Mechanics Research Communications 96 (2019) 87–93

Contents lists available at ScienceDirect

Mechanics Research Communications

journal homepage: www.elsevier.com/locate/mechrescom

Mechanochemical aspects of skin wound healing in microgravity

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ARTICLE INFO

Article history:
Received 2 March 2019
Accepted 19 March 2019
Available online 23 March 2019

Keywords:
Skin wound healing
Microgravity
Residual stress
Interfacial growth
Wrinkling
Nutrient chemistry

ABSTRACT

A coupled biomechanical-chemical growth model is proposed to study regeneration of residual stresses and appearance of wrinkling during cutaneous wound healing in a microgravity environment. A novel free energy density is introduced which couples mechanics, nutrient chemistry, and microgravity, assuming both skin and wound to be nonlinear elastic membranes. A simple boundary-value-problem is formulated and solved to obtain quantitative results on effects due to short-term and long-term microgravity exposure on stress generation and wrinkle formation, while emphasizing the interplay between elasticity, nutrient concentration, and microgravity.

1. Introduction

Skin is a vital mammalian organ which maintains the physiological and biochemical balance of the body by means of external protection, thermal regulation, sensation, and endocrine function [17,25]. Any injury or abnormality in skin may imbalance these functions leading to discomfort and deteriorating health conditions. The nature of the problem becomes even more critical in unfamiliar environments such as those encountered in outer space. Skin related disorders, such as fissuring of finger tips, skin boils, skin irritation, skin rash, skin dryness, and contact dermatitis have been reported for humans in space [19,34]. An astronaut on-board International Space Station (ISS) showed coarsening of epidermis, thinning of skin, ageing, and decreased skin elasticity [35]. A study with mice showed dermal atrophy and deregulation of hair follicle cycle subjected to prolonged microgravity [21]. Other works have reported wound atrophy resulting from a decreased production of growth factors, inferior cellular activities, and impaired collagen formation [7,12,22], on one hand, and decreased skin tension and subsequent impaired wound healing due to significant mechanical unloading, on the other [18,22]. The purpose of this article is to extend a recently proposed model of coupled biomechanical-chemical growth to understand regeneration of skin tension and appearance of wrinkling during the cutaneous wound healing process in an altered gravity environment. The latter is central to understand the nature of scar formation. The present model, which considers both skin and wound as nonlinear elastic membranes, incorporates the effects due to modified cellular activity, mechanical unloading, and nutrient availability during both short-term and long-term exposure to a microgravity environment.

We begin by discussing a few wound healing related observations in microgravity experiments. First, we note the alteration in cellular and extracellular elements involved in the healing response thereby impairing the healing dynamics [12]. A change in the haemostatic phase of wound healing, which results into a downward shift in platelet quantity and its function, has been observed in a microgravity environment [12]. The production of platelet derived growth factors (PDGF), and various other inflammatory cells required in the inflammation stage, has also been observed to diminish [9]. The proliferation of wounded structures is dependent on the interplay of many growth factors, e.g., transforming growth factors (TGF), PDGF, and epidermal growth factors (EGF), whose function and production are directly affected due to microgravity exposure. Second, mechanical unloading impairs wound healing [6,10,22]. A hind-limb unloading experiment simulating weightlessness reveals that keratinocyte and endothelial cell growth and function may be inhibited during the wound healing process [22]. Skin being a mechano-sensitive tissue, the nature of wound healing is strongly influenced by mechanical forces. This is because these forces, intrinsically and extrinsically, stimulate fibroblasts, myofibroblasts, and endothelial and epithelial cells in granulation tissues [7]. According to Ingber [18], “Gravity sensation may not result from direct activation of any single graviorecceptor molecule. Instead, gravitational forces may be experienced by individual cells in the living organism as a result of stress-dependent changes in cell, tissue, or organ structure that, in turn, alter extracellular matrix mechanics, cell shape, cytoskeletal orga-

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https://doi.org/10.1016/j.mechrescom.2019.03.005
0093-6413/

nization, or internal pre-stress in the cell-tissue matrix." Therefore, whenever living organisms are exposed to microgravity, they respond by a substantial decrease in pre-stress at the macroscopic scale. Third, nutrition also plays a pivotal role in wound healing. Whereas carbohydrates are required to supply the glucose requirement during healing, proteins are necessary for the development of granulation tissue, and fatty acids are required for the synthesis of new cells [15]. Moreover, vitamin-C helps in synthesis of collagen, vitamin K assists in formation of blot clot, vitamins of the B complex are the precursors of enzymatic reactions, collagen cross linking, and the release of energy from carbohydrates, and vitamin A assists in collagen cross-linking and proliferation of epithelial cells [15]. It is expected that wound healing in microgravity will be impaired due to the absence of vital nutrients apart from other cellular responses as a result of gravitational unloading and physiological alterations.

The earlier biomechanical models of cutaneous wound healing [16,20] treated the healing process as a multi-component diffusion problem, while ignoring both the nonlinear elasticity of skin (and wound) and the consideration of an explicit wound-skin interface. This has been rectified in several recent models [2,31,32,36] which have been otherwise motivated from the prolific literature on biomechanical growth. Our recent work [31,32] has addressed issues related to residual stress generation and wrinkling in the skin, adjacent to the wound, and wound rupturing during the healing process. The distinguishing aspect of our work has been to use an incoherent interfacial growth framework which provides a natural setting to discuss the aforementioned issues. More recently, we have proposed a biomechanical-chemical growth model which couples mechanical aspects (stress related) of interfacial biological growth to nutrient chemistry [30,33]. It is this model that we now extend to incorporate the role of microgravity in the wound healing process and related elastic instabilities. It is pertinent to note that there is no biomechanical model in the literature which can be currently used towards this end. Our interest, in particular, is to study the effect of both short-term and long-term microgravity exposure on the residual stress generation and wrinkle formation in the healing skin. The interplay between mechanical and chemical ingredients of the theory are emphasized throughout.

In rest of the article, we begin by formulating the problem in Section 2. In particular, we introduce a novel coupled mechanical-chemical free energy density function which also includes several parameters which can potentially depend on microgravity. The mechanical and chemical balance laws are discussed in detail and used to formulate a boundary value problem. The results are discussed in Section 3 in the light of available experimental information.

2. Problem formulation

The healing of skin wound occurs through four major phases: haemostasis, inflammation, proliferation or wound closure, and remodelling [24]. Our model considers the wound closure stage alone [31,32]. The fundamental role played by the wound edge during wound healing is taken as the basis in our model [31]. The basic biomechanical framework for the problem, as formulated below, will be taken from our earlier work [31,32]. The biomechanical-chemical coupling will also be derived from a more general setting proposed in our recent work [31,33]. In the following we will avoid repetition and directly make use of expressions from these papers. The interested reader is referred to these works for more details. It is important to emphasize that these earlier models have been enhanced here to incorporate effects due to microgravity. Such dependencies are, in particular, included through

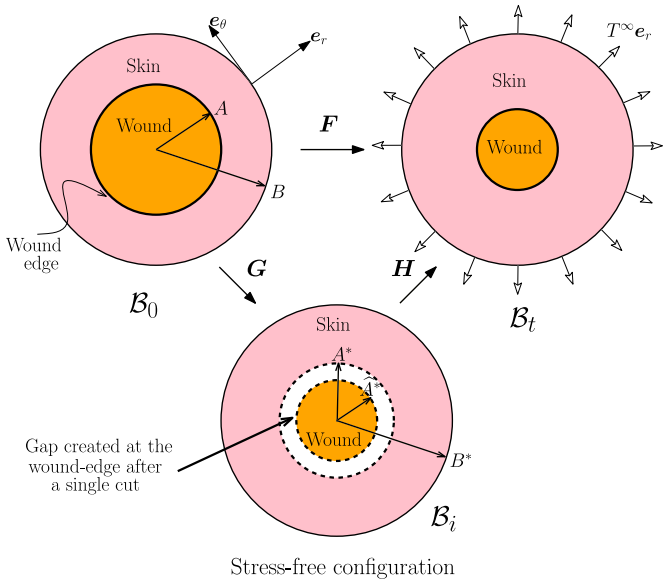

Fig. 1. The kinematic model for wound healing in microgravity, where $\mathcal{B}_0$ is the reference configuration, $\mathcal{B}_i$ is the intermediate configuration, and $\mathcal{B}_t$ is the current configuration.

the free energy density function, the far field skin tension, the healing rate, and the growth strains.

2.1. Kinematics and growth

The wound healing model considers growth of the healthy skin, and resorption of the wound, governed by a mass source at the wound-skin interface. The wound is taken as a thin circular disk and the surrounding skin as a thin circular disk with an annulus, both made of nonlinear elastic membranes, see Fig. 1. The problem is assumed to be axisymmetric, both geometrically and in mechanical-chemical response. The skin area in the vicinity of the wound is assumed to be large enough so that the traction at the skin boundary is obtainable from the known pre-stress in healthy skin. The essential feature of growth kinematics is the multiplicative decomposition of deformation gradient into an elastic and a growth part. However, unlike the models of bulk growth [23], both mass addition and deformation incompatibility in our framework is restricted to a sharp interface between wound and skin.

The wound region is of radius A, $\hat{A}^*$, and a in reference configuration $\mathcal{B}_0$, in intermediate stress-free configuration $\mathcal{B}_i$, and in current configuration $\mathcal{B}_t$, respectively. It is necessary that $a < A$ for wound healing. The intermediate configuration is obtained from $\mathcal{B}_t$ by relieving it of all the stresses. In the present model, a single cut at the skin and wound interface is sufficient to achieve the zero-stress state, see Fig. 1. The skin region surrounding the wound has an outer radius B, B^*, and b in the respective configurations as shown in the figure. Moreover, due to the assumed nature of growth, the inner radius of skin region in $\mathcal{B}_i$, given as A^* is not identical to wound radius $\hat{A}^*$. Keeping axisymmetric nature of the problem in mind, the position vector of a point in the reference, intermediate, and current configuration are taken as $\boldsymbol{X} = R\boldsymbol{e}_r(\theta)$ (with $0 \le R \le B$, $0 \le \theta \le 2\pi$), $\boldsymbol{X}^* = R^*\boldsymbol{e}_r(\theta)$ (with $0 \le R^* \le B^*$ such that $R^* = k_w R$ for $0 \le R \le A$ and $R^* = k_s R$ for $A \le R \le B$), and $\mathbf{x} = r(R)\mathbf{e}_r(\theta)$ (with $0 \le r \le b$), respectively, where k_w and k_s are growth parameters independent of the position. The biological nature of these parameters has been discussed earlier [31,32]. The unit vectors $\boldsymbol{e}_r$ and $\boldsymbol{e}_\theta$ are along radial and circumferential directions, respectively. The preceding maps can be used to derive the total deformation gradient $\boldsymbol{F} = r'\boldsymbol{e}_r \otimes \boldsymbol{e}_r + (r/R)\boldsymbol{e}_\theta \otimes \boldsymbol{e}_\theta$, away from the

interface, where the superscript prime denotes a derivative with respect to R; the inelastic growth distortion $\mathbf{G} = k_a(\boldsymbol{e}_r \otimes \boldsymbol{e}_r + \boldsymbol{e}_\theta \otimes \boldsymbol{e}_\theta)$; and elastic distortion $\boldsymbol{H} = \boldsymbol{F}\boldsymbol{G}^{-1} = (r'/k_a)\boldsymbol{e}_r \otimes \boldsymbol{e}_r + (r/k_aR)\boldsymbol{e}_\theta \otimes \boldsymbol{e}_\theta$. Here, and elsewhere, the subscript a stands for either w or s to accordingly represent wound and skin domains, respectively. It should be noted that both $\boldsymbol{H}$ and $\boldsymbol{G}$ are incompatible in the sense that the jump in their values at the wound-skin interface is not of a Hadamard rank one form as long as we take $k_s \neq k_w$ [31,32].

2.2. Free energy, stress, and chemical potential

We postulate a bulk free energy density, per unit area of the intermediate configuration, coupling bulk nutrient concentration, bulk elastic deformations, and microgravity, as

$$\Psi = 2\tau_a(\lambda_1 + \lambda_2 + 1/\lambda_1\lambda_2 - 3) + m\Psi_c(C) + \Lambda_a\lambda_1\lambda_2(C - C_0), \tag{2.1}$$

where λ_1 and λ_2 are elastic stretches along the radial and circumferential directions. In the present case $\lambda_1 = r'/k_a$ and $\lambda_2 = r/(k_aR)$. The elastic part of the energy is that of a Varga hyperelastic membrane, which supports wrinkling instability but prohibits cavitation [29], where τ_a represents the shear modulus. The second term in the energy density $\Psi_c(C)$ is the chemical energy density, where $C = C(R)$ is the bulk nutrition concentration field, and m is a dimensionless factor which decides the amount of biochemical energy available during growth. The factor m in fact is used to capture the depletion in nutrient energy level in the presence of microgravity; we will take $m < 1$ for growth in a microgravity environment and $m = 1$ for growth in normal gravity. This is motivated by the simple fact that, during microgravity exposure, the available amount of nutrients in a biological body depletes from its usual state. The third term in the free energy density couples elasticity with nutrient chemistry. It represents a contribution to the total energy from a mutual dependence of nutrient distribution and elastic deformation. The coupling is important for microgravity simulations, since a decreased nutrient chemistry may directly lead to wound atrophy. The simple form of this term is assumed due to analytical convenience, where Λ_a is the diffusive mobility and C_0 is the haemostatic bulk chemical concentration. The material constants τ_a, Λ_a, and C_0 may also depend on microgravity. They are, in particular, expected to be affected during a long-term exposure to microgravity.

The excess free energy density, per unit length of the interface in the intermediate configuration, at the interface is assumed to have contribution only due to nutrient concentration:

$$\psi = m\psi_c\big(\widetilde{C}\big), \tag{2.2}$$

where $\widetilde{C}$ is an excess nutrient concentration distribution on the wound-skin interface.

The non-trivial Cauchy stress components (in their usual notation), as derived from (2.1), are [29]

$$T_{rr}(R) = (1/\lambda_2)\partial_{\lambda_1}\Psi = \left((2\tau_a/\lambda_2)\left(1 - \frac{1}{\lambda_1^2\lambda_2}\right) + \Lambda_a(C - C_0)\right) \text{ and} \tag{2.3}$$

$$T_{\theta\theta}(R) = (1/\lambda_1)\partial_{\lambda_2}\Psi = \left((2\tau_a/\lambda_1)\left(1 - \frac{1}{\lambda_1\lambda_2^2}\right) + \Lambda_a(C - C_0)\right). \tag{2.4}$$

Most importantly, the stress components depend explicitly on the concentration fields in addition to elasticity. The stress field can therefore appear even when the elastic strains are absent, in response to nutrient concentration in excess to the haemostatic concentration value. On the other hand, for the growth strains as considered in the preceding section, the bulk and the interfacial chemical potential can be derived from (2.1) and (2.2), respectively, as [33]

$$\mu(R) = k_a^2\partial_C\Psi = k_a^2(m\partial_C\Psi_c + \Lambda_a\lambda_1\lambda_2) \text{ and} \tag{2.5}$$

$$\tilde{\mu} = k_s\partial_{\widetilde{C}}\psi = k_sm\partial_{\widetilde{C}}\psi_c. \tag{2.6}$$

The bulk chemical potentials, again, are related to not only concentration fields but also to elastic stretches. In all these expressions, subscript a should be replaced by w or s depending on whether the domain of interest is wound or skin, respectively. Moreover, due to the axisymmetric nature of the problem, both $\widetilde{C}$ and $\tilde{\mu}$ will be constant.

2.3. Governing equations

The two unknown fields in our framework are deformation $r(R)$ and concentration $C(R)$. All the other fields of interest can be derived in terms of these variables. In the following we will derive the governing equations for these including jump conditions and boundary conditions. We will differentiate between two cases of unwrinkled and wrinkled membrane. The equations for the latter will be derived using tension field theory. Assuming zero body forces and neglecting the inertia (quasi-static deformations) the linear momentum balance for the problem at hand is satisfied if [32]

$$\frac{(T_{rr})'}{r'} + \frac{(T_{rr} - T_{\theta\theta})}{r} = 0, \tag{2.7}$$

wherever the stress components are differentiable, i.e., away from wound-skin or unwrinkled-wrinkled skin interfaces, and $[\![T_{rr}]\!] = 0$, i.e., the continuity of T_{rr} across any interface of stress discontinuity. Here, the bracket $[\![f]\!]$ represents the jump in a piecewise continuous bulk field f across an interface such that $[\![f]\!] = f^+ - f^-$, where f^+ is the limiting value of f as it approaches the interface from the bulk side into which the normal points and f^- is the limiting value when approached from the other side of the interface.

2.3.1. Unwrinkled solution

The wrinkling in the membrane appears in response to appearance of compressive stresses. It is only the non-negative stress fields which allow thin elastic membranes to maintain their stability [27]. Compressive stresses in such membranes can be accommodated by localized buckling in the form of infinitesimal wrinkles. During skin wound healing, these wrinkles are reported to occur in the circumferential direction alone and only in the skin domain [5,13]. We will restrict our considerations in line with these observations by choosing appropriate material parameters. In particular, we will require the radial stresses T_{rr} to remain tensile everywhere. Moreover, we allow wrinkling only in the skin domain. Keeping these in mind, we begin by first assuming that there is no wrinkling in the skin. Using the stress expressions (2.3) and (2.4), and the assumed expressions for elastic stretches, we have

$$T_{rr}(R) = 2\tau_ak_a(R/r) - 2\tau_ak_a^4\big(R/rr'\big)^2 + \Lambda_a(C - C_0) \text{ and} \tag{2.8}$$

$$T_{\theta\theta}(R) = 2\tau_ak_a\big(1/r'\big) - 2\tau_ak_a^4\big(R/rr'\big)^2 + \Lambda_a(C - C_0). \tag{2.9}$$

Substituting these into (2.7), we can reduce it to

$$4\tau_ak_a^4R^2\big(rr'\big)^{-3}\Big(rr'' + \big(r'\big)^2 - (r/R)r'\Big) + \Lambda_aC' = 0 \tag{2.10}$$

for $0 \le R < A, A < R \le B$. This equation can in fact be readily integrated to obtain a solution for membrane deformation. Indeed, let $p = \lambda_1\lambda_2 = rr'/(k_a^2R)$. Then (2.10) can be rewritten as $2\tau_a(1/p^2)' =$

$\Lambda_a C'$, which can be integrated to get an expression for p and subsequently for r'. Another integration yields the required formula, which of course would still require the unknown $C(R)$ to be resolved completely.

2.3.2. Wrinkled solution using tension field theory

The wrinkled skin domain will in general appear between the wound domain and the healthy skin domain. The outer radius of the wrinkled domain can be obtained by calculating the radius R, say R_c, for which $T_{\theta\theta}$ obtained above becomes zero. The governing equation in the wrinkled region, $A \le R \le R_c$, follows on using the tension field theory as proposed by Pipkin and Steigmann [28]. Towards this end, a 'natural width' $n(\lambda_1)$ of the membrane is calculated by imposing $T_{\theta\theta} = 0$ in (2.4) and solving for λ_2 in terms of λ_1. We get $n(\lambda_1) = (\lambda_1 + \gamma_a \lambda_1^2 (C - C_0))^{-1/2}$, where $\gamma_a = \Lambda_a/(2\tau_a)$. A regularized energy is then derived from (2.1) as

$$\begin{aligned}\Psi_r(\lambda_1, C) &= \Psi(\lambda_1, n(\lambda_1), C)\\ &= 2\tau_a\left(\lambda_1 + 2\sqrt{\lambda_1^{-1} + \gamma_a(C - C_0)} - 3\right) + m\Psi_c(C). \quad (2.11)\end{aligned}$$

The stresses in the wrinkled region are given by $T_{rr} = (1/\lambda_2)\partial_{\lambda_1}\Psi_r$ and $T_{\theta\theta} = 0$. The equilibrium Eq. (2.7) is then reduced to $rT_{rr} =$ const., or equivalently $R\partial_{\lambda_1}\Psi_r = \text{const}$. This provides us with the governing equation for deformation in the wrinkled region.

2.3.3. Nutrient balance and chemical equilibrium

The nutrient balance, away from a singular interface, is considered in the following form as derived in our recent paper [33, §5]:

$$K_0 \triangle \mu = (g(C)/\mu) E_{\theta\theta}(E_{rr} + E_{\theta\theta}), \quad (2.12)$$

where K_0 is a positive material constant, $\triangle$ is the two-dimensional Laplacian operator, $g(C)$ is a positive function, and E_{rr} and $E_{\theta\theta}$ are the radial and circumferential components of the elastic Eshelby stress tensor. Using the definition of the former [33], i.e., $E = k_a^2(\Psi 1 - H^T \partial_H \Psi)$, and (2.1) we can obtain

$$E_{rr} = k_a^2(2\tau_a(\lambda_2 + (2/\lambda_1\lambda_2) - 3) + m\Psi_c(C)) \text{and} \quad (2.13)$$

$$E_{\theta\theta} = k_a^2(2\tau_a(\lambda_1 + (2/\lambda_1\lambda_2) - 3) + m\Psi_c(C)) \quad (2.14)$$

in the unwrinkled region and

$$\begin{aligned}E_{rr} = k_a^2\Bigg(2\tau_a\Bigg(2\sqrt{\lambda_1^{-1} + \gamma_a(C - C_0)} + \frac{1}{\lambda_1\sqrt{\lambda_1^{-1} + \gamma_a(C - C_0)}} - 3\Bigg)\\ + m\Psi_c(C)) \text{and} \quad (2.15)\end{aligned}$$

$$E_{\theta\theta} = k_a^2\left(2\tau_a\left(\lambda_1 + 2\sqrt{\lambda_1^{-1} + \gamma_a(C - C_0)} - 3\right) + m\Psi_c(C)\right) \quad (2.16)$$

in the wrinkled domain. The bulk chemical potential μ in (2.12) is given by (2.5) in an unwrinkled region and by the same relation, but with λ_2 replaced by $n(\lambda_1)$ in the wrinkled domain. After substituting the bulk chemical potential and the components of Eshelby tensor in (2.12) we get the other differential equation, in addition to the equilibrium condition derived in the preceding section, to form the complete system of coupled differential equations in the bulk, away from the interface, for the determination of r and C. On the other hand, the nutrient balance at an interface is considered in the form [33, §5]

$$K_0[\![\mu']\!] = h(\widetilde{C})(2\tilde{\mu} - k_s\psi), \quad (2.17)$$

where $h(\widetilde{C})$ is positive. Here, μ can be written in terms of $r(R)$ and $C(R)$ using (2.5), both from unwrinkled and wrinkled regions, with suitable modifications for the latter. The interfacial chemical potential $\tilde{\mu}$ is given in terms of $\widetilde{C}$ from (2.6). These relationships are simplified further by considering chemical equilibrium. Accordingly, we require the bulk chemical potentials to be continuous across any surface of discontinuity, i.e., $[\![\mu]\!] = 0$, and that the value of the interface chemical potential $\tilde{\mu}$ be equal to the value of μ at the interfacial position. The former of these is to be used as a boundary condition while the latter is used to obtain an expression for $\widetilde{C}$ in terms of C.

2.3.4. Boundary value problem

In the preceding two sections, we have derived a set of coupled ordinary differential equations for the determination of deformation $r(R)$ and concentration $C(R)$. Different set of equations were derived depending on whether the domain of interest was free of wrinkling or otherwise. We now briefly summarize a choice of the boundary conditions which can be used to determine the final solution. At the centre of the domain, we assume the deformation to vanish, i.e. $r(0) = 0$, thereby precluding cavitation in the wound [32]. At the outer edge of the skin region (at $R = B$), the radial tension in the skin is specified as $T_{rr}(B) = T^\infty (> 0)$, where T^∞ is the magnitude of the far field stress in the unwounded skin. At the interface of wound and skin, or of unwrinkled and wrinkled domains, both the deformation r and the radial stress T_{rr} are continuous. These continuity conditions provide additional boundary conditions on the deformation. It is also important to note that the current position of the wound edge (given by a) is usually available from experimental observations [4]. In particular, the velocity of healing or the rate of contraction is known to decrease with time [4]. This motivates us to take $a = A\zeta^{d-1}$, where ζ is the healing constant ($\zeta < 1$ for healing) and d is the number of days; $d > 1$, assuming that there will be no proliferation of wound during the first day. In addition to the above, we need boundary conditions related to concentration field. Towards this end, we take the concentration gradient C' to be zero both at the centre of the wound ($R = 0$) and at the outer edge of the skin domain, far from the wound boundary. At every interface we consider chemical equilibrium, requiring continuity of bulk chemical potential, and interfacial nutrient balance.

3. Discussion

Our interest is to develop a comparative understanding of the appearance of wrinkling, residual stresses, and nutrient distribution in the wound-skin domain during the healing process with respect to normal gravity, instantaneous (short-term) microgravity, and long-term microgravity conditions. Towards this end, we will consider different sets of parameter values for solving the boundary value problem involving stress and nutrient distribution. The interplay between wrinkling, in a nonlinear elastic membrane, and nutrient distribution, even in a normal gravity situation, is previously unexplored [33]. During the following solution process we consider $\Lambda_a = 0$, for numerical convenience, thereby excluding any explicit coupling between elastic and chemical responses. With this assumption we can obtain analytical solutions for stress in the wrinkling domain and hence study the qualitative nature of stress and nutrient fields within a relatively simplistic framework. The nutrient distribution is still solved using a numerical procedure. The deformation and stress solutions are obtained following our previous work [31,32].

We first collect the values of various parameters, and forms of functions, which appeared in our model. The considerations in this paragraph will be assumed to hold invariant of the gravity conditions. For the form of chemical potentials we take $\Psi_c = \alpha(C^2/2)$ and $\psi_c = \beta(\widetilde{C}^2/2)$, where $\alpha = 1$ kJm^2/n^2 and $\beta = 0.001$ kJm/n^2. In the nutrient balance equations we consider $K_0 = 1$ n^2/kJms,

Table 1
A comparative effect of normal gravity, instantaneous microgravity and prolonged microgravity on wrinkling, stresses, and incompatibility. The stress T_w is the value of both radial and hoop stress inside the wound. R_c is the outer radius of the wrinkled domain.

Parameter values	Gravity condition	R_c/A	k_w	T_{rr} at $R = R_c$ kPa-mm	T_w for $R/A < 1$ kPa-mm
$T^\infty = 0.5$ kPa, $\zeta = 0.95$, $m = 1$, $k_s = 1.05$, $\tau_s = 10$ kPa	On earth	2.158	0.8929	1.0129	2.232
$T^\infty = 0.1$ kPa, $\zeta = 0.95$, $m = 0.8$, $k_s = 1.05$, $\tau_s = 10$ kPa	Short-term	6.082	0.92	0.2	1.241
$T^\infty = 0.1$ kPa, $\zeta = 0.99$, $m = 0.6$, $k_s = 1.01$, $\tau_s = 8$ kPa	Prolonged	1.985	0.9779	0.20	0.3999

$g(C) = 0.1C^3$, $h(\widetilde{C}) = \widehat{h}(C_w) = (k_w^2\alpha_w C_w/2k_s)^4$. Here n is the number of cells and hence nutrient concentration C is essentially the number of cells per unit area (n/m^2). In our analytical solutions we take $B = \infty$, however for numerics we take $B = 10A$. We have taken $d = 2$ to investigate the nature of healing after the first day.

The parameters, varied to capture the effect of different gravity conditions, are reported in Table 1. The choice of elastic parameters is based either on the available data or from the qualitative nature of biological observations. For instance, the value of τ_s on ground is taken from the available experimental results [14] while $\tau_w = 0.7\tau_s$ is chosen based on the assumption that wound is less stiffer than the skin. The value of healing constant ζ is motivated from the available wound healing data [4]. We have considered $\zeta = 0.95$, assuming the rate of wound closure to be 5%, to signify normal healing of a skin wound. The value of k_s, which essentially captures the growth strain in skin region, has been chosen in the range of 1.01–1.05. A large value of k_s would imply a large opening at the wound edge after making an incision and vice-versa. Even though no experimental data is available for k_s, we solve our problem with data which does not create larger openings. The skin pre-tension values (T^∞) considered are lower than those reported in the literature [11,14]. This is to prevent non-existence of solution in the wound. This restriction is an outcome of the simple hyperelastic model chosen for our analytical convenience. It should be noted that various biochemical parameters chosen for the problem are solely hypothetical in nature and with an intent to capture the significant aspects of the phenomena.

To mimic the conditions of wound healing when astronauts just reach an outer space orbit or are exposed to short-term microgravity (e.g., a week), we assume the skin pre-stress to reduce by 80% and the available chemical energy to reduce by 20%, while keeping all other parameters to remain same as those on earth. This assumption is based on the observation that the astronauts take at least a week for adapting themselves to microgravity. The immediate effect of the space environment is hence only in mechanical unloading (decreased skin tension) [6,7,10,18,22] and change in physiological conditions and body metabolism [8,26]. The body metabolism and nutrient deficiency would alter the healing rate and proliferation of cells, however it would depend on how fast the body adapts to weightlessness. On the other hand, when we simulate wound healing during prolonged microgravity exposure, we alter the parameters to capture the decreased elasticity of skin [3,21,35] (reduced by 20%), reduced skin growth deformation ($k_s = 1.01$) indicating decreased cellular proliferation and cellular migration [1,7,9,12], and a reduced healing rate ($\zeta = 0.99$) due to complex interplay of healing dynamics [9,10,12,22] with reduced nutrients and body metabolism in space ($m = 0.6$) [15,26]. The skin pre-tension value during prolonged microgravity is kept same as that during instantaneous orbital conditions ($T^\infty = 0.1$ kPa) since the mechanical unloading is due to weightlessness in space and it is expected to remain more or less constant over time.

The radius of the wrinkled domain (R_c), wound growth strain (k_w), and the stresses obtained from the solution during wound healing for all the three simulated conditions of microgravity are reported in Table 1. In Figs. 2–4, stress, nutrient concentration, and chemical potential gradient in skin and wound domain are plotted against the normalized radius R/A, respectively. A comparison between the wrinkling radii in Table 1 shows that instantaneous microgravity produces large wrinkled domains whereas the wounds formed during prolonged microgravity have wrinkled domains of sizes similar to those formed under normal gravity conditions. The large wrinkled region, in a short-term microgravity exposure, owes

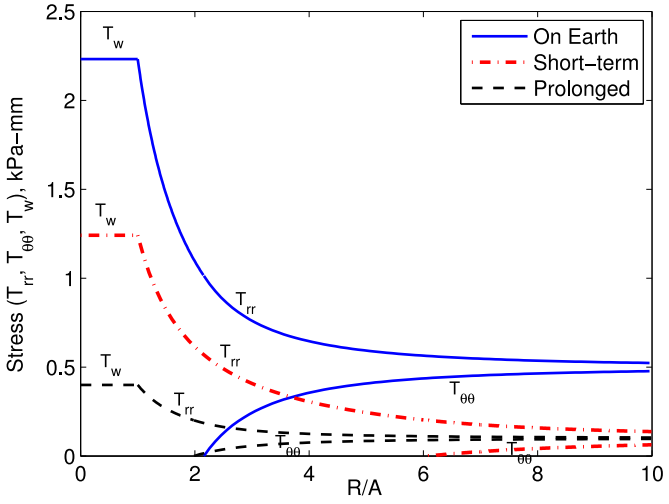

Fig. 2. The radial (T_{rr}) and circumferential ($T_{\theta\theta}$) stresses in the skin domain for the three gravity conditions. Both these stresses are same in the wound domain, denoted by T_w.

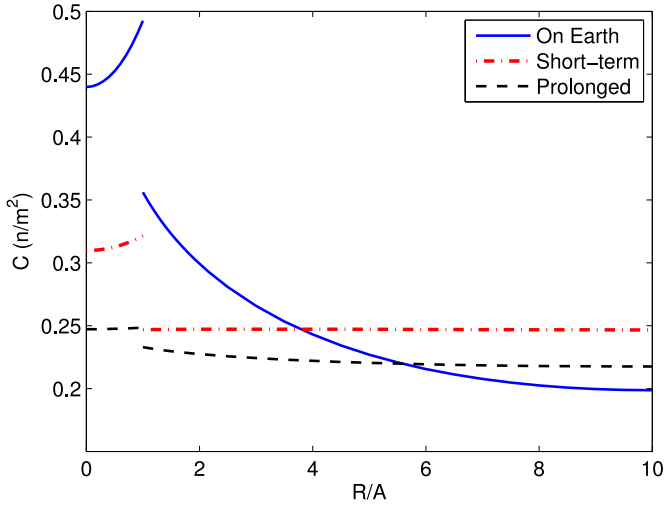

Fig. 3. Nutrient concentration distribution for the three gravity conditions. Here, $n = 10^{15}$.

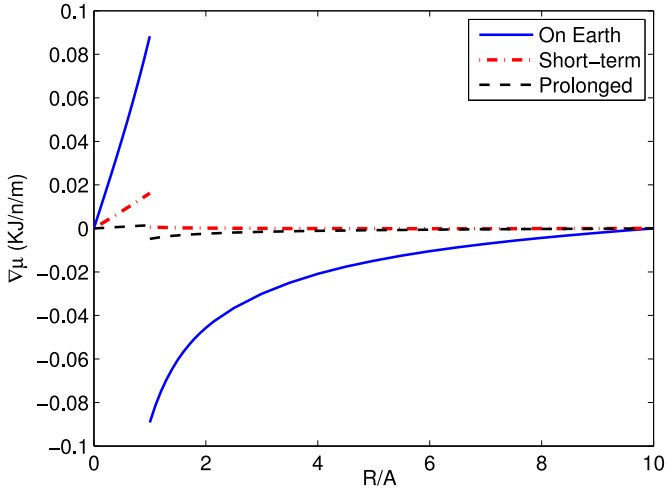

Fig. 4. Distribution of chemical potential gradient for the three gravity conditions.

to a sudden loss of skin pre-tension due to mechanical unloading. The region is however shrunk during prolonged microgravity due to slow rate of healing, slow rate of cytokine synthesis, and cellular production. The short-term microgravity being a temporary phenomena, the nature of wrinkling is not expected to cause permanent scar formation. Moreover, since prolonged microgravity does not show any increase in the wrinkled region, the scar sizes on earth and in space would be similar.

A comparison between stress values in skin and wound domain, for all the three cases as reported in Table 1 and Fig. 2, indicates a decreasing trend in radial stresses with increased microgravity exposure. In fact, the radial stress reduces substantially during long duration exposure to microgravity. Although the skin pre-tension in this situation is similar to short-term microgravity situation, other mechanical and biochemical factors act together to reduce the stress in the system. The difference $k_s - k_w$, a measure of incoherency at the wound edge, also decreases in space indicating diminishing of residual stresses. The reduced nature of stresses seen in microgravity is good for scar control, however the lower levels of skin pre-stress and system stresses may hinder the biochemical cascades which may lead to wound atrophy. The biochemical observations provided in the introduction support this inference. Moreover, the simulated results are qualitatively in good agreement with the experimental observations in space.

The nutrient concentration distribution, shown in Fig. 3, indicates depletion in the biochemical concentration inside the wound during wound healing in a space environment. The depletion is substantial during prolonged microgravity. The depletion might be due to the after effects of decreased availability of chemical energy and reduced stress values in the wound region. A direct implication of the reduced nutrient concentration is decrease in cell proliferation, cell migration, and production of growth factors. This is in agreement with the existing observations in space [1,7,9,12]. The magnitude of chemical potential gradient in the wound and skin domains indicates the nature of cellular activities in the respective domains. It is clear from Fig. 4 that the biochemical activity in the wound and at the wound edge, the latter represented by the jump in chemical potential gradient, reduces in space. A prolonged microgravity exposure significantly influences the chemical potential gradient inside the wound. These observations indicate that the wound would be in a state of atrophy in such a situation.

4. Concluding remarks

We have developed a general framework for understanding the nature of internal stress, wrinkling, and nutrient concentration distribution during cutaneous wound healing process in microgravity environments. The essential ingredient of our theory is a coupled biomechanical-chemical free energy and a nutrient balance law, in addition to the usual equations of nonlinear elastic membranes. This free energy, in particular, has several chemical and mechanical variables which can depend upon microgravity. The coupling of nutrient chemistry with mechanical deformation is central to our understanding of wound healing in space. In fact, a deviation of the available nutrients in the system from the haemostatic requirement affects the healing or atrophic state of the wound. A boundary value problem has been formulated considering the wound and skin to be two-dimensional nonlinear elastic membranes. The problem is solved and analysed for two cases of affected gravity, short-term and long-term, and compared with gravity condition on earth. Most importantly, the results demonstrate that wound formation in long-term microgravity would be in atrophic state as compared to the other two conditions.

Acknowledgements

The authors acknowledge the financial support from the ISRO-IITK Space Cell Grant No. STC/ME/2015098 titled “Growth and aging of tissues under microgravity environment”.

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