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# Modelling Keloids Dynamics: A Brief Review and New Mathematical Perspectives

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## Abstract

Keloids are fibroproliferative disorders described by excessive growth of fibrotic tissue, which also invades adjacent areas (beyond the original wound borders). Since these disorders are specific to humans (no other animal species naturally develop keloid-like tissue), experimental *in vivo/in vitro* research has not led to significant advances in this field. One possible approach could be to combine *in vitro* human models with calibrated *in silico* mathematical approaches (i.e., models and simulations) to generate new testable biological hypotheses related to biological mechanisms and improved treatments. Because these combined approaches do not really exist for keloid disorders, in this brief review we start by summarising the biology of these disorders, then present various

types of mathematical and computational approaches used for related disorders (i.e., wound healing and solid tumours), followed by a discussion of the very few mathematical and computational models published so far to study various inflammatory and mechanical aspects of keloids. We conclude this review by discussing some open problems and mathematical opportunities offered in the context of keloid disorders by such combined *in vitro/in silico* approaches, and the need for multi-disciplinary research to enable clinical progress.

**Keywords:** keloid disorders, review, mathematical modelling and computational approaches, modelling cancer and wound healing, inflammation, biomechanics

## 1 Introduction

Since 2018, the World Health Organization defines keloids as a member of a group of disorders “characterized by increased deposition of fibrous tissue in the skin and subcutaneous tissue” [1]. Accordingly, keloids are considered not just pathological scars, but rather the outcome of an abnormal wound healing process with features similar to that of chronic inflammatory diseases and cancer [2]. Clinically, keloids present as a fibrotic tissue that proliferates beyond the primary injured area and persist over time without natural regression. This fibrotic tissue also exhibits inter-lesional and intra-lesional heterogeneity [3]. Keloids may cause pain and pruritus, and seriously affect patient quality of life when they are located in visible areas [4]. Keloids may result from different skin injuries, including surgery, burns, trauma, piercing, and folliculitis, though their location appears mainly confined to chest, shoulder, neck, and ear [5]. The lack of effective treatments clearly reflects our poor understanding of keloid pathogenesis, though keloid histopathology has been extensively described in the past decades [6]. Despite this, keloid aetiology and pathogenesis remain largely unknown.

Since keloid disorders are exclusive to humans, existing *in vivo* and *in vitro* studies that are based on different animals cannot induce keloid scar formation, although they can induce the formation of a nodule-like mass formed of keloidal collagen [3]. As emphasised in [7], this lack of biological models that could mimic all human characteristics of keloid disorders has hindered research efforts aimed at prevention and therapeutic interventions. Therefore, new *in vitro* human biological models are required to advance the research in this field [8]. These *in vitro* human models could be complemented by *in silico* approaches focused on mathematical models of these biological systems and computer simulations. These combined *in vitro/in silico* perspectives have become quite common for studies on wound healing and cancer evolution (disorders that have similar biological mechanisms as keloids [2, 9]), but they have not usually been used for keloid disorders.

The goal of this brief review is to present the complex problem of keloid disorders in the context of related disorders such as wound healing and solid tumour growth and spread, and to propose new multi-disciplinary approaches (that include mathematical modelling and simulations), which could bring new perspectives and solutions. To this end, we structure this review as follows. In Section 2 we discuss the biology of keloid

disorders with an emphasis on inflammatory and bio-mechanical aspects. In Section 3 we review a variety of mathematical models that have been developed over the last decades to describe and investigate wound healing, solid tumours, and keloid scars. In Section 4 we discuss some open problems in the context of modelling and computational approaches for these multi-scale disorders. We conclude in Section 5 with a summary of the main aspects reviewed in this study and some future perspectives.

## 2 Biological aspects of keloid disorders: inflammation and biomechanics

The set of causes (aetiology) for keloid formation is still not fully understood. However, several studies have postulated different hypotheses on the pathogenesis of keloid formation [3, 9, 10]. Historically, these hypotheses range from the keloid triad hypothesis (which encompasses three risk factors that must be simultaneously present and interacting to trigger keloid formation, namely genetics, infection with pathogens such as bacteria or viruses, and external factors such as surgery) [3, 11, 12], to the incomplete malignancy hypothesis (suggesting that keloids could be a type of incomplete malignancy that has undergone only a few tumorigenic changes) [3], the viral hypothesis (suggesting that keloids could be triggered by a normally quiescent, unknown virus) [3, 13], the stiffness gap hypothesis (suggesting that keloids could be the result of an enlarged gap between the extracellular matrix stiffness and cellular stiffness) [3], the immuno-nutritional hypothesis (suggesting that keloids could be the result of nutritional imbalance that promotes prolonged inflammation) [3], the metabolic hypothesis (suggesting that keloids could be the result of an increased metabolic activity of fibroblasts) [3], the chronic inflammation hypothesis [3, 14], and the neurogenic inflammation hypothesis [3, 15].

We mentioned these different hypotheses here since some of them have been investigated through mathematical models, as discussed in Section 3 below. However, in the following we focus on the “keloid triad” that combines both intrinsic inflammatory aspects as well as bio-mechanical external aspects [11], since we aim to emphasise the importance of understanding the connection between these two aspects in the context of keloid scars. Note that over the last few years the importance of interplay between inflammation and mechanical stress has become clear during wound healing, where immune responses regulate myofibroblast differentiation and overall tissue contraction [16]. Moreover, it is expected that the emerging field of mechano-immunology will bring further understanding of how mechanical cues at the level of the tissue regulate immune responses at the level of cell to improve the outcomes of various disorders [17], including keloid disorders. In regard to these keloid disorders we note that on one hand, excessive inflammation has been associated with abnormal skin wound healing and keloid development [18]. On the other hand, keloids are known to occur specifically on skin areas subjected to high mechanical stress [19]. Therefore, we believe that both dysregulation of inflammation and cell mechano-responses to tissue environment could synergize to trigger and regulate keloid growth.

**Inflammatory aspects related to keloids.** Central to keloid tissue formation there is the keloid fibroblast (KF) – see also Table 1 – a key cell submitted to

both inflammatory and mechanical stimuli. In consequence, and compared to normal skin fibroblasts, KFs have an increased proliferation rate [8, 20] and a reduced apoptosis rate [21, 22]. Moreover, KFs are more responsive to growth factor activation (i.e., by TGF- $\beta$ 1 and PDGF) than their normal counterparts [23–25], and this leads to higher production of type I and III collagens (the ratio I/III in keloid tissue being 17:1 versus 5:1 in normal skin) [26]. During wound healing, extracellular matrix (ECM) degradation and remodelling processes are controlled by a family of enzymes called matrix metalloproteinases (MMPs). MMPs are synthesised by fibroblasts, keratinocytes, and macrophages, and their activity is regulated by tissue inhibitors of matrix metalloproteinases (TIMPs). Dysregulation of such a MMP/TIMP equilibrium may lead to ECM over-accumulation. In keloids, the levels of MMP-1 and -13 (collagenase), MMP-2 (gelatinase) and TIMP-1 and -2 increase, whereas the level of MMP3 (stromelysin) decreases, compared to the respective levels in normal scars [26–28]. The TGF- $\beta$ 1/Smad signalling pathway is pivotal in the process of keloid fibrosis. TGF- $\beta$ 1 regulates fibroblast-to-myofibroblast conversion,  $\alpha$ -SMA expression, and collagen synthesis during the development of fibrosis. TGF- $\beta$ 1 is found in a higher quantity in keloids compared to normal scars [29–31]. Accordingly, a variety of therapeutic strategies (drugs, siRNA, shRNA, miRNA, etc.) have been designed to target the TGF- $\beta$ /Smad signalling pathway in order to interfere with fibroblast-mediated keloid progression; e.g., by suppressing the proliferation, activation and migration of keloid fibroblasts, or by reducing collagen synthesis [32]. However, further investigation of these strategies is necessary to fully understand the specific molecular mechanisms and the potential side effects [32].

Other inflammatory cells involved in wound healing and aberrant scar formation, which impact also the formation and evolution of keloids, are the macrophages, T lymphocytes, mast cells, and neutrophils [3, 18]; see also Table 1. All these inflammatory cells that have been found in higher numbers in keloids [3], are able to cross-talk with KFs all along the abnormal healing process via different cytokines (e.g., IL-4, IL-6, IL-10, IFN- $\gamma$ ), chemokines (MCP-1), and growth factors (e.g., TGF $\beta$ , VEGF, bFGF) [18].

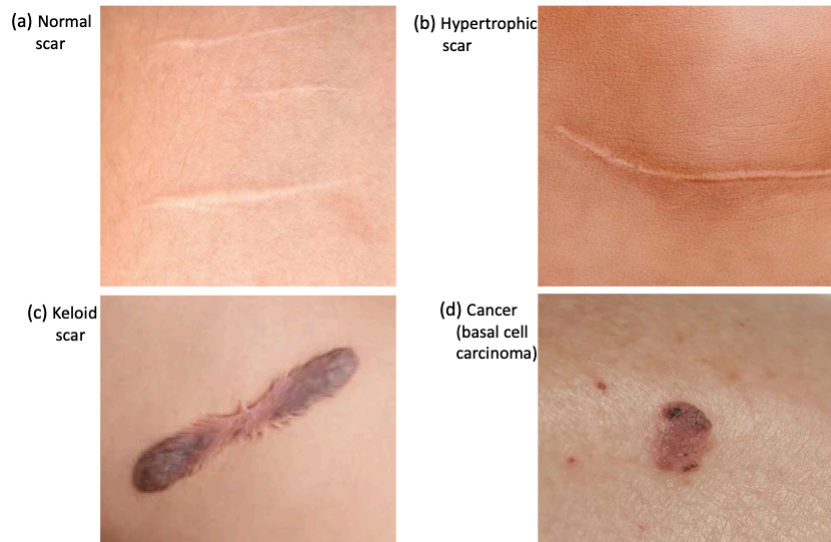
**Table 1** Some of the inflammatory cells and molecules most important in keloids, whose kinetics and interactions could be modelled mathematically.

| Cells                          | Behaviour during keloid evolution  | References   |
|--------------------------------|--|--------------|
| Fibroblasts                    | ↑cell numbers, ↑proliferation, ↑migration, ↑metabolism; ↓apoptosis, ↑ECM degradation | [3]          |
| Myofibroblasts                 | ↑cell numbers  | [3]          |
| Keratinocytes                  | ↑cell numbers  | [3]          |
| Macrophages                    | ↑cell numbers (in particular M2 cells)   | [3]          |
| T cells                        | ↑cell numbers  | [3]          |
| Mast cells                     | ↑cell numbers  | [3]          |
| Molecules                      | Behaviour during keloid evolution  | References   |
| Cytokines                      | ↑IL-6; ↑IL-8; ↑IL-18; ↑TNF- $\alpha$ ↓IL-10  | [18, 33]     |
| Growth factors                 | ↑TGF- $\beta$ ; ↑PDGF; ↑VEGF   | [18, 29, 34] |
| Chemokines and their receptors | ↑CCR1; ↓CCR7; ↑CXCL9; ↑MCP-1   | [18, 33]     |
| Collagen                       | ↑type-I:type-III ratio   | [35]         |

**Bio-mechanical aspects related to keloids.** All cells inside skin tissues are subjected to various mechanical forces that could be intrinsic (e.g., due to orientation of collagen fibres in the ECM, or due to cytoskeletal structures) or extrinsic (e.g., forces generated through muscle movement). These mechanical forces include stretching tension, shear force, scratch, compression, as well as hydrostatic and osmotic pressures [5]. In [5, 19] it was shown that keloids are more likely to develop in highly mobile anatomic regions subjected to skin stretching/contraction and with different stiffness/thickness characteristics, such as the anterior chest region or the scapular region. Moreover, the resulting keloid tissues have different mechanical properties compared to the healthy skin tissues: lower extensibility and higher rigidity for keloid tissues [36]. In addition, mechanical forces at the tissue level can modulate inflammatory cellular behaviours via the activation of mechanoreceptors on fibroblasts and immune cells, which can further increase these cells' roles in keloid scar formation and spread [37]. Some of the most studied cellular mechanoreceptors are the integrins (at cell-ECM junctions) and the cadherins (at cell-cell junctions), which are known to play an important role in wound healing and fibrosis [38]. In response to the activation of various mechanoreceptors, the mechanical signal is transferred and interpreted inside the cell through a mechanotransduction process (that transforms mechanical inputs into biochemical signals), which then leads to the modulation of molecular signalling pathways such as the FAK-ERK-MCP-1 pathway [38] or the TGF- $\beta$ /Smad pathway mentioned above [37, 38]. Since the mechanotransduction process has a big impact on cell proliferation, survival, differentiation or motility, a recent study [39] hypothesised an important role for the mechanical microenvironment on macrophage dysfunction in the context of keloid formation. In particular, it was suggested that tissue stretching combined with ECM stiffness can perturb the balance between M1 and M2 macrophages, which could then lead to sustained and concomitant pro- and anti-inflammatory signalling [40, 41].

Before discussing the mathematical approaches already applied (or those that could be applied) to modelling keloids disorders, we mention briefly some of the differences and similarities between keloids and scars (either normal or abnormal), and between keloids and benign as well as malignant tumours. For a visual comparison between normal and abnormal scars (including keloids) and cancers, we refer the reader to Figure 1. For a more in-depth comparison of these disorders we refer the reader to the references cited below. This brief discussion below will help us understand the applicability of mathematical modelling approaches for wound healing presented in Section 3.1, and those modelling approaches for cancer growth and invasion into surrounding tissue presented in Section 3.2, in the context of keloid research. We also note here that the cellular and biochemical processes involved in wound healing are similar to those involved in tumour development and invasion, and for this reason in [42] it was suggested that tumours are “wounds that will not heal”. Also for this reason, the type and structure of mathematical models for wound healing and cancer discussed in Sections 3.1 and 3.2 will be quite similar.

**Differences and similarities between keloids and scars.** Since various studies investigate keloid scars from the perspective of abnormal scars [9], in the following



**Fig. 1** Illustration of (a) normal scar; (b) abnormal hypertrophic scar; (c) abnormal keloid scar; (d) skin cancer (basal cell carcinoma).

we mention briefly some of the differences and similarities between keloids and hypertrophic scars (i.e., the two types of abnormal scars); for a more detailed comparison see [9].

- *Similarities.* Both hypertrophic and keloid scars are fibroproliferative disorders characterised by excessive and disorganised production of ECM (in particular increased type-I collagen production), as a result of abnormal proliferation and differentiation of fibroblasts [9, 18]. In addition, both types of scars are characterised by different inflammatory immune cells that infiltrate the tissue (mast cells, macrophages, T cells, dendritic cells), increased epidermal thickness, increased presence of myofibroblasts, increased TGF- $\beta$  and VEGF levels [9]. They are also characterised by increased levels of some matrix metalloproteinases such as MMP-2, and increased levels of MMP inhibitors TIMP-1 and TIMP-2 [9]. For more similarities see [9].
- *Differences.* There are various differences between scars (in particular hypertrophic scars) and keloids in terms of clinical presentation, epidemiology, histologic findings [43]; see also Figure 1. For example, hypertrophic scars do not exceed the original injury site, while keloid scars grow and invade adjacent tissue, beyond the original injury site. Moreover, while hypertrophic scars could regress spontaneously over time, this does not happen for keloids [18, 44]. Also, hypertrophic scars show lower levels of hypoxia, as opposed to keloids that are characterised by increased hypoxia [45]. Moreover, as mentioned above, keloids usually develop at certain

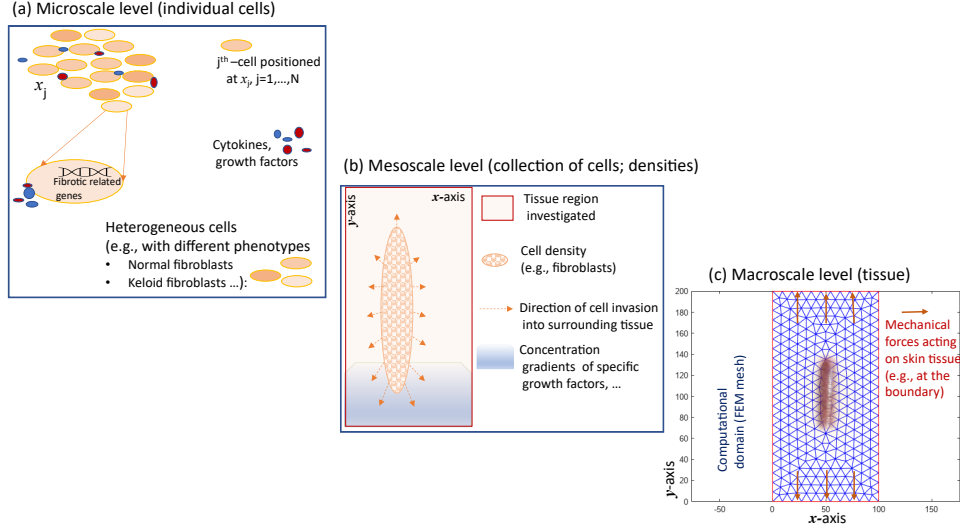
anatomical sites (e.g., chest, shoulder; characterised by certain mechanical properties) and are not associated with skin contracture, while hypertrophic scars occur more commonly at joints and are associated with skin contracture. In regard to the keloid extracellular matrix, the ratio of type-I to type-III collagen is much higher (17:1) compared to the same ratio in normal scars (6:1) [2], or even hypertrophic scars dominated by type-III collagen [44]. For more differences see [9, 44].

**Differences and similarities between keloids and solid tumours.** Since various studies mentioned the importance of investigating keloids from the perspective of benign and malignant tumours [2, 46, 47], in the following we briefly discuss this aspect by focusing on their differences and similarities. To start this discussion, we note that the word “cancer” appears to be coined by Hippocrates 2400 years ago, who compared the disease to a crab that adheres to its surroundings with its claws [48, 49]. The word “keloid” seems to have been coined by [50], who described the resemblance of this disease with a crab’s claws while also acknowledging its tissue-invasive similarities with cancers. In fact, Alibert initially referred to keloid scars as “*cancroides*”, and when it became clear that these lesions were not cancerous he changed their name to “*kéloïdes*” [51]. This shared etymology underlines the fact that, at first sight, keloids and malignant tumours present a close resemblance.

- *Similarities.* We start this discussion by emphasising that while the phenotype of keloids is similar to that of benign dermal tumours [2, 47], the morphology and clinical aggressive behavior of keloids make them somewhat similar to malignant tumours [2, 52]. In fact, keloids can exhibit to a large extent some of the hallmarks of cancers: uncontrolled cell proliferation, ECM deposition, invasiveness into surrounding non-lesional tissue, lack of spontaneous regression, relapse after surgical excision and presence of similar biomarkers [2, 53]. In addition to the clinical similarities between keloids and some specific skin tumours, such as dermatofibrosarcoma protuberans [46, 54], keloidal basal cell carcinoma [52] and keloidal atypical fibroxanthom [55], a few studies reported that abnormal levels of cytokines and (keloid-promoting) growth factors usually associated with cancers might induce also keloid development, leading to the question of whether keloids could be seen as a para-neoplastic phenomenon [56]. In this context, we mention a recent clinical study that showed an increased risk of cancer development in patients with keloids [57]. Moreover, keloids can respond to a certain extent to cancer treatments such as radiotherapy, chemotherapy, targeted immunotherapy and virotherapy [2, 58].
- *Differences.* Even though in some clinical situations keloids look very aggressive due to their volume and location, they differ from cancers in the following major points: (i) keloids cannot occur spontaneously (without any skin wound), are benign and do not lead to metastasis [56]; and (ii) they are specific to humans, no other animal species developing naturally keloid tissues [7, 59]. In addition to this, the similarities between keloids and scars discussed above emphasise even more the differences between keloids and cancers, and thus contribute to the usual classification of keloids as abnormal scars and not as neoplasms [2].



### 3 Current mathematical modelling approaches



**Fig. 2** Keloid dynamics can be investigated at different spatial scales: (a) *microscopic level*: focus on the kinetics of individual cells, or on interactions between individual cells via cytokines/growth factors; (b) *mesoscopic level*: focus on the evolution of densities of cells, and their interactions with gradients of cytokines/growth factors; (c) *macroscopic level*: focus on skin tissue, and how mechanical forces on the skin impact the evolution of the whole keloid.

Since many of the biological processes involved in keloid disorders are, at first sight, relatively similar to those characterising benign and malignant tumours [2], as well as to those characterising wound healing [3], in the following two subsections we start by briefly summarising the current mathematical approaches used to model normal and/or hypertrophic scars (see Section 3.1), and the approaches used to model solid tumours (see Section 3.2). Then, we discuss briefly the mathematical and computational models used to describe keloid dynamics (see Section 3.3).

**Types of modelling approaches.** The modelling approaches used to describe collective cell behaviours at different scales can be classified as (see also Figure 2): (a) *discrete (agent-based) models* that focus on individual cells; (b) *continuum models* that focus on densities of cells; (c) *hybrid models* that connect the dynamics of individual cells with continuum gradients of cytokines/growth factors or continuum densities of extracellular matrix or other cell populations. In addition to these three types of mathematical models, usually described by ordinary differential equations (ODEs), partial differential equations (PDEs) or integro-differential equations (IDEs), which are then discretised and simulated numerically, there is also a fourth type of models that we will refer to as (d) *computational models*. These computational models focus mostly on cell and tissue bio-mechanics, where specific rules describing mechanisms or processes at cell/tissue levels are incorporated directly into a numerical software (e.g., cellular automata models for individual cell dynamics [60, 61], or finite element implementation

of constitutive equations for tissue-deformation [62]). Note that the dichotomy between computational models and mathematical models was discussed in more detail in [61, 63], where it was emphasised that while computational models formulate hypotheses about mechanisms and processes, mathematical models formulate hypotheses about relations between variables and about changes in their magnitudes. Throughout this review we follow the same terminology regarding mathematical and computational models.

Due to the huge amount of mathematical and computational modelling of both wound healing and cancers (for some reviews we refer the reader to [64–70], as well as to [71–76] and the references therein), in the following two subsections we only mention briefly some of these studies, while emphasising the multi-scale aspects of these models as well as the bio-mechanical vs. immunological/inflammatory approaches considered. In each section, we split the discussion between

- mathematical/computational models for microscale (molecular-level) dynamics, i.e., models described by ODEs and PDEs, for changes in the densities of receptors on a cell surface, or the concentrations of molecules inside/outside a cell that control specific signalling pathways (see also Fig. 2(a));
- mathematical/computational models for mesoscale (cell-level) dynamics, i.e., models described by ODEs and PDEs for changes in the number or densities of cells (see also Fig. 2(b));
- mathematical/computational models for macroscale (tissue-level) dynamics, i.e., models usually described by constitutive equations for various mechanical forces acting on tissues (see also Fig. 2(c)).
- mathematical/computational models for multi-scale dynamics, which consider both bio-mechanical and immunological/inflammatory aspects.

The specific models discussed below in sub-sections 3.1 and 3.2 are chosen somewhat randomly, to illustrate how various modelling approaches in wound healing and cancer can also provide different insights into keloid disorders. For each of these chosen models we briefly present them, we mention the numerical approach used to discretise them (to emphasise the importance of simulations in the investigation of temporal and spatio-temporal dynamics displayed by these models), and then we briefly state how these models could be relevant to keloids.

**Remark 1.** *We acknowledge the huge mathematical literature on collective cell movement that focuses on the biological mechanisms behind cell-cell interactions and cell migration in development and disease; see, for example, the reviews in [73, 77–80] and the references therein. There are also even more studies on the collective movement of animals in ecological settings [81]. However, to keep this review focused, here we focus exclusively on models developed explicitly for wound healing, for solid tumours, and for keloids, and ignore related models investigating general collective movement of cells, or collective movement of cells in tissue development or other diseases.*

### 3.1 Modelling wound healing

Numerous mathematical and computational models have been developed since the 1990s to explain the various phases of wound healing: from angiogenesis and inflammation, to wound closure and tissue remodelling. While many of these models focus only on angiogenesis [82, 83] and inflammatory aspects related to wound healing [70, 84–87], others focus on generic interactions between cells and extracellular matrix [88–90] and/or on bio-mechanical aspects related to wound healing [91–93] without considering the impact of inflammation. Many other models combine both inflammatory and mechanical aspects [94–96]. Most of these models are continuum, but there are also a few discrete models [84, 85] and some hybrid discrete-continuum models [89, 97]. Moreover, while most of these wound healing models are local, there are also a few non-local models [98] that incorporate long-range (i.e., almost tissue-level) effects of mechanical forces acting on cells (e.g., cell-cell adhesion forces).

In the following we discuss in more detail a few examples of older/newer models for wound healing, to emphasise that: (i) older models are simpler but also very relevant to current studies (including studies on keloids); and (ii) newer models encode complex inflammatory-mechanical interactions, but these models are difficult to be investigated analytically and the results are difficult to be tied back to specific biological mechanisms (due to the multitude of parameters that could be responsible for the same results). Among these models, some are continuum and some are discrete, to emphasise the variety of choices. However, for more pedagogical reviews of modelling wound healing we refer the reader to [64, 66]. Also, for each model discussed below we also mention the numerical approaches used to simulate model dynamics (if such simulations were performed) and discuss parameter estimation.

**Microscale dynamics.** The mathematical models for signalling pathways inside cells or between cells during wound healing are relatively complex, as they consider the various interactions between the components of these pathways or between different pathways. One such signalling pathway that is important in wound healing [99] (as well as in cancers [100] and keloids [101], due to its overall importance in cell proliferation) is the MAPK pathway. In the context of coordinated cell movement during wound healing, the study in [102] developed a 7-equations PDE-ODE model for the interaction between the Epithelial Growth Factor (EGF) and the Reactive Oxygen Species (ROS), which can diffuse in the extracellular space and phosphorylate the EGF membrane receptor (EGFR) and further activate the MAPK pathway. The authors recognised that the complexity of their model required an investigation through numerical simulations (using a staggered three-point finite difference scheme for space, and an explicit Euler discretisation for time). Such numerical simulations showed spatial wave-like behaviours in the dynamics of MAPK. The model matched some (but not all) of experimental data, as it could not capture a decrease in the MAPK activity. Among the modelling aspects that were deemed important by the authors in [102] and required further improvement were: (i) the determination of the ROS source function from the data (which was difficult due to conflicting experimental results, some suggesting that this function is negligible, while other suggesting the opposite), and (ii) the modelling of the positive feedback between MAPK signalling

and cell deformation due to bio-mechanical forces resulting from cell contraction/extension during movement towards wound closure.

This type of model that focuses only on microscale (i.e., molecular-level) dynamics could be relevant also for keloids, to investigate changes in those signalling pathways that are dysregulated in keloids vs. normal wounds (since, to our knowledge, such a modelling approach does not exist yet for keloids; see sub-section 3.3).

**Mesoscale dynamics.** One of the earliest models for cell dynamics in wound healing was introduced in [88] to describe the changes in the density of epithelial cells as a result of linear/nonlinear cell migration and mitotic regeneration. Model fitting to available data led to the identification of the cell diffusion coefficient. However, since a one-equation PDE model could not accurately reproduce data showing a decrease in wound radius with respect to time (i.e., could not reproduce a lag phase followed by a linear phase in the reduction of wound radius), the authors in [88] have then considered a two-equations PDE model for the changes in epithelial cell density in response to a generic mitosis-regulating chemical. The authors then performed numerical simulations on a radially-symmetric circular geometry (using, most likely, a finite difference discretisation – although the numerical method was not specified in [88]). Due to a lack of biological details related to wound healing, the simulated solutions were fitted to experimental data on wound radius to investigate the role of a generic chemical, namely inhibitor or activator of cell mitosis. The very good fit between the solution of the new model and the data did not allow the authors to distinguish between the two mitosis mechanisms, but nevertheless supported the view that biochemical regulation of cell mitosis is fundamental to wound healing. We emphasise here that given the very simple models in [88] that involved very few parameters, it was possible to estimate all parameters (linear and nonlinear diffusion coefficients, cell mitotic rate, chemical half-life) using available experimental data. In addition, the authors also estimated the wave speed of epidermal wound healing, which was found to be of the same order of magnitude as in previous experimental studies. This very early study on wound healing suggests that simple 1-equation or 2-equation models with a few number of parameters could be useful also for the exploration of keloid dynamics when more detailed data is not readily available.

In addition to such simple models, the mathematical literature for wound healing includes also more complex models that have been derived to consider various inflammatory aspects. For example, [85] developed an agent-based model for the behaviour of individual epithelial cells in response to the cross-talk between two signalling pathways: EGFR and TGF- $\beta$  (which, as we have seen above, are important not only in wound healing, but also in cancer and keloids). The cells were characterised by intracellular proteins and cell surface receptors (e.g. EGFR, TLR-4 integrins), and could produce diffusible factors (e.g., EGF). A “scratch” was introduced into the computational model to create a wound edge, and cells at this edge were assumed to produce reactive oxygen species (ROS), damage associated molecular patterns (DAMPs), and adenosine triphosphate (ATP) that stimulated more epithelial cells. Note that this model could actually be considered a multiscale model, due to the fact that cell dynamics was controlled by molecular-level processes. The NetLogo algorithm used for numerical simulations encoded various rules for cell migration, as well as rules for

interactions with other cells and with extracellular matrix (ECM). The simulations proposed new testable hypotheses on the crosstalk between TGF- $\beta$  and EGFR (with a possible point of regulation at the receptor tyrosine kinase level) that could lead to scratch healing. However, the simulation results that lead to this hypothesis depended on model parameters, which were “calibrated” in the sense that they were chosen from plausible parameter ranges to produce behaviours similar to the *in vitro* cell migration data and wound closure percentage.

Thus, even if this model was relatively complex (spanning both microscale-mesoscale dynamics) and could not be properly parametrised for quantitative predictions, it was used to explore model behaviour and to generate new theoretical hypotheses related to some biological mechanisms controlling wound healing. Such modelling approaches could be relevant also in the context of keloids, where detailed data is not always available.

**Macroscale dynamics.** [92] considered a 10-equation model for growth and contraction in the dermal layer of the skin during wound healing. The model combined differential equations for changes in tissue deformation and radial stress, balance of linear and angular momentum, a constitutive stress-strain relationship for an incompressible hyperelastic material, as well as the time-evolution equation of a growth tensor. The boundary conditions modelled contraction forces as exerted by fibroblast migration (considered implicitly). Numerical results, obtained using a finite difference discretisation with a forward Euler scheme, investigated changes in stress and growth at various spatial positions, changes in wound radius, total tissue volume and tissue thickness as functions of time. In particular, the simulations reproduced the three healing phases of a wound: the initial recoil; a proliferative and contracting phase; and a final phase characterised by slower wound closure. The authors in [92] have also simulated numerically the remodelling of the tissue after wound closure, to investigate the unclear mechanism by which the dermis fails to close completely. The results showed that over the remodelling period the three components of the stress tensor (i.e., radial stress, circumferential stress and axial stress) approach steady-state values. Local sensitivity analysis was also performed to investigate the effect of four model parameters (radial, circumferential, and axial growth, and shear elastic modulus) on tissue remodelling time, and identified the shear elastic modulus as the parameter with the greatest impact. This bio-mechanical model, which gives access to stress states at every point in the tissue (and at any time), was then used to perform two computational experiments that were difficult to be performed *in vitro/in vivo* to understand the underlying mechanisms: re-wounding (i.e., re-cutting a wound at the same location) and pressure treatment experiments (e.g., pressure therapy via pressure bandages, for the management of hypertrophic scars or keloids [103]). The re-wounding computational experiment allowed the authors to hypothesise that a new (second) wound is characterised by a greater retraction of its edges when dermal tissue is subject to low growth and high contraction, compared to the case when dermal tissue is subjected to high growth and low contraction. The computational experiment for the investigation of the pressure needed for effective wound healing treatment, which is still an open clinical problem (although pressure values are known to vary between 0.001-0.01MPa [92]), suggested that pressure does not seem to impact the

wound radius, but it has an impact on total tissue volume and on tissue thickness. Overall, this study could have potential implications for the macroscale modelling of keloid dynamics, as it is known that keloids can develop only in specific anatomic regions characterised by specific viscoelastic parameters [19], but the bio-mechanical mechanisms behind their development are not fully understood due to difficult experiments.

**Multiscale dynamics & the interplay between inflammation and biomechanics.** Such models combine differential equations for changes in cell densities, sometimes as a result of changes in the concentrations of inflammatory molecules, with constitutive equations for mechanical forces acting on tissue. One of the earliest models on this topic, which focused only on biomechanics, was introduced by [91], who considered a fibroblast cell population that can proliferate logistically, migrate randomly and can also undergo passive convection with the extracellular matrix (ECM), whenever ECM also undergoes convection. Finally, a constitutive equation described the mechanical force balance between traction forces exerted by the cells and forces associated with the properties of ECM. A finite difference method was used to discretise the equations, and optimal parameter values were determined by using a nonlinear least squares regression fit to compare the predicted numerical solution with the experimental data on wound area. Since the behaviour of the model – showing an expansion of the wound boundary followed by a relaxation to its initial position as fibroblasts repopulate the wound – could not explain the features of a real wound (i.e., a first plateau phase in the wound area, followed by an exponential decrease), the authors incorporated implicitly inflammatory responses. Then they investigated numerically different scenarios and observed that an increased steady-state concentration of an inflammation-derived growth factor associated with the wound, which influenced the traction force, the maximum ECM concentration or the cell chemotaxis, could lead to simulations qualitatively consistent with wound healing contraction. The final discussion in [91] also emphasised that the simple incorporation of inflammatory responses can create ambiguity in comparing the numerical results since identical inflammatory mechanisms would not lead to the same chemotactic gradient in different wound geometries. Our discussion in Section 2 also emphasised the complexity of the inflammatory response in wound healing characterised by multiple types of immune cells, cytokines, growth factors, etc. (see also Table 1), which could lead to more ambiguity if simpler models are used. Such relatively simple models that investigate explicitly and/or implicitly the interplay between biomechanics and inflammation could be relevant also for keloids since, as we mentioned in Introduction, this interplay is not fully understood.

A more detailed and more complex multi-scale model for cell-level and tissue-level dynamics was developed in [104] in the context of modelling skin grafts to cover excised burns. To investigate the long-term deformation of dermal tissues and the development of residual stresses within these tissues, the authors in [104] modelled tissue as an isotropic heterogeneous, morphoelastic solid, and inside the tissue the focus was on the spatio-temporal dynamics of fibroblasts, myofibroblasts, collagen molecules and a generic signalling molecule. Partial differential equations for the conservation of cell densities and the concentration of molecules were coupled with a conservation

equation for the linear momentum of the dermal layer, an evolution equation for the infinitesimal strain changes over time, and a visco-elastic constitutive relation for the relationship between the Cauchy stress tensor and the effective strains and displacement velocity gradients. Most of the parameter values used in [104] were estimated or taken directly from previous studies. Numerical simulations using a moving-grid finite-element method have investigated the displacement field as well as the displacement velocity field, for different rates of morphoelastic change and different levels of signaling molecules. The simulations showed a good agreement between the time-evolution of the numerically-calculated wound surface area and some clinical data on the relative surface area of the wound. Therefore, even if molecular-level and cellular-level data (related to concentration of molecules and densities of cells) was missing, the authors have used tissue-level data (related to wound surface) to test the model. Such a modelling approach could be relevant also for keloids, where molecular-level and cellular-level data is not always available, but tissue-level data on keloid spread is available.

### 3.2 Modelling solid tumours

As mentioned in the previous sections, the similarities between keloids and solid tumours suggest that some of the modelling approaches used for tumours could be applied to a certain extent also to keloids. Moreover, since the cancer modelling field is more mature and already reached translational application [105, 106], it can pave the way for keloid translational research.

The development of mathematical models for solid tumours dates back to 1950's [107]. While earlier models focused on the growth of avascular tumour spheroids due to diffusion of nutrients [108–110], later models focused also on the growth of vascular spheroids in response to angiogenesis [111], as well as on tissue invasion and metastasis [112, 113], or on interactions with immune cells in the environment [74]. Some models were discrete [114, 115], others were hybrid [116], while many more models were continuum [110, 111]. Moreover, while the majority of models developed until a decade ago focused on cancer dynamics at one scale (molecular, cell or tissue scale), the last decade has seen the development of multiscale models for cancer invasion into surrounding tissues [117–119]. Among this extremely rich field of cancer modeling, some studies focus on inflammatory and bio-mechanical aspects common to both cancers and keloids: e.g., the roles of TGF- $\beta$  and macrophage populations [120], the importance of collagen fibre orientation [121], or the role of mechanical stimulation [122].

As in the previous section, we now discuss in more detail a few examples of older/newer models for cancer growth and invasion, to emphasise that: (i) older models are simpler (and can be investigated analytically), but they are still relevant to current studies on keloids; and (ii) newer models encode complex inflammatory-mechanical interactions that can be investigated only numerically and not analytically, and the results are difficult to be tied back to specific biological mechanisms (due to the multitude of parameters that could be responsible for the same results). We present both continuum and discrete models, to emphasise the range of modelling approaches that could be used for the same problem. Again, for each model discussed below we mention

briefly the numerical approaches used to simulate model dynamics, and the relevance of the models and/or the results to the keloid problem.

**Microscale dynamics.** In the context of wound healing, in the previous section we have presented a microscale-level model for the interaction between the EGFR and the MAPK pathways. Here, we present a microscale-level model [123] focused on the same EGFR pathway and its interactions with the ERK and AKT signalling pathways in the context of targeted cancer therapies (with cetuximab) for two different gastric cancer cell lines with different mutation patterns, that respond or not to the therapy. The mathematical model, described by an ODE system for the dynamics of 22 variables representing the different components of these pathways (in addition to 5 variables assumed to be conserved), was calibrated using different datasets for time and dose responses of proteins (e.g., EGFR, pEGFR, pERK and pAKT), obtained via quantitative immunoblotting or obtained from published data for different cancer cell lines. The authors first performed a maximum likelihood parameter estimation and a parameter uncertainty analysis that led to the conclusion that less than 50% of parameters were identifiable and therefore they would need more experimental data. Then, to assess the predictive power of the model, the authors in [123] studied causal differences between the cancer cell line responding to cetuximab and the non-responder cell line, and suggested that such differences could be caused by the presence of a mutation (MET) as well as differences in the receptor internalisation and recycling. Finally, they validated the model predicted response to a MET inhibitor. (As a side note, we mention that for the numerical discretisation of this model the authors have probably used a classical finite difference scheme; however, this information was not specified in [123]).

Overall, this particular model shows how new biological hypotheses can be generated by numerical simulations combined with some available molecular-level data. This modelling approach could be relevant also for keloid disorders, where similar signalling pathways seem to be important (but to our knowledge they were not modelled; see also sub-section 3.3 below).

**Mesoscale dynamics.** Most of the published models for tumour growth and spread focus on the dynamics of tumour cells, as well as on their interactions with immune cells involved in inflammation [74, 124], with ECM components [112], etc. In the following we present briefly a discrete model [125] and a continuum model [120] for immune responses to cancer.

A simple agent-based model for immune responses against colorectal tumours was introduced in [125] to investigate the interactions between different individual cells: stem cells, non-stem tumour cells, and cytotoxic T lymphocytes. This computational model (a cellular automata model) encoded various rules for cell dynamics and cell-cell interactions: cell proliferation and death, cell migration, tumour cell killing by immune cells. To parameterise the model, some parameters were taken from previous studies, others were measured by histology, and the remaining parameters were set to some biological plausible values. Then, numerical spatial distribution patterns of immune and tumour cells were compared visually with histological colorectal cancer tissue samples. Numerical simulations showed different types of tumours infiltrated with immune cells, i.e., tumours with few infiltrated immune cells, tumours with large



numbers of infiltrated immune cells, tumours with an immune cell rim around them, or tumours almost eradicated by the immune cell, which matched histological data. Moreover, simulations suggested a possible connection between immune cell numbers and stromal permeability: increase in stromal permeability without an increase in lymphocyte numbers could lead to faster tumour progression, while tumour eradication occurred only in the case with high stromal permeability and high lymphocyte numbers. Therefore, the authors in [125] concluded that the stroma (which arises as a result of post-inflammatory fibrosis) has an important role in tumour regression. This conclusion could be important also for keloid disorders, where the structure of the keloid stroma could impact the infiltration of various immune cells and the subsequent evolution of the keloid.

To account for pro-inflammatory and anti-inflammatory roles of immune responses to cancer, in [120] the authors derived a continuum model (described by 14 ordinary differential equations and 59 parameters) for the time-evolution of colorectal cancer, which considered not only the densities of cytotoxic T lymphocytes but also the densities of naive, helper and regulatory T cells, densities of macrophages, naive and activated dendritic cells, and various cytokines such as  $\text{IFN-}\gamma$  and  $\text{TGF-}\beta$ , carcinogenic cytokines (such as IL-6) and immuno-suppressive agents (such as IL-10). To parameterise the model the authors used clinical data from the Cancer Genome Atlas (TCGA) project of Colon Adenocarcinoma, and estimated the fraction of each immune cell type in each tumour, tumour dimensions, densities of cancer cells and ratio of cancer to immune cells for different clusters of patients' data with similar immune patterns. Sensitivity analysis was then performed to investigate the impact of variability in model parameters on tumour-immune outcomes and identified cancer proliferation and death rates as the most sensitive parameters. Numerical simulations (performed in Python using the "odeint" function that implements the LSODA algorithm) confirmed different patterns of tumour growth based on the immune infiltration level and on the parameters characterising various immune responses in various clusters of patients: fast tumour growth associated with a high density of cytotoxic T cells and dendritic cells and a low growth rate of macrophages; slow tumour growth associated with low densities and growth rates of naive and active dendritic cells and cytotoxic T cells. The authors in [120] also found some contradictory results about the role of macrophage activation rates for different patient clusters: in some clusters a high activation rate leads to a high density of cancer cells, while in other clusters the high activation rate leads to a lower density of cancer cells. These results emphasise the fact that cancer evolution cannot be captured only by a single immune biomarker but rather a combination of tumour and immune biomarkers, which need to be identified from the data (that was limited, given the very large number of parameters). Taking into consideration the complexity of keloid disorders, we suspect that similar aspects should be characterising keloids evolution, and deriving similar complex models for the dynamics of cells and cytokines inside keloid tissues will require a relatively large amount of data for model parametrisation, to be able to distinguish between various biological mechanisms responsible for the observed dynamics.

**Macroscale dynamics.** One of the earlier models for the growth and deformation of avascular tumour spheroids in response to available nutrients was introduced in [126]. This moving-boundary mathematical model was described by an equation for the internal pressure of the spheroid in response to cell division and death, which then led to the motion of cellular material. A second equation described the steady-state level of nutrients at the outer boundary of the spheroid. In addition, it was assumed that (i) cell-cell adhesion led to a surface tension at the outer boundary of the spheroid, which balanced the internal expanding pressure; (ii) cell mass was conserved; (iii) rate of nutrient diffusion through the outer spheroid surface was equal to rate of nutrient consumption inside the spheroid. Analytical results investigated the stability conditions for growing tumours under small environmental perturbations, and showed that these conditions depend on various model parameters related to tumour proliferation, nutrient consumption, and the tension on the spheroid surface. However, no numerical simulations were performed for this simple model (although the authors stated that such simulations should be performed). Note that we decided to mention this model here because keloids are also characterised by moving boundaries that invade the adjacent healthy tissues, and thus such a simple modelling approach could be relevant for keloids as well, by combining it not only with linear/nonlinear stability analysis but also with numerical simulations, to test the predictions of the analytical results about the factors responsible for the deformation of the boundary.

A more complex poro-mechanical model for the dynamics of a tumour spheroid as a result of internal tumour pressure was recently developed in [122]. The model considered the tumour as a porous multiphase system, with the ECM representing a solid scaffold while the interstitial fluid and the tumour cells being modelled as fluid phases. Equations described the mass conservation of these three phases, a momentum conservation equation for the full system, and an advection-diffusion equation for the oxygen within the interstitial fluid (here the oxygen represented the nutrient that limits the growth of tumour cells). Some model parameters were quantified using an experimental protocol called the Cellular Capsule Technology (CCT), where multicellular tumour spheroids were cultured with spherical porous alginate capsules which work as mechanosensor. Other model parameters were taken from previous numerical studies, and their averaged values were set as initial guesses for parameter identification. Finite element simulations were performed using the FEniCS framework [127] for an identified parameter set, to further investigate model dynamics in terms of oxygen profiles, necrotic fraction, interstitial fluid pressure, ECM displacement, as well as tumour cell pressure and saturation. The numerical simulations in [122] showed that the model outputs could predict experimental tumour cells saturation and its necrotic fraction, despite the fact that these quantities were not exploited for model calibration. These simulations also showed that necrotic cells moved from the proliferating rim towards the core of the tumour spheroid.

This 3D poro-mechanical model could be relevant to keloids modelling due to the various phases incorporated here (as keloids are also formed of heterogeneous fibroblast populations across different spatial regions within and around the keloid scars [128]), and the detailed calibration performed for parameter identification and further predictions.

**Multiscale dynamics & the interplay between inflammation and biomechanics.** A hybrid model for cancer growth and spread was introduced in [121] to investigate the spatial structure of the extracellular matrix (ECM), and in particular the density and orientation of collagen fibres, on the evolution of solid cancers. To this end, the authors combined an off-lattice agent based modelling framework *MultiCell-LF* [129] for individual tumour cell dynamics (where each cell was characterised by internal variables such as age, growth, division stage), with a multi-scale continuous framework [130] for the dynamics of the two phases of the extracellular matrix (ECM), i.e., the fibrous phase (described, for example, by collagen and elastin [131]) and non-fibrous phase (described, for example, by proteoglycans and glycoproteins [131]). The coupling of the discrete model with the continuum model was realised through mechanical cell-matrix adhesive forces that acted non-locally in a neighbourhood of each individual cell, and through the re-arrangement of matrix fibres by the cancer cells. The numerical approach connected, at specific time stages, the agent-based algorithm for individual cell dynamics with the finite difference algorithm for the discretisation of the continuous ECM [121]. Numerical simulations were performed with some parameter values taken from the literature and other values guessed. The results showed different cell invasion patterns depending on (i) cell-cell and cell-matrix adhesive forces, (ii) cells sensing radius, and (iii) spatial structure and directionality of fibres in the ECM. A continuum version of this hybrid model, that incorporated also pro-tumour immune responses caused by M2 macrophages was introduced in [132], and later generalised in [133] to include also the M1 macrophages and their re-polarisation into M2 cells as tumour progresses, as well as nutrients in the micro-environment. In contrast to the hybrid model in [121], the continuum models in [132, 133] focused on the changes in the densities of cells (tumour and macrophages) as a result of cellular random movement, directed movement generated by non-local fluxes due to cell-cell and cell-ECM adhesive forces, and as a result of cell proliferation and death. The modelling of the two phases of the ECM was similar as for the hybrid model in [121]. These continuum models (discretised using high-resolution finite volume schemes) were used to explore numerically various biological scenarios that could not be found in the biological literature: from the impact of adhesion between macrophages and tumour cells, or between macrophages and ECM [121]; to the impact of random vs. directed ECM fibres on the invasion speed of tumour cells into the surrounding healthy tissue [121]; and even to the spatial dependency of M1→M2 cell re-polarisation [133]. All these results were only qualitative, as none of these multiscale hybrid or continuum models were parametrised with actual data (due to model complexity and a lack of relevant multi-scale data).

We chose to present here these multi-scale models to emphasise that (a) bio-mechanical forces resulting from cell-cell and cell-ECM interactions (which are relevant also for keloid fibroblasts), could be incorporated in an implicit way into the mathematical models (as opposed to their explicit incorporation in most of the models presented above), and that (b) one could incorporate also detailed remodelling of ECM by cells in the microenvironment (e.g., fibroblasts, macrophages), an aspect very important in keloids that are characterised by the overproduction of collagen.

### 3.3 Modelling keloids

Despite the numerous biological and clinical studies on keloids that have been published since the 1800s [50, 134], very few mathematical/computational models have been proposed to focus exclusively on keloid formation and/or growth. Moreover, since we could not find any models focused exclusively on microscale dynamics, in the following we present all existent keloid models that are focused on mesoscale, macroscale and multiscale dynamics.

**Mesoscale dynamics.** The few models for the temporal and spatio-temporal evolution of cell densities focus mainly on the inflammatory aspects involved in keloid progression [135–137]. For example, starting with some experimental studies [138, 139] on the role of nitric oxide (NO) in wound healing (NO being produced by both fibroblasts and macrophages), [135] proposed an ODE model for the temporal interactions between fibroblasts, collagen, oxygen, nitric oxide (for a simpler model), as well as macrophages, TGF- $\beta$  and blood vessels (for a more complex model). Numerical simulations (using a stiff ODE solver) performed for both models suggested that keloid scarring could be the result of increased NO concentrations (as opposed to hypertrophic scarring that does not seem to be associated with increased NO). In addition, simulations suggested that reducing NO levels in conjunction with surgical excision might lead to normal scars. A different modelling approach was considered in [136, 137], where the authors used the kinetic theory of active particles (KTAP) to propose a model for keloid formation from the perspective of malignant cells. Therefore, their integro-differential model described the interactions between virus particles, immune cells, normal fibroblasts, keloid fibroblasts and malignant cells. All these cells were characterised by an activity variable that described the proliferation ability of fibroblasts, the aggressiveness of virus particles, the activation of immune cells and the progression ability of malignant cells. Numerical simulations (using most likely a finite difference discretisation method – although this was not stated explicitly in [137]) were performed to investigate the behaviour of cell variables in response to changes in different parameters, and with respect to the activity variables describing the phenotypes of these cells [136, 137]. Finally, a very recent study [140] introduced a 2D non-local mathematical model to investigate the interactions between a growth factor (TGF- $\beta$ ), fibroblasts, macrophages and ECM in the context of normal and abnormal wound healing. The model, described by a local PDE for the dynamics of the growth factor, two non-local PDEs for the dynamics of the two cell types (where the bio-mechanical forces caused by cell-cell and cell-ECM adhesion were incorporated implicitly in the non-local terms), and a local ODE for the dynamics of ECM, was discretised using the finite element method. Numerical simulations (where the parameter values were chosen randomly, due to a lack of relevant keloid data) showed the possibility of having both normal and abnormal wound healing. While normal scars were obtained with the assumption of a logistic growth for both fibroblasts and macrophages, abnormal scars were obtained with the assumption of a truncated logistic growth for these cells (i.e., cell growth did not become negative, but stayed constant as soon as cell density increased above the carrying capacity due to non-local cell-cell and cell-ECM adhesive interactions). The abnormal scars were raised (i.e., fibroblasts densities were

above the carrying capacity) and were spread beyond the original wound margins, thus suggesting a hypertrophic or even a keloid scar.

**Macroscale dynamics.** In addition to the above few mathematical models focused on the dynamics of specific cells and aggregations of cells, there are also some computational models of keloids that focus mainly on the constitutive equations that describe the relations between different mechanical forces acting directly on the tissue, the tissue displacement, and the material properties of the tissue (see also the above discussion on computational models for skin) [62, 141–143]. The computational domain representing skin formed of both healthy and keloid tissue (each being characterised by different mechanical parameters), is then discretised using a finite element approach. For example, in [62] the authors used a finite element analysis to investigate the relationship between the keloid growth pattern and the stretching tension, and concluded that (i) keloid centers were regions of low tension, while keloid edges were regions of high tension; (ii) keloid expansion occurred in the direction in which was pulled, and the crab’s claw-shaped invasion pattern was the result of increased stretching tension; (iii) adhesion to subcutaneous hard tissue increased the tension in the keloid. In [141] the authors considered a computational (finite element) model for the simulation of skin tissue and various stress fields in the vicinity of a keloid scar in the presternal area of the body, and used it to predict the likely directions of evolution of this keloid based on the mechanical stress field. In [142] the authors considered a 2D hyperelastic bi-material model of the keloid tissue and the surrounding healthy tissue. A finite element solver was then used to identify the mechanical parameters that characterise soft tissue based on *in vivo* experiments of uni-axial displacement, and to investigate model sensitivity with respect to the displacement field and the reaction force measurement. Since the domain for all these tissue-level models of keloids is defined computationally (in contrast to the previous models for wounds and tumours where the domain – i.e., the ECM – was described mainly by time-evolving equations), a particular aspect that needs to be investigated is the boundary between the keloid scar and the healthy skin, which might require the refinement of the finite element mesh to improve the accuracy of numerical predictions. For a more detailed discussion of this open problem, see section 4.

**Multiscale dynamics & the interplay between inflammation and biomechanics.** One of the earlier mathematical models that was derived to investigate fibro-proliferative wound healing disorders such as hypertrophic scars and keloids was proposed in [144]. The model was described by partial differential equations for the spatio-temporal dynamics of fibroblasts, myofibroblasts, collagen and a generic growth factor. The cells were also assumed to be passively convected by the strained tissue, and thus the equations for changes in the densities of these cells (as a result of inflammation) were coupled with a conservation law for tissue displacement (as a result of mechanical forces). For the numerical simulation of this 1D spatial model, the authors considered a finite difference discretisation based on the method of lines and the Gear’s method [144]. Numerical simulations were performed in the context of normal wound healing and pathological responses characterised by increased fibroblast, myofibroblast, growth factor and collagen levels, using non-dimensionalised parameter values taken from [145] (as both studies [144] and [145] used the same mathematical model).

For the usefulness of these non-dimensionalised parameter values in numerical simulations, as well as the use of same non-dimensional parameter values for different models, see the discussion in Section 3.4. Analytical bifurcation approaches were also considered to investigate the changes in model steady states with respect to various parameters, and a travelling wave analysis was performed to calculate the minimum wave velocity.

### 3.4 Available data and parameter estimation

An important aspect in modelling normal/abnormal wound healing and cancers is related to parameter identification using available data. In the following we start by revisiting some of the models described in more detail in the previous sections, and discussing some approaches used to estimate model parameters and further validate the models. At the end of this section, we discuss the availability of keloid data vs. cancer/wound healing data.

- **Wound healing data.** We mentioned in Section 3.1 that the very first mathematical studies on wound healing [88] have identified some of the parameters characterising wound healing (e.g., cell diffusion coefficient, or speed of the decrease in wound radius) by fitting very simple mathematical models with very few parameters to available data on wound radius, using non-linear least squares regression methods [91]. However, for more detailed mathematical models with more parameters the situation is more complex. For example, to parameterise and validate another (relatively) early modelling study for wound contraction [145], the authors have started by reducing the large number of model parameters (i.e., more than 30) via some simplifying assumptions and non-dimensionalisation. Such an approach was considered because of a scarcity of data available to uniquely identify all model parameters, which was leaving multiple parameter combinations for characterisation [91]. Then the authors in [145] estimated the remaining dimensional model parameters using various published experimental data on fibroblasts random motility rate, their size and doubling time, as well as data on collagen turnover in response to certain levels of TGF- $\beta$ . Sensitivity analysis was performed on model parameters, and the results showed that small variations in parameters whose values were estimated from experimental data or theoretical calculations led to small quantitative changes in the numerical solutions. The numerical results of the model in [145] were further compared with different types of experimental data: the rate of change in the area of circular excisional wounds in rats, and the clearance rate of platelet-derived growth factor (PDGF); and the comparison showed good matching.

We note here that the non-dimensionalised parameter values from [145] were later used in [144]. This was appropriate because both studies used the same mathematical model. In general, non-dimensionalised parameters associated with a model cannot be used in a different model, since the non-dimensionalisation could be based on different combinations of parameters. Nevertheless, many current modelling studies (for both wound healing and cancer) consider parameter values that were published in different models, and thus the results in those studies show only examples of possible model dynamics and cannot be used for model validation and

further clinical predictions.

For the multiscale morphoelastic model introduced in [104] to describe the development of contractures in wound healing (and discussed above in Section 3.1), the authors used dimensional parameter values taken from previous experimental and modelling studies. Again, the numerical results were compared with clinical data on the time evolution of surface areas of skin grafts. A lack of data on cell densities and collagen concentration profiles, did not allow the authors to perform a more in-depth model validation.

- **Cancer data.** In contrast to the relatively scarce wound data, much more data exists to calibrate and validate cancer models. For example, the agent-based model introduced in [125] and presented in Section 3.2 above in the context of cell-level dynamics of solid tumours, was calibrated using human samples of colorectal carcinoma. Digitized histological staining of various tissue sections were used to estimate parameters such as tumour cell proliferation and apoptosis rates, immune cell proliferation and apoptosis rates, and distance to necrotic areas. In addition, *in vitro* immune cell migration experiments were performed to estimate migration speeds. The remaining free parameters (not estimated from data) were set to biologically plausible values. Finally, the simulation results were validated using publicly available histological data on different tissue composition and morphology, from colorectal adenocarcinoma human patients. Note that some parameters (i.e., immune cell numbers, stromal permeability) were varied to assess their impact on the dynamics of these solid tumours. However, no rigorous sensitivity and uncertainty analysis was performed in [125], to investigate the impact of the variability in model parameters (at least for the free parameters).

A continuum mathematical model that was first calibrated and then validated using different cancer data sets was presented in [122] (see the detailed discussion in Section 3.2 above). In this study, a poro-mechanical model for multi-cellular tumour spheroids was calibrated using tumour volume data from mouse colon carcinoma and data on radial displacement of spherical porous alginate capsules surrounding the spheroids. The model was then tested and validated on a different data set for thick and thin encapsulated tumour spheroids. Additional data on cell states (proliferating or dead) inside tumour spheroids was used to quantitatively cross-validate the model. A sensitivity analysis (using Sobol's index) was performed to assess the sensitivity of the finite element solution to model parameters. Then some of the selected parameters were identified (via an optimisation algorithm) from the numerically-calculated sensitivity profiles, and cross-validated on experimental results with thick and thin encapsulated multi-cellular tumour spheroids.

- **Keloid data.** We conclude this discussion by focusing now on keloid data and its use to parameter estimation. First, we note that the cell-level model in [135] had some of the parameters estimated within ranges corresponding to normal scars, while other parameters were given values above the levels assumed to describe normal scars. Due to a lack of cell-level data to validate the model, the simulation results were only qualitative and were used to propose new hypotheses on the role of nitric oxide in keloid scarring.

A similar qualitative approach was considered also in [62], where a finite element

model was built starting from photographs of keloid scars. Stress-related parameters for different tissues (keloid, normal skin and fat) were given some physically-realistic values. Then bio-mechanical parameters were varied to test different hypotheses: from the role of shrinking and stretching on keloid tissue tension, to the impact of keloid adhesion to hard tissue on the overall keloid tissue tension.

**Data availability.** We conclude this discussion by emphasising the huge amount of microscale/mesoscale/macroscale *in vitro* and *in vivo* data related to various aspects of cancer development and evolution, and data related to wound healing, for both animal and human patients. All this data can be used to parametrise the various mathematical models for cancer and wound healing developed over the past decades, with the ultimate goal of making quantitative predictions about the evolution of these medical disorders, and the success of various therapies. However, since keloids are exclusive to humans, there is a lack of keloid data at different scales, which does have an impact on the validation of existent (and future) models for keloids. As we have seen above, some studies attempted to overcome this issue by looking at variables and parameters that have elevated values in keloids compared to normal scars. However, many such parameters have elevated values in both keloids and hypertrophic scars (e.g., increased cellular density, increased deposition of collagen I and III, decreased MMP expression, myofibroblasts become the predominant cell type [9]), which makes it difficult to separate the mechanisms behind each of these two types of disorders. Thus, if we are to make some progress with understanding the formation and evolution of keloids, we require more *in vitro* and *in vivo* keloid data to calibrate and validate *in silico* keloid models.

## 4 Computational and data-related issues

Despite the various modelling approaches summarised in the above sections, there are still many open problems related to model formulation (e.g., the choice of specific functions to describe interactions between model components, the important variables to be considered in the model, etc.), as well as analytical and numerical investigation of wounds/tumours/keloids. There are also open problems related to data availability and model parametrisation. Before mentioning briefly some of these open problems in Sections 4.1 and 4.2 below, we need to return to the models discussed above and to notice that while the simpler earlier models (for wound healing and cancer) focused also on analytical results, the later more complex models focused almost exclusively on numerical results. The complexity of these newer multiscale models makes it sometimes very difficult to investigate them analytically (in terms of pattern formation, bifurcations, travelling waves, etc.). Also the discrete/hybrid models are investigated only computationally, since the analytical approaches to study them still represent open problems. However, since this review did not present in more detail the various analytical approaches considered so far to investigate the various discrete/hybrid/-continuum models for wounds, cancers and keloids, we prefer to focus our discussion on open problems only on some specific issues related to computational and data collection and assimilation approaches.



## 4.1 Numerical issues.

For all studies presented above in more detail we mentioned briefly the numerical method used to discretise them. However, what we could not discuss was the choice of those particular numerical schemes, since the authors do not usually present the reasons behind their choices (e.g., for their convenience, or due to numerical issues encountered when using other types of schemes). As a general conclusion, we can only say that earlier studies as well as studies that modelled the impact of inflammation on wound healing, cancer and keloids, used mainly finite difference schemes for the discretisation of their mathematical models. In contrast, newer studies that modelled various biomechanical aspects of tissues, used the finite element method for the discretisation of their models.

In the following we discuss briefly some numerical issues related to continuum as well as discrete/hybrid mathematical models describing the dynamics of cells and tissues.

**Continuum models.** Regarding the numerical resolution of tissue-level constitutive equations, as well as the resolution of many 2D/3D PDEs for mesoscale/macoscale-level dynamics, the finite element method (FEM) is the way most frequently used. FEM implies, however, specific challenges:

- The gradients of the unknown fields (strain field, chemical gradients, etc.) are discontinuous across the scar/skin or tumour/tissue interface because the physical properties of the keloid/tumour are different from that of the skin.
- Field gradients can be large at the interface between the skin and the scar/tumour.
- The skin/scar interface evolves in time [146–149].
- Computing the velocity field along the interface may be challenging because of difficulties in resolving the gradient fields across the interface [150, 151].

One approach that has been used to address some of these issues is the goal oriented mesh adaptation to improve efficiently the accuracy of the predictions [143, 148]. The recent study in [143] has shown the feasibility of goal oriented mesh adaptation to improve the accuracy of the prediction, in the context of numerical simulations of mechanical responses in a keloid scar. As stated in [143], the Dual Weighted Residual (DWR) method that allowed to compute with high accuracy a quantity of interest related to tissue displacement, was also capable of detecting rather automatically the interface between the healthy skin and the keloid.

**Discrete & hybrid models.** The main challenge of these models is to simulate very large numbers of cells. It is known that a  $1 \text{ cm}^3$  of tissue can contain between  $10^8 - 10^9$  cells, depending on cell diameter [152]. Despite the huge increase in computational power over the last few years, simulating numerically the behaviour of  $10^8 - 10^9$  cells that can interact linearly/non-linearly with other cells in a 3D environment, and which might be characterised by some internal variables (describing, for example, their phenotype or activation state), is still computational prohibitive. In fact, this computational issue led to the development of hybrid models that combined the detailed dynamics of individual cells with some coarse-grained representation of other cells or of the environment (e.g., concentrations of chemicals, densities of extracellular matrix components) [153].

Another issue with some of the discrete models is that the lattice-based models are

at risk with potential grid-based artefacts [115]. For example, the number/position of neighbours with whom a cell can interact, could lead to different results regarding the evolution of an aggregation of cells (fibroblasts, cancer cells, etc.).

We note here that while it would be tempting to replace such discrete models with hybrid and continuum models with well-calibrated parameters, for the purpose of avoiding such computational challenges, such an approach might not always be feasible. First, the current technological advances towards the development of organoids and organs-on-chips [154], as well as the current quest towards the development of digital twins in medicine (see Section 4.2 below) will lead to situations where mathematical models will be derived to reproduce experiments that start with a low number of cells that keep proliferating until they form 3D structures resembling tissues and organs. Such models would then be used to test *in silico* various personalised therapies, to understand how they impact the heterogeneous cells found at various depths inside these 3D biological structures. However, different mathematical studies on collective cell/particle behaviours have shown that numerical simulations with discrete models do not always match numerical simulations obtained with the continuum versions of these discrete models [155, 156]. Second, the calibration of discrete and continuum models with data from different scales (cell scale vs. tissue scale) is still an open problem due to the availability of such data (see discussion below), which could lead to more issues related to the quantitative predictions made by such discrete vs. continuum models.

## 4.2 Multiscale data collection and model parametrisation

Despite the multitude of mathematical models for wound healing and cancer that can be applied (perhaps in slightly modified ways) to investigate keloid dynamics, one of the main challenges of these models is the large number of parameters, sometimes modelling dynamics across multiple scales (molecular, cellular and tissue scales), and the limited data sets. For example, in [104] the authors validated the tissue-level component of their multi-scale morphoelastic model using clinical data for the time-evolution of wound surface area, but could not find data on cell densities or collagen concentrations to validate also the cell-level components of their model. Such a model validation using different data sets is extremely important due to the very large numbers of parameters: e.g., 35 parameters in [104]. However, even if one manages to estimate some of these parameters in a multiscale model using different data sets (usually obtained through different experiments on different types of cells and molecules), there is still the problem of investigating the uncertainty in model outcomes to parameters across multiple scales. [157] presented an overview of various single-scale sensitivity analysis methods and approaches that could be used for multiscale models (i.e., all-in-one sensitivity approaches, intra/inter-compartmental sensitivity approaches and hierarchical sensitivity approaches), while discussing the strong and weak points of each approach.

The latest experimental developments towards the use of microfluidics and lab-on-a-chip technologies to establish microenvironments to study wound healing [158], cancer [159] and other diseases such as keloids, will generate much more single-scale and multi-scale data. These technologies enable researchers to vary local molecular,

cellular and environmental parameters in a controlled way, which can then be replicated by the mathematical and computational modelling approaches to match the experimental settings through the development of “digital twins” (DT) [160]. The current push for the development of DT for precision medicine [161] will impact also keloids research (especially due to the lack of appropriate murine models for keloids, as discussed above). This will eventually allow the use of real-time single-scale and multi-scale keloids data to parametrise multiscale models for keloid dynamics. Nevertheless, the computational challenges discussed above will have to be solved before the development of such DT.

## 5 Summary and Conclusions

Keloids are unique human disorders, as no other animal species can develop naturally such keloid scars. This particular aspect has impacted the lack of current treatments for these keloid disorders. However, since keloids display many molecular and cellular characteristics similar to cancers and wound healing, it is normal to look at this other two disorders when trying to understand keloid evolution. Moreover, if *in vitro* and/or *in vivo* experiments are not possible, one can still use *in silico* approaches to propose and test various biological hypotheses.

The goal of this review was to present the state-of-the art in modelling and simulations of keloid disorders. To this end, we started with a review of the biology of these disorders while emphasising the similarities and differences at molecular, cellular and tissue scales between keloids, wound healing, and cancer. Moreover, since there is a huge amount of theoretical (mathematical and computational) studies for both wound healing and cancer, it was normal to consider the possibility of such theoretical approaches to drive keloid research further. Thus, in Sections 3.1 and 3.2 we started by listing a multitude of studies for wound healing and cancer, to emphasise the very active research in these two areas; then we discussed in more detail some examples of models developed in these studies, which could be relevant also to keloids. Our discussion of these specific models aimed to present both older and newer models, so we could (i) emphasise the simplicity of older models (that could be investigated also analytically) vs. the complexity of newer models (that are investigated mainly numerically); and (ii) emphasise the lack of multiscale data to parametrise all these models, especially the more complex ones. By stressing the advantages and disadvantages of simpler vs. complex models in cancer and wound healing, we aimed to put into perspective the new mathematical models that would have to be developed for keloids. More precisely, by presenting some validated models that could be used for quantitative predictions in cancer/wound healing, as well as models that could be used only for qualitative predictions, we aimed to show the reader the the range of modelling approaches that one can consider. Then, in Section 3.3 we presented briefly most of the mathematical/computational models we found on keloids. The literature review we did in this section showed that at this moment there are more mathematical/computational approaches to investigate tissue-level keloids dynamics, compared to cell-level dynamics. This is in contrast to the modelling studies on wounds and cancers, where cell-level dynamics dominates. This trend can probably be explained by the relatively

few *in vitro* experiments and almost a lack of *in vivo* experiments on keloids, which can be used to parametrise mathematical models for cell-level dynamics.

To conclude, we believe that clinical progress with this keloid disorder (as well as with other similar human-specific fibro-proliferative disorders [162]) can be ensured only through the development of new single-scale cell-level mathematical models and/or multi-scale cell-level/tissue-level mathematical models for keloids, combined with the generation of experimental data to parametrise all these models.

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