Modeling the Effects of Dehydration on Cellular Growth and Wound Repair

I. Introduction

The impacts of dehydration on cellular growth have been studied, but not formed into a computational model that could inform medical treatments and in vitro experiments that involve growing tissue [1]-[5]. Dehydration is defined as a reduction of the total concentration of water in the body, such that the body weight is reduced [6]. Acute and chronic forms of dehydration can cause a variety of symptoms [6],[7]. Mild to moderate dehydration is common in athletes and the elderly [4]. Both groups are also more likely than the average population to get injured [4],[8],[9]. A comprehensive and functioning model describing the impacts of dehydration on tissue growth could be used when studying and designing treatment plans for groups vulnerable to dehydration and to inform decisions on environments for growing cell cultures and tissue in vitro. The expected model will seek to combine, simplify, and modify two computational model: a continuum model and a partial differential equation model [1],[2],[3]. Due to the composition of the two computational models, which will act as a base for the combined or resulting model, the resulting computational model is a set of ordinary differential equations. The resulting model has the same limitations as the continuum model and the partial differential equation model. Any areas where the limitations of the two models overlap could be areas of concern, as any errors may be compounded. Physiologically, the final model references the known role of dehydration on inflammation [5],[10],[11], circulation [4], [5], and the extracellular matrix [1],[2],[4]. The final model highlights and helps explain the differences between wound repair while the patient is healthy and while the patient is dehydrated, which is of medical significance as it could help inform medical opinions on wound care and as a factor in medical studies on wound repair [4],[5],[12],[13].

This project is done via computational modeling, due to the unfeasibility and invasiveness of any other method. This project studies the movement and growth of living cells, which is difficult to study experimentally. Biopsies could be used, to a limited extent. However, in order to control for variables, such as medical conditions, lifestyle factors, and age, each subject would have to be biopsied multiple times. This still would not have perfect comparability, as the biopsy would be a slightly different area each time. Additionally, as the study involves wound repair, taking repeated biopsies of the area could slow the healing of the wound by damaging the scab or enlarging the wound itself. There are, to the knowledge of this paper, no scans that could be used over the course of the study that would provide the required information.

This model focuses on the impact of dehydration on wound repair, specifically seeking to determine the differences between wound repair in a healthy patient and wound repair in a dehydrated patient. Previous work on this subject includes two computational models. One model [1],[2] describes cell density by modeling the tissue as a compressible fluid in a two-dimensional continuum model with the extracellular matrix as a vector array. The final equation of which is shown in Equation 1. The continuum model simulates the intralayer

elastic couplings, the adhesion of cells, the forces of the lamellipodia, and the rate of apoptosis and replacement of cells within a cell sheet. Specifically, the left side is the derivative of the cell density in terms of time. The first term on the right is the ratio of the residual bulk modulus to the adhesion of the epithelial cells (κ) multiplied by the change in cellular density ($\Delta\rho$). The second term is the growth factor of the equation ($g(\rho)$), which is a function of the cellular density. During cellular expansion there are four boundary conditions, shown in Appendix A. The variables are the same as in Equation 1; additionally, φ is a situationally defined constant and $\rho 0$ is the initial cell density. The model and boundary conditions are based off a series of assumptions. The conditions are assumed to be steady state. The acceleration of each cell is assumed to be negligible compared to its velocity. The model assumes that the cell layer responds passively and instantaneously to any force acted on it. The model also assumes that $\rho(x,0)$ is constant and the initial density is relative to the prestress created by the action of the lamellipod in the interior of the cell sheet at confluence [1],[2]. The second of the two computational models that is used as a base for the resulting model is not a continuum model, but a partial differential equation which is shown in Equation 3. The left side of the equation represents the cellular density derivative over time when the trajectories are always perpendicular to the surface. The terms on the right describe how the cells diffuse tangentially along a tissue surface that is not a straight vector, the influence of tangential velocities of individual cells and the

$$(1)\ \partial\rho/\partial t = \kappa\Delta\rho + g(\rho)$$

$$(2)\ g(\rho) = \alpha\rho(1 - \rho/\rho_k)$$

$$(3)\ (\partial\rho/\partial t)_n = D(\partial^2/\partial t^2)\rho - \rho u_n\kappa - \partial/\partial l(\rho(v_s + u_s))$$

tangential velocities over the tissue surface, the collective effect of cell crowding or cell spreading, and the rate of change of the number of cells present due to tissue synthesizing cells, respectively. The parameter D is a constant for diffusive flux, ρ symbolizes cellular density, un is the surface velocity's tangential component, κ is the local mean curvature, vs is the individual cell's tangential component, t is time, and l is the arc length. In addition to steady state assumptions, the partial differential equation model assumes that the initial cell density distribution and initial radius are arbitrary and subject to a boundary condition of $\rho(-\pi,t) = \rho(\pi,t)$. It is assumed that the cells are subject to a tangential cell velocity field that depends on the length of the cavity wall [3]. These two models will be combined with precedence given to the continuum model. The parameters already in the combined model will be modified to reflect how dehydration effects them based upon a literature review. Specifically, the cellular density decreases [14] and the adhesion constant increases [11], depending on the severity and duration of dehydration. In addition to these impacts, dehydration can reduce circulation [4],[5], prevents enough water from being absorbed into the extracellular matrix [4], increases inflammation [5],[11], decrease blood pressure [7], decreases the volume of plasma [6],[13] and increases the heart rate [12].The relationship between these changes and the

modeled parameters has not been well defined in literature.

II. Materials and Methods

The project is done via computational modeling, specifically, a continuum model. The general pattern of cell density change within wound healing can be defined as cell spreading or cellular growth in terms of the literature. Figure 1 shows how dehydration impacts the physiology of the body based off of literature defined relationships. Literature defines this growth in terms of logarithmic growth and partial differential equations. The creation of the final mathematical model is shown in Figure 2. The final mathematical model is made up of a primary linear first order partial differential equation and four boundary equations.

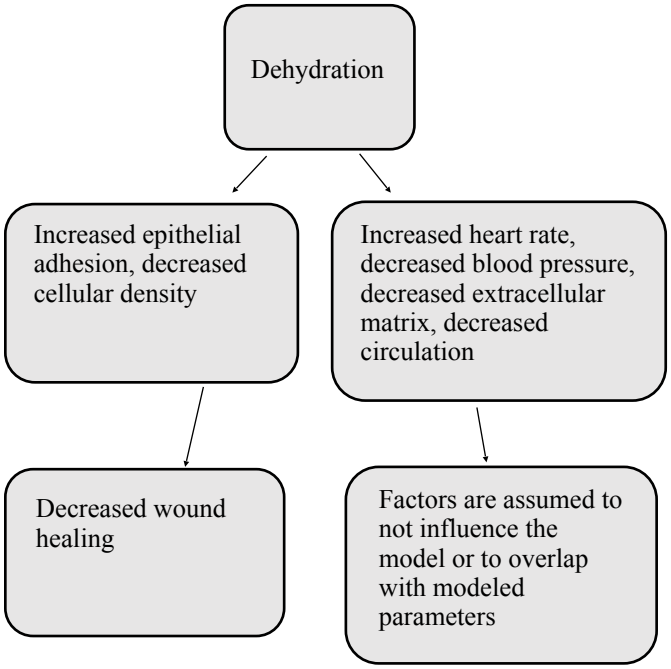

Figure 1: The flow diagram showing how dehydration impacts the body and the model.

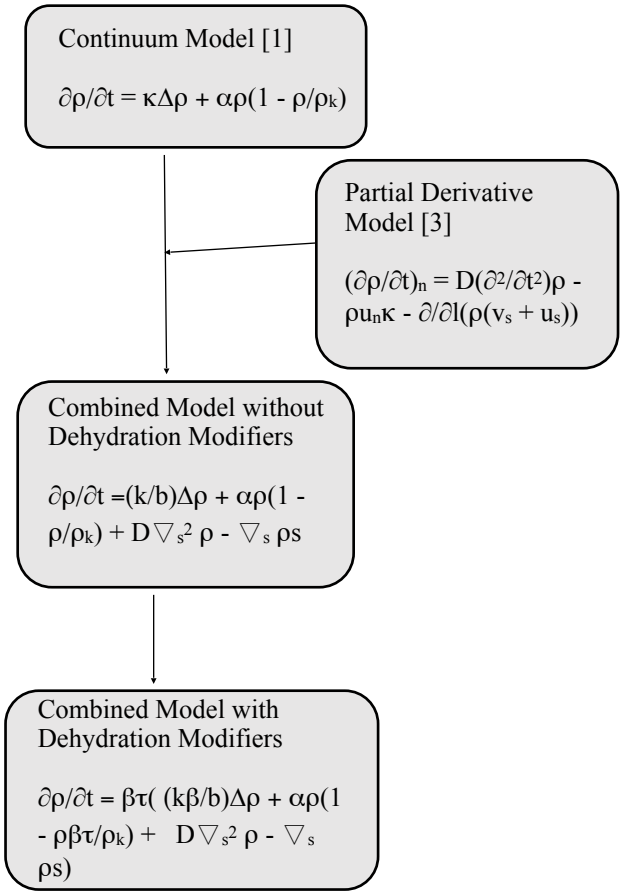

Figure 2: The flow diagram showing how the final mathematical model is derived. The equations are Equations 1, 2, 5, and 6.

The equations are originally based off of two computational models, whose final equations are shown in Equations 1 and 3. The continuum model shown in Equation 1 and 2 was used as the primary model and the secondary model, shown in Equation 3 was used to modify the continuum model. The original continuum model describes the main forces that control cell migration of a cell sheet. Specifically, the intralayer elastic couplings, the adhesion of cells, the forces of the lamellipodia, and the rate of apoptosis and replacement of cells [1],[2]. The secondary model describes how cells diffuse tangentially along a tissue surface that is not a straight vector, the influence of tangential velocities of individual cells and the tangential velocities over the tissue surface, the collective effect of cell crowding or cell

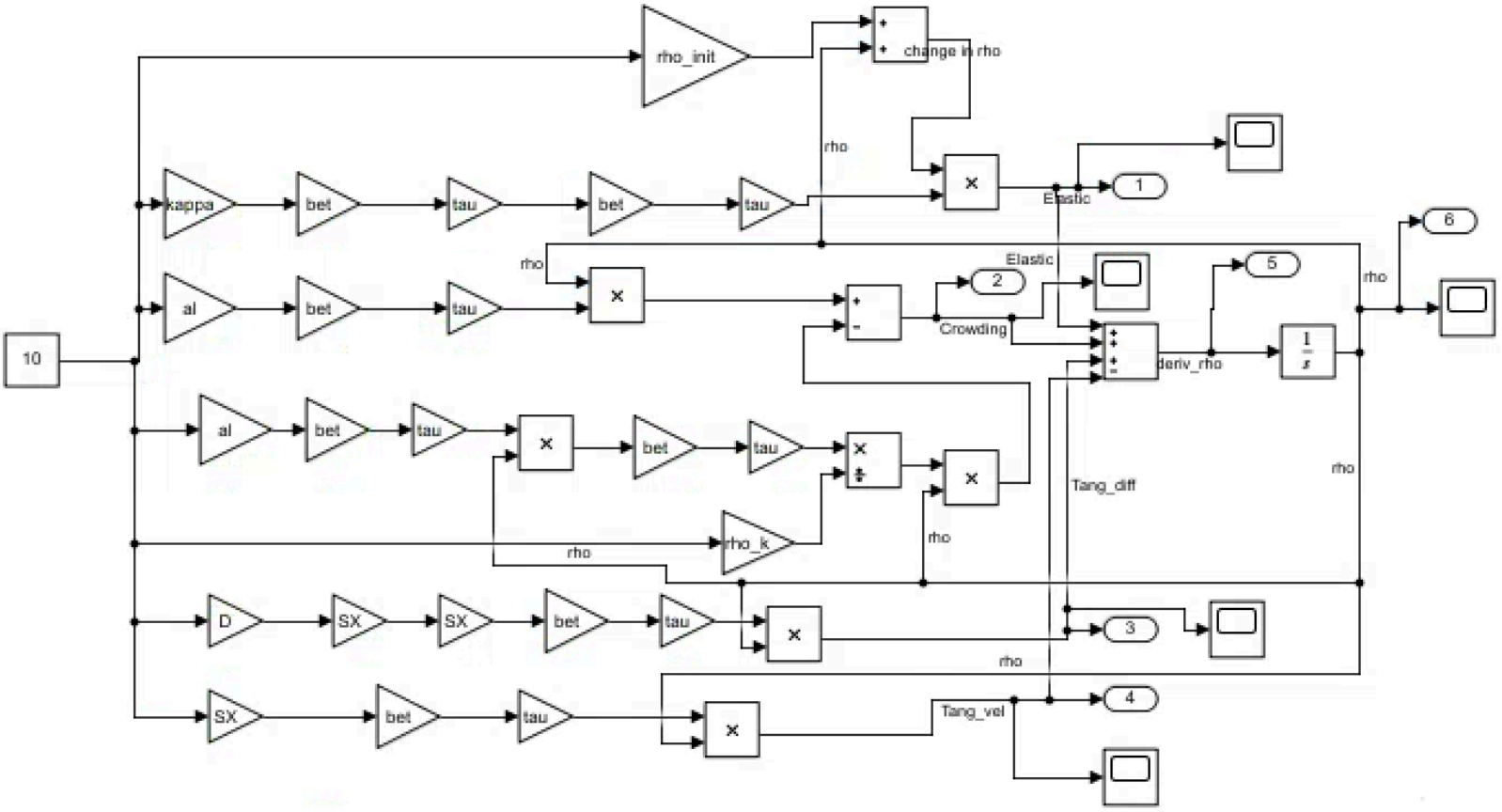

Figure 3: The simulation model for the parameters and the dehydration modifiers. The severity (bet) and duration (tau) modifiers are assigned a value of X, as this is changed in each simulation. The other values are from the continuum model [1],[2] and the partial differential model [3].

spreading, and the rate of change of the number of cells present due to tissue synthesizing cells [3]. The additional factors of the secondary model are incorporated into the primary model by modifying the growth of the cellular density segment of the continuum model's main equation. The growth segment is assumed to be Equation 2 during cell-colony expansion, which would be present during wound repair [1],[2]. The equation is assumed to be logistical growth in this model during tissue growth. The parameter ρk is the limiting cell density and α is a situationally defined growth constant. This equation already has some factors that overlap with the factors of the secondary model, namely the rate of cell growth and apoptosis and ratio of the cell density and the limiting cell density. To simplify the final equation and prevent from overweighting these factors in the final equation, they are assumed to be analogous. Specifically, the factors from the continuum model that are assumed to be analogous to the partial differential equation model are, respectively, the rate of change of the number of cells present due to tissue synthesizing cells is assumed to be analogous to the rate of apoptosis and replacement of cells and collective effect of cell crowding or cell spreading is assumed to be analogous to the ratio of the cell density and the limiting cell density. The secondary model is not a continuum model, so it looks at the movement of individual cells and the surface area in two separate parameters [3]. The continuum model lumps these areas into the movement of the tissue as a whole [1],[2]. To allow for more direct comparability between the results of this model and the continuum model that serves as a base, the parameters for the cell and

surface area will be lumped together. The additional factors were added to the equation. The final growth equation is shown in Equation 4. The parameters are the same with s being an additional parameter which is the surface that is used in the gradient. This becomes part of the combined model, shown in Equation 5 and 6. Equation 5 has the residual bulk modulus (k) and cellular adhesion (b) combined into a constant, κ. Equation 6 elaborates to show the adhesion constant, which has been shown to be modified by the dehydration [1],[2],[3],[11]. The combined model uses the assumptions that both models used in their own creation, in addition to the ones stated. These assumptions keep the final equation and boundary conditions simple enough to model and analyze.

(4) $g(\rho) = \alpha\rho(1 - \rho/\rho_k) + D\nabla_s^2 \rho - \nabla_s \rho s$

(5) $\partial\rho/\partial t = \kappa\Delta\rho + \alpha\rho(1 - \rho/\rho_k) + D\nabla_s^2 \rho - \nabla_s \rho s$

(6) $\partial\rho/\partial t = (k/b)\Delta\rho + \alpha\rho(1 - \rho/\rho_k) + D\nabla_s^2 \rho - \nabla_s \rho s$

The factor of dehydration was added to the combined model [1],[2],[3],[11],[14], [15]. The literature review indicated how each of the parameters in the model changes in dehydrated conditions. Specifically, the cellular adhesion of the epithelial layer increases with dehydration [11] and cellular density decreases with time in and severity of dehydrated conditions [14]. Partially based on models for dehydration, the dehydration factors were added as dimensionless multiplied modifiers for the parameters [1],[2],[3],[15]. The equation is shown in Equation 7. Two dehydration modifiers were used to alter Equation 7. The parameters were modified solely by the severity of dehydration or by the severity and the duration of dehydration [11],[14]. Both modifiers are defined as being from 0 to 1, with the lower bound being non-inclusive. The severity modifier is labeled β. A value of 1 is defined as normal hydration. A lower value is defined as some level of dehydration. The duration modifier is labeled as τ. A value of 1 is defined as no time spent dehydrated. A lower value is defined as some time spent dehydrated. For both modifiers, a value of 0 is assumed to be fatal. This approach assumes a direct and linear correlation that impacts the parameter with even the slightest dehydration and does not have a limit to how much it changes. Dehydration has been linked to other symptoms as well. Depending on severity and duration of dehydration it reduces circulation [4],[5], prevents enough water from being absorbed into the extracellular matrix [4], increases inflammation [5],[11], decrease blood pressure [7], decreases the volume of plasma [6],[13] and increases the heart rate [12]. The relationship between these changes and the modeled parameters has not been well defined [4],[6],[7],[11], [12],[13]. This model assumes that the factors either do not impact the rate of wound repair or are described by the change in the parameters that are modeled.

(7) $\partial\rho/\partial t = (k\beta/b)(\Delta\rho\beta\tau) + \alpha\rho\beta\tau(1 - \rho\beta\tau/\rho_k) + D\nabla_s^2 \rho\beta\tau - \nabla_s \rho\beta\tau s$

The final equation was translated to a SIMULINK model and MATLAB code. The general code for the input values is in Appendix H. The code allows the parameters to be easily changed and the output to be captured. All but the created

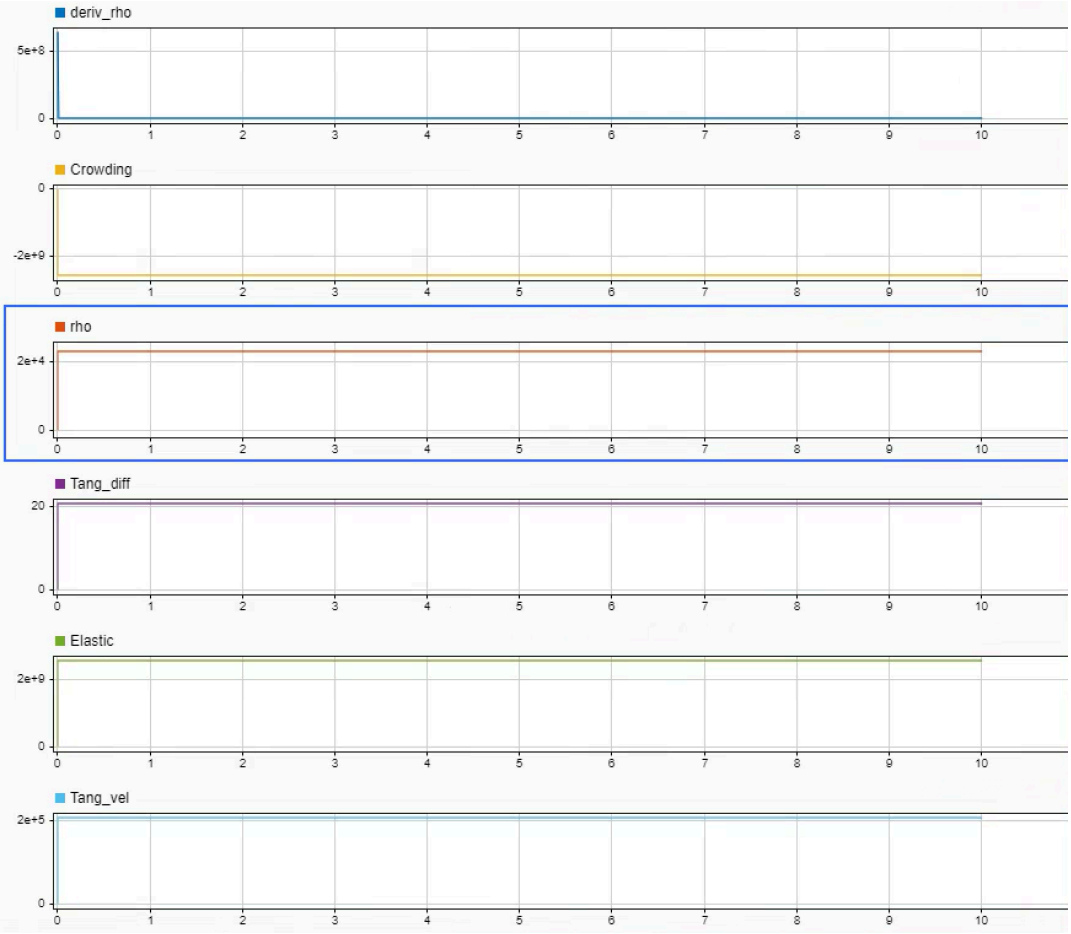

Figure 4: The results of the model when run to model fully hydrated conditions. The tau and beta were both set to one. The other parameters are the test values declared in Appendix H. This is used as a control for the dehydrated simulations to be run against. It is also used to compare against the continuum and partial differential model to test the accuracy of the model. This model shows that cell crowding and elastic couplings components have the largest influence on the model. The rho value shows that the cellular density of this model is higher than expected.

dehydration modifiers are filled with test values from the two models the model is derived from and a literature review, as shown in Appendix H. This allows the model to be run and validated based on standard averages and general trends. Additionally, the boundary conditions was coded into the model [16],[17]. The SIMULINK model is shown in Figure 3. The model uses a node as the sink to capture the values in the code for analysis. The source used is a constant, as the model assumes that the internal cellular factors that dictate cell and tissue growth do not change as the wound heals. The model will be validated by using a set of literature values and various values of dehydration. The comparison of the different outputs should reveal that the rate of change of cellular density over time decreases and thus show a decline in the rate of wound healing as dehydration increases in severity and duration. The final model has six nodes to capture the model's final results and to allow the analysis of the components of the model. There is one node for each of the four grouped segments of the equation that are combined via addition and subtraction to make the final model. There is also one node to look at the cellular density and one to

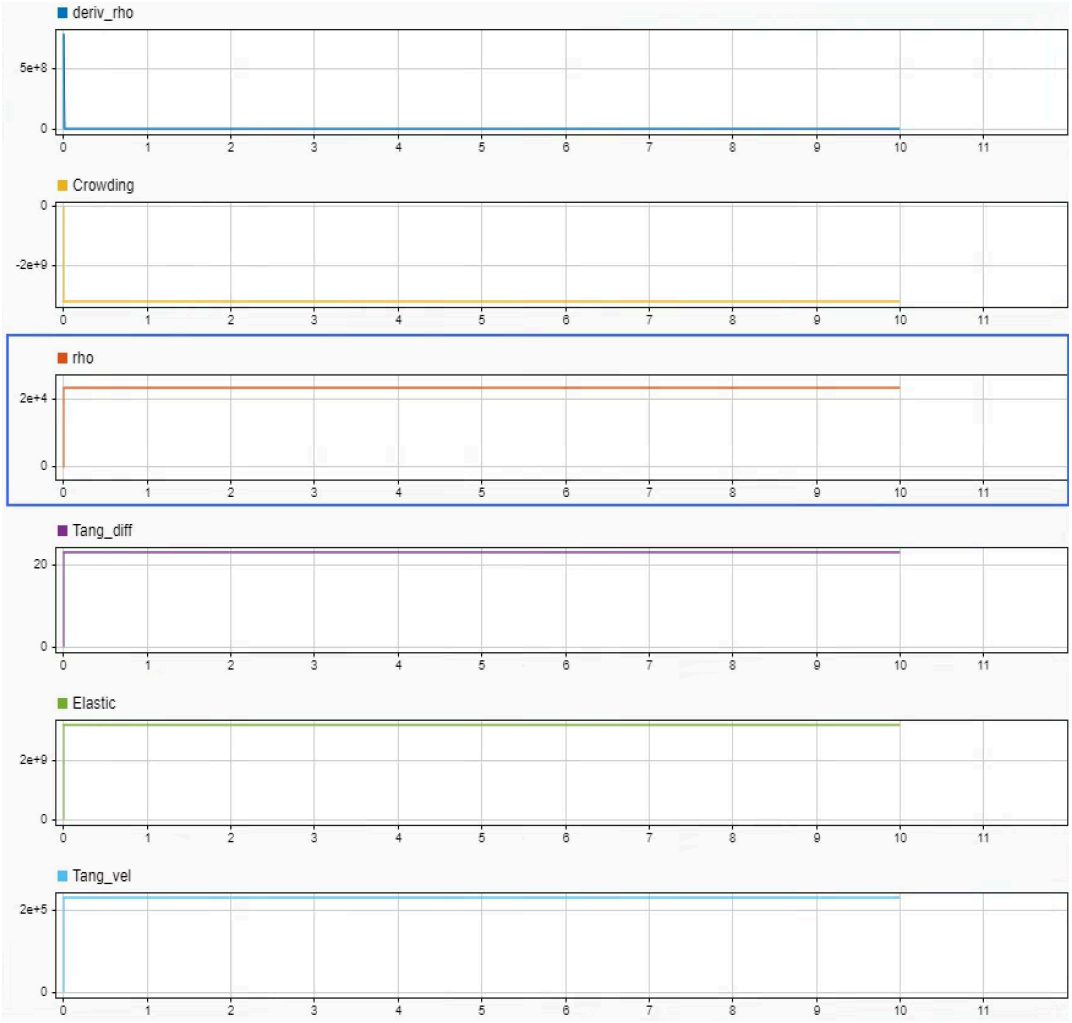

Figure 5: The results of the model when run to evaluate the effects of changing the duration modifier. The beta was set to one, the tau was set to 0.9. The other parameters are the test values declared in Appendix H. The simulation shows the same pattern of decreasing values and slowed wound repair as Appendices B, D, and E.

observe the derivative of the cellular density in terms of time.

III. Results

The simulation was tested in three ways in addition to a control. The control was to run the model at fully hydrated values. The first type of modification was changing the severity constant while keeping the duration constant at 1. The second type was changing the duration constant while keeping the severity constant at 1. The first two types were not based on anatomical values. Instead they were controlled attempts to model the impact of each variable on the model as a whole. The third type involved changing both parameters. These values were not based on experiments. Instead they were based on theoretical situations and assigned theoretical values. This created a possible source of error where any situations that were not anatomically possible could have created results that were not anatomically possible and did not reflect physiological relationships. Despite the lack of physiological relevance, the trials proved that the modifiers were influencing the model independently and the model produced a single type of output.

The simulation at fully hydrated values is the closest to the models that were used to derive this model. The resulting lines all reach a visually steady state, with minor oscillations found when the data is

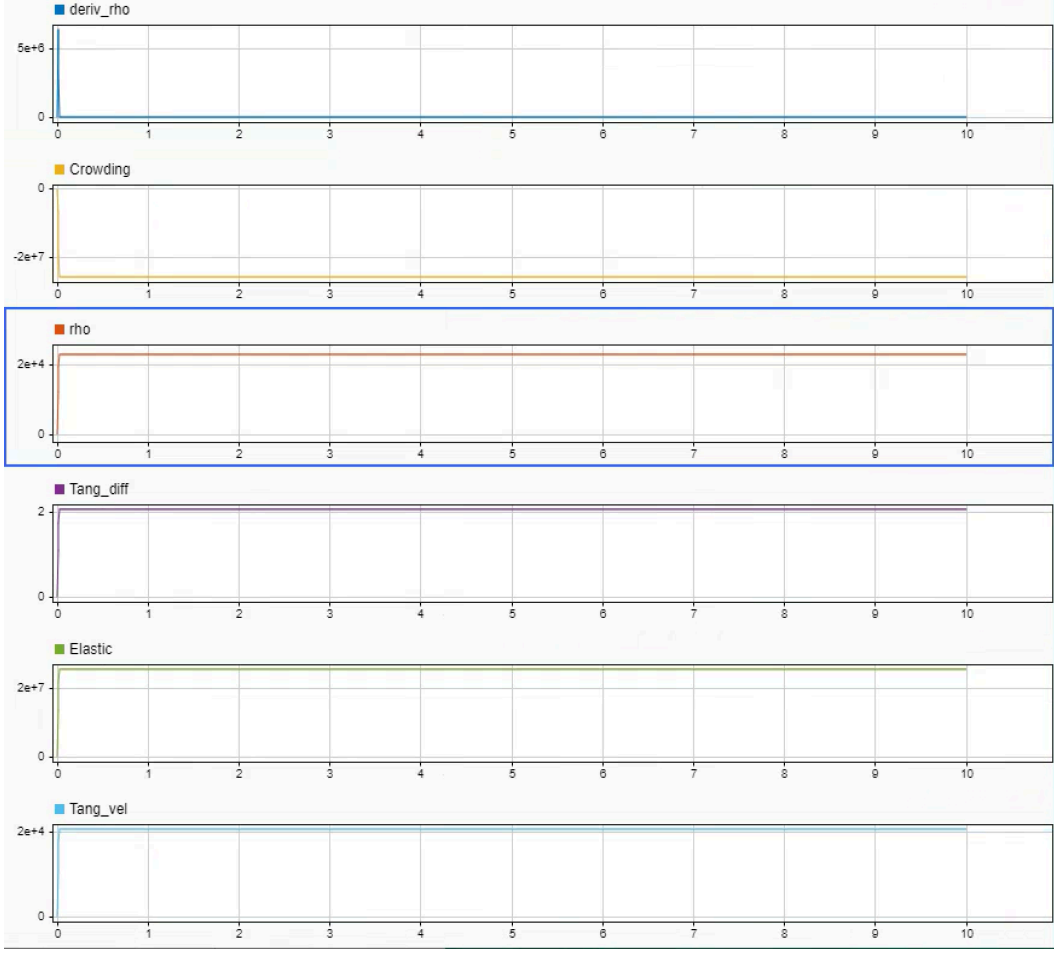

Figure 6: The results of the model when run to simulate acute dehydration. The beta was set to 0.1, the tau was set to 0.9. The other parameters are the test values declared in Appendix H. This simulation shows that acute dehydration does not have the same level of impact as severe dehydration, but it does decrease the components. This indicates that wound healing would be slowed, but not significantly.

examined. The node that is attached to the part of the model that represents the elastic couplings between layers shows that the steady state is a large, positive value. Based on the simulations, no change smaller than a factor of ten has any notable effect. Comparatively to the other values, the elastic couplings have a large influence on the change of density over time. The part of the model that represents the effects of cell crowding and the synthesis and apoptosis of cells resulted in a large, negative value. Both of these factors having this level of influence makes sense with the continuum model, as they are some of the primary factors considered by the continuum model [1],[2]. Additionally, it has been indicated that dehydration increases adhesion forces, which would impact the influence of the elastic couplings, and decreases the overall cellular density, which would impact the grouped effect of cell crowding and cell synthesis [11]. The part of the model that represents tangential diffusion along non-straight lines is a small, positive value at the steady state. Compared to the rest of the model, tangential diffusion has a small effect on the change of cell density over time. The part of the model that represents the tangential velocity of cells and tissue returns a medium, positive value at steady state. Tangential velocity appears to have less influence on the model than the elastic couplings or cell crowding, but notably more than the tangential diffusion. These factors were only considered by the partial differential equation model [3]. The steady state value of the cellular density, ρ, was approximately 2.3 * 104 cells/mm^3. when rounded to accommodate for oscillations.

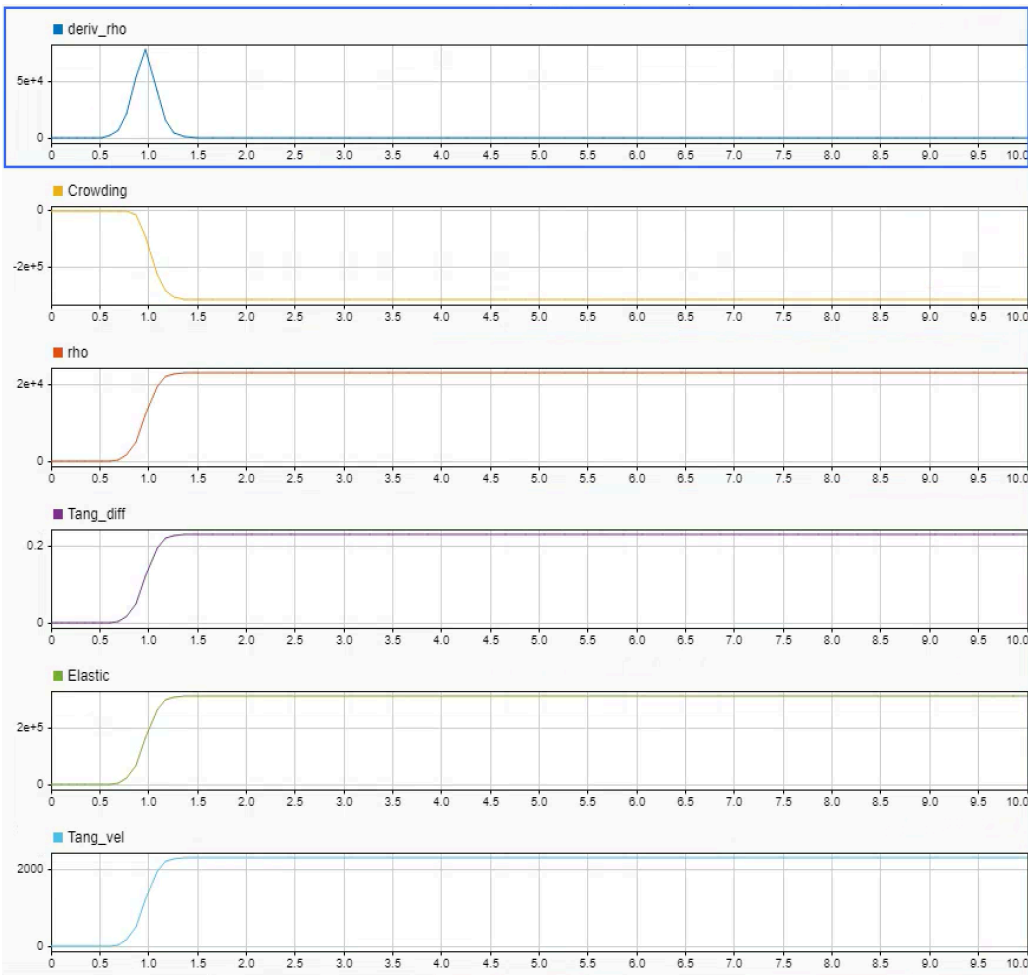

Figure 7: The results of the model when run to simulate severe dehydration during a long period of time. The beta was set to 0.1, the tau was set to 0.1. The other parameters are the test values declared in Appendix H. This simulation is slower to reach steady state than any other simulation. The change in the steady state values shows that the rate of wound healing would be slower than when fully hydrated, but faster than when acutely dehydrated.

This is larger than the upper end of the cellular density found in the continuum model, which ranged from 1000 to 9000 cells/mm^3 [1],[2]. Mathematically, this difference is partially accounted for by the addition of the tangential diffusion along non-straight lines and the tangential velocity of cells and tissue. Generally, adding more elements makes models more accurate [2], [15], but some factors may have been overweighted in the creation of this model due to unintentional overlap.

To test the behavior of the model and the influence of the individual modifiers, two sets of trials were run where one modifier was set to a value of 1 and the other was set to 0.1, 0.5, and 0.9. The severe value was chosen as the largest value that does not exceed one decimal place, the mild was chosen as the smallest value that does not exceed one decimal place, and moderate was chosen as the halfway point. There is no direct physiological correlation, however severe is assumed to be the most the human body can take before dying and mild is assumed to be the smallest amount of dehydration that will impact the body. All of these were physiologically unfeasible trials as they would involve either a person being some degree dehydrated while not having been dehydrated for any length of time or being dehydrated for some length of time while not suffering from dehydration. Both sets of trials maintained the same type of behavior that was exhibited in the fully hydrated simulation. For both sets of trials, the farther the dehydration constants got from fully hydrated values, the lower the eventual steady state values of the equations

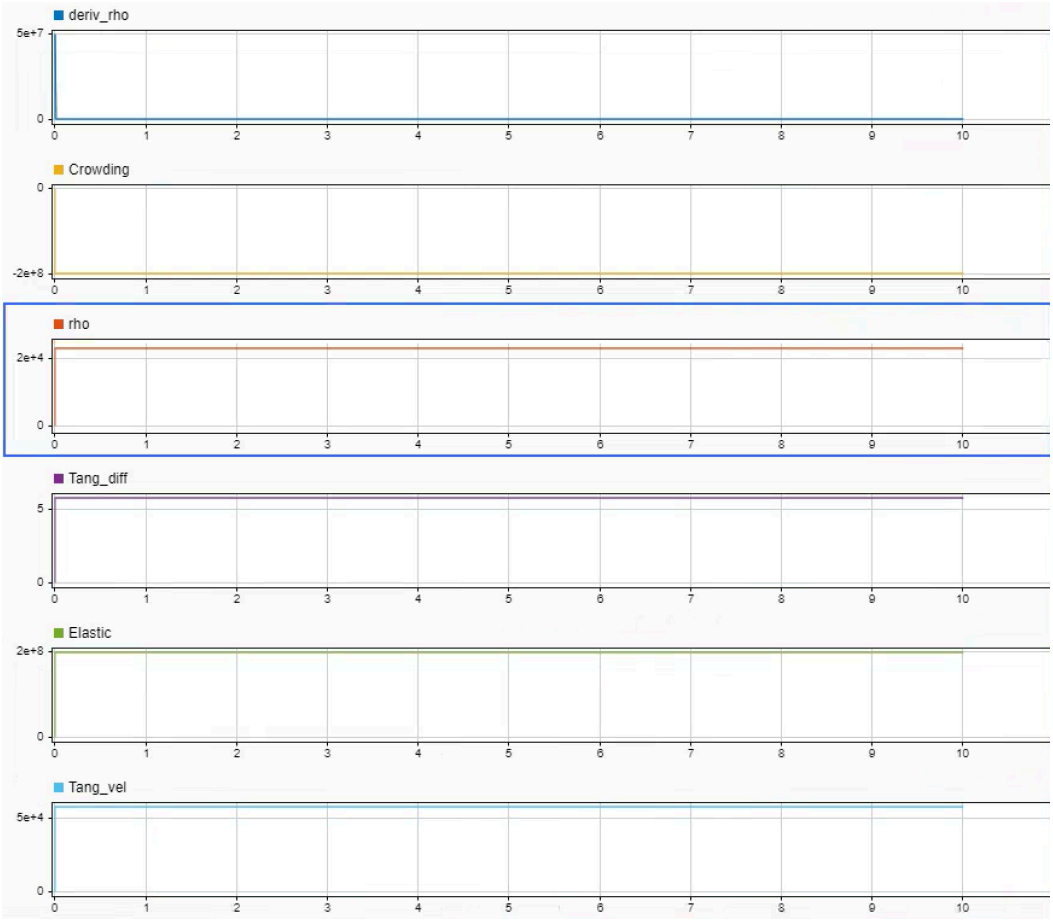

Figure 8: The results of the model when run to simulate moderate dehydration for a medium length of time. The beta was set to 0.5, the tau was set to 0.5. The other parameters are the test values declared in Appendix H. This simulation's values are show that the moderate dehydration would allow wound's to repair faster than during severe or acute dehydration.

were. This matches the expected trends from literature [4],[6],[7],[11],[12],[13]. The lowering of the modifiers, for the most part, produced similar behaviors and steady states, as shown in Appendices B, D, E, and Figure 5. When one modifier was set to 0.5, the differences were more apparent as shown in Appendices C and F. The trial where the duration modifier was set to 0.5 showed larger values for all of the components of the equation than the trial where the severity modifier was set to 0.5.

There were three simulations where both modifiers were altered. The first modeled the subject during acute dehydration, severe in duration and short in time. For this situation, the severity modifier was set to 0.1 and the duration modifier was set to 0.9. This is shown in Figure 6. The resulting cellular density was very similar to the fully hydrated value. The derivative of the cellular density in terms of time, the tangential diffusion along non-straight lines, the elastic couplings between layers, and the tangential velocity of cells and tissues were all decreased. The effect of cell crowding was increased to a less negative number. This may be because a section of tissue with lower cellular density has less issues with cell crowding. The second simulation was of the body during severe dehydration after a long period of time. For this situation, the severity and duration modifiers were set to 0.1. This is shown in Figure 7. The modifiers significantly slowed the exponential curves, so it took until approximately 1.4 seconds to achieve the approximate steady state that the fully hydrated model achieved in approximately 0.1 seconds. The modifiers also decreased all the values except the cell crowding,

which increased, and the cellular density, which changed very little. The third simulation was of a person who had been moderately dehydrated for a medium length of time. This had both modifiers set to 0.5 and is shown in Figure 8. The graphs show the same pattern as Figure 7, though not as severely. In both simulations where both modifiers were set to the same value, the cellular density did not drop significantly, which would have been expected with the established literature correlation. However, the derivative of the cellular density in terms of time did, which matches the slowed rate of wound healing that was predicted by literature [4],[5],[6],[7],[11],[12],[13].

The model can be characterized as exponential. Each component exhibits either an exponential growth or decay curve. The curve that represents the cellular density, the tangential diffusion along non-straight lines, the effect of intralayer elastic couplings, and the effect of the tangential velocities of individual cells and the tissue as a whole are a growth curve. The grouped effect of cell crowding and cell synthesis and apoptosis is an exponential decay curve. The derivative of cellular density in terms of time is most closely characterized as a bi-exponential model. The initial spike is brief, then decays to a steady state value that is greater than the initial value, which is most clearly shown in Figure 7. Based on the resulting graphs when the modifiers are changed from fully hydrated values, the most effected segments are the grouped effect of cell crowding and the effect of cell synthesis and apoptosis and the tangential diffusion along non-straight lines. When the modifiers are altered enough, the curve delays and the peak seen in the final value widens.

IV. Discussion and Summary

The final model and its results demonstrate the impact of dehydration on otherwise healthy tissue growth. The relative influence of various factors of cellular growth were shown in the value of each factor during the fully hydrated simulation. Specifically, after the initial exponential curve the relationship of the steady state values can be used to determine a general relationship between the components of the equation and the final cellular density. While fully hydrated, intralayer elastic couplings are the largest factor that increases cell density, being to a power of nine. A correlation has been shown between higher cell density and higher elastic expression within tissue [18]. This does not guarantee that a higher elastic expression would indicate that the cell density should be higher there, but it suggests the possibility. The influence of the tangential diffusion of cells is comparatively small being only to a power of one [19]. The area chosen was chosen for mathematical simplicity, it is possible that a different surface area would change the level of influence of this factor. The grouped effect of cell crowding and cell synthesis and apoptosis to decrease cellular density has an approximately equivalent amount of effect as the elastic couplings, being to a power of negative nine. The nature of wound repair is likely the reason why this factor is so large. The need to replace cells would be increased, but the number of cells that had been damaged would also be increased. Dehydration reduces circulation, thus reducing the nutrients that would reach the cells, which could decrease the rate of cell synthesis [4]. Additionally, the process of wound healing has been shown to be contingent on cell

movement and the shape of the cell groupings [19]. These combined factors together could cause the cell crowding component to decrease cell density by such a large amount. The influence of the tangential velocity of cells is the next most influential component to decrease the cellular density. Physiologically, it's likely that the movement of the cells allows them to spread out and decrease the cellular density at any one point [19]. Mathematically, the cell crowding component and elastic forces appear to effectively cancel each other out in all of the simulations. This leaves the tangential diffusion and the tangential velocity to determine the change in cellular density.

The simulations that only change one of the dehydration modifiers were used to determine the relative level of influence of the two modifiers. The change of both factors independently produced the same general trends for the components of the equation. The effect of crowding became less negative. It is possible hydration, to some extent, disrupts the natural movement and shape changes that are necessary for a wound to repair itself [19]. Cellular adhesion increases with dehydration, which could change how the movement of cells and their extrusion [11],[20]. The value of tangential diffusion and tangential velocity decreased. Both are types of cell migration, so any factor that would impact cell movement would impact them both [20]. The same increase in cellular adhesion that could impact the effect cell crowding could impact the tangential diffusion and velocity components [11]. Additionally, dehydration decreases circulation, which reduces the amount of nutrients [4]. This could impact any cell movement. The value for the elastic couplings decreased. This could be due to the increase in adhesion forces or the possible correlation between cell density and elastic couplings [11],[18],[19]. While the same trends appearing with both individual simulations could indicate an error in the model, the correlation between the factors makes sense, as the factors both are indicative of the effect of dehydration and generally work in tandem. The correlation being due to a modeling error is less likely because of the differences between results. While when one value was set to 0.1 or 0.9 the results were identical, they were not always. When the severity modifier was set to 0.5, both the cell crowding factor and the derivative of the cellular density had higher initial values and the rest of the factors has higher steady states than when the time constant was set to the same, as shown in Appendices C and F. This could indicate that the severity of dehydration is more important than the duration of dehydration.

The relative influence of the equation components on the change in cellular density due to dehydration can be examined by how much the factors change between fully hydrated values and when the modifiers are both set to 0.1, simulating severe dehydration. The cell crowding component and the elastic component changed by the largest factor. Both changed by a power of four, the cell crowding component becoming less negative and the elastic couplings component increasing. Mathematically, the two cancel each other out. Both the tangential diffusion and tangential velocity decreased by a power of two.

The results for the cellular density were unexpected. When the model was run with the dehydration modifiers set to fully hydrated values, the cellular density was higher than the upper end of the range found by the continuum model by approximately a power of ten [1],[2]. Whether this is due to a modeling error or a different set of initial conditions is unclear. When run to simulate dehydrated conditions, the cellular density did not change significantly between levels of dehydration. Dehydration has been determined to decrease the cellular density due to the change in circulation and diameter of blood vessels [14]. The minimal variance could be due to a modeling error. The model relies on a series of simplifications and assumptions. Either one could have been made incorrectly or multiple assumptions could have compounded an error. The model could also have some degree of truncation errors from the computation, which prevents the decrease from being as large. The model never reaches a full steady state, so the oscillations could hide a smaller decrease. Alternatively, no literature could be found that gives an exact range of possible human cellular densities, but it is possible that the cellular density can only change within certain parameters.

The results of the model provide some illumination on the differences between wound repair while hydrated and dehydrated. Previous work on this subject has shown the cellular density decreases and the adhesion constant increases, depending on the severity and duration of dehydration [11],[14]. In addition, dehydration can reduce circulation [4],[5], prevents enough water from being absorbed into the extracellular matrix [4], increases inflammation [5],[11], decrease blood pressure [7], decreases the volume of plasma [6],[13] and increases the heart rate [12], which creates an overall slower process for wound healing [1],[2]. This model suggests some of the ways that these factors influence and slow the rate of wound repair. By dividing the rate of wound repair into components the effect of the factors can be better observed and explained. The model shows that the severity of dehydration is more detrimental to the rate of wound repair than the duration of dehydration in some situations.

Future tests and simulations could further validate or be used to refine the model. One way would be to run a test under the conditions modeled and compare the end states of both tests. This would likely be unfeasible. The constants could be checked and standardized using the same method that the continuum model used, as shown in Appendix G. The method uses a set of equations that could be used to optimize the constants of the equation. Where zρ and zd is summed over all points and j begins at one. The goal would be to minimize z = zp + zd [1]. If similar models could be found a comparison could be used, similarly to how the simulation could be used with experimentally gathered data.

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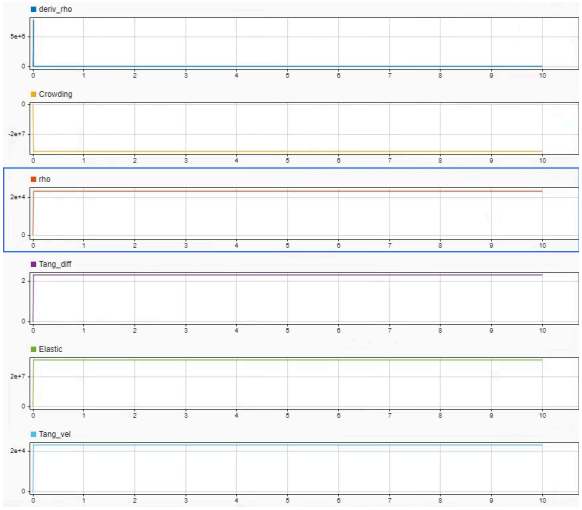
APPENDIX A

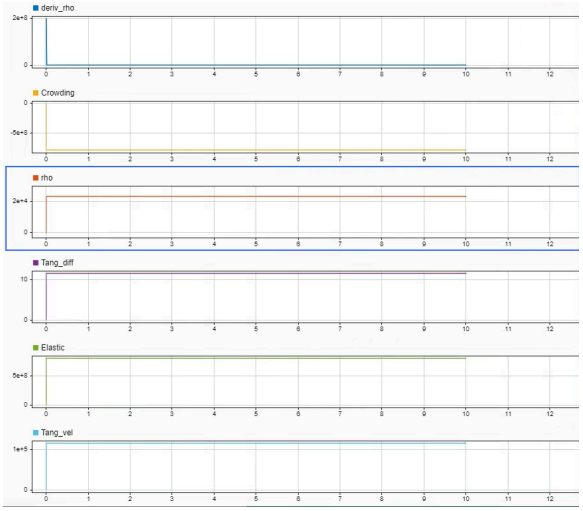
1) At the edge of the coverslip region, Neumann: $\Delta\rho * n = 0$ on an outer boundary
2) At the edge of the observable are, Dirichlet: $\rho = e^{\phi}\rho_0$ on an outer boundary
3) Lamellipodia at wound edge; constant force per unit length; Dirichlet: $\rho = e^{\phi}\rho_0$ on an inner boundary
4) At the moving edge: $v * n = -\kappa e^{\phi}\rho_0^{-1}\Delta\rho n$ on an

APPENDIX B



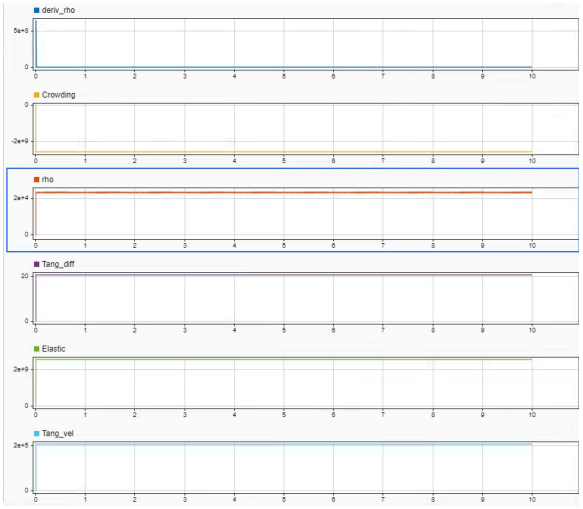
Appendix B: The results of the model when run to evaluate the effects of changing the severity modifier. The tau was set to one, the beta was set to 0.1. The other parameters are the test values declared in Figure 3.

APPENDIX C



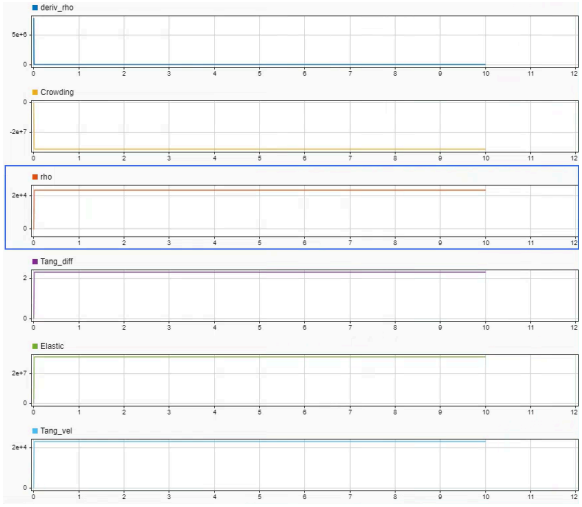
Appendix C: The results of the model when run to evaluate the effects of changing the severity modifier. The tau was set to one, the beta was set to 0.5. The other parameters are the test values declared in Appendix H.

APPENDIX D



Appendix D: The results of the model when run to evaluate the effects of changing the severity modifier. The tau was set to one, the beta was set to 0.9. The other parameters are the test values declared in Appendix H.

APPENDIX E



Appendix E: The results of the model when run to evaluate the effects of changing the duration modifier. The beta was set to one, the tau was set to 0.1. The other parameters are the test values declared in Appendix H.

APPENDIX F

Appendix F: The results of the model when run to evaluate the effects of changing the duration modifier. The beta was set to one, the tau was set to 0.5. The other parameters are the test values declared in Appendix H.

APPENDIX G

$$z_\rho = \sum \rho_{rmsj}$$

$$z_d = \sum d_{rmsi}$$

APPENDIX H

The below text is the full code. The colors of comments and other types were left in for readability.

```
clc;clear;

%Specify parameters
%parameter values would change
depedning on exact sample being
modeled
%values are test values based on
literature research and assumption
kappa = 13700; % (micro*m)^2/h -
residual bulk modulus/adhesion
constant
rho_init = 0.004876; %cells/?m2
%rho = ; %cellular density - thing
being found
%chng_rho = rho - rho_init; %change
in cellular density - thing being
found
al = 0.0913; %growth constant
rho_k = exp(1.158)*rho_init;
%limiting cell density
D = 0.0001; %cellular diffusion
constant - literature - assumed
0.0001 for now
SX = 1; %gradient(rho); %surface
gradient of rho - sample value

%dehydration variables
%The variables would change in each
simulation to model different
%situations with different levels
of severity and durations of
dehydrtation
bet = X; %start 1
tau = X; %start 1

%Simulate the model - unfinished
psuedo-code
%The code will run the model,
capture the output, and plot the
output.
a = sim('DehydratedWoundModel');

%the following plots all five
outputs using simulation data
inspector
plot(a.yout);
```

APPENDIX I

Initial Equations to be combined to get Equation 7:

Continuum Model [1]:
$\partial\rho/\partial t = \kappa\Delta\rho + g(\rho)$
Where $g(\rho) = \alpha\rho(1 - \rho/\rho_k)$
Expanded: $\partial\rho/\partial t = \kappa\Delta\rho + \alpha\rho(1 - \rho/\rho_k)$

Partial Derivative Model [3]: $(\partial\rho/\partial t)_n = D(\partial^2/\partial t^2)\rho - \rho u_n\kappa - \partial/\partial l(\rho(v_s + u_s))$
Expanded: $(\partial\rho/\partial t)_n = D\bigtriangledown_s^2\rho - \bigtriangledown_s(\rho(v_s + u_s)) - \rho u_n\kappa + \rho(P - A)$

Assumed equivalencies:

$\alpha = \rho(P - A)$
$\rho/\rho_k = \rho u_n\kappa$
$v_s + u_s = s$

Combination process:

$g(\rho) = \alpha\rho(1- \rho/\rho_k) + D\bigtriangledown_s^2\rho - \bigtriangledown_s(\rho(s))$
$\partial\rho/\partial t = \kappa\Delta\rho + g(\rho)$
$\partial\rho/\partial t = \kappa\Delta\rho + \alpha\rho(1- \rho/\rho_k) + D\bigtriangledown_s^2\rho - \bigtriangledown_s(\rho(s))$
$\kappa = k/b$

Combined Model without Dehydration Modifiers:
$\partial\rho/\partial t =(k/b)\Delta\rho + \alpha\rho(1 - \rho/\rho_k) + D\bigtriangledown_s^2\rho - \bigtriangledown_s\rho s$

Combined Model with Modifiers:
$\partial\rho/\partial t = \beta\tau((k\beta/b)\Delta\rho + \alpha\rho(1 - \rho\beta\tau/\rho_k) + D\bigtriangledown_s^2\rho - \bigtriangledown_s\rho s)$

Equation 7:
$\partial\rho/\partial t = (k\beta/b)(\Delta\rho\beta\tau) + \alpha\rho\beta\tau(1 - \rho\beta\tau/\rho_k) + D\bigtriangledown_s^2\rho\beta\tau - \bigtriangledown_s\rho\beta\tau s$