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How can mathematics be used to improve burn care?

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ABSTRACT

Severe second-degree 'partial thickness' and third-degree 'full thickness' burns are characterized by damage to the dermal layer of the skin. In the dermis, specialized cells called fibroblasts play a crucial role in wound healing. These cells produce collagen, a protein that provides strength and structure to the skin. After burn injury, fibroblasts migrate to the injured area and start producing and depositing collagen to help repair the damaged tissue. While contraction is essential for closing the wound, it can also result in scar contraction (contractures), especially in more severe burns. This contraction creates stresses on the skin, which can deteriorate the mobility of joints near the burn.

This article overviews the most recent research results in computer simulations of scar contraction after burns.

1. Introduction

People often died from burns in the past; however, nowadays, more people survive severe burns because care has improved considerably in recent decades. Since many people survive the burn, there is currently more focus on improving the quality of life of people with burns. Therefore, burn care often aims to prevent or inhibit scar contractures and hypertrophy. In severe burns, it might be necessary to apply skin grafting, where the patient's undamaged skin is used to (partly) cover the burned parts of the patient's body.

The risk and degree of developing scar contractures and hypertrophic scars may be influenced by factors like the size and depth of the burn, the location of the burn on the body, individual factors such as genetics, and individual wound care. Therefore, under- standing how skin responds physiologically to severe burns is essential for improving and optimizing burn care. Developing insights about the physiological evolution of burned skin is, therefore, very important. Such an understanding can only emerge if observations substantiate the developed theory. These observations can be clinical (*in vivo*); however, well-controllable experimental laboratory observations (*in vitro*) are also important. Since such observations include trends and patterns, it is essential to describe them quantitatively. The theory thus contains quantitative relations between various biological parameters. These relations are represented in mathematical relations that can occur in the form of algebraic equations or in terms of random processes. It is often unclear how, when, why, to what extent, and where specific biological processes occur; therefore, random (stochastic) processes are used in mathematical models. Combining mathematical relationships forms a mathematical model that can explain specific trends and make predictions. This modeling is often done in technological, financial, and eco- nomic sciences, but also for weather forecasting and, nowadays, in biomedicine.

Each mathematical model is constructed to compute and reproduce certain trends and outcomes. For example, in the current context, the aim is the degree of skin contraction over time. Since computations use numbers, every mathematical model will also need input parameters (input variables), and with this input, one computes the output variables of interest. There is much variation in the physiological properties of

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patients; therefore, there is an enormous uncertainty in the dermal evolution after a burn. One wonders, for example, why one patient develops a severe contracture while another does not. For the modeling, this uncertainty is expressed in patient-specific values of the input parameters, which then give a patient-specific set of output variables. A significant challenge here is that many of the input variables for the patient are unknown and need to be better or more consistently documented in the literature. After all, measurements always contain uncertainty or a margin of error. The error is often assumed to be statistically distributed according to a normal (Gaussian) distribution. The assumption for a Gaussian distribution results from the fundamental Central Limit Theorem from statistics, which states that the mean of independently identically distributed stochastic variables increasingly resembles a normal distribution as the number of samples increases. That is why it is impossible to give a reliable prediction based on the classical models, and hence, it is necessary to include uncertainty in the modeling. This inclusion of uncertainty can also be seen in weather forecasts. A typical example is the so-called 'plume' for the long-term weather forecast. This plume is based on 51 simulations in which different models are used, and the models are subjected to minor variations in the input parameters. This strategy results in several simulated output scenarios, which estimate the probabilities of certain weather types.

To address this uncertainty, mathematical models are used to predict the evolution of skin after a severe burn injury. The idea is to implement different surgical treatments in the modelling to estimate the quantitative impact of different treatments on the evolution of post-burn skin. This opens the door to finding optimal treatments that aim to maximize patients' quality of life by minimizing the extent of hypertrophy and contracture. The computational framework provides the burn-treating community with an experimental tool that is an alternative to animal models. Animal skin typically behaves significantly differently from human skin, and with the in-silico framework, an ethical alternative is provided. The uncertainty in input values as a result of patient-to-patient variations necessitates the probabilistic and statistical assessment of the results from the simulations in terms of maximized probability of successful treatment.

In this article, we will outline the biophysical background of skin evolution, describe key model developments, and place all this in the context of clinical practice.

2. Biophysical background

Skin consists of three main layers: epidermis, dermis, and subcutis, each with specific functions[1,2]. The outermost layer, the epidermis, contains specialized cells called keratinocytes and forms a tight barrier against external factors. The dermis layer underneath the epidermis consists of a network of extracellular matrix, mainly collagen and elastic fibers, providing strength and elasticity to the skin. The dermis also contains blood vessels, nerves, immune cells, hair follicles, and sweat glands. The deepest layer in the skin is the subcutis, which mainly consists of adipose tissue, providing energy storage and insulation, and forms the interface between the skin, organs, and muscles. In a severe burn, i.e., second-degree 'partial thickness' and third-degree 'full thickness' burns, at least the (entire) dermis is damaged, meaning that the extracellular matrix (collagen), blood vessels (capillaries), and epidermis must be regenerated[3,4]. In the dead, damaged skin, contaminants (pathogens) and bacteria are cleared by immune cells, including neutrophils and macrophages. The burned skin contains substances (e.g., tissue plasminogen activators) that break down the burned skin and/or fibrin. Subsequently, the macrophages, which act like 'generals' in the immune system, secrete, among others, transforming growth factor β (TGF-β) captured by fibroblasts in the dermis[5,6]. This growth factor stimulates fibroblasts to migrate to the damaged region and produce, and deposit collagen so the wound can close and the regenerated skin regains its integrity and firmness. Furthermore, the macrophages also secrete vascular endothelial growth factor (VEGF), which attracts the endothelial cells. The endothelial cells are the backbone of small blood vessels. As a result of VEGF, the endothelial cells migrate to the damaged region and create a new blood vessel network (neovascularization/angiogenesis). So far, only the two growth factors (TGF-β and VEGF) stimulating fibroblasts and endothelial cells have been described. In reality, there are many different growth factors, each of which has its function. It is unknown which growth factors, exactly how many circulate in skin and body, and which behavioral patterns they influence in body cells. Furthermore, if all growth factors are known, the mathematical model would be prohibitively complicated because of the excessive size of the mathematical problem. Poor knowledge of input values would further increase the amount of uncertainty. Hence, a very complicated, detailed mathematical model is not necessarily a useful model.

In the presence of specific growth factors and because of local tensions in the immediate environment of fibroblasts, fibroblasts can differentiate into myofibroblasts. Myofibroblasts exert relatively high tensile forces and produce collagen at a relatively high rate[7,8]. However, the collagen these cells produce differs from the collagen undifferentiated fibroblasts. The fibroblasts produce the collagen characteristic for undamaged (embryonic) skin, the so-called type I collagen. The collagen produced by myofibroblasts is the so-called type III collagen. The production of this collagen by the myofibroblasts is much faster than that of type I collagen. This provisional collagen quickly provides the skin with integrity. However, it also leads to topographical changes in the skin. In addition, this type of collagen has different mechanical properties (type III collagen fibers are thinner and less durable than type I collagen fibers).

At about the same time, the epidermis is regenerated. It is known that there is communication between the different cell types, the so-called 'keratinocyte-fibroblast crosstalk', responsible for the closure of the epidermis and regeneration of the dermis[9]. However, the way this communication is processed is not completely clear. The basement membrane separates the dermis from the epidermis. Once the epidermis has been restored, the wound is closed, and clinicians refer to the damage as a scar instead of a wound. This new scar tissue has a different structure than undamaged skin; therefore, residual stresses will remain in the scar tissue and its immediate vicinity even once the myofibroblasts have died by apoptosis[10]. While the collagen regenerates, the endothelial cells regenerate the circulatory system. In the long term, type III collagen is replaced by type I collagen. However, the last-mentioned (remodeling) process can take years.

As noted earlier, myofibroblasts exert tensile forces that cause the scar tissue to contract. This contraction creates tension in the scar tissue and the surrounding tissue. The damaged area is then subject to contraction. The stresses, in turn, may enhance further differentiation of fibroblasts to myofibroblasts. Hence, a chain reaction may occur. Mathematical modeling aims to quantitatively understand the underlying biophysical processes and predict possible scenarios that occur after a burn. An example of such a scenario is a scar contracture.

3. A description of the mathematical models

Many mathematical formulations that simulate physical phenomena are based on conservation laws. One can think of classical physical laws such as mass, energy, or momentum conservation. These relations are then typically expressed in so-called partial differential equations, and these models can be applied on a larger scale, in the scale of centimeters or decimeters. These types of models are called continuous-scale or macro-scale models. A continuous-scale example is morphoelasticity, widely used in biological modeling to describe elastic growth. In contrast to elastic deformations, morphoelasticity describes skin deformation as plastic. This model consists of partial differential equations representing conservation laws for momentum, chemokine, (myo)fibroblasts, and collagen. It includes migration (by chemotaxis and

random walk), cell proliferation (cell growth and division), cell differentiation, cell death, and the production and decay of collagen and chemokine. Furthermore, it includes tensions, inertia, and cell forces in the tissue, as well as changes in microstructure that result in permanent deformation. This model is discussed in detail in [11,12], and the general equations are shown in the Appendix.

In order to use the model for the simulation of the biophysical process, one has to approximate the solution to the partial differential equations. Alternative models are used for modeling on smaller scales, such as millimeter scales or even smaller ones. In these alternative models, one models cells as individual entities (agents) that are involved in particular biological processes such as cell division or cell traction. These small (micro)-scale models are no longer purely based on partial differential equations. Some of these models even include the deformation of cells that takes place during migration. An example of this type of micro-scale modeling can be found in [13], which models how cells migrate through narrow curved channels. This model is then used to describe how cancer cells migrate to another part of the body and thus cause cancer to metastasize (spread). In models where many cells are treated, the geometry of the cells is often taken constant during simulation [14]. These models are comparable to the so-called particle models that are used in computational physics.

Furthermore, the tensile forces exerted by the cells in their immediate vicinity are included in the models. This model type cannot be applied on a large macro scale since the simulations require too much computing power. In particular, if one wants to quantify the uncertainty in a statistically sound manner, this type of model is not yet applicable on a macro scale.

The microscale models contain many random processes since, in large colonies, it is unknown whether and when individual cells divide, differentiate, or die. It is not known how they migrate because the tissue always contains unpredictable inhomogeneities, and the behavior of cells is, to some extent, unpredictable. Therefore, processes such as cell division, differentiation, cell death, and migration are modeled as random processes, meaning that inherent to this model formulation, uncertainty will occur in the outcome space. We are also interested in the mathematical analysis of the transition between small and large-scale models. This transition is also known as upscaling. The research in upscaling is done in two ways. On the one hand, the transition is proved rigorously with mathematical principles from functional analysis based on averaging compositions of regularized localized point sources and forces (mathematically by using Dirac delta distributions) and, for example, using the hydrodynamic limit. On the other hand, statistical procedures, such as machine learning or alternative regression procedures, are applied to sets of microscale parameters by averaging the results obtained from computer simulations. Both methods should lead to obtaining mathematical relationships of cell densities, traction forces, and other quantities that describe cell behavior. The first mathematical steps were taken in [15].

Numerical techniques approximate the solution of mathematical problems, particularly partial differential equations. In these techniques, the differential equations are converted into algebraic equations. In order to maintain optimal freedom in geometry in numerical approximations, the finite element method is often used, which in turn is combined with time integration methods to solve the problem over time. The principle behind the finite element method is that the computational area is divided into discrete points where one approximates the solution of the partial differential equations. Furthermore, the problem often contains non-linearities, so additional numerical so-called fixed point techniques must be used to estimate the solution using successive approximations (called iterating). We have described this in more detail in [16]. Furthermore, the model has been mathematically examined for stability (i.e., the extent to which small perturbations in the data affect the final computational results) in [17,18].

4. Handling the uncertainty

As noted earlier, many input parameters in the mathematical models are subject to variations from patient to patient. In addition, many input parameters need to be better documented in the literature, where contradictory values are often found. Since measurements always contain unpredictable errors, measured quantities are modeled as random variables. Therefore, (the average of) a measured quantity is often expressed in terms of a (95 %) confidence interval. A 95 % confidence interval expresses that the likelihood is 95 % for the value of the measured parameter to have a value within this interval. In any case, this variability creates uncertainty that affects the model's outcomes. Since the values of the input parameters impact the results from the mathematical model, it is necessary to consider this uncertainty. After all, a single simulation only provides a possible scenario (This principle is similar to flipping a coin only once, where one toss only results in a head or a tail. Flipping the coin only once cannot be used to determine whether the coin is fair.), in which this scenario only forms a point in the output space (mathematically, one should speak of the set of outcomes, however, in this manuscript, we deal with these probabilistic concepts more loosely). Hence, the probability of occurrence of this scenario is, in fact, zero, which can be seen as follows. Represent the continuous outcome space as a line segment with length H, say between $x = 0$ and $x = H$, or the interval $(0, H)$. We used the word continuous here in the following sense: suppose that $\omega \in (0, H)$ is a possible event in the outcome space. Then for each (arbitrary) $\epsilon > 0$, but sufficiently small such that the interval $(\omega - \epsilon, \omega + \epsilon)$ is contained within the interval $(0, H)$, all points within the interval $(\omega - \epsilon, \omega + \epsilon)$ are also possible events. Then, there are infinitely many points on this line interval. All these points correspond to an event. According to Laplace's definition of probability for events that are all equally probable, we suppose that the total number of possible events is given by N, then the probability of each single event, say ω is given by

$$P(\omega) = \frac{1}{N} \tag{1}$$

We mentioned earlier that an interval has infinitely many points; hence, N is unbounded. Dividing by an infinite number gives a zero. Hence, the probability of each single event is zero. For the statistical gourmet, we note that this assumes a statistically uniform distribution for simplicity of presentation. In practice, the assumption of uniformity of the statistical distribution has proved to be a poor starting point. Therefore, we have to change this assumption in the real calculations. However, the conclusion for this part remains the same, and hence, for the sake of the illustration of our argument, we keep on using uniformity. To consider the probability of a single simulation, let us take the length of the interval to zero (since we take a point as an interval of length zero). In other words, h is sent to zero. Let $P(G)$ be the probability of event G; then this means that $P(a \leq x \leq a + h) \to 0$ if $h \to 0$. Therefore, the probability of this outcome is equal to zero, meaning that a single simulation is insignificant. We will, therefore, have to perform large numbers of simulations to estimate the mean outcome, spread, and statistical distribution. This large number of simulations is needed even if the only objective is to delineate the outcome space (outcome collection) and to estimate the probabilities of certain scenarios (to be regarded as subsets of the outcome collection), hence allowing us to estimate the probability that a contracture is more severe than a certain threshold value.

From an arithmetic point of view, statistical distributions are assumed for the input parameters. The a priori statistical distributions are then estimated based on data from the literature or based on (intuitive) arguments. Furthermore, several simulations are performed, in which the input parameters are sampled from the statistical distributions that they follow. A (single) scenario is then computed, and the idea is that this procedure is done repeatedly. This principle fits within the so-called Monte Carlo method. The output parameters are analyzed once

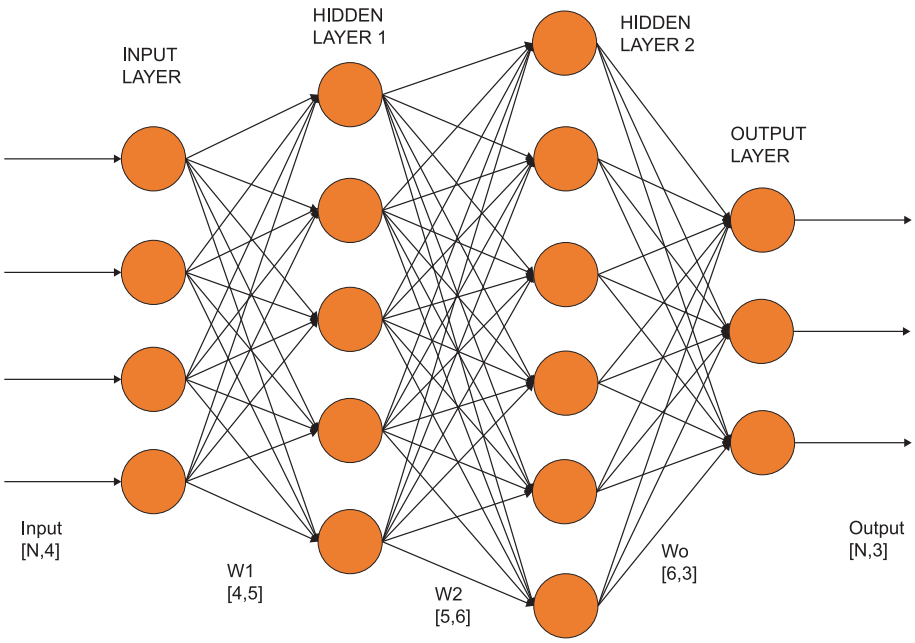

Fig. 1. Schematic representation of a feed-forward neural network. One can see the input layer, hidden layers, and output layer. Information flows from left to right. Information entering a node is algebraically processed and passed to all nodes in the next layer (to the right of the node).

the Monte Carlo simulations have been done. It is possible to determine correlations between the output parameters and between the output and input parameters. In this way, one gains insight into the reciprocal dependencies. One can, for example, compute the covariance matrix between input and output parameters and carry out the so-called Proper Orthogonal Decomposition (POD) to determine which linear relationships of components correlate mostly with each other. The POD, also called Principal Component Analysis, is based on Singular Value Decomposition, which can be interpreted mathematically as a 'transformation of data on principal axes'. In this way, one can describe the data; thus, data compression (by filtering out the components with small correlations) can be obtained, which can be easily handled and stored. Through the computations, the output can also be treated statistically by putting the results in a histogram, which provides graphical insight into the statistical distribution of the output parameters. One can then statistically test whether the outcome follows a certain probability distribution. For example, the output data can also be used to estimate the probability that the wound will contract by more than a certain percentage. On the other hand, one can use the so-called Kernel Density Method to formulate a numerical-algebraic expression for the probability distribution of an outcome parameter. Subsequently, improved estimates can be constructed through bootstrapping (sampling (draws) from the obtained numerical-algebraic probability distribution) for various statistical variables (such as variance and mean, amongst others). In any case, the uncertainty causes the modeler a significant amount of work, translating into computer-intensive computations that can take a very long time and require a heavy computer infrastructure. These high computational costs are undesirable in a clinical setting. How we deal with this will be discussed in the next section.

5. Artificial intelligence to speed up computations

Artificial intelligence is the idea that a computer can perform decisive and inferential tasks that humans normally do. These tasks can be, for instance, recognizing patterns, such as faces or spoken (written) words, raising verdicts, or reproducing numbers from given data. The process of making the computer or machine capable of performing these tasks is referred to as machine learning. As mentioned, the (numerical) computation times can be excessively long. Since clinicians prefer quick results without a heavy computer infrastructure, it is necessary to look for fast alternatives. Artificial intelligence can provide a platform for such a fast alternative. The algorithmic infrastructure for this alternative is based on a neural network. Using this neural network, one simulates the model, which in itself already provides a simulation for reality. This neural network forms a tool to quickly reproduce the simulations from the more complex (numerical) model. In turn, bundling neural network simulations can be used to estimate specific statistical parameters randomly (i.e., with samples).

The idea of a neural network can be explained as follows. We consider a network with an input and output parameters layer. Suppose the complex mathematical model contains 25 input parameters; then, the input layer consists of 25 input nodes. Moreover, suppose we are interested in simulations over 365 days; then, the output layer consists of 365 nodes. This output layer, in turn, depends on the number of variables we want to examine. However, for convenience, we will assume that only a single output parameter is analyzed at different times (days). One uses so-called hidden layers between this input and output layer, which all contain a certain number of nodes. At each node, information comes in from all nodes from the layer in front of it (except the input layer). The information is algebraically processed through a so-called transfer function in which the coefficients are called weights and biases. Then, the processed information is passed to all nodes in the next layer (except the output layer). The idea of a neural network and its principle is shown in Fig. 1. The neural network relates a set of input values to a set of output values by evaluating a sequence of algebraic expressions. The algebraic operations, referred to as transfer functions, are characterized by coefficients, which, in turn, are referred to as weights and biases. A random set of weights and biases in the transfer functions relates the input set to a random output set. Based on the results from the complex mathematical model, the idea is to estimate the values of the coefficients in the transfer functions (weights and biases) to obtain the results of optimally describing a complex mathematical model. This estimation is called *training* the neural network model. Subsequently, the optimal configuration of the network is also sought. This optimal configuration then reflects on the number of nodes per hidden layer and the number of hidden layers in the network.

All in all, training and optimizing a neural network can be seen as an advanced regression procedure from a statistical perspective. A trained

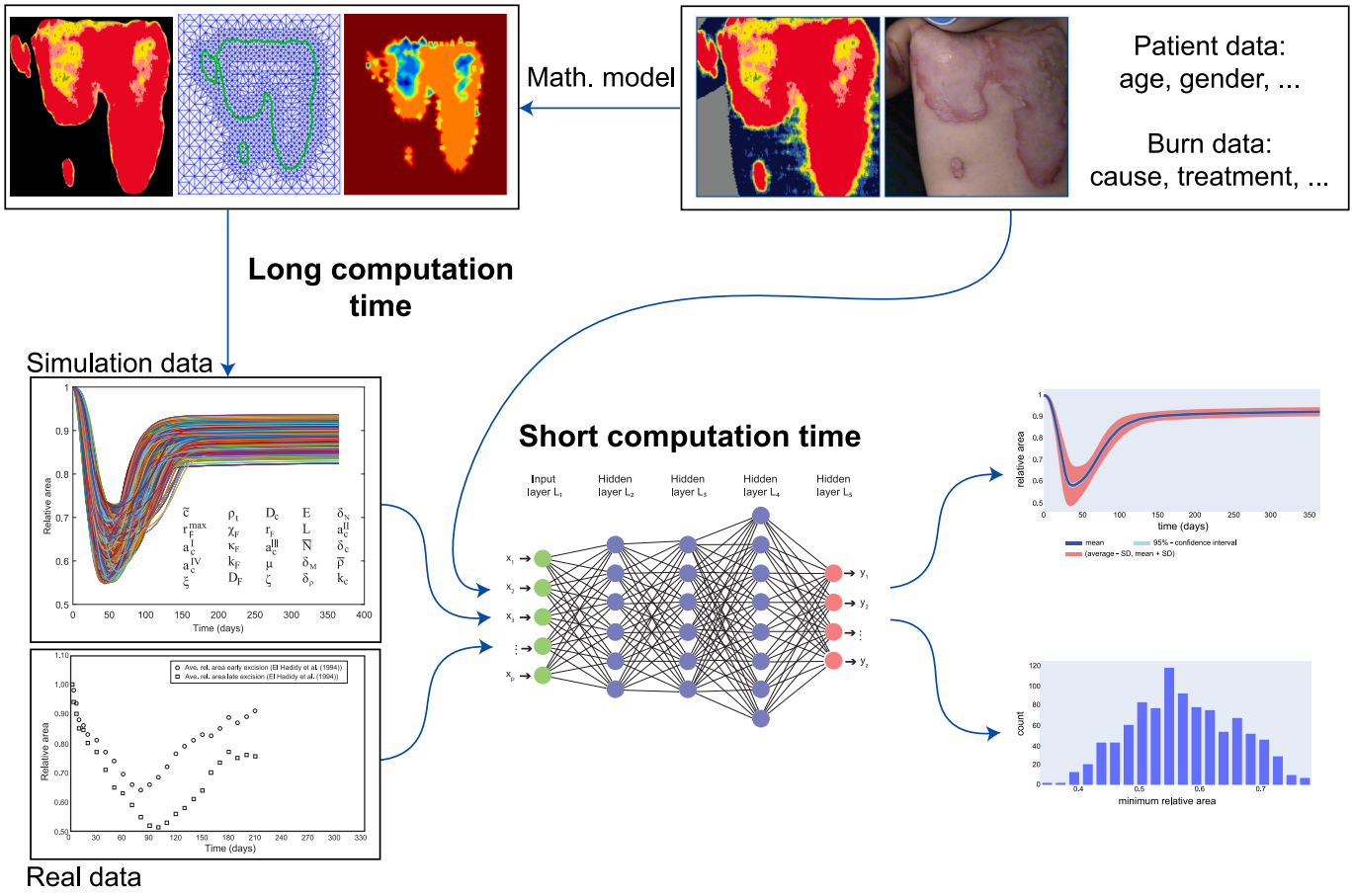

Fig. 2. A schematic representation of integrating the mathematical model and the neural network in clinical practice. For example, with a relatively long computation time, the mathematical model predicts the degree of contraction regarding scar size versus time for many simulations with sampling from probability distributions for the patient and burn data. After training the neural network based on the mathematical model results and, in addition, accurate (follow-up) data, the neural network reproduces these results in a relatively short computation time, providing the practitioner with an estimated probability distribution of various scenarios.

and optimized neural network can mathematically be considered an advanced interpolation or mapping routine. Our results show that a spectacular computational acceleration can be achieved [19]. Because these computations are so much faster than the computations with the complex mathematical model, we expect this to be the way to integrate simulations into medical practice.

However, it should be noted that the machine learning models are limited in the sense that if one changes the mathematical model, then one has to redo the training of the neural network and associated configurational optimization. There are also important limitations on the validity of results if input values fall outside the network training set limits.

6. Clinical-social and future perspective

Mathematical modeling offers many possibilities for predicting how the skin will develop over time. In addition, the mathematical model (*in silico* model) can replace or reduce the number of laboratory animals needed to perform tests. We hope that in the future, we will make a tool for the practitioner that can provide guidelines in advance for the treatment that should be implemented. This idea is our long-term objective; hence, much work remains. Our models are unique in the literature since we combine the mechanics with shrinkage and change of skin structure, which in turn is coupled with a biochemical model for cells, growth factors (chemokines), and collagen.

The current model describes clinical observations very neatly. However, the model is not complete yet. In a future model, we want to implement the different types of collagen and integrate the functioning of the immune system into the current model. This implementation will mimic the complexity in reality even more. We feel a certain reluctance to add more complexity to the models since more complex models also imply the need for additional input parameters and, in this way, introduce more uncertainty. After all, it is unclear how various links between sub-processes occur and what parameter values should be used for this purpose. A complex model is, therefore, not always a good model.

6.1. *Bridging the gap: Towards enhanced clinical utility*

On the other hand, we also see that the models are still limited because only a few treatment methods can be included in the computational models. To address this matter, future research will focus on incorporating crucial surgical interventions such as debridement, skin grafting, and splinting. These interventions are essential for managing burn injuries, with debridement removing damaged tissue, skin grafting replacing lost epidermal skin, and splinting aiding in proper healing and function.

Incorporating these treatments into our model poses a significant challenge, requiring careful consideration of how to represent them mathematically. For example, debridement could be modeled by modifying initial conditions for chemokine concentrations, skin grafting by adding a source term for grafted keratinocytes and collagen, and splinting by adjusting mechanical boundary conditions.

By incorporating these extensions, our model will be able to predict the impact of surgical timing, optimize graft characteristics, and

evaluate splinting strategies. Ultimately, these advancements will enable more accurate predictions of patient outcomes and inform clinical decision-making, providing surgeons with a valuable tool to compare predicted outcomes of different interventions, identify patients at higher risk of complications, and make more informed decisions tailored to each patient's unique needs.

6.2. The role of artificial intelligence

We also see that there is still much work to be done in the artificial intelligence framework, which has proven to be a necessary tool to facilitate a probabilistic approach to the outcomes of the simulated scenarios. Here, multidimensional cases with more complex wound geometries must be dealt with, and further experiments may be conducted with so-called physics-informed networks.

When these concepts have been further developed, the idea is that a practitioner can scan the burn wound, for example, using laser Doppler imaging (LDI). This scan includes the shape (geometry) of the injury. It gives a picture of the amount of blood flowing through the blood vessels in the burned area, which helps predict the wound healing time and indirectly gives information about the severity of the injury. This scan must, of course, be performed non-destructively on a patient. After all, the patient should not be bothered by it. In general, such a scan contains (much) noise. Image processing is required to filter out the noise. Alternatively, it is possible to resort to artificial intelligence here as well. Of course, we must always test whether the artificial intelligence-based results have been obtained with input data within the domain of the training set. The idea is then that the obtained scan is used as an initial condition for the simulations with the neural network model mimicking the mathematical model. The practitioner should then quickly see a histogram of the intensity of the expected skin contraction (and any other variables of interest). We also want to include the treatments so the practitioner finds the optimal treatment according to the model. The idea is shown schematically in Fig. 2.

Of course, we still have to deliver a considerable effort and be modest. Practitioners are often experienced physicians who know very well from their observations and colleagues what the most likely scenarios are. Therefore, a clinician should always maintain skepticism regarding model results. Common sense must always come first, and model results can never be blindly adopted. In addition, the model predicts probabilities in specific scenarios. We must remember that improbable events can happen. In other words, the (almost) impossible can happen! Hence, common sense must prevail despite the modeling efforts and the beauty of mathematical modeling.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix. Mathematical model equations

This paper discusses mathematical models at continuous and macro scales. While the main text focuses on the conceptual understanding of these models, this appendix provides a glimpse into the underlying mathematical equations for interested readers.

Continuous-Scale Example: Morphoelasticity The continuous-scale model, exemplified by morphoelasticity (plastic skin deformation), is represented by the following system of equations:

$$\begin{aligned} \rho_t\left(\frac{\mathrm{D}\boldsymbol{v}}{\mathrm{D}t}+\boldsymbol{v}[\nabla\bullet\boldsymbol{v}]\right) &= \nabla\bullet\sigma+\mathbf{f},\ \text{in}\ \Omega,\ t>0,\\ \frac{\mathrm{D}\boldsymbol{\varepsilon}}{\mathrm{D}t}+\boldsymbol{\varepsilon}\mathrm{skw}(\nabla\boldsymbol{v})-\mathrm{skw}(\nabla\boldsymbol{v})\boldsymbol{\varepsilon}+(\mathrm{tr}(\boldsymbol{\varepsilon})-1)\mathrm{sym}(\nabla\boldsymbol{v}) &= -\alpha\boldsymbol{\varepsilon},\ \text{in}\ \Omega,\ t>0,\\ \boldsymbol{v}(\boldsymbol{x},t) &= 0,\ \text{on}\ \partial\Omega,\ t>0. \end{aligned} \tag{2}$$

In these equations, ρ_t denotes the total mass density of the dermal tissues, σ represents the viscoelastic relationship for the Cauchy stress tensor, f is the body force exerted by myofibroblasts pulling on the extracellular matrix, and α is a non-negative constant controlling tissue recovery. When $\alpha = 0$, the tissue fully recovers to its original shape.

and volume once the force is removed. Furthermore, the term $\frac{\mathrm{D}\boldsymbol{y}}{\mathrm{D}t}=\frac{\partial\boldsymbol{y}}{\partial t}+\boldsymbol{v}\bullet\nabla\boldsymbol{y}$ is the material derivative, accounting for changes in a property y over time.

These equations describe $\boldsymbol{v}$, the velocity of points within the computational domain (including both damaged and healthy tissue) due to contraction, and $\boldsymbol{\varepsilon}$, the effective strain, a local measure of the difference between the current tissue configuration and a virtual equilibrium configuration.

Essentially, Equation (2) can be thought of as an advanced version of Newton's law ($F = m \bullet a$). It describes how forces exerted by cells cause the tissue to move and de- form. The second equation describes how the tissue's microstructure changes due to cell forces and collagen production.

While not shown here, the complete mathematical model includes additional equations governing other essential components of the tissue. These are the collagen density (de- scribes the amount of collagen present in the tissue), the (myo)fibroblast density (de- scribes the concentration of cells responsible for wound contraction), and the signaling molecule concentrations (describes the concentration of chemical signals that influence cell behavior). These equations, along with detailed explanations and analyses, can be found in the references cited in the main text [11,12].

Note: A deep understanding of these equations is not necessary to grasp the main concepts of the paper. This appendix serves as a resource for readers interested in exploring the mathematical underpinnings of the discussed models.

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