. It decreases over time. Thus, this expression is not useful for calculations. Instead, we may notice that the perimeter P is approximately constant during wound healing. Therefore, we can write *P=2L* instead (note that $P \sim S^0$). If we substitute this expression in Eq.1 and notice that *dx=vdt,* we can write

$$dS = -2Lvdt \quad (5)$$

If we integrate both parts and reshuffle terms, we will get

$$S = S_0 - 2Lvt \quad (6)$$

The wound healing time will be $T = S_0/2Lv = W/2v$

3.3 The Generalization to Simple Shapes

For a rectangular wound, we can find an exact solution to the wound closure problem. If we consider the rectangle with the length *L* and width W ($L \geq W$) and the wall is moving with the speed *v*, then the unclosed area of the wound at time *t* will be

$$S = (L - 2vt)(W - 2vt) = W^2(L/W - 2vt/W)(1 - 2vt/W) \quad (7)$$
$$\text{for } 0 \leq t \leq W/2v.$$

If we introduce the wound healing time $T = W/2v$ and normalized time $\tau = t/T$ then we can obtain an expression for the normalized surface area *s*:

$$s = \frac{S}{S_0} = (1 - \tau W/L)(1 - \tau) \quad (8)$$

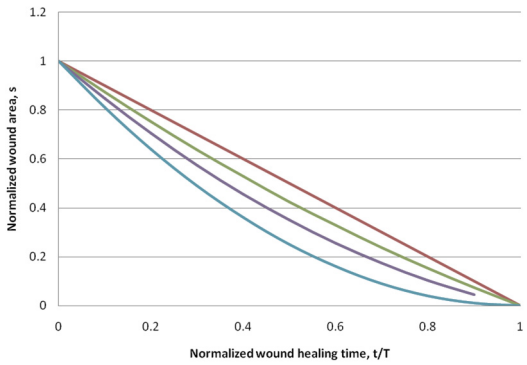

Figure 4: Wound healing trajectories for a rectangular wound for various values of *W/L* ratios: 0 (red curve), 0.3 (green curve), 0.6 (purple curve), and 1 (blue curve).

In Figure 4, one can see several wound healing scenarios for various *W/L* ratios.

The case *W/L->0* corresponds to the 1D case considered above. If *W/L=1*, then it is a square wound, which is very similar to the round wound considered in the 2D section.

3.4 The Generalization to Complex Shapes

2D and 1D cases can be generalized differently if we consider the wound margin as a fractal curve with a dimension d_f, where $1 \leq d_f \leq 2$. One can see that the perimeter *P* can be expressed through wound area *S* as

$$P = aS^{\frac{d_f - 1}{2}} \quad (9)$$

where *a* is a constant. In particular, this expression holds in the case of *d=2* and *d=1*. This expression can be used to calculate d_f for a specific curve. We need to visualize the curve at several pixel sizes, calculate *P* and *S* for each of them, and plot these values against each other (*P* vs. *S*). Then, the parameter *a* and the fractal dimension d_f can be found numerically using curve fitting.

If we substitute Eq.9 in Eq.1, divide both parts on $S^{(d_f-1)/2}$ and integrate them, we will get

$$S_0^{\frac{3-d_f}{2}} - S^{\frac{3-d_f}{2}} = \frac{3 - d_f}{2}avt \quad (10)$$

Thus, we can obtain an explicit expression for the area *S* at any given time *t*

$$S = (S_0^{\frac{3-d_f}{2}} - \frac{3-d_f}{2} avt)^{\frac{2}{3-d_f}} \quad (11)$$

This expression holds for *d=2* (see Eq.4) and *d=1* (see Eq.6). Similarly, we can get an expression for the normalized area *s*:

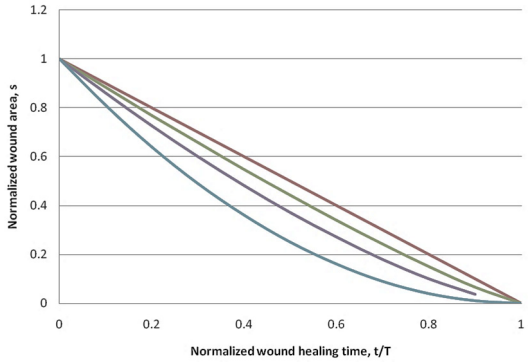

Figure 5: Wound healing scenarios for various fractal dimensions d_f: 1 (red curve), 1.3 (green curve), 1.6 (purple curve), and 2 (blue curve).

$$s = \frac{S}{S_0} = (1-\tau)^{\frac{2}{3-d_f}} \quad (12)$$

In Figure 5, one can see several wound healing scenarios for various fractal dimensions d_f. Note that the wound healing time, in this case, will be

$$T = 2S_0^{\frac{3-d_f}{2}} / av(3-d) \quad (13)$$

4 DISCUSSION

From simple geometrical considerations, one can see that the wound healing time is determined by the shortest dimension (the width) of the wound. That is why the surgical closure of the wound (wherever possible) is the best strategy. However, within that time, the wound healing trajectory can be different. Our simple calculations show that the wound's shape may have significant implications on a wound healing trajectory. For example, in the middle of the wound healing process (t/T=0.5), the 1D wound model predicts 50% closure, while the 2D model predicts 75% closure (25% remaining).

We have proposed two approaches to account for the wound shape: a) based on the *W/L* ratio and b) based on the fractal dimension. Both methods do not require any clinical workflow changes if the wound were measured using digital photography.

The rectangular wound model can be easily extended to any elliptical shape. In this case, the wound trajectory (Eq.8) will be the same. The fractal model can be extended to more complex shapes, which include concave segments. Thus, the models are complementary, and the combination of these two models covers the broad range of wound shapes.

We also found that the wound perimeter is a fairly important factor in the wound healing process. For example, the perimeter can be linked with the wound area through a fractal dimension of the shape. Note that the "fractal dimension" term is used quite loosely here. We don't expect wound shape similarity extended through multiple scales.

The proposed approach also helps identify which wound healing rate used in clinics is the most informative. As we mentioned in the introduction, the current wound healing tracking methods based on wound area *S* are imprecise. Partially it can be explained by the fact that they do not account for the wound shape. The more relevant metric could be a linear healing rate *D* proposed in (Gilman, 1990), which can be calculated as $D=\Delta S/P$ from the change in the area ΔS and mean perimeter *P*. It can be seen that *D,* which was originally termed as “the advance of the wound margin toward the wound centre,” is an experimental measure for the wound closure rate *v*.

In particular, a study on 49 wounds found (Gorin, 1996) that the linear healing rate does not correlate with the initial wound area, perimeter, and *W/L* ratio. Thus the linear healing rate is independent of the wound shape. These results were confirmed in (Cukjati, 2001) on 300 wounds. Therefore, these results can be considered as experimental confirmation of the validity of the proposed model.

To validate these theoretical predictions further, experimental verification is required, particularly for complex shapes.

There are certain limitations to the proposed model. Firstly, it was derived under the assumption that wound epithelization occurs for all wound perimeter points. From a physiological point of view, it means that wound healing is not impaired. While it can be the case for an acute wound, it is not apparent for chronic wounds. For example, the revascularization of the ischemic wound can be impossible without revascularization surgery. Secondly, the wound healing rate may depend on the wound thickness. In the case of superficial wounds, the vascular network may stay almost intact. Thus only re-epithelization is required. Therefore, the rate of wound closure is limited by keratinocytes migration only (up to 20 μm/h) and can be higher than for partial-thickness wounds (10-16 μm/h). For the full-thickness wounds, which require collagen deposition, the wound closure rate will be even slower.

The linear healing rate was assessed in several studies. Pecoraro et al. (Pecoraro, 1991) found 0.064 mm/day on diabetic foot patients. Margolis et al. (Margolis, 1993) found 0.093 mm/day on venous ulcers. Gorin et al. (Gorin, 1996) found a similar result of 0.11 mm/day on venous ulcers. Cukjati et al. (Cukjati, 2001) found 0.068 mm/day for the wound of unknown etiology. All these values are 2-4 times lower than the angiogenesis-limited healing rate. Thus, one can expect that these rates are limited to slower collagen-deposition processes or presence areas with impaired healing.

These considerations can be helpful while analyzing clinical data or designing clinical or pre-clinical experiments.

5 CONCLUSIONS

Wound shape has significant implications on a wound healing trajectory, which is not taken into account by metrics currently used for wound healing progress tracking. Wound area (closure) and wound area (closure) as a percentage of the initial wound area are important clinical endpoints. However, they do not account for wound shape and do not allow an accurate comparison of different wounds and treatment methods. With the ubiquity of smartphones and digital wound measurements, it is time to start developing more accurate wound healing metrics. The smallest size of the wound (width) and a linear wound healing rate can be the basis for such metrics.

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