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Modelling Keloids Dynamics: A Brief Review and New Mathematical Perspectives

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ABSTRACT

The keloids are fibroproliferative disorders described by an 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), the experimental *in vivo*/*in vitro* research has not lead 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. Since 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 the keloids. We conclude by discussing the open problems and 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, 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" (WHO, 2022). 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 (Tan et al., 2019). 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 (Limandjaja et al., 2020a). Keloids may cause pain and pruritus, and seriously affect patient quality of life when they are located in visible areas (Butler et al., 2008). Keloids may result from different skin injuries, including surgery, burns, trauma, piercing, and folliculitis, though their location appears mainly confined to chest, shoulders, neck and ears (Ogawa, 2011). Today, the lack of effective treatments clearly reflects our poor understanding of keloid pathogenesis, though keloid histopathology has been extensively described in the past decades (Jumper et al., 2015). Despite this, keloid aetiology and pathogenesis remain largely unknown.

Since keloid disorders are exclusive to humans, existent *in vivo* and *in vitro* studies that are based on different animals are not quite relevant to humans (as skin physiology, immunology and cell and tissue biomechanics are different between animals and humans (Limandjaja et al., 2020a)). Therefore, new *in vitro* human biological models are required to advance the research in this field (Suttho et al., 2017). 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 the keloids (Limandjaja et al., 2021; Tan et al., 2019)), but they are not usually 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 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 (Limandjaja et al., 2020b; Bayat et al., 2005; Limandjaja et al., 2021). These hypotheses, which touch on inflammation and/or bio-mechanics (Limandjaja et al., 2020a), range from the keloid triad hypothesis (which encompasses three risk factors that could trigger the keloids, namely genetics, inflammation and external factors such as surgery), to the incomplete malignancy hypothesis (suggesting that the keloids could be a type of incomplete malignancy that has undergone only a few tumorigenic changes), the viral hypothesis (suggesting that the keloids could be triggered by a normally quiescent, unknown virus), the stiffness gap hypothesis (suggesting

that the keloids could be the result of an enlarged gap between the ECM stiffness and cellular stiffness), the immuno-nutritional hypothesis (suggesting that keloids could be the result of nutritional imbalance that promotes prolonged inflammation), or the metabolic hypothesis (suggesting that keloids could be the result of an increased metabolic activity of fibroblasts). We mentioned these different hypotheses here since some of them have been investigated though 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 (Agbenorkul et al., 1995), since we aim to emphasise the importance of understanding the connection between these two aspects.

Inflammatory aspects related to keloids. In the middle of the "keloid triad" 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 (Suttho et al., 2017; Shi et al., 2019) and a reduced apoptosis rate (Lu et al., 2007; Zhou et al., 2020). Moreover, KFs are more responsive to growth factors activation (i.e., by TGF-β1 and PDGF) than their normal counterparts (Babu et al., 1992; Bettinger et al., 1996; Haisa et al., 1994), and this leads to higher production of type I and III collagens (the ratio I/III in keloid is 17:1 versus 5:1 in normal skin) and extracellular matrix (ECM) accumulation (Xue and Jackson, 2015). During wound healing, ECM degradation and remodelling is controlled by a family of enzymes called matrix metalloproteinases (MMPs). MMPs are synthesised by fibroblasts, keratinocytes and macrophages, and their activity is regulated by the tissue inhibitors of matrix metalloproteinase (TIMPs). Dysregulation of such MMP/TIMP equilibrium may underlie 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 (Xue and Jackson, 2015; Ulrich et al., 2010; Aoki et al., 2014). The TGF-β1/Smad signalling pathway is pivotal in the process of keloid fibrosis. TGF-β1 regulates fibroblast-to-myofibroblast conversion, α-SMA expression and collagen synthesis during the development of fibrosis. TGF-β1 is found in higher quantity in keloid than in normal scar (Desmouliére et al., 1993; Jagadeesan and Bayat, 2007; Carthy, 2018). Accordingly, a variety of therapeutic strategies (drugs, siRNA, shRNA, miRNA, etc) have been designed to target the TGF-β/Smad signalling pathway in order to interfere with fibroblast-mediated keloid progression (Zhang et al., 2020).

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 (Limandjaja et al., 2020a; Wang et al., 2020); see also Table 1. All these inflammatory cells that have been found in higher numbers in keloids (Limandjaja et al., 2020a), are able to cross-talk with the KF all along the abnormal healing process via different cytokines (e.g., IL-4, IL-6, IL-10, IFN-γ), chemokines (MCP-1) and growth factors (e.g., TGFβ, VEGF, bFGF) (Wang et al., 2020).

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 (Ogawa, 2011). In (Ogawa, 2011; Ogawa et al., 2012) 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 regions. Moreover, the resulting keloid tissues have different mechanical properties compared to the healthy skin tissues: lower extensibility and higher rigidity for the keloids (Chambert et al., 2019). In addition, mechanical forces at the tissue level, can modulate inflammatory cellular behaviours via the activation of

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	(Limandjaja et al., 2020a)
Myofibroblasts	↑cell numbers	(Limandjaja et al., 2020a)
Keratinocytes	↑cell numbers	(Limandjaja et al., 2020a)
Macrophages	↑cell numbers (in particular M2 cells)	(Limandjaja et al., 2020a)
T cells	↑cell numbers	(Limandjaja et al., 2020a)
Mast cells	↑cell numbers	(Limandjaja et al., 2020a)
Molecules	**Behaviour during keloid evolution**	**References**
Cytokines	↑IL-6; ↑IL-8; ↑IL-18; ↑TNF-α ↓IL-10	(Shan et al., 2022; Wang et al., 2020)
Growth factors	↑TGF-β ; ↑PDGF; ↑VEGF	(Wang et al., 2020; Desmouliére et al., 1993; Niessen et al., 1999; Fujiwara et al., 2005)
Chemokines and their receptors	↑CCR1; ↓CCR7; ↑CXCL9; ↑MCP-1	(Shan et al., 2022; Wang et al., 2020)
Collagen	↑type-I:type-III ratio	(Abergel et al., 1985)

mechanoreceptors on fibroblasts and immune cells, which can further increase cells' roles on scar formation and spread (Huang and Ogawa, 2022). Some of the most studied cellular mechanoreceptors are the integrins (at cell-ECM junctions) and cadherins (at cell-cell junctions), which are known to play an important role in wound healing and fibrosis (Kuehlmann et al., 2020). In response to mechanoreceptors activation, 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 (Kuehlmann et al., 2020) or the TGF-β/Smad pathway mentioned above (Huang and Ogawa, 2022; Kuehlmann et al., 2020). Since the mechanotransduction process has a big impact on cell proliferation, survival, differentiation or motility, a recent study in (Zhou et al., 2022) hypothesised an important role for the mechanical microenvironment on the 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 (Li et al., 2017; Xu et al., 2020).

Before discussing the mathematical approaches applied (or those that could be applied) to modelling keloids disorders, we mention briefly some of the differences and similarities between the keloids and the scars (either normal or abnormal), and between the keloids and the cancers. For more in-depth comparisons 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 for cancer growth and invasion of 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 Dvorak (1986) suggested that tumours are "wounds that will not heal". Also for this reason, the type and structure of the 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 different studies investigate the keloids from the perspective of abnormal scars (Limandjaja et al., 2021), in the following we mention briefly some of the differences and similarities between the keloids and the hypertropic scars (the two types of abnormals scars); for a more detailed comparison see (Limandjaja et al., 2021).

- *Similarities.* Both hypertrophic and keloid scars are fibroproliferative disorders characterised by excessive and disorganised production ECM (in particular increased collagen type-I production), as a result of abnormal proliferation and differentiation of fibroblasts (Wang et al., 2020; Limandjaja et al., 2021). 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-β and VEGF levels (Limandjaja et al., 2021). They are also characterised by increased levels of some matrix metalloproteinases, such as the MMP-2, and increased levels of MMP inhibitors TIMP-1 and TIMP-2 (Limandjaja et al., 2021). For more similarities see (Limandjaja et al., 2021).
- *Differences.* There are various differences between the scars (in particular hypertrophic scars) and keloids in terms of clinical presentation, epidemiology, histologic findings (Ghazawi et al., 2018). For example, the hypertrophic scars do not exceed the original injury site, while the keloid scars grow and invade adjacent tissue, beyond the original injury site. Moreover, while the hypertrophic scars could regress spontaneously over time, this does not happen for the keloids (Wang et al., 2020; Bran et al., 2009). Also, the hypertrophic scars showed lower levels of hypoxia, as opposed to the keloids that are characterised by increased hypoxia (Vincent et al., 2008). Moreover, as mentioned above, the keloids usually develop at certain anatomical sites (e.g., chest, shoulder; characterised by certain mechanical properties) and are not associated with skin contracture, while the hypertrophic scars occur more commonly at joints and are associated with skin contracture. In regard to the keloid 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) (Tan et al., 2019), or even hypertrophic scars dominated by type-III collagen (Bran et al., 2009). For more differences see (Limandjaja et al., 2021; Bran et al., 2009).

Differences and similarities between keloids and cancers. Since various studies mentioned the importance of investigating the keloids from the perspective of benign cancers (Tan et al., 2019; Kimura et al., 2014), 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 (Hajdu, 2011; Lonardo et al., 2015). The word "keloid" seems to have been coined by Alibert (1806) and/or Addison (1854), who described the resemblance of this disease with the crab's claws, while acknowledging its tissue-invasive similarities with cancer.

- *Similarities.* Both cancers and keloids show hyper-proliferative cell behaviours, and cell invasion into the adjacent surrounding healthy tissue (in patterns that resemble crabs' claws), which are fuelled by alterations in cytokine/growth factors levels Tan et al. (2019). Neither cancers nor keloids can regress spontaneously, and their surgical excision is followed by a relapse. Same as tumours, the keloids are vascularised through angiogenesis Tan et al. (2019). Moreover, both keloid fibroblasts and cancer cells seem to use similar bioenergetics based mainly on glycolysis (as opposed to non-keloid fibroblasts that use mainly oxidative phosphorylation) (Vincent et al., 2008). In fact, due to their similar clinical presentations, in some cases the keloids have been misdiagnosed as skin tumours, while in other cases the tumours have been misdiagnosed as keloids (Kimura et al., 2014). In addition to the clinical similarities between keloids and some specific skin tumours (e.g., dermato

fibrosarcoma protuberans, keloidal dermatofibroma (Kanitakis, 2013), keloidal basal cell carcinoma and keloidal atypical fibroxanthom (Tongdee et al., 2016)) a few studies reported that abnormal levels of cytokines and (keloid-promoting) growth factors that are associated with cancers, might induce also keloids development, leading to the question of whether the keloids could be seen as a para-neoplastic phenomenon (He et al., 2011). This question is also supported by the fact that the keloids can exhibit to a large extent the hallmarks of cancer (Tan et al., 2019): sustained proliferative signalling, evasion of growth suppressors, angiogenesis, resisting cell death. Moreover, the keloids can respond to a certain extent to cancer treatments such as radiotherapy, chemotherapy and targeted immunotherapy and virotherapy (Kim, 2021; Tan et al., 2019).

- *Differences.* The main differences between keloids and cancers are that (i) the keloids cannot occur spontaneously and cannot metastasise (He et al., 2011), and (ii) they are specific to humans, no other animal species developing naturally keloid tissues (Marttala et al., 2016). In addition to this there are the similarities between the keloids and scars mentioned above, which only emphasise the differences between the keloids and cancers and contribute to the usual classification of keloids as abnormal scars and not as neoplasms (Tan et al., 2019).

3 CURRENT MATHEMATICAL MODELLING APPROACHES

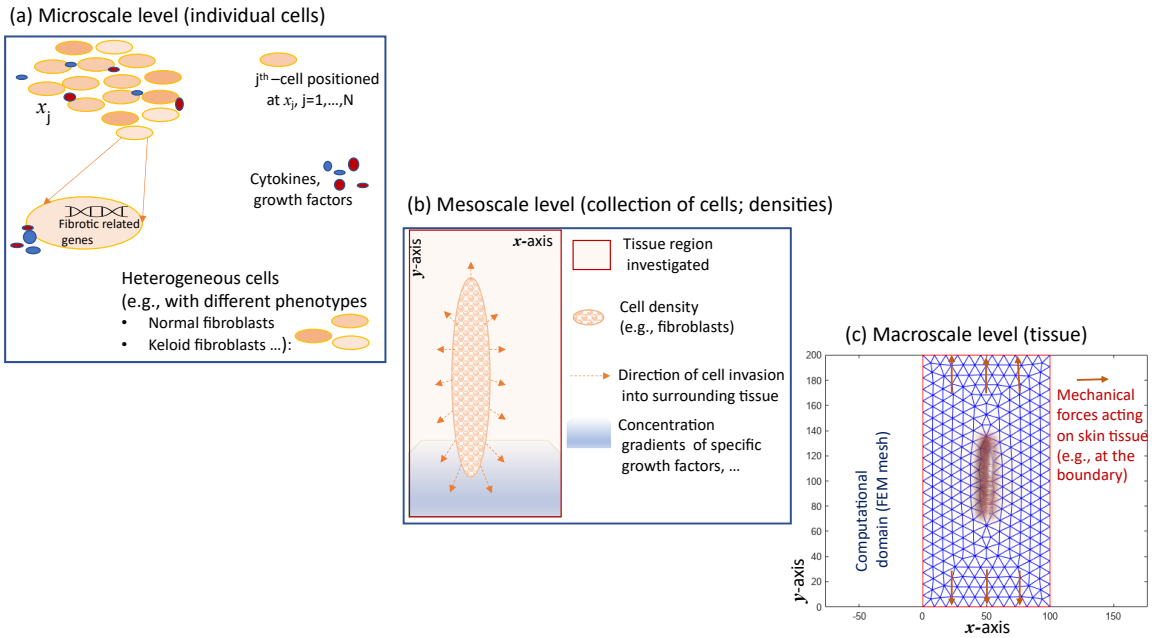

Figure 1. Keloid dynamics can be investigated at different spatial scales: (a) *microscopic level:* focus on the kinetics of individual cells, or interactions between individual cells via cytokines/growth factors; (b) *mesoscopic level:* focus on the evolution of densities of cells, and their interactions with gradients of cytokines/growth factors; (c) *macroscopic level:* focus on the skin tissue, and how the mechanical forces on the skin impact the evolution of the whole keloid.

Since the biological processes involved in keloid disorders are similar to those characterising benign cancers and wound healing, 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 the keloids 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 1): (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; (d) *computational models* that focus mostly on cell and tissue bio-mechanics. The discrete, continuum and hybrid models are usually described by ordinary differential equations (ODEs), partial differential equations (PDEs) or integro-differential equations (IDEs) for the changes in the position of cells (or densities of cells), their differentiation, proliferation, death, etc., which are then simulated numerically. Some discrete models (e.g., cellular automata models) avoid the use of equations for changes in cell positions/velocities by focusing on the computational rules that govern such changes in one cell following interactions with other cells, or due to cell death, proliferation, etc. These cell behavioural rules are then implemented directly into the numerical code, and so they can be considered as computational models. Other computational models consider fixed cell densities inside tissues and focus on mechanical forces acting on these tissues (forces usually described by constitutive equations).

Due to the huge amount of mathematical and computational modelling of both wound healing and cancers (for some reviews we refer the reader to Arciero and Swingdon (2013); Buganza Tepole and Kuhl (2013); Flegg et al. (2015); Jorgensen and Sanders (2016); Sherratt and Dallon (2002); Thackham et al. (2009); Ziraldo et al. (2013), as well as to Altrock et al. (2015); Bekisz and Geris (2020); Chen et al. (2020); Eftimie et al. (2011); Enderling and Chaplain (2014); Yin et al. (2019) 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 cell-level dynamics (i.e., models described by ODEs, PDEs for changes in the number or densities of cells) and mathematical/computational models for tissue-level dynamics (i.e., models usually described by constitutive equations for various mechanical forces acting on tissues).

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 Buttenschön and Edelstein-Keshet (2020); Camley and Rappel (2017); Chen et al. (2020); Deutsch et al. (2020); Maini and Baker (2014) and the references therein. There are also even more studies on the collective movement of animals in ecological settings (Abaid et al., 2022). However, to keep this review focused, here we focus exclusively on models developed explicitly for wound healing, for cancer, 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 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 the angiogenesis (Pettet et al., 1996; Gaffney et al., 2002) and inflammatory aspects related to wound healing (Mi et al., 2007; Stern et al., 2012; Ziraldo et al., 2013; Vodovotz et al., 2004; Waugh and Sherratt, 2006), others focus on generic interactions between cells and extracellular matrix (Sherratt and Murray, 1990; Dallon et al., 1999, 2000) and/or on the bio-mechanical aspects related to wound healing (Tranquillo and Murray, 1993; Bowden et al., 2016; Maroudas-Sacks and Zemel, 2018) without considering the impact of inflammation, and many other models combine both inflammatory and mechanical aspects (Cumming et al., 2010; Tepole and Kuhl, 2016; Koppenol et al.,

2017). Most of these models are continuum, but there are also a few discrete models (Mi et al., 2007; Stern et al., 2012) and some hybrid discrete-continuum models (Dallon et al., 1999; McDougall et al., 2006). Moreover, while most of these wound healing models are local, there are also a few non-local models (Webb, 2022) that incorporate the long-range (i.e., almost tissue-level) effects of mechanical forces acting on the 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; and (ii) newer models encode inflammatory-mechanical interactions but these are still difficult to understand due to model complexity. However, for more pedagogical reviews of modelling wound healing we refer the reader to Arciero and Swingdon (2013); Flegg et al. (2015).

Cell-level dynamics. One of the earliest models for cell dynamics in wound healing was introduced by (Sherratt and Murray, 1990) to describe the changes in the density of epithelial cells as a result of linear/nonlinear cell migration and mitotic regeneration. Since a one-equation PDE model could not accurately reproduce the data about the decrease in wound radius with respect to time, the authors in (Sherratt and Murray, 1990) have then considered a two-equations PDE model for the changes in epithelial cell density in response to a generic mitosis-regulating chemical. Due to a lack of biological details related to wound healing, numerical simulations combined with experimental data on wound radius were then performed to investigate the role of the generic chemical: inhibitor or activator of cell mitosis. We note that given the very simple model, which involved very few parameters, the authors have estimated these parameters (e.g., linear and nonlinear diffusion coefficients, cell mitotic rate, half-life of the chemical) using available experimental data. They also estimated from the wave speed of epidermal wound healing.

A very recent mathematical study (Webb, 2022) also used a one-equation model for the collective movement of cells to investigate the impact of cell-cell adhesion and cells sensing radius on the incomplete wound closure. The cell-cell adhesion was implemented (using the same modelling framework introduced by Armstrong et al. (2006)) via non-local terms describing the tissue-level effects of these adhesive interactions on the surrounding cells. Numerical simulations performed with this nonlocal advection-diffusion-reaction model showed the existence of a critical value of the sensing radius and a critical interval for the adhesion force that ensured complete wound closure. Reducing the adhesion force below this interval allowed for wound closure for every value of the sensing radius. This theoretical study did not used data to parametrise the model.

More complex models have been derived to consider various inflammatory aspects involved in wound healing. For example, Stern et al. (2012) developed a discrete model for the movement of individual epithelial cells in response to the cross-talk between two signalling pathways EGFR and TGF-β. The cells were characterised by intracellular proteins and cell surface receptors (e.g. EGFR, TLR-4 integrins), and they can produce diffusible factors (e.g., EGF). A "scratch" was introduced into the 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) which stimulated more epithelial cells. Note that this model could actually be considered a multiscale model, due to the dynamics of cells - at cell level - that is controlled by molecular-level processes. Numerical simulations proposed new testable hypotheses on the crosstalk between TGF-β and EGFR (with a possible point of regulation at the receptor tyrosine kinase level) that could lead to scratch healing. The simulation results that lead to this hypothesis depended on model parameters, which were "calibrated" in the sense that they were chosen from the plausible parameters to produce behaviours similar to the in vitro cell migration data and wound closure percentage.

Tissue-level dynamics. Bowden et al. (2016) considered a 10-equations model for growth and contraction in the dermal layer of the skin during wound healing. The model combines 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 investigated the changes in stress and growth at various spatial positions, changes in wound radius, total tissue volume and tissue thickness as functions of time. 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.

Multiscale cell-level and tissue-level dynamics. These types of models combine differential equations for changes in cell densities with constitutive equations for mechanical forces acting on the tissue. One of the earliest models on this topic was introduced by Tranquillo and Murray (1993), 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 is which 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. Since the behaviour of the model – showing an expansion of the wound boundary followed by relaxation to its initial position as fibroblast 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. To this end, they investigated numerically different scenarios and observed that an increased steady-state concentration of an inflammation-derived growth factor associated with the wound, that influences 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 Tranquillo and Murray (1993) also emphasised that the simple incorporation of the inflammatory responses can create ambiguity in comparing the 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.

A more detailed model was introduced by Koppenol et al. (2017) to investigate numerically the formation and subsequent regression of hypertrophic scar tissue following dermal wounding. The authors used a constitutive stress-strain equation for the explicit modelling of the dermal layer of the skin as a heterogeneous isotropic and compressible neo-Hookean solid. In addition, they used partial-differential equations for the spatio-temporal evolution of a generic fibroblast population, a myofibroblast population, and a generic signalling molecule produced and degraded by both fibroblasts and myofibroblasts. The collagen molecules are produced by both fibroblasts and myofibroblasts (and this production rate is enhanced by the signalling molecule), but collagen does not move as it is assumed to be attached instantly to the ECM. Finite element numerical simulations and their comparison with clinical measurements suggested that a relatively high apoptosis rate of myofibroblasts can lead to normal scar tissue, while a low apoptosis rate can lead to hypertrophic scar tissue. However, the results depended strongly on the parameter models: some chosen from the published biological and mathematical literature (even if those experimental studies were performed under different conditions), some resulting from other parameter values, and some guessed. Therefore the numerical results, however interesting and informative in terms of new possible experiments, were valid only for those parameter sets.

3.2 Modelling solid cancers

The development of mathematical models for solid cancers dates back to 1950's (Araujo and McElwain, 2004). While earlier models focused on the mechanisms explaining the growth of avascular tumour spheroids due to diffusion of nutrients in the environment (Thomlinson and Gray, 1955; Laird et al., 1965; Greenspan, 1972, 1976; Roose et al., 2007), later models focused also on the growth of vascular spheroids in response to angiogenesis (Chaplain et al., 2006), as well as on tissue invasion and metastasis (Anderson et al., 2000; Quaranta et al., 2008; Sfakianakis and Chaplain, 2021), interactions with the immune cells in the environment (Eftimie et al., 2011), or cancer response to treatments (Yankeelov et al., 2013). Some of these models are discrete (Macnamara, 2021; Metzcar et al., 2019), others are hybrid (Rejniak and Anderson, 2011), and many more models are continuum (Chaplain et al., 2006; Roose et al., 2007). Moreover, while the great 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 numerous multiscale models for cancer invasion into the surrounding tissues (Quaranta et al., 2008; Stolarska et al., 2009; Diesboeck et al., 2011).

Again, as in the previous section, we 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 so can be investigated analytically), but they are still relevant to current studies; and (ii) newer models encode inflammatory-mechanical interactions, but these are still difficult to understand due to model complexity (including also large numbers of parameters that need to be estimated). For many more models for tumour growth, invasion and interactions with other components of the tumour microenvironment (including stromal and inflammatory cells) we refer the reader to the reviews in Araujo and McElwain (2004); Chaplain et al. (2006); Anderson et al. (2000); Quaranta et al. (2008); Eftimie et al. (2011); Sfakianakis and Chaplain (2021); Yankeelov et al. (2013); Macnamara (2021); Stolarska et al. (2009); Diesboeck et al. (2011); Rejniak and Anderson (2011); Friedman (2004); Metzcar et al. (2019) and references therein.

Cell-level dynamics. The last few decades have seen the development of a large variety of mathematical models describing the temporal and spatio-temporal evolution of tumour cell populations, as well as its interactions with other cell densities: e.g., various immune cells involved in inflammation (Eftimie and Barelle, 2021; Eftimie et al., 2011), endothelial cells involved in angiogenesis (Chaplain et al., 2006), extracellular matrix components (Anderson et al., 2000). In the following we present two models, a discrete and a continuum model for immune responses to cancer.

An agent-based model for immune responses against colorectal tumours was introduced in Kather et al. (2017) to investigate the interactions between stem and non-stem tumour cells, and T lymphocytes. The immune cells that have killed successfully five time are assumed to lead to the increase in tumour stroma, which then reduces cell migration. To parametrise the model, some parameters were taken from previous studies, others were measured histologically, and the remaining parameters were set to some biologically plausible values. Then the numerical spatial distribution patterns of immune and tumour cells were compared visually with histological colorectal cancer tissue samples. Numerical simulations showed different types of tumour infiltrated with immune cells, and suggested a possible connection between immune cell numbers and stromal permeability: increase in stromal permeability without an increase in lymphocytes led to faster tumour progression.

The inflammatory immune responses to cancer do not include only lymphocytes but also many more types of immune cells, some triggering inflammation others reducing inflammation. In Kirshtein et al. (2020) the authors have derived a continuum model for immune responses to colorectal cancer (described

by ordinary differential equations), 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 IFN-γ and TGF-β, carcinogenic cytokines (such as IL-6, IL17, IL-21) and immuno-suppressive agents (such as IL-10). To parametrise 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 were used to investigate the temporal dynamics of cells in colorectal tumours, and confirmed different patterns of tumour growth based on the immune infiltration level. The simulations also showed that some immune-related parameters, such as the macrophage activation rates, have different effects on tumour growth depending on immune infiltration level.

Tissue-level dynamics. One of the earlier models for the dynamics (and deformation) of avascular tumour spheroids in response to available nutrients was introduced by Greenspan (1976). 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 leads to the motion of cellular material. A second equation described the steady-state level of nutrients at the outer boundary of the tumour spheroid. In addition, it was assumed that (i) cell-cell adhesion led to a surface tension at the outer boundary of the spheroid proportional to the mean curvature of the boundary, tension which balanced the internal expanding pressure; (ii) cell mass is conserved; (iii) the rate of nutrient diffusion through the outer spheroid surface is equal to the rate of nutrient consumption inside the spheroid. Analytical results for this model investigated the stability conditions for the growing tumours, i.e., the conditions (on tumour spheroid radius, nutrient level,) for which the tumour preserves its "almost-spherical" shape under small environmental perturbations and does not desegregate into smaller cell colonies. No numerical simulations were performed for this simple model.

A more complex poro-mechanical model for the dynamics of a tumour spheroid as a result of internal tumour pressure was recently developed by Urcun et al. (2021). 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 multi-cellular tumour spheroids were cultured with spherical porous alginate capsules which work as mechanosensor. Other model parameters were taken from multiple previous numerical studies, and their averaged values were set as initial guesses for parameter identification. A sensitivity analysis (using Sobol's index) was performed to asses the sensitivity of the finite element solution to the parameters. Then some of the selected parameters were identified (via an optimisation algorithm) from the sensitivity profiles, and cross-validated on experimental results with thick and thin encapsulated multi-cellular tumour spheroids. Finally, numerical simulations were performed with the identified parameter set to investigate model dynamics in terms of oxygen profiles, necrotic fraction, interstitial fluid pressure, ECM displacement, as well as tumour cell pressure and saturation.

Multiscale cell-level and tissue-level dynamics. A hybrid model for cancer growth and spread was introduced in Suveges et al. (2021) 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* (Kim et al., 2014) for individual tumour cell dynamics, with a multi-scale continuous framework (Shuttleworth and Trucu, 2019) for the dynamics of the two phases of the extracellular matrix (ECM) (i.e., the fibrous and non-fibrous phases). The coupling of the discrete model with the continuous model was realised through mechanical cell-matrix adhesive forces that act non-locally in a neighbourhood of each individual cells, and the re-arrangement of matrix fibres by the cancer cells. Note that the density and directionality of the ECM fibre phase (as well as the non-fibres phase) are specified across the whole spatial domain representing the tissue. 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 the cell-cell and cell-matrix adhesive forces, cells sensing radius, as well as on the spatial structure and directionality of fibres in the ECM. The complexity and multiscale aspect of this particular model makes it difficult to be parametrised.

A different type of hybrid model was developed by Kim et al. (2007) to describe the growth of a tumour spheroid. The model considered a discrete representations of cells in the outer region of the spheroid, where the majority of growth and cell division occurred, and a continuum constitutive description of cells in the quiescent and necrotic regions of the tumour, and a continuum description of the extracellular matrix (i.e., surrounding gel). Finally, the dynamics of two nutrients, glucose and oxygen, was described by reaction-diffusion equations. The outside gel and the interior (quiescent and necrotic) tumour regions were assumed to be viscoelastic with different material properties, and their behaviour was described by constitutive equations. While these constitutive equations were solved using the finite element method with a triangular mesh, the reaction-diffusion equations for the nutrients were solved using an alternating-direction implicit finite-difference scheme on a regular grid. In regard to the discrete cells, they were assumed to be subjected to various forces caused by cell-cell and cell-ECM adhesion (which could deform the cells), could move with a specific velocity, and could undergo proliferation depending on the nutrient and stress levels. The connection between the regions with discrete cells and continuum cell fields was computed numerically by first determining the location, magnitude and direction of force exerted by individual cells onto the boundary of the continuum fields. Then finite element interpolation functions were used to distribute point forces from individual cells (at the boundary of the continuum field) onto the nodes of the finite elements (that cover the continuum field). This nodal force distribution was used as a boundary condition for the stress distribution in the continuum continuum regions of the domain (Kim et al., 2007). The continuum regions were also updated through the generations of a new mesh, to account for discrete proliferating cells not receiving enough nutrients and thus becoming quiescent and entering the continuum field. Numerical simulations of this model investigated the temporal changes in the size of different regions of the tumour, as well as the impact of gel stiffness on tumour growth rates. Again, the model was not parametrised using experimental data.

3.3 Modelling keloids

Despite the numerous biological and clinical studies on keloids that have been published since 1800s (Alibert, 1806; Addison, 1854), very few mathematical/computational models have been proposed to focus exclusively on keloid formation and/or growth. We briefly mention all these models below.

Cell-level dynamics. The few models for the temporal and spatio-temporal evolution of cell densities focus mainly on the inflammatory aspects involved in keloid progression (Cobbold and Sherratt, 2000; Bianca, 2011; Bianca and Fermo, 2011). For example, starting with some experimental studies (Schäffer

et al., 1997a,b) on the role of nitric oxide (NO) in wound healing (NO being produced by both fibroblasts and macrophages), Cobbold and Sherratt (2000) proposed an ODE model for the temporal interactions between fibroblasts, collagen, oxygen, nitric oxyde (for a simpler model), as well as macrophages, TGF-β and blood vessels (for a more complex model). Numerical simulations performed with 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 by Bianca (2011); Bianca and Fermo (2011), who used the kinetic theory of active particles (KTAP) to proposed 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 were performed to investigate the behaviour of cell variables in this kinetic system in response to changes in various parameters, and with respect to the activity variables describing the phenotypes of these cells (Bianca, 2011; Bianca and Fermo, 2011).

Tissue-level 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 the skin) (Akaishi et al., 2008; Chambert et al., 2012; Sutula et al., 2020; Marie et al., 2022). The computational domain, representing the 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 Akaishi et al. (2008) 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 the keloid edges were subjected by 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 Chambert et al. (2012) the authors considered a computational model for the simulation of the skin 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 Sutula et al. (2020) the authors considered a 2D hyperelastic bi-material model of the keloid tissue and the surrounding heathy 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 the sensitivity of model parameters with respect to the displacement field and the reaction force measurements. Since the domain for all these tissue-level models for keloids is defined computationally (in contrast to the previous models for wounds and tumours where the domain/ECM was described 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 prediction. Such an issue can be addressed using, for example, the Dual Weighted Residual (DWR) technique (Marie et al., 2022).

Cell-level and tissue-level dynamics. One of the earlier mathematical models that were derived to investigate fibro-proliferative wound healing disorders such as hypertrophic scars and keloids was proposed by Olsen et al. (1996). The model is 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 the 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). Numerical simulations were performed with some arbitrary parameter values in the context of normal wound healing and pathological response characterised by increased fibroblasts, myofibroblasts, growth factor and collagen values. Analytical bifurcation approaches were 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.

4 OPEN PROBLEMS

Despite the various modelling approaches summarised in the above sections, there are still many open problems related to the modelling, as well as the 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 issues related to computational and data collection and assimilation approaches.

4.1 Numerical issues.

Continuum models. Regarding the numerical resolution of tissue-level constitutive equations as well as many PDEs for cell-level dynamics, the finite element method (FEM) is the way most frequently used. FEM implies, however, specific challenges: the widely varying skin-scar or skin-tumour stiffness leads to large displacement field gradients at the interface, knowing this interface evolves in time (Duddu et al., 2008). Moreover computing the velocity field along the interface may be challenging because of difficulties in resolving the gradient fields across the interface (Bordas and Duflot, 2007; Bordas et al., 2008):

- 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 are different from that of the skin.
- Field gradients can be large at the interface between the skin and the scar.
- The skin/scar interface evolves in time (Bui et al., 2017, 2018; Duprez et al., 2020).
- Computing the velocity field along the interface may be challenging because of difficulties in resolving the gradient fields across the interface (Bordas and Duflot, 2007; Bordas et al., 2008).

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 prediction (Duprez et al., 2020; Marie et al., 2022). The very recent study in Marie et al. (2022) 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.

Discrete & hybrid models. The main challenge of these models is to simulate very large numbers of cells. It is known that a 1cm^3 of tissue can contain between $10^8 - 10^9$ cells, depending on cell diameter (Monte, 2009). 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) (Kim et al., 2007).
Another issue with some of the discrete models is that the lattice-based models are at risk with potential grid-based artefacts (Metzcar et al., 2019). 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.).

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 number of parameters, sometimes modelling dynamics across multiple scales (molecular, cellular and tissue scales), and limited data sets. 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), there is still the problem of investigating the uncertainty in model outcomes to parameters across multiple scales. Renardy et al. (2019) 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), 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 (Monfared et al., 2021), cancer (Liu et al., 2021) 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) (Eftimie et al., 2022). The current push for the development of DT for precision medicine (Venkatesh et al., 2022) will impact also the research for keloids (especially due to the lack of appropriate murine models for keloids). 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 the 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 and 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 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, and then we mentioned in more detail some of the models developed in these studies. In our discussion we aimed to present both older and newer models, so we can (i) emphasise the simplicity of older models vs. the complexity of newer models; (ii) emphasise the lack of multiscale data to parametrise all these models. 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 be probably 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. We believe that clinical progress with this keloid disorder 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 these models.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

This review article was originally conceived and structured by RE. All authors contributed to the writing of this manuscript.

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