5-2019

Geometric Aspects of Wound Healing

Julio Urenda
The University of Texas at El Paso, jcurenda@utep.edu

Vladik Kreinovich
The University of Texas at El Paso, vladik@utep.edu

Comments:

Technical Report: UTEP-CS-19-45

Geometric Aspects of Wound Healing

Julio Urenda[1,2] and Vladik Kreinovich[2]
[1]Department of Mathematical Sciences
[2]Department of Computer Science
University of Texas at El Paso
500 W. University
El Paso, TX 79968, USA
jcurenda@utep.edu, vladik@utep.edu

Abstract

In this paper, we show that many aspects of complex biological processes related to wound healing can be explained in terms of the corresponding geometric symmetries.

1 Formulation of the Problem

Geometric aspects of wound healing: a brief descrption. When a wound appears, the body starts a complex process of healing the wound; see, e.g., [1, 4, 6]. Among other important related processes, two processes affect the geometric shapes:

- within the first few minutes of injury, cells called platelets move to (and along) the wound boundary and change their shape to cover ("clot") this boundary – thus protecting the remaining part of the body; see, e.g., [5, 8];
- some time after that, epithelial (skin-forming) cells change their shape to elongated and slowly move in the direction orthogonal to the skin's boundary to cover the tissues exposed by the wound; see, e.g., [3].

A challenge. Wound healing is a very complex well-choreographed, and often, very successful process. However, in contrast to many other complex biological processes, it occurs very naturally, without a complex behavior coded into a DNA molecule, without a complex multi-neural nervous system controlling different stages. Most of this complex choreography occurs on the level of cells themselves. How can we explain this unexpectedly complex behavior of such a seemingly control-less system?

What we do in this paper. In this paper, we show that the geometric aspects of wound healing can be naturally explained by analyzing the corresponding local geometric symmetries.

2 What Are Natural Symmetries Here and What Are the Resulting Cell Shapes: Case of Undamaged Skin

Natural local symmetries of the undamaged skin surface. To understand the wound healing process, let us start with analyzing the natural local symmetries of the undamaged skin surface.

Locally, a skin surface is flat, so we can locally represent it as a plane. In general, a plane has the following geometric symmetries: rotations, shifts in two directions, and scaling $x \to \lambda \cdot x$. Overall, we have a 4-dimensional group of symmetries.

There are also discrete symmetries: reflections across a line, and mirror reflections – reflections across a point.

Out of the continuous symmetries, rotations are the only symmetries that can be *exact*, in the sense that it is quite possible to have a circular piece of skin which is perfectly invariant with respect to all rotations around its center. In contrast, shifts and scalings are only *approximate* symmetries: there is no way to select a piece of skin which would be invariant with respect to all shifts or with respect to all possible scalings: such an invariant region would have to coincide with the whole infinite plane.

Symmetry of skin cells: case of undamaged skin. A skin in not a homogeneous medium, it consists of cells. The cell shapes are usually somewhat complicated, but in the first approximation, we can describe their shapes in geometric terms.

We want to describe the shape of a cell boundary. In this description, we take into account that while the plane itself has a 4-dimensional symmetry group, the cell boundary cannot have all these symmetries: e.g., if it was shift-invariant, then with any point on this boundary, we would have all the points obtained from it by shift; thus, the cell boundary would take over the whole plane. Thus, to form a cell, some original symmetries must be broken.

Symmetry breaking is a process which is ubiquitous in real world and thus, well studied in physics. According to physics, the most probable are the transitions that break the smallest number of symmetries (and thus retain the most symmetries); see, e.g., [2, 7]. For example, when we heat a well-structured well-symmetric crystal, we do not directly get a fully amorphous gas stage; first, we get a liquid stage, in which some structure is retained.

The main symmetries here are rotations – since they are the only symmetries which are exact. The only shape which is invariant with respect to rotations is a circle. And skin sells indeed form a circle-type shape, with approximately the same size in all directions. (Of course, they are not exact circles, since skin cells cover the whole skin surface, and it is not possible to cover a planar area with non-intersecting circles.)

3 What If the Skin Is Damaged: Resulting Symmetries and Cell Shapes

What happens when there is a wound. A typical wound is a cut. Locally, a cut is a straight line. Thus, locally, instead of a plane, we have the shape of a half-plane, an area of the plane which is to one side of the cut line.

Cell shapes at different locations: discussion. At a location distant from the wound boundary, locally, the skin still has the same shape. So locally, we have the same symmetries, and thus, we expect that the cells retain the same shape.

However, for cells at the wound boundary, not all local symmetries hold: e.g., there is no longer invariance with respect to rotations. Since symmetries are different, we expect the shapes to be different as well. To find the resulting shapes, let us analyze what are the resulting symmetries.

What are natural symmetries of the damaged skin surface. As we have mentioned, the half-plane is no longer invariant with respect to rotations. Of all the shifts, it is only invariant with respect to shifts parallel to the cut. It is also still invariant with respect to scalings. Thus, instead of the original 4-dimensional symmetry group, we now only have a 2-dimensional symmetry group. In this case, both symmetries are approximate, since, as we mentioned, a finite region cannot be exactly shift-invariant or scale-invariant.

The new configuration also has some remaining discrete symmetries: namely, it is invariant with respect to a reflection across any line which is orthogonal to the wound boundary.

Resulting cell shapes. What are the cell shapes in the vicinity of the wound boundary? Similarly to the case of cell shapes for the undamaged skin, the typical cell shapes for the damaged skin should be invariant with respect to at least some of the original symmetries.

Let us first look for the shapes which are invariant with respect to both shifts and scaling. To simplify our analysis, let us take a coordinate system in which the wound boundary has the form $y = 0$, and the remaining skin is located in the half-plane $y > 0$. In these coordinates, if the cell boundary contains a point (x_0, y_0) with $y > 0$, then:

- due to shift-invariance, it will contain the points (x, y_0) for all possible values x, and thus,
- due to scale-invariance, it will contain all the points (x, y) with $y > 0$ – i.e., it will coincide with the whole skin.

Since each cell is only a part of the skin, this means that for the maximally symmetric cell shapes, we cannot have points with $y > 0$. Thus, these cells must be located in the area $y = 0$ – i.e., on the boundary of the wound.

Since we are considering cells on the boundary of the wound, the cell must contain at least one point on this boundary $y = 0$, i.e., a point $(x_0, 0)$ for some

x_0. Due to shift-invariance, we can conclude that the cell must contain all the points $(x, 0)$ for different x – i.e., that the cell must fit the wound boundary.

What if we only have some symmetries? If we have shift-invariance, then we get the same shapes – elongated cells that cover the boundary. What if we only have scale-invariance? In this case, if we take, as the origin of the x-axis, the point where the cell intersects with the boundary, then this intersection point will have the coordinates $(0, 0)$. A cell is not a single point, it has to have some other points. If (x_0, y_0) is such a point, then, due to scale-invariance, it must also contain all the points $(\lambda \cdot x_0, \lambda \cdot y_0)$. In other words, the cell must contain all the points on a half-line (ray) that goes from $(0, 0)$ to this point (x_0, y_0). So, we have an elongated cell at some angle to the wound's boundary.

Most of such lines are only scale-invariant. However, some of these lines – namely, the ones which are orthogonal to the wound boundary – have an additional discrete symmetry: namely, the configuration including such line and the wound's boundary is invariant with respect to reflections across this line.

Conclusion: resulting shapes listed in the order of their relative frequency. According to our symmetry-based geometric analysis, the most frequent – and the first to appear – will be the maximally symmetric shapes, i.e., the elongated cells which are located directly on the boundary of the wound. As we have mentioned, this is exactly what we observed in the wound healing process: in the beginning, such cells indeed appear.

Next come cells which have the largest number of remaining symmetries – namely, the cells which are elongated and perpendicular to the wound boundary. This is also indeed what happens at the second stage of the wound healing.

So, the shapes of the emerging cells and the order in which these cells appear can indeed be explained by geometric symmetries.

Comment. After the above two major types of cells, we may have cells with fewer remaining symmetries – namely, elongated cells which are oriented at an angle to the wound boundary. Such cells have indeed been observed; see, e.g., [1, 4, 6].

4 Geometric Symmetries Also Explain Observed Cell Motions

For undamaged skin, cells do not move. In the undamaged skin, a cell is surrounded by other cells, so it has nowhere to move.

The situation is different on the wound boundary. When there is a wound, there is an open space to which cells can move. Let us use geometric symmetries to describe the most probable directions of the cells' movement.

How to find the most probable motion direction: main idea. To find the most probable direction of the cell's motion, it is reasonable to use the

same idea when describing the cells' shapes: namely, we look for directions that maximally preserve the corresponding symmetries.

Case of maximally symmetric cells. The cells on the boundary are invariant with respect to both shift along the boundary and scaling. Thus, the line describing the direction of their most probable motion should also be invariant with respect to the same two symmetries.

One can easily see that the only such line is the line of the boundary itself. Thus, we conclude that these cells will most probably move along the wound's boundary.

Of course, this motion is only possible is there is space to move – i.e., if there is a part of the boundary which is not yet covered by such cells. So, the reshaping of the corresponding cells and their motions will continue until there is no more space to move – i.e., until the whole boundary is covered by such cells. This is exactly what is needed to form a cover for protecting the remaining part of the skin.

Case of second generation cells. Let us now consider the "second generation" cells, elongated cells whose direction is orthogonal to the wound's boundary. These cells are invariant with respect to scaling and reflection across their own line. Thus, the most probable line of their motion should be invariant with respect to the same symmetries.

One can see that the only such line is the line coinciding with the line of the cell itself. Thus, most probably, the cell will move in the same direction – orthogonal to the line of the boundary.

From the pure symmetry viewpoint, it can move in both directions: it can move towards the boundary, or it can move away from it. However, from the physical viewpoint, it cannot move away from the boundary – there the skin in intact, and there is no place to move. So, the only physically possible movement will be across the wound boundary. This way, such cells will spread into the wound area and cover it – this is exactly what we observe in the wound healing process.

Conclusion. So, a seemingly complex process of wound healing indeed requires no central control – its seemingly well-choreographed steps can be naturally explained by the corresponding geometric symmetries.

Acknowledgments

This work was supported in part by the US National Science Foundation via grants 1623190 (A Model of Change for Preparing a New Generation for Professional Practice in Computer Science) and HRD-1242122 (Cyber-ShARE Center of Excellence).

The authors are greatly thankful to Dr. Brandilyn Stigler and to all the participants of the 2019 Southwest Local Algebra Meeting SLAM'2019 (El Paso, Texas, February 23–24, 2019) for valuable discussions.

References

[1] R. A. F. Clark (Ed.), *The Molecular and Cellular Biology of Wound Repair*, Kluwer Academic Publishers, Dordrecht, 1996.

[2] R. Feynman, R. Leighton, and M. Sands, *The Feynman Lectures on Physics*, Addison Wesley, Boston, Massachusetts, 2005.

[3] H. G. Garg, *Scarless Wound Healing*, Marcel Dekker, New York, 2000.

[4] R. G. Gourdie and T. A. Myers (eds.). *Wound Regeneration and Repair: Methods and Protocols*, Humana Press, New York, 2013.

[5] H. Rasche, "Haemostasis and thrombosis: an overview". *European Heart Journal Supplements*, 2001, Vol. 3, Supplement Q, pp. Q3–Q7.

[6] B. Stigler, "Algebraic model selection and identification using Groebner bases", *Abstracts of the 2019 Southwest Local Algebra Meeting SLAM'2019*, El Paso, Texas, February 23–24, 2019.

[7] K. S. Thorne and R. D. Blandford, *Modern classical physics: optics, fluids, plasmas, elasticity, relativity, and statistical physics*, Princeton University Press, Princeton, New Jersey, 2017.

[8] H. H. Versteeg, J. W. Heemskerk, M. Levi, and P. H. Reitsma, "New fundamentals in hemostasis", *Physiological Reviews*, 2013, Vol. 93, No. 1, pp. 327–358.