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Mathematical Modelling of Dermatological Disease and Recovery

by

Najida Begum

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy of Loughborough University

23rd March 2010

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Abstract

The National Health Service in the UK, spends over £1 bn every year treating dermatological conditions such as chronic wounds. These wounds exhibit poor vascularisation prone to polymicrobial infections where slow or non-healing are typical, and spend prolonged periods in the inflammatory stage. Chronic wounds such as leg and foot ulcers develop in patients with illnesses such as diabetes, where circulation is compromised and regular treatment and monitoring are essential. Many management strategies and new therapies have been introduced to combat chronic wounds and include growth factor therapy and skin substitutes. Although one of the greatest concerns is preventing an acute wound becoming chronic, and retrieving the normal healing before amputations are needed. Other dermatological conditions such as psoriasis affects 2-3% of the UK’s population and shares some common traits with the wound healing phenomena, however mathematical models in this area are scarce.

The thesis proposes a number of new mathematical models, to describe dermatological skin growth and recovery in both the epidermal and dermal membranes. The resulting models consist of nonlinear highly coupled system of partial differential equations (PDEs) studied using analytical and numerical methods. There are two broad themes (1) epidermal growth and recovery and (2) dermal and epidermal healing between the proliferative and repaired states.

The epidermal model based on the keratinisation process studied the interaction of cell behaviour, cell binding and a generic signal in superficial wounds. The model predicted epithelial recovery and the reformation of the well defined live and dead cell regions, regulated by growth factors and cell-cell binding properties. A simple extension of the model included the inflammatory response to describe psoriasis, and highlights abnormalities in cell maturation leading to hyperproliferation. Potential treatments based on manipulating the growth factors IGF and IGFBP-3 are investigated.

The dermal model captures the entire healing process by considering the interaction of keratinocytes, fibroblasts, signals and nutrients that work collectively to ensure skin homeostasis. This allows the recovery of the damaged dermis and replaces the wound medium with granulation tissue. Manipulating the key parameters responsible for vasculature sufficiency, clotting ability, infiltration of bacteria into the wound and loss of dermal tissue provided distinct wound scenarios. They demonstrated the transition from normal to delayed/abnormal healing profiles, where comparisons between the two states were possible. Prospective intervention methods based on treatments available were considered to study their effectiveness on compromised healing. The additional supply of nutrients, signals and fibroblasts led to many interesting outcomes particularly in the presence of bacteria. The growth factor treatment applied to the densely infected wound case given in our model was unsuccessful, as hypergranulation prevents keratinocyte migration and stalls wound coverage; this can only be retrieved
with fibroblast treatment resembling skin substitutes such as dermagraft.
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A.1 Mesh grid for finite schemes highlighting the initial point $u_{i,j}$, where $i$ is the spatial and $j$ the temporal index of the mesh point [118].
Abbreviations

- BM: Basement membrane
- ECM: Extracellular matrix
- FDM: Finite differences method
- GF: Growth factors
- MMP: Metalloproteinases
- NHS: National Health Service
- PDE: Partial differentiating equations
- PMD: Post mitotic differentiating
- ROS: Reactive oxygen species
- SC: Stem cells
- TA: transit amplifying
- TJP: Tight junction proteins
- TIMP: Tissue inhibitor MMPs
- TW: Travelling wave
- WH: Wound healing
Glossary

- **Actin**: Protein found in muscle tissue.
- **Chemotaxis**: Characteristic movement or orientation of an organism or cell along a chemical concentration gradient either towards or away from the chemical stimulus.
- **Connective tissue**: Also known as fascia, it is a framework of fibres that provide support to body tissues and organs.
- **Cytokines**: Regulatory proteins released by cells of the immune system.
- **Cytotoxic**: Extent to which a substance is toxic to living cells.
- **Desquamation**: Cell shedding at the skin's surface.
- **Endotoxin**: Toxins excreted by microorganisms e.g. bacteria.
- **Eschar**: Necrotic tissue mass at the wound site.
- **Exotoxin**: Toxins that appear in the presence of particular microbes.
- **Granulation tissue**: Perfused connective tissue that replaces the fibrin clot in a wound.
- **Growth factors**: Chemical proteins made by the body that function to regulate cell division and proliferation.
- **Hyperoxia**: Excess oxygen in organs or tissues.
- **Hypoxia**: Deficient oxygen supply
- **ROS**: Includes oxygen ions, free radicals and peroxides which are generated by macrophages and neutrophils to terminate bacteria that they engulf.
- **Signal Transduction**: Signal movement from outside to inside the cell.
- **Sloughing**: The skin's natural renewal process of skin shedding.
- **Toxin**: Harmful substance produced by living cells or organisms.
- **Quorum Sensing**: The ability of bacteria to communicate and co-ordinate behaviour via signalling molecules.
Chapter 1

Introduction: Skin

1.1 Brief History

It has taken many centuries to appreciate and recognise the importance, functionality and role in terms of structure and complexity of the skin. Many early civilisations believed that the primary role of the skin was to cover the body and prevent it from violation from external agents. They looked unfavourably at cutting open a human body, and even now many societies consider it as a taboo. This continuous belief impeded the study of human anatomy in both the classical world and in Christian Europe [17, 139]. Embalming was practised by the Ancient Egyptians indicating proficiency of activity inside the body, however the individual responsible for the incisions was ostracised from society. They believed in protecting the skin even after death as the skin provided the soul's integrity [92, 17]. The skin was idealised in classical Greek culture and considered to protect the body's solidarity, and also strongly believed in the non-violation theory. Aristotle described skin formation by referring to the loss of moisture and desensitised actions [17]

"by the drying of the flesh, like scum upon boiled substances; it is so formed not only because it is on the outside, but also because what is glutinous, being unable to evaporate, remains on the surface."

References are made in Hippocratic texts emphasising the skin's functional role of removing impurities from the body and the pores show great physicality. This initiated models demonstrating fluid transport from various parts of the body to another and fluid secretion. The Greek and Romans have adopted a variety of names to describe the different forms and aspects of skin which we still use today, as listed below [17].

- **Derma (ςέρμα)**: Greek word for hide.
- **Cutis**: Latin term describes the living skin and the skin that protects.
It was conjured from Aristotle's theory that the skin was the last organ to form, which was widely accepted by early followers and has taken many centuries to dislodge. The science and study of the skin is collectively termed dermatology, although in the earlier hospitals they used the term “cutaneous” disease. There was leniency towards dismembering of corpses in the third century BC, as the study of human anatomy progressed in medical schools. Although research was conducted to gain insight into structural details of the human body, they ignored the importance of examining the skin itself [17, 92].

Galen provided the doctrine on how to study the human body, based on knowledge obtained by examining animals. Students were instructed to consider the bones first as they form the shape of the body, then the muscles and the veins, arteries and nerves. He was not attentive to the remaining bodily components. This form of studying human anatomy went on for centuries after, and the skin was not studied in detail until the 16th century by Vesalius (using early microscopes), who defined the cuticle (epidermis), the derma (dermis), and the fat (hypodermis) and also described the flesh membrane separating skin from bodily constituents which he referred to as “panniculus carnosus”. He contested Aristotle’s statement of the skin being senseless, as examination highlighted nerves extending from the skin to the body, intimating the skin’s involvement in sensations such as touch. This helped develop the knowledge and appreciation of the skin’s role in anatomy, prompting researchers to consider the organ both structurally and physically. Towards the end of the 18th century, when the microscopes were more refined and commonly used amongst scientists the skin was considered more and more as an organ and a permeable membrane. It was no longer considered as just an integument, where thermoregulation was believed to accompany its excremental properties [17, 92].

Many books dedicated to the skin followed, which discussed the structure and function, but also began to classify skin diseases. Joseph Plenck, a military surgeon treated many skin diseases and identified 114 of them, based on their anatomical location and characteristic lesions. This was then shortlisted to only 10 (scurf, scale, scab, stigma, papula, rash, macula, tubercle, vesicle and pustule) by Robert Willan who wrote the book On Cutaneous Diseases, helping him name and define a range of skin conditions; and his work was continued even after his death by his student Thomas Bateman who introduced the first atlas of skin conditions. It should be highlighted that the skin was considered independently, and conditions/diseases identified were based on how they surfaced ignoring the underlying pathological cause [17].

In this introductory chapter we will discuss the skin anatomy and review details regarding the healing process and skin diseases that may occur.
1.2 Skin Anatomy

The skin is a multilayered organ with intricate structure and physiology with the ability to continuously self repair. This complex produces various distinctive derivative appendages including hair follicles, sweat glands and sebaceous glands each consisting of miscellaneous cell types and extracellular components as presented in Figure 1.1. It acts as a physical barrier of protection by separating the external environment from our internal constituents and accounts for 16% of the body's mass. The non-uniform appearance and thickness implies that the skin depth, composition and density of appendages will vary in accordance to anatomical sites, the sole of our feet is much thicker (6mm) when compared to the eyelids (1mm) for example. The skin distinguishes itself from other epithelial tissue as it prevents fluid loss and the ingress of noxious chemicals and micro-organisms [34, 40].

The three functional layers (of the skin) are the epidermis, dermis and hypodermis which all are unique in their cellular, structural and functional composition as shown Figure 1.1. Such layers interact and work collectively, to help develop and maintain homeostasis, although each membrane will be discussed independently in more detail [50, 139].

![Figure 1.1: The skin and its functional membranes [109]](image)

The skin has numerous functions and the main ones are [11, 40, 17].

- Thermoregulation.
- Structural integrity to the body.
- Mechanical protection.
1.2 Skin Anatomy

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The skin has numerous functions and the main ones are [11, 40, 17].

- Thermoregulation.
- Structural integrity to the body.
- Mechanical protection.
• Removing waste products of metabolism.

The remainder of this chapter will explore the skin and related topics to provide information relevant to the biological ideas and mathematical modelling that will form the background of the work presented in this thesis.

### 1.2.1 Epidermis

The epidermis is a stratified multilayered protective medium ranging from 0.07-1.5mm in thickness, providing an initial interface between the body and its external environment, characterised by both regenerative and differentiable properties and the first membrane affected by injury, damage or loss to skin [11, 15].

![Diagram of the keratinisation process in the epidermis](image)

**Figure 1.2: Keratinisation process in the epidermis [40].**

There are many types of cells that reside in the epidermal membrane, of which 80-95% consist of keratinocytes. Other key cells include melanocytes and Langerhans cells which are also important in terms of protection and homeostasis. This superficial membrane comprises of five sublayers, which are described below and presented in Figure 1.2 (starting with the layer

The epidermal cells in particular keratinocytes become proliferative and differentiable, allowing the formation and renewal of this membrane.
nearest to the basement membrane) [15, 46, 128].

- **Basal layer (stratum basale):** This is the only sublayer where keratinocytes can mitotically divide, they appear columnar/cuboidal and rigid in appearance. One daughter cell produced from every mitotic division is forced to move upwards (see Figure 1.3), which results from the growth pressure created and the presence of actin².

- **Prickle layer (stratum spinosum):** The epidermal cells present in this layer appear more polyhedral. Keratin synthesis produces keratin filaments, which are resilient bundles/cables that anchor cell-cell attachments namely desmosomes³ allowing equal distribution of tensility over the entire tissue.

- **Granular layer (stratum granulosum):** The epidermal cells morph into diamond structures and acquire granules/keratohyalin, which continue to differentiate. Although enzymes contained in this sublayer begin to dehydrate cytoplasmic organelles (such as the nuclei) and they are filled with keratin filaments to form a more dense intracellular framework.

- **Clear layer (stratum lucidum):** The epidermal cells become more elongated, and cells begin to disintegrate as they come nearer to the skin’s surface releasing sphingolipids; which are oily droplets that occupy the intracellular space.

- **Horny layer (stratum corneum):** The epidermal cells are elongated further and appear flat in appearance although still polygonal. In this layer the cells are completely lifeless and are referred to as corneocytes, forming a protective barrier against pathogens and water. Corneocytes are removed from the skin’s surface through desquamation/sloughing.

![Figure 1.3: The behaviour and relevance of stem cells (SC). SC divide asymmetrically producing two daughter cells, one which will be retained in the basal layer whilst the other will become a transit amplifying (TA) cell, to enhance its progeny. It is the post mitotic differentiating cells (PMD) that detach from the basal layer and move into suprabasal layers [11, 40].](image)

²Keratinocytes contain actin, enabling comfortable motility in tissue and active migration upwards.

³The desmosomes connecting cells appear as "prickles" hence the name [15].
The upper layers are characterised by the production and accumulation of keratin proteins. There are approximately 20 keratins derived from the independent genes [11, 15, 40], with molecular weight ranging from 40-70 kDa. This provides necessary rigidity of the dead cells in the upper layer to undertake their protective functions.

Epidermal cell growth in the lower sublayers balances those lost from the outer medium to maintain consistency in epidermal thickness provided there are no abnormalities. The whole keratinisation process ranges from 4-6 weeks; once the daughter cell leaves (see Figure 1.3) the basal layer it takes 2-3 weeks to reach the granular layer and a further 2-3 weeks to desquamate (cell shedding/sloughing).

**Cellular Attachments**

Cell-cell and cell-ECM attachments provides the structural integrity in tissues and organs. They determine the tensility and binding strength intra- and intercellularly. These cellular attachments can be categorised by three groups namely desmosomes, tight junctions and gap junctions as illustrated in Figure 1.4.

Desmosomes are common in epithelia especially skin and have three structural forms described below [9, 119].

1. **Spot desmosomes**- Cells are mechanically connected via interconnecting filament structures.

2. **Hemidesmosomes**- Half desmosomes that attach epithelial cells to the basement membrane and act as anchors for cells.

3. **Belt desmosomes**- Continuous band between interacting cells, loosely connected to

![Figure 1.4: The different types of junctions in the epidermis looking at two adjoining cells [119].](image-url)
filaments on the cytoplasmic part of the membrane.

Tight Junction Proteins (TJP) are a group of integral and impermeable proteins, typically located on the boundaries, of both the granular and horny sublayers. They allow neighbouring cell to communicate without sharing their contents. Gap junctions are important especially during injury/wounding, and protect healthy cells by separating them from the damaged/dying ones [9, 11, 119].

**Basement Membrane**

The basement membrane (BM) distinguishes the epidermis and dermis which are biologically active. Once this membrane is disrupted particularly in wounds, it must be reformed to regain normal functionality as the BM provides physical support, provision for cellular attachments and is involved in almost every pathological process including neoplasia, inflammation, wound healing and immunological reactions [11, 40].

1.2.2 **Dermis**

The dermis is the thickest functional membrane ranging between 0.6-3mm, that comprises of its own vasculature and intricate structure, where you will find hair follicles, sweat glands and sensory receptors. It supplies the epidermis with essential nutrients and growth factors as the epidermis does not have a vasculature of its own. It can be defined by two regions, which are the papillary and reticular layers as discussed below [11, 40, 56, 92].

- **Papillary Layer**: Located below the epidermis and composed of loose connective tissue. This layer contains dermal papillae such as nerve endings, capillaries and Meisner corpuscles e.g. touch receptors. Papillae indents the epidermis and provides the fingerprint projection observed on the skin's surface. The dermo-epidermal junction allows keratinocytes to be embedded in the dermal papillae, and interaction with basal membrane produces a framework able to trap collagen fibres.

- **Reticular Layer**: Is the thicker of the two dermal layers occupying approximately 80% of the entire membrane, and is densely populated with connective tissue containing collagen and elastic fibres. There is a plentiful supply of blood vessels, nerves and Pacinian corpuscles which are deep tissue receptors that sense pain and pressure.

The principal dermal cells are fibroblasts which are primarily found in the papillary layer, and low cell densities can be seen in the reticular layer. They are responsible for collagen and elastin production which provides tissue integrity, tensility, and play crucial roles to the wound healing complex, as they restore blood supplies and promote tissue growth. There are

---

4Dermo-epidermal junction is an area between the epidermis and dermis and includes the basement membrane.
different forms of fibroblasts such as fibrocytes and myofibroblasts whose activity is mostly observed [2, 26, 56], during tissue damage and repair.

1.2.3 Hypodermis

The hypodermis is also known as subcutaneous fascia. This membrane contains loose connective tissue and fat deposits, where nerves, blood vessels and hair follicles reside as shown in Figure 1.1. The cells contained are mainly of adipocytes, macrophages and fibroblasts. It acts as an energy reserve which contributes to insulation, conservation of body warmth and protecting internal organs after injury. The thickness of the hypodermis varies around the body, and is absent in the eyelids and the shins [46, 56]. We will not consider this membrane in the modelling to come, however it is useful to envisage the skin in its entirety.

1.2.4 Cell Cycle and Development

Cells are essential for the growth and development of all organisms, achieved by cell division. A selection of cell cycle activities is presented in Table 1.1. There are checkpoints within the cycle which control cell division to ensure all steps have been successful, preventing unwanted overproduction of cells, refer to Figure 1.5. Failure of certain checkpoints results in complications such as tumour growth, abnormal healing and skin conditions e.g. psoriasis [119].

Figure 1.5: Cell cycle: the phases. G1 - Gap 1: Duration can range from 10-400 hours. In this phase we observe the growth and preparation of chromosomes mediated by cyclin-dependent kinases (Cdks), ready for the preceding stage. S- DNA synthesis: Discontinuous process and duration is relatively constant in most cells, where the genome is duplicated and controlled by S-phase promoting factor (SPF). G2 - Gap 2: Cells prepare for mitosis. M- Mitosis: Cell division. Go - Gap 0: Cells are in a quiescent state, which can enter the G1 phase in response to proliferation or other factors. This diagram has been reproduced with the permission of Sai Liu [77].
<table>
<thead>
<tr>
<th>Anatomical location</th>
<th>Type of cell division</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow (produces blood cells)</td>
<td>Constant renewal</td>
</tr>
<tr>
<td>Gonads (gametes production)</td>
<td>Constant renewal</td>
</tr>
<tr>
<td>Epithelia (epidermis and gut lining)</td>
<td>Constant renewal</td>
</tr>
<tr>
<td>Skin (epidermis and dermis) after injury</td>
<td>Active when needed</td>
</tr>
<tr>
<td>Liver (part removal encourages growth)</td>
<td>Active when needed</td>
</tr>
<tr>
<td>Nerve cells</td>
<td>Never</td>
</tr>
<tr>
<td>Brain cells</td>
<td>Never</td>
</tr>
</tbody>
</table>

Table 1.1: Type of cell division in distinct parts of the body [119].

1.3 Growth Factors/cytokines

Growth factors (GF) are naturally occurring proteins released by a variety of cells and regulatory proteins, stimulating many cellular and physiological processes including proliferation, differentiation, reproduction and general growth and development. Cytokines are a distinct family of GFs, secreted from immune cells such as leukocytes and macrophages; they stimulate the immune responses [40, 67].

These chemicals bind to specific high affinity receptors found on cell membranes when activated, to allow signal transduction which describes intra- and extra-cellular signal movement. Signal transduction initiates many intracellular processes, including a series of phosphorylation reactions that take place in the cell’s nucleus and induces gene expression. These intracellular events result in protein synthesis, alter cellular activity and may also affect the proliferation of cells. Many GFs have multiple roles, where distinct concentration levels initiate different biological responses both inhibitory/stimulatory seen during wound healing, skin diseases and other physiological impairments (see Table 1.2) [11, 40, 67].

Skin characteristics are maintained by many chemical mediators, which include epidermal GF (EGF), fibroblast GF (FGF), platelet derived GF (PDGF), transforming GF (TGF)-β and insulin GF (IGF). Their functions overlap and many GFs contribute to the same process [11, 15, 40, 119]. Table 1.2 shows a list of selected growth factors involved in skin regulation and wound healing and highlights their functions and activities.

GFs allow cells to communicate intracellularly and exert their effects in four ways: endocrine, paracrine, autocrine and juxtacrine. Endocrine signals act on distant cells, paracrine signals target adjacent cells and stay in close proximity to the emitting cell, autocrine signals affect cells of the same cell type and juxtacrine signals are channelled along the cell membrane directly to adjacent cells via protein/lipid constituents [40, 67].

9
<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cell source</th>
<th>Signalling</th>
<th>Function</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF</td>
<td>Platelets, MC, macrophages, keratinocytes EC, fibroblasts</td>
<td>Autocrine</td>
<td>Stimulates angiogenesis &amp; proliferates dermal cells. Regulates migration &amp; differentiation. Role in activating signalling &amp; receptors interacts with heparan sulfate proteoglycans</td>
<td>+</td>
</tr>
<tr>
<td>EGF</td>
<td>Macrophages, eosinophils, EC, keratinocytes &amp; fibroblasts</td>
<td>Paracrine or juxtacrine</td>
<td>Stimulates keratinocyte migration. Important role in re-epithelialisation &amp; granulation tissue formation.</td>
<td>+</td>
</tr>
<tr>
<td>VEGF</td>
<td>Keratinocytes, macrophages MC, fibroblasts platelets, EC</td>
<td>Paracrine</td>
<td>Stimulates angiogenesis &amp; granulation tissue formation. Regulates lymphangiogenesis &amp; acts as a chemoattractant.</td>
<td>+</td>
</tr>
<tr>
<td>Angio-poietins</td>
<td>Platelets, MC, Ang-2 macrophages keratinocytes, fibroblasts, EC</td>
<td>Paracrine</td>
<td>Ang-1 needed to stabilise blood vessels; acts as a destabilising factor loosening cell-cell and cell-ECM contacts allowing EC motility.</td>
<td>+</td>
</tr>
<tr>
<td>IGF</td>
<td>Platelets, macrophages, fibroblasts</td>
<td>Autocrine, paracrine or endocrine</td>
<td>Stimulates growth &amp; differentiation of dermal and epidermal cells. Promotes wound healing &amp; tissue regeneration.</td>
<td>+</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Platelets, MC, macrophages keratinocytes fibroblasts, EC</td>
<td>Paracrine</td>
<td>Mitogenic for fibroblasts, but inhibits keratinocyte proliferation. Attracts macrophages to wound site, stimulating them to secrete additional cytokines: FGF, PDGF, TNFα and IL-1.</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 1.2: Cytokines, cell source, functions and the positive/negative effect during wound healing and repair [88, 138].
Wound healing (WH) is an ongoing area of intense research that has developed substantially over the last few decades. A major concern in research is establishing an accurate insight into the biochemical and cellular mechanisms exhibited by wounds, and differentiating between normal and abnormal healing processes. This would contribute greatly to the development of more effective therapies and improvements to existing wound management strategies, especially for chronic and slow healing wounds [117, 124]. Figure 1.6 illustrates GF and cell activities, that allow successful re-epithelisation by replacing the fibrin clot in a wound following the normal healing course.

1.4.1 Phases of Wound Healing

Wound healing is a complex dynamic process defined by a number of well orchestrated series of events, often presented as a three stage process, namely the inflammatory, proliferative and maturation phases. These phases may overlap in a single wound, although it provides a guideline when assessing and monitoring wound healing behaviour [11, 25]. The cellular activity incorporated in one phase provides the environment necessary for successful entry to the proceeding phases [40].
Inflammatory Phase

The inflammatory phase is the body's initial response and the two governing processes are haemostasis (clotting response which reduces further blood loss) and inflammation (protective reaction to injury signified by redness and swelling). The most important cytokines are PDGF and TGF-β in this initial phase and following an injury large quantities are released into the affected area, acting as chemoattractants for many cells. The inflammatory response is essential to recruit fibroblasts and immune cells to restrict infection and initiate the repair process [2, 11, 15]. In this subsection, an overview of the normal healing process will be discussed.

At the onset of injury, platelets released from the compromised vasculature will form an eschar (or scab) comprised of fibronectin and fibrinogen to prevent further blood loss, cover the wound from infections and provide temporary support to restrict further damage. The resulting clot formation acts as a scaffold for migrating cells, to rebuild tissue in the damaged area [11, 15]. The hydration of the fibrin clot determines the migration path of keratinocytes, and a moist clot is favourable for normal healing to persist.

Neutrophils become active between 2-3 days after injury to help remove foreign bodies and recruit further leukocytes to the wound bed. Monocytes transform to macrophages and further phagocytose bacteria/foreign material and ingest inactive neutrophils, also secrete more GFs to encourage the migration of cells, such as fibroblasts essential for healing and preparation for the next phase. A flow chart schematic of key events during inflammation is given in Figure 1.7.
They increase cell proliferation & migration to wound site

INJURY

They increase cell proliferation & migration to wound site

They increase cell proliferation & migration to wound site

They increase cell proliferation & migration to wound site

Figure 1.7: Inflammation process [11, 25].

Proliferative Phase

This phase will be discussed in more details here, as it is the focus of the modelling in Chapters 5 and 6, where we will consider dermal healing between the proliferative and remodelling/maturation stages of healing.

Fibroblasts begin to migrate into the wound bed from surrounding tissue in response to cytokines, growth factors, activated neutrophils and macrophages towards the end of the inflammatory phase and signifies the beginning of this stage [15].

Fibroblasts are key to the repair process and have a multiple roles in wound healing contributing to the production of the extracellular matrix (ECM), collagen synthesis producing fibronectin and proteoglycans such as hyaluronic acid. During ECM production, the wound margin is decomposed by matrix metalloproteinases (MMPs) and plasminogen activators. These MMPs are essential to all stages of wound healing and are regulated by tissue inhibitor metalloproteinases (TIMPs) ensuring that excess matrix degradation does not take place, which may be one of the contributors to abnormal wound healing [11, 56, 138].

The key components in this stage are neoangiogenesis/neovascularisation, granulation tissue formation, collagen synthesis, contraction and epithelisation; the most active cytokine in this
phase are TGF-β and PDGF. First two events occur simultaneously and interdependently occupying open spaces on the wound and producing new capillaries [2, 11].

Granulation tissue production replaces the initial fibrin clot and depends on neovascularisation which allows blood vessels to proliferate in tissue that does not usually contain them. Neovascularisation is a combination of angiogenesis and vasculogenesis, and replaces the damaged blood vessels to establish a supply of oxygen and nutrients in the wound area. Angiogenesis is the physiological process where new blood vessel growth results from pre-existing vessels, mediated by many angiogenic factors (e.g. VEGF) and capillary production resulting in arteriole formation that revascularises the injured area [2, 11, 15].

Keratinocytes present at the wound edge undergo a transformation, which enables them to phagocytose debris and migrate into the wound site and also promotes the proliferation rate. This allows the wound to contract and granulation tissue to develop further. This combination prompts re-epithelisation and wound closure [56] and Figure 1.8 summarises the sequence of events in the proliferation phase.

Figure 1.8: Proliferation process [11, 40].

These GFs stimulate fibroblast proliferation, collagen production and re-epithelisation (supported by EGF). Continual supplies of both are usually available throughout the whole healing duration [4, 15, 67, 138].
Remodelling/Maturation Phase

In the final phase of wound healing, collagen and ECM synthesis continues to take place, the key cytokine here is TGF-β and the primary cells are still fibroblasts. In adults, the remodelling of the granulation tissue often leads to scar tissue formation, which may take months or years to complete, whereby the tensile strength of the repaired tissue is increased by further collagen deposition and restructuring [11, 56].

1.4.2 Wound Types

Skin mass can be lost in many ways, mechanically through piercing or scraping, by burning from flames or chemicals or from blistering. There are a vast number of ways for injuries to occur and the effects on the skin’s functional layers is varied and dependent on the severity of the wound. The depth, size and management of wounds, contributes greatly to the healing time and likelihood of infections [5, 11].

Wounds can be classified into four categories as follows [5, 11, 69].

- **Superficial thickness**: Injuries affect the first functional membrane (epidermis), where the epidermal cell population is not greatly affected, leaving an adequate blood supply and encourages prompt re-epithelisation.

- **Superficial partial thickness**: The epidermis and the upper layers of the dermis are affected and appear as abrasion or blisters. The moisture in these wounds should be controlled to prevent contamination and promote the healing process.

- **Deep partial thickness**: Injuries extend further into the dermis, where the destruction of nerve endings, epidermal and dermal cell population affects regeneration. Second degree burns are in this category.

- **Full thickness**: Wounds that destroy both the epidermal and dermal layers, finding its way into the subcutaneous layer (hypodermis) and may damage any underlying structures such as muscle, tendon or bone. These injuries may appear as craters.

1.5 Chronic Wounds

A slow or non healing wound is referred to as a chronic wound, and the normal wound healing pathology is severely impaired. The healing rate ranges from weeks to years and is dependent on many factors, such as age and severity, which affect wound pathology. Loss of large skin mass poses a great threat to an individual’s life, by significantly impairing their lifestyle in terms of independence and quality as they will experience great discomfort and distress.
Typical sources of chronic wounds include pressure ulcers, diabetic ulcers and burn wounds affecting both epidermal and dermal layers [11].

The annual cost to the National Health Service (NHS) from regular monitoring and patient care is approximately £1 bn, whilst in the USA it is significantly greater and is estimated at $150 bn. Patients with chronic illnesses like diabetes are likely to suffer more as they have certain dysfunction and impairments which inhibits normal repair. According to the UK Health Episode Statistics (2005), it was reported at one time that only a quarter of the 400,000 leg ulcer sufferers were being treated due to resource limitation and prioritising patient needs [56, 100].

There are many factors contributing to the onset of chronic wounds and it is believed that the ability of keratinocytes and fibroblasts to proliferate, migrate and synthesise specific growth factors and cytokines essential for the recovery reduces immensely. Also, keratinocytes exhibit partial activation and differentiation in the wound medium resulting in impaired healing. Overexpression of c-myc in the basal layer produces the chronic wound phenotype and reduces the local epidermal stem cell population [124, 128]. This may be a result of the hypoxic medium a chronic wound exhibits, and the accumulation of dead tissue and cellular exudate present [8]. Typical characteristics of chronic wounds are given below [11, 32, 124].

- Vascular insufficiency and inadequate supply of oxygen and nutrients.
- Polymicrobial contamination (bacterial or fungal infections).
- Tissue degradation from the toxic chronic wound fluid created in the damaged area.
- Elevated levels of ROS (reactive oxygen species) and proteases
- Reduction in essential GFs
- Impaired keratinocyte migration.

ROS include superoxide radical and hydrogen peroxide and are known to be cytotoxic, they are believed to affect central cellular processes such as proliferation and apoptosis. Increased levels of ROS that follow immediately after an injury, reach high levels within chronic wounds affecting many key processes [133].

Chronic wounds remain for prolonged periods in the inflammation phase because of the persistent infections which affect the clotting mechanism and begin to “attack” healthy tissue. In acute wounds, the concentration of inflammatory cytokines is carefully controlled by antagonists, which favour inhibition. However, in chronic wounds, many proinflammatory cytokines are released but are not regulated, which may be responsible for further tissue damage [7, 11, 34].

\[\text{c-myc}\] is a oncprotein that is responsible for the transcription of growth associated genes.
Chronic wounds express an imbalance between the proteolytic enzymes and their inhibitors, from the over-expression of MMPs. The disparity of MMPs and TIMPs can lead to abnormal degradation of the ECM, GFs (including EGF, PDGF and TGF-β) and adhesion proteins such as fibronectin when TIMP levels are relatively low. Cell exposed to chronic wound fluid demonstrates low mitotic activity as DNA synthesis is impaired. It has also been suggested that macromolecules present in chronic fluid accumulate in the wound bed, which may bind or trap GFs making them unavailable for the healing process [34, 139, 124].

There are many observations that indicate differences between normal and chronic wounds, but little is known regarding which factors are the cause and which are simply the symptom responses to the situation. Poor vascularisation and bacterial infections commonly occur in chronic wounds, and the inability to improve a healthy normal wound medium will cause further complications in the healing process [134].

**Role of Bacteria**

Infections are likely to occur in deep partial and full thickness wounds, because of the hostile environment provided, and accumulation of nonviable tissue. Bacteria can invade the wound in three stages as listed below [11, 71, 116]

- **Contamination**: Microbes present in low quantities but can reproduce. This is common in all wounds and provided the bacteria are kept in check complete healing is observed.

- **Colonisation**: A more established bacterial population exists which is polymicrobial, and extensive proliferation may occur. They are localised to the superficial compartment of the wound. On the surrounding skin, exposure to external stimuli and endogenous factors including mucous membranes are potential microbial sources, contributing to colonisation.

- **Infection**: Bacterial colonies begin to expand and are no longer localised to the superficial membrane, invasion begins deeper into the skin tissue affecting the dermis, damaged tissue and vascularisation. Infection may become systemic (gangrene and septicaemia).

Invasion into the wound area, especially the deep tissue compartments, results in infections and contributes to the development and prolongation of chronic wound healing. Microbes produce destructive MMPs, exotoxins and endotoxins to the host and this creates a pro-inflammatory environment, which aggravates tissue damage as discussed above. Common wound pathogens of aerobic nature include *Staphylococcus Aureus* and *Pseudomonas Aerius* and anaerobic ones include *Peptostreptococcus* spp and *Porphyromonas* spp [11, 71]. Chronic wounds such as diabetic foot ulcers have a higher proportion of anaerobes compared to aerobes, which makes it more difficult to follow the normal healing process and requires vigorous intervention methods [71, 116].
Table 1.3: The types of wound dressing available [59].

1.6 Treatments

Chronic wounds are usually treated by means of wound debridement and applications of dressings which will prevent infection, contamination and promote healing. Wound debridement involves the removal of necrotic tissue and microorganisms, and may be applied through surgical/other methods to restore normal healing, some of which will be discussed in this section [11, 14]. The use of maggots for wound debridement has been in place since from as early as 1557, where they not only clean the wound but also stimulate granulation tissue formation and prevent septicaemia. Their use declined with the introduction of antibiotics, but in recent years we have seen an increase in their application [14, 125, 126].

Advancing techniques in tissue engineering has led to development of skin substitutes such as the trademarked products Myskin and Dermagraft, which initiate complete healing when combined with other care management strategies. Myskin is an autologous epidermal substitute which uses living skin cells from patients, and is administered in a viable state on a polymer coating. It has been successful in burn wounds, ulcers and other non-healing wounds by initiating healing and expressing natural GFs needed for repair. Dermagraft is a cryopressed dermal substitute, that comprises human derived fibroblasts, extracellular matrix (ECM) and a bioabsorbable scaffold. Its primary purpose is to promote re-epithelialisation in full thickness wounds particularly diabetic foot ulcers after implantation, as living cells proliferate and also express essential GFs [1, 44, 90].

Many wound dressings are available and include adhesive film, alginate, hydrogel and hydrocolloid and their usage is largely dependent on wound type and pathology, as summarised in Table 1.3. It is common to use more than one type of dressing for a single wound and these dressings target to maintain moisture within the wound, absorb excess exudate, provide thermal insulation and prevent bacterial contamination [59].
1.7 Skin Conditions

The skin can be affected in many ways, whether it is hormonal, hereditary or contribution from environmental factors (sun, chemicals or personal habits) resulting in spots, rashes, plaques and lesions which surface visibly on the skin. Some common skin diseases include eczema, dermatitis and psoriasis, which can range from being highly localised or cover large areas of the body's surface [11, 40]. In chapter 4, we will propose a model for psoriasis and this condition warrants further discussion.

1.7.1 Psoriasis

Psoriasis is a common immunological chronic skin disease, characterised by hyperproliferation, impaired keratinisation and dermal inflammation, affecting both genders and is neither contagious nor infectious. Although this condition was described in the early 19th century; it is only within the last three decades that detailed investigations have been conducted [75, 115].

In the UK, 2-3% of the population are affected by the condition and there are 7.5 million sufferers in the US. In males, it most often develops in two age groups, namely 15-22 and 60-69 years old, and typically for females it is younger. The disease can be very intermittent, with periods of remission and relapse lasting weeks or years.

This condition is characterised by red scaly lesions referred to as plaques and is believed to be multi-factorial (combination of genetic and environmental factors contribute and trigger this disease), although the heredity pattern is still under investigation. Factors that may contribute to the onset and perpetuation of psoriasis include, chemical injury, throat infections, stress and alcohol, which may stimulate or activate particular immune cells such as T-lymphocytes, which surface to the skin. Patients with this condition may also develop psoriasis arthritis causing pain, swelling and stiffness of the joints [75, 108].

The most common forms of psoriasis, affecting 80% of all sufferers is known as Plaque psoriasis (psoriasis vulgaris). The characteristics of this form include raised inflamed skin and silvery white scales which vary in thickness. Upper scales come away easier than those deep within the skin as shown in Figure 1.9. Typical locations include elbows, knees, scalp and lower back. Less common forms include guttate, pustular and erythrodermis psoriasis that have differing characteristics and severity [93, 108, 123].

Psoriasis affects both the epidermal and dermal membranes, but it is the former where it is most noticeable. The disease exhibits high infiltration of immune cells within the epidermal membrane, and is commonly believed to be a T-cell mediated autoimmune disease. Although many GFs are believed to be involved; two of the most significant ones are IGF-1 and IGFBP-3 [78, 108, 123].
IGF-1 promotes epithelial cell division and motility in both normal and abnormal skin states e.g. wound healing, whilst IGFBP-3 inhibits IGF-1 and prevents cell proliferation and differentiation. These chemicals in balance are important for skin structure, however, a large presence of immune cells producing IGF-1 in the epidermis will upset this, perhaps causing the symptoms described [11, 28, 119].

Figure 1.9: Keratinisation process in normal and psoriatic epidermis [11, 40, 78]

Table 1.4 presents the activities of IGF-1 and IGFBP-3 in the epidermal membrane at the different layers, comparing normal and psoriatic skin. This results in chaotic maturation as the turnover period is shortened to 7-10 days, where both live and dead cells coexist at the skin's surface presented in Figure 1.9, although the severity and location contribute to the onset [28, 50, 61, 75]. Cells proliferate in the basal layer as well as one or two of the suprabasal layers, which would not normally proliferate accompanied by increased IGF levels as IGF-IR (IGF-insulin receptor) expression is more extensive. Figure 1.9 presents the keratin composition of normal and psoriatic epidermis and keratin types 6 and 16 [66] are those typically present in a wound responding to inflammation [28, 75]. This suggests that the body's immune system is initiated during the development of psoriatic plaques [78].
NORMAL | PSORIASIS
--- | ---
IGF-1 | Produced by fibroblasts and melanocytes. It acts on basal keratinocytes. | Produced by fibroblasts, melanocytes and inflammatory cells. Acts on basal and suprabasal keratinocytes.
IGFBP-3 | Produced by keratinocytes SC and TA. Expression in PMD may be suppressed by TGFs and acts as an inhibitor. | Produced by SC only and is low in TA and PMD cells.
IMMUNE CELLS | Present in lower epidermal layers. | Infiltrates in lower and upper epidermal layers.

Table 1.4: The difference in IGF-1, IGFBP-3 and immune cell behaviour in normal and psoriatic involved epidermis, where SC-stem cells, TA-transit amplifying and PMD-post mitotic differentiating cells [73, 75, 50, 66].

1.8 Thesis Synopsis

This chapter provides the background to dermatology and its associated components relevant for our research, highlighting many integrated factors whose knowledge will benefit the understanding behind the terminology and mathematical model development. This includes introduction to skin, wound healing, chemical mediators, treatments and bacteria in the wound medium. The problems associated with skin conditions such as chronic wounds or diseases, are discussed as a means of expressing the economic burden and strain on sufferers, also stating the common characteristics associated with these conditions. In the chapters to proceed the literature, mathematical models and development will be detailed.

Chapter 2 examines existing mathematical models that investigate epidermal, dermal wound healing and psoriatic behaviour. There is a vast range of literature covering the modelling of wound healing, although many are specific and have only looked at in some depth a narrow part of the healing processes such as angiogenesis or wound closure. Quite understandably, modelling the entire healing process has generally been avoided, as the resulting model would be somewhat unwieldy and a considerable challenge to investigate mathematically.

Chapter 3 introduces a mathematical model which investigates re-epithelisation of superficial wounds by considering the keratinisation process, which controls self-renewal properties of the epidermis defining live and dead cell states. A 1D reaction-diffusion-advection PDE system is applied by incorporating aspects of cell binding tissue, velocity, signal distribution and cell growth. The model predicts that during re-epithelisation the live cell layer builds up first (regulated by a signal, GF or nutrient) and the keratinised layer after (governed by cell-cell binding strength and sloughing), which is in agreement with [15, 43].

Chapter 4 builds on the ideas and results from the re-epithelisation study to formulate a model
for the onset of psoriasis affecting the keratinisation process, characterised by hyperproliferation and parakeratosis. We introduced IGF-1, IGFBP-3 and immune cells, in addition to those variables already presented in Chapter 3, as this reflects the inflammatory response observed on the skin’s surface. The problem is demonstrated by concentrating on immune cell activities and we assumed a promoter-inhibitor relationship between IGF-1 and IGFBP-3, to examine and differentiate between normal and psoriatic involved epidermis. Simulations were obtained in the same manner as Chapter 3 and show that the model can describe many of the psoriatic characteristics discussed in medical literature. The model predicts that a topical application of IGFBP-3 can combat the psoriasis, leading to a recovered epidermal layer.

Deep tissue wounds was the focus of Chapter 5 and we identified keratinocytes, fibroblasts, granulation tissue, signals, nutrients, normal healthy and damaged ECM as the key contributors to the healing process, during the proliferative phase and the processes towards wound closure. Many different wound scenarios were considered including the effects of key parameters that detract the normal healing course and the impact a change in geometry of wound bed exerts. Two parameters of particular interest in healing impairment, were \( \gamma_b \) and \( \beta_{im} \) responsible for nutrient sufficiency and quality of clotting matrix in the wound domain. From the dermal components introduced at the wound site, we found a small bolus of nutrients in the wound was far more effective at enabling healing, than similar more generous treatments of GFs and fibroblasts. However “drip feeding” of GFs and fibroblasts from special dressings (observed in our model) and skin grafts can significantly improve healing.

Chapter 6 builds on the modelling of Chapter 5, to investigate the role of bacteria in the system and their contribution to chronic wound development. The bacteria in the model interfere with dermal and epidermal repair with the ability to kill epithelial and fibroblast cells, also the breakdown of underlying tissue and the latter process can lead to an expanded wound area. The model predicts that bacteria can disrupt the normal healing course and as suspected, the greater the uptake of bacteria from the environment leads to increased wound impairment; which would result if a wound is poorly managed. A very interesting prediction of the model is the hypergranulation of tissue which may result when introducing GFs into an infected wound environment; this is illustrative of how a subtle interaction between GFs and bacteria can lead to considerable variety in wound pathology.
Chapter 2

Overview of Mathematical Modelling

2.1 Introduction

There are still countless open questions regarding wound healing, and potential avenues for improved treatment and reduced scarring. Many features are very difficult to observe and measure in situ, and mathematical models play a useful part in attempting to establish a quantitative understanding of the important mechanisms involved in the healing process. Some of the most common wound healing factors investigated are the roles of skin cell proliferation and migration, growth factors, wound contraction, angiogenesis, extracellular matrix (ECM) alignment and bacterial infections [2, 7, 8, 74, 92].

Mathematical modelling of wound healing have been undertaken for 30-40 years or so [92] and involved a wide variety of mathematics and computations, ranging from descriptive models (including curve fitting to data [19, 103, 107, 134]) and mechanistic descriptions discussed below. In this chapter, we will give an overview of the relevant models to the areas considered in the thesis.

2.1.1 Epidermal Wound Models

There are a number of mathematical models investigating wound healing of the cornea, [20, 21, 41, 42, 113] and others. Corneal wound healing is simpler in many ways to that of the skin as there is no angiogenesis, innervation and other complicated biological processes are also absent [41, 92, 101]. However it is relatively simple to investigate experimentally and data is readily available for model comparison. The most common approach is to assume
a continuum of cells and usually a system of reaction-diffusion-chemotaxis type models are derived. All these models predicted emergence of travelling wave (TW) solutions of wound closure; the speed and profile shape of which can be affected by chemical factors regulating mitosis [20, 21, 41, 42, 92, 101, 113] and cell migration [20, 21, 41, 72]. The results of these models agree qualitatively in broad terms with experimental observations. However some of the details of the predictions of the earlier models [20, 21, 113], were shown by Gaffney [41] not to compare well with experimental observations, particularly in the timing and location of enhanced proliferation. He proposed a more detailed model, principally by distinguishing between quiescent and proliferating cells to address the inconsistencies.

Cell invasion problem investigated by Landman [72], extended earlier models [20, 41, 113] using a multi-species continuum approach in which attachment and reattachment of cells during mitosis and migration were considered. The study found that if the attachment, cell division and reattachment activities were enclosed to a limited region of the wavefront, assuming reattachment rate is considerably faster than the detachment rate then the relatively simple and well studied Fisher's equation \(^1\) is adequate in describing a wound healing scrape assay. This was found not to be the case for slower reattachment rates, where a more detailed model would be required.

### 2.1.2 Dermal Wound Models

The dermal membrane is more intricate than the epidermis as it contains blood vessels, lymph vessels, nerves, hair follicles and sweat glands (refer to Figure 1.1). Injury to the dermis may take years to fully repair and will continuously remodel underneath the skin even after reepithelisation and scar formation, to regain optimum tensile strength. The healing processes in the dermis poses more problems in complexity, and mathematical modelling tends to focus on a small aspect or a single stage of the process.

Wound contraction and scar formation has been a continued focus of many mathematical models, with the aim of understanding how wound could heal so not to leave scars and why hypertrophic scars and keloids occur; this being the main target designing treatments for dermal healing [15, 22, 92]. Initial dermal wound models introduced in the late 80s, investigated the mechanisms involved in wound contraction (e.g. [83, 92]). Since then the mathematical models have advanced greatly looking at multiple cells types and dermal functions [92].

There are many reasons why dermal wounds may be disrupted; fibro-proliferative disorders such as keloids or hypertrophic scars resulting from overactive fibrous tissue may be one of them. In hypertrophic scars, healed wound tissue exceeds that of normal skin and this may be caused by problems in the keratinisation process where cell death occurs at a later stage.

\(^1\)The Fisher Equation takes the form \( \frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} + ru \left( 1 - \frac{u}{K} \right) \), and has been employed to describe many situations in biology and ecology, including wound healing [92, 120].
than expected. In keloids, scar formation goes beyond the original wound margins and exhibits elevated levels of collagen deposition and cellular activity. Deterministic models in [60, 97] were used to help understand dermal wound invasion and fibro-proliferative disorders respectively. Olsen [97] study was an extension of an earlier model developed looking at fibroplasia and wound contraction; the central processes between normal and abnormal skin were identified. The findings suggest that spatiotemporal dynamics of such disorders, highlights the mechanisms from which these pathologies may occur, develop, regress and may provide details/recommendations for clinicians to develop effective management strategies.

GFs mediate the wound healing process and the two that appear to have a central role in regulating normal behaviour are TGF-β and PDGF which have been studied in [22, 60] using ODE systems. Dales et al [22] found that early topical application of TGF-β in adult dermal wounds reduces the ratio of collagen I:III 2, improving wound quality and less visible scarring on the surface. The wound invasion model [60], indicates that PDGF concentrations stimulate fibroblast proliferation and enhance chemotaxis. The additional role of wound geometry was considered by Vermolen et al (2008) [131] to investigate the "Critical Size Defect" (CSD), showing that irregularities in GF production and cell proliferation can lead to the observed phenomena.

Angiogenesis was the focus of [101, 111] using PDE models and both highlight the significance of oxygen concentrations for healing. In [101], ingrowth of new blood vessels at the wound site were represented by travelling wave (TW) solutions, implying that varying cell death rate could help determine the healing prospect of a wound. Schugart (2007) introduced a nonlinear PDE model used to investigate wound angiogenesis by focusing on the role of oxygen tension w. Other interacting factors considered were capillary sprouts n, capillary tips b, fibroblasts f, inflammatory cells m, chemoattractants α and extracellular matrix p. The aim of the model was to provide a realistic model, supported by experimental data to resemble the success of angiogenesis in cutaneous wounds and highlight the key activities of oxygen. This study presented angiogenic behaviour in cutaneous wounds that compare well with experimental observations from patient based studies [111].

More challenging wounds are prone to persistent infections and polymicrobial contamination because of the hostile environment presented as mentioned in 1.2.4 and a number of studies use PDE models to describe its effects [16, 69, 74, 101]. Pseudomonas aeruginosa 3 has been identified as an important microbe, which has led to high mortality from burn wounds. The earlier models [16, 74], focused on reviewing bacterial activity in terms of exoprotein production, which are at high concentrations in infected wounds and the natural immune response (e.g phagocytes that ingest bacteria and prepare the wound domain) is unable to manage increasing levels, when bacterial growth is sufficiently large. A more recent study

2Collagen III is the type seen in granulation tissue and collagen I is present in normal skin.

3This is a virulent opportunistic pathogen and has become increasingly resistant to antibiotics. [69]
[69] investigated the role of quorum sensing (QS) in *Pseudomonas aeruginosa*, which is a cell mechanism that regulates pathogenic activity. Effects of QS on the wound environment and the infection process are integrated into the model. It was found that the QSM diffusion within the wound impedes the blood supply, which could contribute to the development of infections. The model proposed that QSM degrading components could prevent further infection as it would inhibit the signalling system and release of virulent agents into the wound environment. Although the complexity of the model was simplified using logical assumptions, it can be extended to account for bacterial invasion (which was not considered in this model) into healthy tissue and the blood supply. Such knowledge would be appreciated in this area.

Although it is common knowledge that chronic wounds are characterised by persistent bacterial infections, the number of mathematical modelling studies presenting such investigations are limited.

2.1.3 Psoriatic Models

Psoriasis affects both the dermis and epidermis, however the characteristics are primarily seen in the epidermal membrane and it is commonly believed that hyperproliferation takes place, inhibiting cell loss [62, 49]. There are only a small number of studies conducted in this area [49, 62, 115, 75], which has focused on the spatial domain typically using partial differential equation (PDE) systems.

One of the first models [62], explored cell renewal of the epidermis using data from normal and psoriatic patients, focusing on migration, cell loss and proliferation of the basal layer. Findings suggest that there is reduction in cell cycle time or increased GF distribution, and may lead to a less active stratum corneum and premature desquamation. This is supported by [75], where it was found that desquamation and cell detachment from the skin surface is greatly perturbed and abnormality in the keratinisation process leads to parakeratosis. Other factors such as Nitric Oxide (NO) [115] have been reviewed, which is an important signalling molecule that is highly active in this skin condition. The model predicts that there is a decline in NO flux followed by intense degree of erythema, which increases the release rate into psoriatic plaques, whether this is a cause or effect is still unclear.

2.2 Summary

The factors considered in these models do not account for the complete wound healing processes, of any of the three phases known and discussed in Chapter 1. They focused on specific

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*QS is a mechanism used by bacteria to determine their population density to influence their behaviour appropriately. This is achieved by the production and monitoring of signalling molecules.

*Redness of skin, which may result from inflammation.
processes of healing such as chemical regulators e.g. EGF, PDGF and TGF-β or cell densities of keratinocytes and fibroblasts, thought to be essential for repair.

Many mathematical models have been discussed in this chapter that highlight key findings from a selection of existing epidermal, dermal wound healing and psoriatic models using PDE, ODE systems and deterministic approaches to name a few. They provide scope and support for the investigation that will commence in this thesis.

The models proposed in Chapter 3-6, build on some of their ideas, with the focus on regular and irregular healing activity of the epidermal and dermal membranes.
Chapter 3

Re-epithelisation

3.1 Introduction

The epidermis provides skin protection and is the first barrier between the internal organisms and the outside environment, preventing external stimuli entering the body and is particularly important during wound healing. In this chapter our main focus is re-epithelisation, which describes recreation of the intact epidermal layers through the process of keratinisation. As discussed in Chapter 1, keratinocyte reproduction occurs only in the basal layer. Cell differentiation and death takes place in the subsequent layers mediated by GFs, as they move towards the skin surface and undergo morphological and structural changes (see Figure 1.2).

To investigate superficial wounds which includes cuts, grazes and general wound recovery, we explore the keratinisation process in the latter stages of repair. This will help interpret the normal behaviour of skin repair, and identify the key components involved in re-epithelisation and wound closure. The model differs from other epidermal models as it focuses on key events in the re-epithelisation process, where keratinisation is highlighted. The modelling in this chapter, will provide insight and a foundation for further research, discussed in the chapters to follow where we consider skin conditions and deep tissue wounds.

3.2 Mathematical Modelling

3.2.1 Introduction

The mathematical modelling to come in this section will focus on epidermal recovery in the re-epithelisation stage of wound healing. Although we have discussed numerous biological factors involved in mediating the normal epidermal activities, simplifications will be made.
We present a simple model that takes into account growth at the basal lemma, the passage of
keratinocytes from live to dead cell states, cell-cell binding and a regulator (e.g. EGF, KGF). Despite the complexity of the resulting model, it can be analysed in a biological reasonable
limit discussed in 3.3.1.

The main aims of the modelling to come are

- To describe the reepithelisation process.
- Obtain insight into the epidermal behaviour of keratinocyte cell binding and signal usage.
- Obtain insight into the effects of GFs on skin characteristics.
- Obtain insights into the GFs in impaired healing e.g. chronic wounds.

The one dimensional PDE system derived below will be used to investigate the relative im-
portance of signal molecules (could be GFs or nutrients) on live cell density (keratinocytes),
intracellular binding strength and cellular velocity, arising from the volume creation of cells at
the basal membrane. The model traces the evolution of the keratinocytes as they grow from
the basal layer and eventually slough off at the surface. The mitotic activity near the basal
layer will not be considered in detail and will contribute as a boundary condition.

### 3.2.2 Governing Equations

The epidermis is defined in the spatial domain $0 < x \leq H_0$, where at $x = 0$ cells in the basal
layer region enter the domain and $x = H(t)$ is the skin's surface (see Figure 3.2). The skin
domain is assumed to consist only of live cells (fraction $n$), dead cells (fraction $m$) and water
(fraction $w$), hence

$$n + m + w = 1. \quad (3.1)$$

We will therefore ignore for simplicity sweat glands, hair follicles and fine epidermal structures,
such as undulating basal membrane [40]. The variables to be used in our mathematical model
of the epidermis are listed in Table 3.1.
Modelling Skin Growth

The main modelling assumptions regulating live cells, dead cells and water are

1. Live and dead cells have fixed volumes where $\phi$ is the ratio of dead and live cell volume and is given by

$$\phi = \frac{\text{Volume of dead cells}}{\text{Volume of live cells}}.$$  

2. When a cell dies, a fraction $\phi$ forms the dead cell and $1 - \phi$ becomes water where $0 \leq \phi \leq 1$.

3. If all the epidermal cells are alive, then water fraction is given by $1 - n_{\text{max}}$ as shown in Figure 3.1.

4. If all the epidermal cells are dead, then water fraction is given by $1 - m_{\text{max}}$ as shown in Figure 3.1

![Live cells at the basal layer](image1)

![Dead cells near the skin's surface](image2)

**Figure 3.1:** Representative skin tissue illustrating water fractions when all epidermal cells are live or dead.

5. The water fraction is lower in dead skin, hence $n_{\text{max}} < m_{\text{max}}$.

6. We assume that the water fraction is a linear function of $n$ and $m$ refer to (3.1) and Figures 3.1 and 3.2

7. Live and dead cells move at a local velocity $v$, generated by growth in the basal layer and water fraction in between cells at a velocity $v_w$ as presented in Figure 3.2. The velocity of epidermal cells changes from the live cell state to the dead cell states, where we expect $v_n > v_m$.

8. Cell death is regulated by a signal molecule sourced from the basal region. Cell death is enhanced as signal decreases.

9. Only live cells maintain cell-cell binding material.
From (3.1) we can immediately write down \( w = 1 - m - n \) and the remaining constitutive relations will result from these assumptions, to provide equations for cell and water velocity. Applying these assumptions the equations for live and dead cells are

\[
\begin{align*}
\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}(vn) &= -k_d(c)n, \\
\frac{\partial m}{\partial t} + \frac{\partial}{\partial x}(vm) &= k_d(c)n \phi,
\end{align*}
\]

in \( 0 < x < H(t) \), which states that the rate of change of \( n \) and \( m \) in this medium is governed by the death rate function \( k_d \), defined by the Hill function \([82]\)

\[
k_d(c) = \Omega \left( 1 - \frac{\sigma c^\eta}{c_c^\eta + c^\eta} \right),
\]

where \( \Omega, c_c, \eta \) are positive constants and \( \sigma \) is a constant such that \( 0 < \sigma \leq 1 \). This is a monotonic decreasing function of \( c \), so that the death rate is reduced as \( c \) increases. Since the source of \( c \) is at \( x = 0 \), we expect the level of dead cells to increase as \( x \) increases. From (3.2) and (3.3), low \( c \) concentrations will result in higher death rate and live cells will die with lowering signal concentrations.

From (3)-(6) in the above assumptions, we obtain the following constitutive equation

\[
w = (1 - n_{\text{max}}) \frac{n}{n_{\text{max}}} + (1 - m_{\text{max}}) \frac{m}{m_{\text{max}}},
\]
which combined with (3.1) implies
\[ \frac{n}{n_{\text{max}}} + \frac{m}{m_{\text{max}}} = 1, \quad (3.6) \]
hence \( w \) and \( m \) can be expressed as an explicit function of \( n \).

The velocity \( v \) is created by cell movement between the basal layer and skin's surface. Cell growth at the basal membrane will drive motion at velocity \( v_0 \) at \( x = 0 \), therefore \( v(0, t) = v_0 \).

A typical cell is approximately 10\,\mu\text{m} and it takes about 1 day for the cell to reproduce, we expect \( v_0 \approx 0.01 \text{mm/day} \) and \( v(x, t) \) will vary in relation to loss or death of cell volume. To derive an expression for the velocity field \( (v) \) generated by cell movement we divide (3.2) and (3.3) with \( n_{\text{max}} \) and \( m_{\text{max}} \), respectively, giving
\[ \frac{\partial n}{\partial t} + \frac{\partial (vn)}{\partial x} = -k_d(c)\frac{n}{n_{\text{max}}}, \tag{3.7} \]
\[ \frac{\partial m}{\partial t} + \frac{\partial (vm)}{\partial x} = k_d(c)\phi \frac{n}{m_{\text{max}}}, \tag{3.8} \]
which results on addition and using (3.6) the velocity field of
\[ \frac{\partial v}{\partial x} = k_d(c)n \left( \frac{\phi}{m_{\text{max}}} - \frac{1}{n_{\text{max}}} \right), \tag{3.9} \]
We note from the assumption \( \phi \leq 1 \) and \( n_{\text{max}} < m_{\text{max}} \), that
\[ \left( \frac{\phi}{m_{\text{max}}} - \frac{1}{n_{\text{max}}} \right) < 0, \]
so that \( \partial v/\partial x < 0 \) and hence the skin cell movement velocity decreases as cells move towards the surface.

Water is only generated when a cell dies and is given by
\[ \frac{\partial w}{\partial t} + \frac{\partial (v_w w)}{\partial x} = k_d(c)n(1 - \phi), \tag{3.10} \]
where \( v_w(t) \) (advection) is the local water velocity. Adding (3.2), (3.3) and (3.10) gives
\[ \frac{\partial}{\partial x} (v(n + m) + v_w w) = 0, \tag{3.11} \]
where \( V(t) \) is a time dependent function that defines the combined net material flux
\[ v(n + m) + v_w w = V(t), \tag{3.12} \]
suggesting that volume is conserved in the skin medium.
Modelling Cell Binding

We will combine the various cell binding components into a single variable \( b \), which represents a suitably averaged concentration of desmosomes, gap junctions and tight junctions in the local epidermal medium. We assume that binding proteins are generated by live cells, and decay naturally in the skin medium and move at a velocity \( v(x,t) \). We propose that

\[
\frac{\partial b}{\partial t} + \frac{\partial (v b)}{\partial x} = \mu b - \delta b, \tag{3.13}
\]

where \( \mu \) and \( \delta \) are positive constants. Here

- \( \mu \) - Production rate of binding proteins by live cells
- \( \delta \) - Death/natural loss of binding proteins.

The steady state at \( x = 0 \)

\[
b = \frac{\mu m_{\text{max}}}{\delta + v_x}, \tag{3.14}
\]

where

\[
v_x = \frac{\partial v}{\partial x} = k_0(c) m_{\text{max}} \left( \frac{\phi}{m_{\text{max}}} - \frac{1}{n_{\text{max}}} \right),
\]

is therefore taken to be the normal binding state between healthy cells.

Modelling Signals (GFs)

We consider a generic signal that mediates essential epidermal activities. Cells in the epidermis like all epithelia do not contain blood vessels, and rely on diffusion from the dermis and hypodermis to supply nutrients and chemical mediators.

The general conservation equation for signal concentration is given by

\[
\frac{\partial c}{\partial t} = -\frac{\partial J_c}{\partial x} - \lambda n k_c(c). \tag{3.15}
\]

where \( J_c \) is the signal flux and we assume that living cells degrade the GFs (e.g. by proteolysis which is degradation of proteins into smaller simpler molecules) and use nutrients available.

The random motion of the GFs will be modelled by Fickian diffusion and water advection. Assuming the signals are present intra and extra-cellularly quickly approach an equilibrium, the flux \( J_c \) is given by

\[
J_c = -D_c \frac{\partial c}{\partial x} + v_w wc + v(n + m)c = -D_c \frac{\partial c}{\partial x} + V(t)c \tag{3.16}
\]

where using (3.16)

- \( v_w wc \) - Advection in water phase.
• $v(n + m)$ c- Advection of $c$ within live and dead cell phases.

On substitution into (3.11) and using (3.15), the signal concentration is given by

$$\frac{\partial c}{\partial t} + V(t) \frac{\partial c}{\partial x} = Dc \frac{\partial^2 c}{\partial x^2} - \lambda n k_c(c).$$

(3.17)

The function $\lambda n k_c(c)$ is the signal molecule consumption rate by living cells, where we have implicitly assumed that the natural degradation rate of $c$ is negligible (this is reasonable if $c$ is a nutrient). The function $k_c(c)$ is expected to be monotonically increasing to reflect increased consumption with signal concentration. The function we propose is

$$k_c(c) = (\Omega - k_d(c)) = \frac{c^\alpha}{c^\beta + c^\alpha},$$

which has the right qualitative features and is a useful form for the analysis later.

We note that the only source of GFs is from the basal region. We also assume that the damage to the epidermis is fairly minor, such that there is a minimal inflammatory response and signals produced by cells (e.g. GFs) in the epidermis.

**Boundary Conditions**

The boundary conditions imposed on the model are as follows

- At $x = 0$, denotes the end of the basal layer where only living cells are present in preparation for cell maturation, so we impose

  $n = n_{max}$, $c = c_0$, $v = v_0$ and $b = \frac{\mu n_{max}}{\delta + v_x}$.

- At $x = H(t)$ at the skin’s surface, we assume a zero flux boundary condition on $c$ (more details are provided in Appendix B.2.1), hence

  $$\left( \frac{dH}{dt} - V(t) \right) c + Dc \frac{\partial c}{\partial x} = 0.$$  

Desquamation at the skin’s surface is given by

$$\frac{dH}{dt} = v - \frac{F_0}{b},$$

(3.18)

where $F_0$ is a positive constant. Equation (3.18) states that the surface grows at a rate equal to the net difference between local velocity and sloughing rate, which is modelled as simply being inversely proportional to the concentration of binding proteins, hence
we can deduce from (3.14)
\[ F_0 < \frac{\theta \mu_{\text{max}}}{\delta + v_x}. \]  
(3.19)

for \( \delta > 0 \).

Suitable boundary conditions for \( \nu_w \) is unclear. In healthy skin very little moisture escapes through the keratinised layer, suggesting \( \nu_w = 0 \) on \( x = H(t) \), however if the keratinised layer is absent then \( \nu_w > 0 \). In the next section it will be shown that the effects of the water flow seems to be negligible and \( \nu_w \) will decouple from the system, and the complication provided by the flow term will no longer be discussed.

**Initial Conditions**

To close the system we need to impose a set of initial conditions. In the simulation to follow we start with a superficial wound, that has cleared away the keratinised layer and we start with a domain \( x \in (0, H_0) \), which consists of 2-3 layers of live cells at \( x = 0 \). The initial conditions that define this specific problem is defined below

- At \( t = 0 \) (basal layer \( x = 0 \)), we suppose that all dead cells are removed

\[ n = n_{\text{max}}, \quad m = 0, \quad c = c_0 \quad \text{and} \quad b = \frac{\mu_{\text{max}}}{\delta + v_x}. \]

**Full System of Equations**

For purposes of clarity, we present the full system:

\[
\begin{align*}
\frac{\partial m}{\partial t} + \frac{\partial}{\partial x} (vm) &= -k_d(c)n, \\
\frac{\partial m}{\partial t} + \frac{\partial}{\partial x} (vm) &= k_d(c)n\phi, \\
\frac{\partial w}{\partial t} + \frac{\partial}{\partial x} (w) &= k_d(c)n(1 - \phi) \\
\frac{\partial v}{\partial t} + \frac{\partial}{\partial x} (v) &= k_d(c)n \left( \frac{\phi}{n_{\text{max}}} - \frac{1}{n_{\text{max}}} \right), \\
\frac{\partial b}{\partial t} + \frac{\partial}{\partial x} (vb) &= \mu n - \delta b, \\
\frac{\partial c}{\partial t} + V(t) \frac{\partial c}{\partial x} &= D_c \frac{\partial^2 c}{\partial x^2} - \lambda k_c(c),
\end{align*}
\]  
(3.20) \quad (3.21) \quad (3.22) \quad (3.23) \quad (3.24) \quad (3.25)

where the death rate function is given by

\[ k_d(c) = \Omega \left( 1 - \frac{\sigma c^n}{c_0^n + c^n} \right), \]

and

\[ V(t) = v(1 - w) + \nu_w w. \]
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Experimental Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Omega)</td>
<td>Cell death constant</td>
<td>0.5 day(^{-1})</td>
</tr>
<tr>
<td>(\sigma)</td>
<td>Cell death constant</td>
<td>-</td>
</tr>
<tr>
<td>(\mu)</td>
<td>Birth of binding proteins</td>
<td>-</td>
</tr>
<tr>
<td>(c_c)</td>
<td>Death rate in signal concentration</td>
<td>-</td>
</tr>
<tr>
<td>(\lambda)</td>
<td>Natural loss of signal concentration</td>
<td>-</td>
</tr>
<tr>
<td>(\beta)</td>
<td>Natural loss by sloughing</td>
<td>-</td>
</tr>
<tr>
<td>(\delta)</td>
<td>Decay in binding concentration</td>
<td>-</td>
</tr>
<tr>
<td>(D_c)</td>
<td>Diffusion coefficient of signals</td>
<td>4.3 mm(^2) day(^{-1}) [111]</td>
</tr>
<tr>
<td>(\eta)</td>
<td>Cell death rate</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>(H)</td>
<td>Height of the epidermal medium</td>
<td>0.07-1.5 mm [40]</td>
</tr>
<tr>
<td>(m_{\text{max}})</td>
<td>Maximum fraction live cells occupy</td>
<td>80-95% [40]</td>
</tr>
<tr>
<td>(m_{\text{max}})</td>
<td>Maximum fraction dead cells occupy</td>
<td>-</td>
</tr>
<tr>
<td>(\phi)</td>
<td>vol m/vol n</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>(v_w)</td>
<td>Advection in water</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3.2: Parameters considered in the skin model and corresponding experimental values.

This is a nonlinear coupled system of partial differential equations of mixed type defined in the domain \(x \in (0, H(t))\). The dead cell and water fractions are obtained from (3.1) and (3.6). The model parameters are presented and defined in Table 3.2, where values are given for those available and suitable from literature.

### 3.2.3 Nondimensionalisation

We nondimensionalise the system using

\[
\begin{align*}
\{\tilde{x}, \tilde{t}\} &= \left\{ \frac{\Omega x}{u_0}, \frac{t}{\Omega} \right\}, \\
\{\tilde{H}, \tilde{h}, \tilde{v}_w, \tilde{\phi}\} &= \left\{ \frac{\Omega H}{v_0 \mu}, \frac{\delta}{u_0}, \frac{\nu}{u_0}, \frac{\tilde{v}_w}{u_0}, \frac{\tilde{\phi}}{\phi_0} \right\},
\end{align*}
\]

where hatted variables denote dimensionless quantities. Here, time has been rescaled with the maximum cell death rate, and space with the distance a cell would travel in this time near the basal lemma.

Defining the following dimensionless constants as

\[
\begin{align*}
\{\tilde{c}_c, \tilde{\delta}, \tilde{\beta}\} &= \left\{ \frac{c_c}{c_0}, \frac{\delta}{c_0}, \frac{F_0}{\Omega c_0 \mu u_0} \right\}, \\
\{\tilde{\epsilon}, \tilde{\lambda}, \tilde{\mu}\} &= \frac{v_0^2}{D_c} \left\{ \frac{1}{\Omega}, \frac{\lambda}{\Omega}, \frac{\mu}{\Omega} \right\},
\end{align*}
\]
we derive the nondimensionalise system, dropping the hats for clarity,

\[
\frac{\partial n}{\partial t} + \partial (vn) = -\left(1 - \frac{\sigma c^n}{c_1^n + c_1^n}\right)n, \quad (3.26)
\]

\[
\frac{\partial n}{\partial x} = n\left(1 - \frac{\sigma c^n}{c_2^n + c_2^n}\right)\left(\phi \frac{1}{n_{\text{max}}} - \frac{1}{n_{\text{max}}}\right), \quad (3.27)
\]

\[
\frac{\partial b}{\partial t} + \partial (vb) = n - \delta b, \quad (3.28)
\]

\[
\epsilon \left(\frac{\partial c}{\partial t} + V(t) \frac{\partial c}{\partial x}\right) = \frac{\partial^2 c}{\partial x^2} - \lambda n - \frac{c^n}{c_1^n + c_2^n}. \quad (3.29)
\]

In practice the timescales of diffusion of signals across the skin thickness will be considerably less than cell movement through growth (weeks), hence the Péclet number satisfies \(\epsilon \ll 1\); setting \(\epsilon = 0\), equation (3.29) reduces to the quasi-steady equation

\[
\frac{\partial^2 c}{\partial x^2} - \lambda n - \frac{c^n}{c_1^n + c_2^n} = 0. \quad (3.30)
\]

The boundary conditions after nondimensionalisation are given by

• At \(x = 0\), \(n = n_{\text{max}}, m = 0, c = 1, v = 1\) and \(b = \frac{n_{\text{max}}}{\delta + v}\).

• At \(x = H(t)\)

\[
\frac{dH}{dt} = v - \beta
\]

and

\[
\frac{\partial c}{\partial x} = 0.
\]

We note that the rescalings imply

\[
\beta < \frac{\mu n_{\text{max}}}{\delta}. \quad (3.31)
\]

The dimensionless form of the initial conditions discussed in the previous section are

• At \(t = 0\), \(n = n_{\text{max}}, m = 0, b = \frac{n_{\text{max}}}{\delta + v}\) and \(H = 1\), where an initial condition for \(c\) is no longer required due to the quasi-steady equation.

Equations (3.26)-(3.28) and (3.30) together with the set of initial and boundary conditions form a closed system. Table 3.3 presents the nondimensionalised parameters and their "standard value" used in the simulation to follow.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Dimensionless Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda )</td>
<td>Consumption rate constant ( c )</td>
<td>0.2</td>
</tr>
<tr>
<td>( \epsilon )</td>
<td>Péclet number of ( c )</td>
<td>( \ll 1 )</td>
</tr>
<tr>
<td>( \beta )</td>
<td>Natural loss by sloughing</td>
<td>0.001</td>
</tr>
<tr>
<td>( c_\epsilon )</td>
<td>Death rate hill function coefficient</td>
<td>0.01</td>
</tr>
<tr>
<td>( \delta )</td>
<td>Decay rate constant ( b )</td>
<td>2.0</td>
</tr>
<tr>
<td>( \eta )</td>
<td>Death rate hill function exponent</td>
<td>10.0</td>
</tr>
<tr>
<td>( H_0 )</td>
<td>Initial height of the epidermal medium</td>
<td>1.0</td>
</tr>
<tr>
<td>( n_{\text{max}} )</td>
<td>Maximum fraction live cells occupy</td>
<td>0.8</td>
</tr>
<tr>
<td>( m_{\text{max}} )</td>
<td>Maximum fraction dead cells occupy</td>
<td>0.999</td>
</tr>
<tr>
<td>( \phi )</td>
<td>Volume of dead and live cells</td>
<td>1.0</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>Cell death constant</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 3.3: Table of parameters used in the dimensionless epidermal model, together with values used in simulations.

### 3.3 Healthy Epidermis Analysis

#### 3.3.1 Steady State Solutions

The skin in homeostasis is a dynamic steady state. In terms of the model proposed in Section 3.2.2, the components satisfy the steady states of (3.26)-(3.28) and (3.30), namely

\[
\frac{d(vn)}{dx} = -k_d(c)n, \quad (3.32)
\]
\[
\frac{dv}{dx} = nk_d(c)\left(\frac{\phi}{m_{\text{max}}} - \frac{1}{n_{\text{max}}}\right), \quad (3.33)
\]
\[
\frac{d(vb)}{dx} = n - \delta b, \quad (3.34)
\]
\[
\frac{d^2c}{dx^2} = \lambda n k_d(c), \quad (3.35)
\]

subject to

- At \( x = 0 \): \( n = n_{\text{max}}, v = 1, c = 1 \) and \( b = \frac{m_{\text{max}}}{\delta + v_r} \).

- At \( x = H_\infty \):

\[
\frac{\partial c}{\partial x} = 0 \quad \text{and} \quad v = \frac{\beta}{b},
\]

where the free boundary \( H_\infty \) is the thickness of a healthy epidermis at steady state. This system is too complex for analytical solutions in the general case, however, in the limit of \( \eta \to \infty \) and \( \sigma = 1 \); \( k_d(c) \) reduces to the step function enabling progress to be made.
The Limit of \( n_d \to \infty \)

Writing \( k_d(c) \) in terms of the Heaviside step function, by taking the limits \( \eta \to \infty \) and \( \sigma = 1 \) leads to

\[
k_d(c) = 1 - H(c - c_c) = \begin{cases} 
1 & c > c_c \\
0 & c \leq c_c.
\end{cases}
\]

The wound domain \( x \in (0, H_\infty) \) is distinguished by two regions corresponding to \( c > c_c \) and \( c \leq c_c \). We define \( x = x_c \) to be the smallest value \( x \) such that \( c = c_c \), which marks the boundary between the two regions of live and dead cell states. Imposing continuity and\[ continuity as appropriate at flux of \( x = x_c \) we have \]

\[
x = x_c: \quad c(x_c^-) = c(x_c^+), \quad n(x_c^-) = n(x_c^+), \quad b(x_c^-) = b(x_c^+),
\]

\[
\frac{dc}{dx}(x_c^-) = \frac{dc}{dx}(x_c^+) \quad \text{and} \quad v(x_c^-) = v(x_c^+).
\]

The condition at \( x = 0 \) and \( x = H_\infty \) are as above. We will find the solution \( c, n, b \) and \( v \) for the two regions from which we can determine the co-ordinates of the free boundaries \( x = x_c \) and \( x = H_\infty \). The problem is summarised in Figure 3.3.

\( 0 < x < x_c \)

Denoting variables in this region with a superscript \(^-\), where \( k_d = 0 \), gives the system

\[
\frac{d}{dx}(v^- n^-) = 0, \quad \text{(3.36)}
\]

\[
\frac{dv^-}{dx} = 0, \quad \text{(3.37)}
\]

\[
\frac{d}{dx}(v^- b^-) = n^- - b^- \quad \text{and} \quad \frac{dc^-}{dx^2} = \lambda n^- . \quad \text{(3.39)}
\]

Integrating (3.36)-(3.39) and using the boundary conditions at \( x = 0 \) and \( x = x_c \) we obtain

\[
n^- = n_{\text{max}} \quad \text{(3.40)}
\]

\[
b^- = \frac{n_{\text{max}}}{\delta} \quad \text{(3.41)}
\]

\[
v^- = 1 \quad \text{(3.42)}
\]

\[
c^- = c_c + \frac{\lambda n_{\text{max}}}{2} (x_c - x)^2 \quad \text{(3.43)}
\]
where \( c^- (0) = 1 \) provides the location of the free boundary \( x_c \), given by

\[
x_c = \sqrt{\frac{2}{\lambda n_{\text{max}}} (1 - c_c)}.
\]  

(3.44)

\( x_c < x < H_\infty \)

Denoting the variables in this region with a superscript \( ^{++} \), where \( k_d(c) = 1 \), gives

\[
\frac{d}{dx} (v^+ n^+) = -n^+,
\]

(3.45)

\[
\frac{d n^+}{dx} = n^+ \Gamma,
\]

(3.46)

\[
\frac{d}{dx} (v^+ b^+) = n^+ - \delta b^+,
\]

(3.47)

\[
\frac{d n^+}{dx} = 0
\]

(3.48)

where

\[
\Gamma = \left( \frac{\phi}{n_{\text{max}}} \right) - \frac{1}{n_{\text{max}}).
\]

(3.49)

From (3.49) we have \( \Gamma < 0 \) and thus

\[
1 + n \Gamma > 1 + n_{\text{max}} \Gamma = \frac{\phi n_{\text{max}}}{n_{\text{max}}} > 0,
\]

so \( F(n) > 0. \)
A useful function in what follows is $F(n)$, defined as

$$F(n) = \frac{1}{1 + n\gamma}. \quad (3.50)$$

Integrating (3.48) using the boundary conditions at $x = x_c$ and $x = H_0^+$, we obtain immediately

$$c^+ = c_0. \quad (3.51)$$

Equations (3.45) and (3.46) imply,

$$\frac{d(v^+ n^+)}{dx} = - \frac{1}{\Gamma} \frac{dv^+}{dx}, \quad (3.52)$$

$$\Rightarrow v^+ n^+ = n_{max} \quad (3.53)$$

using the condition at $x = x_c$, from which we can deduce

$$v^+ = \frac{F(n^+)}{F(n_{max})} = \frac{(1 + \Gamma n_{max})}{(1 + \Gamma n^+)}. \quad (3.54)$$

Substituting this into (3.45) gives

$$\frac{d}{dx} \left( \frac{F(n^+)}{F(n_{max})} \right) = \Gamma n^+, \quad (3.55)$$

which yields via the chain rule

$$\frac{dn^+}{dx} \cdot \frac{d}{dn} \left( \frac{F(n^+)}{F(n_{max})} \right) = \Gamma n^+, \quad (3.56)$$

leading to the differentiated equation for $n^+$

$$\frac{dn^+}{dx} = - \frac{F(n_{max}) n^+}{F(n^+)^2}, \quad (3.57)$$

using the fact that $F'(n) = -\Gamma/F(n)^2$. We note that $dn^+/dx < 0$, so live cell fraction is monotonically decreasing towards $x = H_0^+$ as expected, with $0 < n^+ < n_{max}$.

By integrating (3.56) we obtain an implicit equation for $n^+$ given by

$$0 = x - x_c - 1 + \frac{F(n^+)}{F(n_{max})} + \frac{1}{F(n_{max})} \ln \left( \frac{n^+ F(n^+)}{n_{max} F(n_{max})} \right). \quad (3.57)$$

For $b(x^+)$ we expand the derivatives in (3.47) and using (3.45) and (3.54), we obtain

$$\frac{db^+}{dx} = \frac{n^+ - \delta b^+ - b^+ v^+}{v^+} = \frac{F(n_{max})}{F(n^+)} (n^+ - (\delta + \Gamma n^+) b^+). \quad (3.58)$$
We now change the independent variable to \( n^+ \), which yields on using the chain rule and (3.56),

\[
\frac{db^+}{dx} = -\frac{n^+ F(n_{\text{max}})}{F(n^+)^2} \frac{db^+}{dn^+},
\]

which results with the following differential equation for \( b^+(n^+) \)

\[
\frac{db^+}{dn^+} - \frac{(\delta + \Gamma n^+)b^+}{n^+(1 + \Gamma n^+)} = -\frac{1}{1 + \Gamma n^+},
\]

substituting for \( F(n^+) \). This has an integrating factor

\[
(1 + \Gamma n^+)^{\delta-1} n^{+(-\delta)},
\]

from which we obtain the solution (using maple)

\[
b(n^+) = \frac{n^+}{\delta - 1} \left( 1 - \frac{(1 + \Gamma n_{\text{max}})^{\delta-1} n^{+\delta-1}}{\delta (1 + \Gamma n^+)^{\delta-1} n_{\text{max}}^{\delta-1}} \right),
\]

using the condition \( b^+(n_{\text{max}}) = n_{\text{max}}/\delta \) at \( x = x_c \). The above analysis assumes that \( \delta \neq 1 \), \( \delta = 1 \) is a very special case that the current analysis will not address.

In order to determine the co-ordinate of the free boundary \( H_x \) from (3.57), we need to determine \( n_\infty \), where \( n_\infty = n^+(H_x) \). Equations (3.54) and (3.58) express \( v^+ \) and \( b^+ \) as functions of \( n \), hence the boundary condition at \( x = H_x \), \( v^+ = \beta/b^+ \) can be expressed at \( P(n_\infty) = v^+(n_\infty)b^+(n_\infty) - \beta = 0 \), where \( P(n) \) is given by

\[
P(n) = \frac{F(n)n}{F(n_{\text{max}})(\delta - 1)} \left( 1 - \frac{F(n)^{\delta-1} n^{\delta-1}}{\delta F(n_{\text{max}})^{\delta-1} n_{\text{max}}^{\delta-1}} \right) - \beta.
\]

We note that \( F(0) = -\beta < 0 \) and

\[
P(n_{\text{max}}) = \frac{n_{\text{max}}}{\delta - 1} \left( 1 - \frac{1}{\delta} \right) - \beta > \frac{n_{\text{max}}}{\delta - 1} \left( 1 - \frac{1}{\delta} \right) - \frac{n_{\text{max}}}{\delta} = 0,
\]

since \( \beta < b^+(x_c) = n_{\text{max}}/\delta \), hence by continuity, there exists a root \( n_\infty \) such that \( P(n_\infty) = 0 \). Suitable roots satisfying \( P(n_\infty) = 0 \) can be routinely computed using, for example the Newton-Raphson method. Having found \( n_\infty \), the steady state for skin thickness \( H_x \) can be found from (3.57), namely

\[
H_x = x_c + 1 - \frac{P(n_\infty)}{F(n_{\text{max}})} - \frac{1}{F(n_{\text{max}})} \ln \left( \frac{n_\infty F(n_\infty)}{n_{\text{max}} F(n_{\text{max}})} \right)
\]

The time it takes for cells to move from the basal layer region to the skin’s surface, \( T_\infty \) can
be obtained from
\[ T_\infty = \int_0^{H_\infty} \frac{1}{v} \, dx. \]  
(3.62)

This can be obtained exactly using the above analysis, where (3.54) gives
\[ T_\infty = \int_0^{H_\infty} \frac{F(n_{\max})}{F(n)} \, dn, \]  
(3.63)

which changing the variable using (3.56), we can solve (3.62) this to get
\[ T_\infty = \int_{n_{\infty}}^{n_{\max}} \frac{F(n)}{n} \, dn \]
\[ = \ln \left( \frac{n_{\max}F(n_{\max})}{n_\infty F(n_\infty)} \right), \]  
(3.64)

which can be computed given \( n_\infty \).

The analysis makes explicit what the model predicts as the key processes governing the epidermal structure. For \( 0 \leq x \leq x_c \), the thickness of the live layer is governed by signal concentration refer to equation (3.44). From (3.61) the thickness of dying and dead layer \( H_\infty - x_c \) is dependent on \( n_{\max} \) and \( n_\infty \); the latter satisfying \( P(n_\infty) = 0 \) from (3.59). This suggests \( n_\infty \) is dependent on the binding parameters \( \beta \) and \( \delta \), and the cell volume parameters \( \Gamma \) and \( n_{\max} \). The thickness of the skin varies in the body, with a tendency to be thinner where skin experiences more wear and tear (e.g. palms of hands and soles of feet).

In the dimensional form of the model, the two parameters which can be altered for the adaptation to the external influence are \( c_0 \) (input signal concentration) and \( \mu \) (binding production rate); as the other parameters such as diffusion and decay rates, are intrinsic physical properties and cannot be changed so easily. In dimensionless terms, \( \lambda \) and \( c_0 \) are inversely proportional to \( c_0 \) and \( \beta \) is inversely proportional to \( \mu \).

We would expect that increasing \( c_0 \) and \( \mu \) would enhance skin thickness. From (3.44), decreasing both \( \lambda \) and \( c_0 \) (\( \equiv \) increasing \( c_0 \)) will increase \( x_c \), thereby thickening the live cell component of the epidermis. It is more difficult to see from the analysis the effects of decreasing \( \beta \) (\( \equiv \) increasing \( \mu \)) and we derive the expected result \( dH_\infty/d\mu > 0 \) (in dimensional terms) by showing the (non-dimensional) equivalent relationship
\[ \frac{dH_\infty}{d\beta} < 0. \]  
(3.66)

We note first that \( \Gamma < 0 \) implies \( F'(n_\infty) = -\Gamma/F(n_\infty)^2 > 0 \). We will now determine the signs of \( dH_\infty/dn_\infty \) and \( dn_\infty/d\beta \) so that (3.66) follows from the chain rule. From (3.61) we have
\[ \frac{dH_\infty}{dn_\infty} = -\frac{F'(n_\infty)}{F(n_{\max})} - \frac{1}{F(n_{\max})} \left( \frac{1}{n_\infty} + \frac{F'(n_\infty)}{F_\infty} \right) < 0, \]
since \( F'(n_\infty) > 0 \). Writing \( P(n) \) in (3.59) as follows

\[
P(n_\infty) = \frac{1}{F(n_{\text{max}})} \left( \Lambda(n_\infty) - \frac{\Lambda(n_{\text{max}})^{\delta}}{\delta \Lambda(n_{\text{max}})^{\delta-1}} \right) - \beta = 0,
\]

where \( \Lambda(n) = nF(n) \). Taking derivatives with respect to \( \beta \) gives

\[
\frac{dP(n_\infty)}{d\beta} = \frac{1}{F(n_{\text{max}})} \frac{dn_\infty}{d\beta} \left( \Lambda'(n_\infty) - \frac{\delta \Lambda'(n_\infty) \Lambda(n_{\text{max}})^{\delta-1}}{\delta \Lambda(n_{\text{max}})^{\delta-1}} \right) - 1 = 0,
\]

hence

\[
\frac{dn_\infty}{d\beta} = \frac{F(n_{\text{max}})(\delta - 1) \Lambda(n_{\text{max}})^{\delta-1}}{\Lambda'(n_\infty)(\Lambda(n_{\text{max}})^{\delta-1} - \Lambda(n_\infty)^{\delta-1})}.
\]

The function \( \Lambda(n) \) is strictly monotonically increasing since \( \Lambda'(n) = F(n) + nF'(n) = 1/(1 + n\Gamma)^2 > 0 \), hence, the denominator is positive (negative) when \( \delta > 1 \) (\( \delta < 1 \)), thus with factor \( (\delta - 1) \) in the numerator \( dn_\infty/d\beta > 0 \). Using the chain rule (3.66) holds, and as expected, upregulating the binding material production (\( \equiv \) decreasing \( \beta \)) will have the effect of thickening skin. This analysis further suggests that the binding factor and signalling molecule should be regulated to control the epidermal structure.

### 3.4 Results

#### 3.4.1 Numerical Methods

For purposes of simplicity we rescale the nonlinear system before computing using finite difference methods (FDM). To accommodate the moving boundary, we write \( t = T \) and \( x = Z/H(t) \) and solve in the \( Z \) domain over the unit interval

Using the chain rule, the rescalings imply

\[
\frac{\partial}{\partial t} = \frac{\partial T}{\partial T} \frac{\partial}{\partial T} + \frac{\partial Z}{\partial T} \frac{\partial}{\partial T},
\]

and

\[
\frac{\partial Z}{\partial x} = 0.
\]

Since \( \frac{\partial Z}{\partial t} = -\frac{\bar{Z}}{H} \) and \( \frac{\partial Z}{\partial x} = \frac{1}{H} \) the rescaled form of equations (3.26)-(3.28) and (3.30)
### Table 3.4: Parameter values used for the superficial wound model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$</td>
<td>0.2</td>
</tr>
<tr>
<td>$c_c$</td>
<td>0.01</td>
</tr>
<tr>
<td>$\delta$</td>
<td>2.0</td>
</tr>
<tr>
<td>$\eta$</td>
<td>5.0</td>
</tr>
<tr>
<td>$n_{max}$</td>
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</tr>
<tr>
<td>$m_{max}$</td>
<td>0.999</td>
</tr>
<tr>
<td>$\phi$</td>
<td>1.0</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>1.0</td>
</tr>
<tr>
<td>$\beta$</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### 3.4.2 Numerical Results

The solutions for the nondimensionalised 1D reaction-advection-diffusion system are discussed in Appendix A.1. The initial conditions applied are

\[ t = 0 : \quad n = 0.8, \quad m = 0, \quad b = 0.8, \quad c = 0.01 \quad w = 0.2 \quad \text{and} \quad v = 0.1 \]
Figure 3.4: Evolution of the (left) live cell fraction (n) and (right) cell-cell binding (b) in the epidermis at steps of \( t = 10 \) (initial curves are represented by the pink line at \( u(x, 0) = b(x, 0) = 0.8 \)) where the first arrow points to initial desquamation and the second arrow indicates the recovered skin thickness. The first dashed line illustrates the point where cells begin to die, the second dashed line (red) show the midpoint where live and dead cells coexist in equal numbers and the third line denotes the upper epidermal layers and development of the horny layer.

The parameter values used in this model to represent healing of a superficial wound, are given in Table 3.4.

The evolution of the model variables (live cell fraction \( n(x, t) \), dead cell fraction \( m(x, t) \), signal concentration \( c(x, t) \) and velocity \( v(x, t) \)) towards the healed/healthy steady state, which defines the removal of all live cells as they reach the skin's surface \( (H_{\infty} \approx 17.59) \) are illustrated in Figures 3.4 -3.5. They appear as hair like profiles protruding away from the solutions that evolve. The simulation suggests that the re-epithelisation process occurs in two stages defined below

1. **Stage 1**- Epidermal cell differentiation to the granular layer.

2. **Stage 2**- Epidermal cell death (and keratinisation \(^1\)) from the granular layer to the skin's surface.

This model predicts full recovery of the live layer before keratinisation takes place [23], after a superficial wound or incision has taken place where the epidermal membrane is lost. As discussed in 3.2.2, the live cell density \( n(x, t) \) is the greatest at the basal layer due to mitotic activity. Cells then progress further into the epidermal medium due to cell division at \( x = 0 \) in an upward directions undergoing maturation and phenotypic changes, where live and dead

\(^1\)Keratinisation is the self-renewal process of the epidermal membrane and provides a protective membrane.
cell regions become more pronounced. The initial stages of desquamating cells defines the transition from live to dying cells and is indicated by the first arrow (refer to figures 3.4-3.5). The steady state recovered thickness $H_\infty \approx 17.59$ (to 2 d.p) is given by the second arrow in the simulations.

In Figure 3.4, we observe the keratinisation process and the two cell states that takes places. A plateau of cells evolves initially with $n \approx n_{\text{max}}$, which falls away when $x \approx 8$ due to a decline in $c(x, t)$ to approximately $c_0 \approx 0.1$ (see Figure 3.5). In turn the binding strength declines at the same point, due to the decreased presence of their live cells producing the material. The model predicts that re-epithelisation process consists of a period in which all cells are alive (between $x = 0$ and $x \approx 8$). Only after a period of time (between $x = 8$ and $x = 12$ both live and dead cells exist), cells prepare for death and there is a full development of the dead (horny) layer between $x = 12$ and $x \approx 17.59$. The time taken for skin cells to move from A to B is given by

$$T_{A \to B} = \int_A^B \frac{1}{v} \, dx,$$

which was approximated numerically using the trapezium method and the values of $v$ obtained from the full system's solutions.

The typical duration of cell keratinisation is estimated to last 2-3 weeks and a further 2-3 weeks for desquamation, our results show an almost equal thickness for the two stages and there is a transitional period where live cells begin to die in the region $8 < x < 12$. In this simulation, a cell traverses the fully live region ($0 < x \leq 8$) in

$$T_{\text{live}} \approx \int_0^8 \frac{1}{v} \, dx = 16 \text{ days},$$

and traverse the dead cell region

$$T_{\text{dead}} \approx \int_8^{H_\infty} \frac{1}{v} \, dx = 27 \text{ days}.$$

The total time taken is approximately 6 weeks which is roughly the time in the thicker epidermal regions, such as the sole of the feet.

At the skin's surface $H_\infty$ there are negligible $b(x, t)$ as only dead cells are present and cell-cell binding is no longer needed (see Figure 3.4), as to be expected with $\beta = 0.001$. We can see over the first few timesteps that $\beta/b(H_\infty) \ll v(H)$ so the model predicts negligible desquaming for a large part of early epidermal healing.

We observe from Figure 3.5 (left simulation) the change in signal behaviour when the re-epithelisation process takes place. It can be interpreted that due to the domain size, $c(x, t)$ is more elevated initially, before more rapidly dropping as the domain size increases ($0 < x < 8$). It is observed that as skin repairs, molecules such as growth factors and nutrients, are at ele-
Figure 3.5: Evolution of the (left) signal concentration \( c \) and (right) velocity \( v \) at steps of \( t = 10 \) (initial curves are represented by the grey line at \( c(x, 0) = 1 \) and pink line at \( v(x, 0) = 1 \) respectively), where the first arrow points to initial desquamation and the second arrow indicates the recovered skin thickness. The first dashed line illustrates the point where cells begin to die, the second dashed line (red) show the midpoint where live and dead cells coexist in equal numbers and the third line denotes the upper epidermal layers and development of the horny layer.

The velocity profile is shown in Figure 3.5 fluctuates between 0.8 and 1 where the velocity generated by cell movement is greatest between the basal and granular layers defined by \( x = 0 \) and \( x \approx 8 \) within the live cell region. The velocity declines as cells die/desquamate due to cell volume loss in the later phase, reflecting dehydration and keratinisation. It should be noted that the velocity incorporates change of live cells as they lose moisture and undergo change in cellular structure within the epidermal membrane. The model predicts also that the velocity becomes constant as it approaches the surface, but never reaches 0, which is supported by literature as cells are in continual movement, until they reach the skin’s surface [11, 40].

Manipulating \( \lambda \) alters the delivery of growth factors to the epidermis, the different scenarios using \( \lambda = 0.05, \lambda = 0.2 \) and \( \lambda = 0.8 \) are presented in Figure 3.6 (left simulation). The standard simulation used \( \lambda = 0.2 \), in which the live and dead cell regions are approximately equal thickness and the parameters were chosen appropriately to ensure this. As \( \lambda \) increases the growth factor delivery becomes less efficient and does not penetrate as deep, impeding full recovery as cell die quickly. The resulting skin has thinner live cell region and a dead cell
region of the same thickness (as expected from the analysis of Section 3.3). The thinness of the live cell layers presumably weakens the skin and makes it more prone to further damage such as infections, as it will be easily exposed if damaged.

The corresponding live cell distributions obtained by altering $\lambda$ are given in Figure 3.6 (right simulation). The plots show that as $\lambda$ increases the thickness of the live cell layer decreases, although the dead cell layers are similar in each case. This is predicted in the analysis in Section 3.3.1 in which $x_c \propto 1/\sqrt{\lambda}$ and the profile of $n(x, t)$ is independent of $\lambda$ for $x > x_c$.

### 3.5 Summary

In this chapter we considered superficial wounds describing epidermal growth and the keratinisation process in the epidermal sublayers as they divide, differentiate and die to ensure epidermal self-renewal. Re-epithelisation is a key process in wound healing, in which the epidermal membrane is reinstated to enable wound recovery and closure, and is a significant means of protection against the external environment from further insults.

A simple model was proposed, describing the evolution and interaction of live cells, cell-cell protein binding concentration and GF signals. The movement due to cell growth and death was accounted for using a velocity variable $V(t)$. The resulting 1D reaction-advection-diffusion model was solved and analytically studied in a steady state limit, also numerically using finite difference methods (refer to Appendix A.1).
The results suggest that the model can produce a quantitatively reasonable description of epithelial recovery and development. In a particular limit we can assess in terms of the model parameters epithelial thickness, thickness of live and dead cells and timescale for growth. The numerical results obtained followed closely profiles expected from biological literature, and provides a replication of the re-epithelisation process after superficial injuries using mathematical modelling. We also investigate the effect of growth factors on recovery rates and skin structure. This provides a basis to look more closely at impaired epidermal healing and will be an area considered in Chapter 4.

The key predictions from the model are as follows

- Re-epithelisation reforms the live cell layer (signal dominated) and once complete builds the keratinised layer which enables cell shedding/sloughing at the skin’s surface (refer to Figures 3.4 left simulation). The time taken for the whole process agrees with biological literature as our model predicted ≈ 6 weeks.

- Signal molecules from the dermis and binding protein production rate are sufficient to regulate the thickness and structure of the epidermis (refer to Figures 3.4 and 3.5 left simulations). A simple extension of the model could make the binding protein production rate a function of signal concentration, which may predict that the whole process can be regulated by a simple signal.

- Elevated signal/GF levels in the skin are not necessarily due to greater production resulting from injury. The geometry of a reduced domain can explain this observation, as signal concentrations are substantial, initially after skin loss (refer to Figure 3.5 left simulation).

The model was aimed at reproducing observed behaviour with minimal complexity. Factors believed to be important that were neglected in the model formulation include

- Independent GFs and their unique activities.
- Specific cellular attachments at the different stages of keratinisation.
- Calcium impact on cell binding or cell movement within the domain.
- Immune cell activity.

Some of the limitations imposed in this model as stated above will be addressed in the next chapter, when we consider the skin disease psoriasis which is characterised by defects in the keratinisation process.
Chapter 4

Psoriasis

4.1 Introduction

This noncontagious chronic, inflammatory, lifelong skin disease is diverse and appears in a variety of forms, severity, location and scaling pattern, with distinct characteristics affecting treatment strategies, as discussed in Chapter 1. The condition cannot be cured and treatment is aimed at reducing the symptoms instead.

This is still a relatively new research area and we are being more knowledgeable about the pathology, biological and physical properties of the constant developments that have been made. Many components have been identified which may be responsible or contribute to the onset of psoriasis and this will aid further expansion in this area. Globally there are over 80 million sufferers with a higher prevalence in Caucasians when compared to populations from South America, Nigeria and China [78, 123].

It is not uncommon to suffer from more than one type of psoriasis simultaneously, or the transition of one form to another mediated by certain trigger factors which are not fully understood [33, 93, 94].

This skin disease is characterised by hyperproliferation and unsystematic cell maturation. It should be noted that unlike Sherratt et al’s model [113], we do not consider blood flow regulation by NO or the dermal membrane, but only the effects exerted within the epidermal membrane. It is believed IGF-1 and IGFBP-3 are important in the abnormal behaviour of keratinocytes [50, 75, 123], and we will investigate normal and psoriatic skin behaviour by focusing on the keratinisation process.
4.2 Mathematical Modelling

4.2.1 Model Discussion

The epidermal model presented in Chapter 3 is extended to incorporate psoriatic components. The effects of this skin disease are visible on the surface in the form of psoriatic plaques, and many biological activities take place in the epidermal membrane as presented in Figure 4.1.

We have introduced additional variables to those stated in Chapter 3, namely immune cells, IGF-1 and IGFBP-3 concentrations (refer to Table 4.1), to obtain greater understanding that will allow comparisons to be made between normal and psoriatic skin.

The main aims of the modelling in addition to those mentioned in Chapter 3 are

- To describe epidermal and abnormal self renewal seen in skin, by focusing on the keratinisation process.
- Obtain insight into the inflammation and immune cell behaviour typical in this skin disease.
- Describe the effects of IGF-1 and IGFBP-3 on normal and abnormal skin development.

A continuum approach will be applied, to model mathematically the normal epidermal renewal process (keratinisation) and abnormal activities that arise from keratinocyte maturation in psoriasis. The model will be discussed in more details in Section 4.2.2 and the full nondimensionalised system will be presented in Section 4.2.3.

![Figure 4.1: Schematic model illustrating normal and psoriatic skin.](image-url)
### Table 4.1: Variables considered in the skin model.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(x, t)</td>
<td>Live cell fraction</td>
</tr>
<tr>
<td>m(x, t)</td>
<td>Dead cell fraction</td>
</tr>
<tr>
<td>w(x, t)</td>
<td>Water fraction</td>
</tr>
<tr>
<td>b(x, t)</td>
<td>Cell-cell binding protein concentration</td>
</tr>
<tr>
<td>c(x, t)</td>
<td>Signal concentration</td>
</tr>
<tr>
<td>v(x, t)</td>
<td>Velocity of cell movement</td>
</tr>
<tr>
<td>A(x, t)</td>
<td>IGF-1 concentration</td>
</tr>
<tr>
<td>B(x, t)</td>
<td>IGFBP-3 concentration</td>
</tr>
<tr>
<td>I(x, t)</td>
<td>Immune cell fraction</td>
</tr>
</tbody>
</table>

### 4.2.2 Governing Equations

In this section we will discuss the model in independent sections for more details regarding their purpose and functionality. The variables and parameters considered in our model are presented in Tables 3.3 and 4.1.

The following assumptions are applied (in addition to those in Chapter 3):

- Cell birth can occur in the presence of IGF-1 and signal molecules [40, 75, 108].
- Binding protein production is reduced in presence of IGF-1 [62, 78]
- IGF-1 is produced by immune cells and removed by the inhibitor IGFBP-3 [49, 75].
- IGFBP-3 is produced by living epithelial cells and removed by immune cells also through the inhibition of IGF-1 [50, 61, 75].
- Immune cells diffuse in the epithelial layer [40, 56, 123].
- Inflammation is simply modelled as increased immune cell presence from the basal region [75, 78].

### Modelling Skin Growth

In psoriatic epidermis there is an excess of IGF-1 secreted and lack of IGFBP-3 in selected keratinocytes. This elevates proliferation of TA cells, expanding the proliferative compartment and allowing hyperplasia and abnormal differentiation. Collectively these events are responsible for the coexistence of live and dead cells at the skin’s surface disrupting the keratinisation process [28, 50, 75].

We assume IGF-1 promotes cell birth [75] and we introduce a birth rate term \( \Theta(c, A) \) given by

\[
\Theta(c, A) = \alpha \frac{c^m}{c^e + c^m} \frac{A^m}{A_e^m + A^m},
\]

53
and the equation for live cells become

\[ \frac{\partial n}{\partial t} + \frac{\partial}{\partial x}(\nu n) = (\Theta(c,A) - k_d(c))n, \]  

(4.1)

bearing mind the equation for dead cells remains unchanged from Chapter 3 hence

\[ k_d(c) = \Omega \left(1 - \frac{\sigma c^\eta}{c^\eta + c^\eta} \right). \]

The constitutive relations (3.5) and (3.6) are unchanged so that water and cell velocity equations become

\[ \frac{\partial w}{\partial t} + \frac{\partial}{\partial x}(\nu w) = k_d(c)n(1 - \phi - \Theta(c,A)n, \]  

(4.2)

\[ \frac{\partial v}{\partial t} = k_d(c)n \left( \frac{\phi}{n_{\text{max}}} - \frac{1}{n_{\text{max}}} \right) + \Theta(c,A) \frac{n}{n_{\text{max}}}, \]  

(4.3)

where the last term results from the volume exchange of water to cells during cell division.

We should note that \( v(0,t) = v_0 \) will be rescaled as before with maximum growth at the basal layer.

**Modelling Cell-Cell Binding**

Applying the assumption that binding protein production rate is reduced during cell division \(^1[40, 56]\), gives the modified equation for \( b \)

The equation for cell-cell binding protein is given by

\[ \frac{\partial b}{\partial t} + \frac{\partial}{\partial x}(\nu b) = \frac{\mu n}{1 + \gamma \Theta(c,A)} - \delta b, \]  

(4.4)

where the factor \( \gamma \) governs the inhibitive effect of mitosis on binding protein production. We note that at the steady-state we have

\[ \nu \frac{db}{dx} = \frac{\mu n}{1 + \gamma \Theta(c,A)} - \delta b - b \frac{du}{dx}, \]  

(4.5)

so that rearranging gives

\[ b = \frac{\mu n_{\text{max}}}{(1 + \gamma \Theta(c,A))(\delta + \nu_x)}, \]  

(4.6)

which will be used in the boundary conditions for \( b \).

\(^1\)Daughter cells from the basal layer are forced to move into the suprabasal layers, so binding proteins production at great quantities are not required.
Modelling Signals

The signal equation (3.17) derived in Chapter 3 and will be the main contributor to birth and death processes within the epidermis. Although this will be distinct from IGF-1 and IGFBP-3 as they contribute to abnormality seen in psoriasis.

Modelling IGF-1

IGF-1 exhibits antiapoptotic properties and overabundance in psoriatic involved skin could lead to disruption in maturation, leaving nucleated cells in the upper epidermal layers which under normal conditions would be absent [11, 28, 40, 78]. For simplicity we assume non-cell and cell associated fGF are at equal concentrations.

The equation for IGF-1 is given by

\[ \frac{\partial A}{\partial t} + V(t) \frac{\partial A}{\partial x} = D_A \frac{\partial^2 A}{\partial x^2} - \zeta_1 AB + \zeta_2 AI, \] (4.7)

where \( V(t) \) is given by (3.12) represents the flux of mass of 'stuff' (cells and water) and

- \( \zeta_1 AB \) represents IGF consumed by IGFBP-3.
- \( \zeta_2 AI \) represent production by immune cells.

Modelling IGFBP-3 expression

IGFBP-3 controls the early stages of keratinocyte differentiation hence acts as an inhibitor displaying apoptotic behaviour. Inefficient IGFBP-3 expression is typical in psoriasis allowing hyperproliferation to persist, as it is unable to counteract the excess IGF-1 levels [28, 40, 78].

The rate of change of IGFBP-3 is given by

\[ \frac{\partial B}{\partial t} + V(t) \frac{\partial B}{\partial x} = D_B \frac{\partial^2 B}{\partial x^2} + \kappa_1 n - \kappa_2 AB - \kappa_3 BI, \] (4.8)

where

- \( \kappa_1 n \) represents the production by keratinocytes.
- \( \kappa_2 AB \) denotes IGFBP-3 consumption by IGF.
- \( \kappa_3 BI \) refers to loss/removal by immune cells.
Modelling Immune cells

The immune system is activated during wound healing and chronic inflammatory conditions such as psoriasis, involving excessive lymphocytes, macrophages and leukocyte recruitment into the skin [11, 40].

Immune cells such as T-cells and Langerhans (they have a uniform distribution in normal epidermis) usually reside in the lower epidermal layers; although they infiltrate upper layers and are present close to the skin’s surface as the inflammatory response is initiated, during the onset of psoriasis [78].

We assume these cells migrate in the epidermal layer and drift with the cells and intracellular fluid. We suggest

$$\frac{\partial I}{\partial t} + V(t) \frac{\partial I}{\partial x} = D_I \frac{\partial^2 I}{\partial x^2} - \rho I, \hspace{2cm} (4.9)$$

where immune cells diffuse into the epidermal medium and are lost via natural means e.g. apoptosis, with the rate constant $\rho$.

Boundary Conditions

The following boundary conditions are imposed

• At $x = 0$, representing the end of the basal layer IGF-1 concentrations and immune cell levels will be at its greatest in response to the presence of live cells, hence

$$n = n_{\text{max}}, \quad c = c_0, \quad v = 0, \quad b = \frac{\mu n_{\text{max}}}{(1 + \gamma \Theta(c, A))(\delta + \nu_x)}, \quad A = A_0, \quad B = 0 \quad \text{and} \quad I = I_0,$$

where $\nu_x$ is given in (4.5) at $x = 0$. We note the basal layer is assumed to be a source for both $A$ and $I$, and a perfect sink for $B$.

• At $x = H(t)$, this represents the skin’s surface, hence zero flux conditions are given by

$$\left( \frac{dH}{dt} - V(t) \right) c + D_c \frac{\partial c}{\partial x} = 0,$$

$$\left( \frac{dH}{dt} - V(t) \right) A + D_A \frac{\partial A}{\partial x} = 0,$$

$$\left( \frac{dH}{dt} - V(t) \right) B + D_B \frac{\partial B}{\partial x} = 0,$$

$$\left( \frac{dH}{dt} - V(t) \right) I + D_I \frac{\partial I}{\partial x} = 0,$$

and desquamation is given by

$$\frac{dH}{dt} = v - \frac{F_0}{b},$$

as defined in Chapter 3.
Full System of Equations

The full system of equations for the extended model are given below

\[
\begin{align*}
\frac{\partial n}{\partial t} + \frac{\partial}{\partial x} (vn) &= \Theta(c, A)n - k_d(c)n \quad (4.10) \\
\frac{\partial m}{\partial t} + \frac{\partial}{\partial x} (vm) &= k_d(c)n\phi \quad (4.11) \\
\frac{\partial w}{\partial t} + \frac{\partial}{\partial x} vt_w &= k_d(c)n(1 - \phi) - \beta(c, A)n \quad (4.12) \\
\frac{\partial v}{\partial x} &= k_d(c) \left( \frac{\phi}{n_{\text{max}}} - \frac{1}{n_{\text{max}}} \right) + \Theta(c, A) \frac{n}{n_{\text{max}}} \quad (4.13) \\
\frac{\partial b}{\partial t} + \frac{\partial}{\partial x} (vb) &= \frac{\mu n}{1 + \gamma \Theta(c, A)} - \delta b \quad (4.14) \\
\frac{\partial c}{\partial t} + V(t) \frac{\partial c}{\partial x} &= D_c \frac{\partial^2 c}{\partial x^2} - \lambda nk_c(c) \quad (4.15) \\
\frac{\partial A}{\partial t} + V(t) \frac{\partial A}{\partial x} &= D_A \frac{\partial^2 A}{\partial x^2} - \zeta_1 AB + \zeta_2 AL \quad (4.16) \\
\frac{\partial B}{\partial t} + V(t) \frac{\partial B}{\partial x} &= D_B \frac{\partial^2 B}{\partial x^2} + \kappa_1 n - \kappa_2 AB - \kappa_3 BI \quad (4.17) \\
\frac{\partial I}{\partial t} + V(t) \frac{\partial I}{\partial x} &= D_I \frac{\partial^2 I}{\partial x^2} - \rho I. \quad (4.18)
\end{align*}
\]

where

\[
\Theta(c, A) = \alpha \frac{c^n}{c_c^n + c^n} \frac{A^n}{A_c^n + A^n}
\]

\[
k_d(c) = \Omega \left( 1 - \frac{\sigma c^n}{c_c^n + c^n} \right)
\]

and

\[
k_c(c) = (\Omega - k_d(c)).
\]

The equations for \(m\) and \(c\) remain the same, and have not been modified for the extended model. Our model consists of a nonlinear coupled PDE system defined on the moving domain \((0, H(t))\) and to close the system we consider the initial conditions stated below. The full list of parameters are shown in Table 4.4.

Initial Conditions

In the following simulation we will consider the self-renewal of the epidermis starting from the end of the basal layer and maturing as it tends towards the skin's surface. The initial conditions are given below

- At \(t = 0\) given at the basal layer \((x = 0)\) all dead cells and IGFBP-3 are absent, hence

\[
n = n_{\text{max}}, \quad m = 0, \quad b = \frac{\mu n_{\text{max}}}{(1 + \gamma \Theta(c, A)) (\delta + v_x)}, \quad A = A_0, \quad I = I_0, \quad c = c_0 \text{ and } B = 0.
\]
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Experimental Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
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<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>$b$ produced by $\Theta(c, A)$</td>
<td></td>
</tr>
<tr>
<td>$\mu$</td>
<td>$b$ production</td>
<td></td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Natural loss/usage of signals</td>
<td></td>
</tr>
<tr>
<td>$D_A$</td>
<td>Diffusion coefficient of IGF</td>
<td>$13.73 \text{ mm}^2 \text{ day}^{-1}$</td>
</tr>
<tr>
<td>$D_B$</td>
<td>Diffusion coefficient of IGFBP-3</td>
<td></td>
</tr>
<tr>
<td>$D_I$</td>
<td>Diffusion coefficient of immune cells</td>
<td>$8.6 \times 10^{-2} \text{ mm}^2 \text{ day}^{-1}$</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Hill function exponent of $c$ in $\Theta(c, A)$</td>
<td></td>
</tr>
<tr>
<td>$\eta_1$</td>
<td>Hill function exponent of $c$</td>
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</tr>
<tr>
<td>$\eta_2$</td>
<td>Hill function exponent of $A$</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$A_c$</td>
<td>Death rate Hill function exponent for $A$</td>
<td></td>
</tr>
<tr>
<td>$\zeta_1$</td>
<td>IGF-1 used by IGFBP-3</td>
<td></td>
</tr>
<tr>
<td>$\zeta_2$</td>
<td>IGF-1 production by immune cells</td>
<td></td>
</tr>
<tr>
<td>$\kappa_1$</td>
<td>IGFBP-3 expression by keratinocytes</td>
<td></td>
</tr>
<tr>
<td>$\kappa_2$</td>
<td>IGF-1 used by IGFBP-3</td>
<td></td>
</tr>
<tr>
<td>$\kappa_3$</td>
<td>IGFBP-3 removal by immune cells</td>
<td></td>
</tr>
<tr>
<td>$\Omega$</td>
<td>Cell birth constant</td>
<td>$0.5 \text{ day}^{-1}$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Natural loss of immune cells</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.2: Parameters considered in the psoriatic model and corresponding experimental values.

4.2.3 Nondimensionalisation

Here, time has been rescaled with cell death and space with velocity over time as before.

$$\{\hat{t}, \hat{t}\} = \left\{\frac{\Omega x}{v_0}, \frac{\Omega t}{\tau}\right\}.$$

In addition to the rescalings in Chapter 3, we apply the following

$$\left\{\hat{A}, \hat{B}, \hat{I}\right\} = \left\{\frac{A}{A_0}, \frac{B}{B_0}, \frac{I}{I_0}\right\}.$$

$$\left\{\hat{\epsilon}_A, \hat{\epsilon}_B, \hat{\epsilon}_I\right\} = \left\{\frac{\epsilon^A}{\Omega}, \frac{\epsilon^B}{\Omega}, \frac{\epsilon^I}{\Omega}\right\}.$$

$$\left\{\hat{\kappa}_1, \hat{\kappa}_2, \hat{\kappa}_3, \hat{\kappa}_4, \hat{\kappa}_5, \hat{\kappa}_6\right\} = \left\{\frac{\kappa_1 n_0}{\Omega}, \frac{\kappa_2 A_0}{B_0 D_B}, \frac{\kappa_3 I_0}{D_I}, \frac{\kappa_4}{\Omega}, \frac{\kappa_5 I_0}{B_0 D_B}, \frac{\kappa_6}{D_I}, \frac{\rho}{\Omega}\right\},$$

where the hatted variables define the dimensionless quantities used to nondimensionalise the system, refer to Appendix B.2 for more details.

Dropping the hats for clarity, the nondimensionalised system becomes

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial x} (\epsilon n) = \epsilon n \frac{c^n}{c^e + c^n} + \epsilon n \frac{A^n}{A^p + A^n} - n \left(1 - \frac{\sigma c^q}{c^e + c^q}\right) n, \quad (4.19)$$

$$\frac{\partial v}{\partial x} = n \left(1 - \frac{\sigma c^q}{c^e + c^q}\right) \left(\frac{\phi}{m_{max}} - \frac{1}{n_{max}}\right), \quad (4.20)$$

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Assuming that diffusion of $c, A, B$ are rapid compared to growth, we expect $\varepsilon_c, \varepsilon_A, \varepsilon_B \ll 1$. Furthermore immune cells are actively mobile and we expect also that $\varepsilon_I \ll 1$. Hence we obtain the quasi-steady approximations. Hence $\varepsilon_c, \varepsilon_A, \varepsilon_B$ and $\varepsilon_I \ll 1$

\begin{align}
0 &= \frac{\partial^2 c}{\partial x^2} - \lambda n \left( \frac{\sigma c^n}{c^2 + c^n} \right), \\
0 &= \frac{\partial^2 A}{\partial x^2} - \zeta_1 AB + \zeta_2 AI, \\
0 &= \frac{\partial^2 B}{\partial x^2} + \kappa_1 n - \kappa_2 AB - \kappa_3 BI, \\
0 &= \frac{\partial^2 I}{\partial x^2} - \rho I.
\end{align}

The corresponding initial and boundary conditions are given

- At $t = 0$ hence $n = n_{\text{max}}$, $b = \frac{n_{\text{max}}}{(1 + \gamma_0 (c, A)((t + \nu_0))}$, $B = 0$ and $m = 0$.
- At $x = 0$ then $m = 0$, $b = \frac{n_{\text{max}}}{(1 + \gamma_0 (c, A)((t + \nu_0))}$, where $\nu_0$ given by (4.5) with $A = 1$, $c = 1$ and $n = n_{\text{max}}$
- At $x = H(t)$
  \[
  \frac{dH}{dt} = v - \beta \frac{b}{b},
  \]
  and from the quasi-steady reduction
  \[
  \frac{\partial c}{\partial x} = 0, \quad \frac{\partial A}{\partial x} = 0, \quad \frac{\partial B}{\partial x} = 0, \quad \frac{\partial I}{\partial x} = 0.
  \]

We note the coupled non-linearity with the $A$ and $B$ equations means that it is not possible to repeat the analysis seen in Section 3.3, in order to get the full solutions in the $\eta \to \infty$ limit of the healthy skin case.

This 1D nonlinear PDE system presented by equations (4.17)-(4.21) and (4.26)-(4.29) is an
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Experimental Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>Production of $\Theta(c,A)$</td>
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</tr>
<tr>
<td>$\lambda$</td>
<td>Natural loss/usage of signals</td>
<td>1.0</td>
</tr>
<tr>
<td>$\epsilon_A$</td>
<td>Péclet number of $A$</td>
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</tr>
<tr>
<td>$\epsilon_B$</td>
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<td>$\ll 1$</td>
</tr>
<tr>
<td>$\epsilon_I$</td>
<td>Péclet number of $I$</td>
<td>$\ll 1$</td>
</tr>
<tr>
<td>$\theta_A$</td>
<td>Death rate Hill function exponent for $A$</td>
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</tr>
<tr>
<td>$\eta$</td>
<td>Hill function exponent of $c$</td>
<td>3.0</td>
</tr>
<tr>
<td>$\eta_1$</td>
<td>Hill function exponent of $c$ in $\Theta(c,A)$</td>
<td>3.0</td>
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<tr>
<td>$\eta_2$</td>
<td>Hill function exponent of $A$</td>
<td>3.0</td>
</tr>
<tr>
<td>$\zeta_1$</td>
<td>IGF-1 used by IGFBP-3</td>
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</tr>
<tr>
<td>$\zeta_2$</td>
<td>IGF-1 production by immune cells</td>
<td>1.5</td>
</tr>
<tr>
<td>$\kappa_1$</td>
<td>IGFBP-3 expression by keratinocytes</td>
<td>2.0</td>
</tr>
<tr>
<td>$\kappa_2$</td>
<td>IGF-1 used by IGFBP-3</td>
<td>2.5</td>
</tr>
<tr>
<td>$\kappa_3$</td>
<td>IGFBP-3 removal by immune cells</td>
<td>0.5</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Natural loss of immune cells</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Table 4.3: Table of parameters in the dimensionless psoriatic model, together with values used in simulations.

extension of skin model discussed in Chapter 3. The boundary conditions defines a closed system and numerical results will be presented below. Table 4.3 presents the nondimensionalised parameters and corresponding values that will be used in the simulations to follow.

**Time: $x = 0 \rightarrow x = x^*$**

In this chapter we modify (3.62), used to derive time taken for cell movement in the keratinisation process, due to the zero boundary condition hence $v = 0$ at $x = 0$ suggesting that there are cells retained in the basal layer which is a reasonable assumption. To overcome this issue, we introduce $x_0$ where

- $x_0$, defines the initial estimated position of the interface where $v \neq 0$ bordering the basal and suprabasal layers.
- $x^*$, defines the interface between live and dead cells.
- The number of cell layers is given by $x^*/x_0$.

This alteration applies to the live cell region and we write

$$T_{live} = \int_{x_0}^{x^*} \frac{1}{v} dx. \quad (4.30)$$
4.3 Results

4.3.1 Numerical Methods

As seen in Chapter 3, we rescale the system using \( t = \frac{l'}{H} \) and \( x = \frac{Z}{H(t)} \) and apply the chain rule to give

\[
\frac{\partial n}{\partial T} + \frac{(v - Z H)}{H} \frac{\partial n}{\partial Z} = \Theta(c, A)n - k_d(c)n;
\]

\[
\frac{1}{H} \frac{\partial v}{\partial Z} = nk_d(c)T - \Theta(c, A) \frac{n}{n_{\text{max}}};
\]

\[
\frac{\partial b}{\partial T} + \frac{(v - Z H)}{H} \frac{\partial b}{\partial Z} = \frac{n}{1 + \gamma \Theta(c, A)} - \delta b,
\]

\[
\frac{1}{H^2} \frac{\partial^2 c}{\partial Z^2} = \lambda n k_c(c),
\]

\[
\frac{1}{H^2} \frac{\partial^2 A}{\partial Z^2} = \zeta_1 AB - \zeta_2 AI,
\]

\[
\frac{1}{H^2} \frac{\partial^2 B}{\partial Z^2} = \kappa_3 BI + \kappa_2 AB - \kappa_1 I,
\]

\[
\frac{1}{H^2} \frac{\partial^2 I}{\partial Z^2} = \rho I,
\]

subject to the initial and boundary conditions

- At \( T = 0, n = n_{\text{max}}, m = 0, B = 0 \) and \( b = \frac{n_{\text{max}}}{(1 + \Theta(c, A)(d + \nu))} \).  
- At \( Z = 0, n = n_{\text{max}}; m = 0, c = 1, I = 1, \nu = 0 \) and \( b = \frac{n_{\text{max}}}{(1 + \gamma \Theta(c, A)(d + \nu))} \).  
- At \( Z = 1 \) then

\[
\frac{\partial c}{\partial Z} = 0, \quad \frac{\partial A}{\partial x} = 0, \quad \frac{\partial B}{\partial x} = 0, \quad \frac{\partial I}{\partial x} = 0,
\]

and

\[
\frac{dI}{dT} = \nu - \frac{\beta}{b}.
\]

Details of the rescalings are given in Appendix A.2.

4.3.2 Normal

In Figures 4.2 - 4.4, we show the re-epithelisation process which replicate the normal keratinisation scenario investigated in Chapter 3. The parameter values given in Table 4.4, and the arrows point to \( H_{\infty} \), hence represents the healed skin surface (\( x \approx 6.2 \) in this case).

The initial conditions are as follow,

\[
t = 0: \quad n = 0.8, \quad c = 1, \quad b = 0.18, \quad \nu = 0, \quad A = 1, \quad B = 1 \quad \text{and} \quad I = 1.
\]
Table 4.4: Standard set of parameter values used in the extended model.

<table>
<thead>
<tr>
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<th>Values</th>
<th>Parameters</th>
<th>Values</th>
</tr>
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<tr>
<td>$c_c$</td>
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<td>$A_c$</td>
<td>1.0</td>
</tr>
<tr>
<td>$\delta$</td>
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<td>$\zeta_1$</td>
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</tr>
<tr>
<td>$\eta$</td>
<td>3.0</td>
<td>$\kappa_2$</td>
<td>2.5</td>
</tr>
<tr>
<td>$n_{\max}$</td>
<td>0.8</td>
<td>$\kappa_3$</td>
<td>0.5</td>
</tr>
<tr>
<td>$m_{\max}$</td>
<td>0.009</td>
<td>$\phi$</td>
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</tr>
<tr>
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<td>$\rho$</td>
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</tr>
<tr>
<td>$\kappa_1$</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We can observe the live and dead cell states in the keratinisation process from Figure 4.2 (left simulation), where cells start to desquamate from $x \approx 2.2$ are almost equal periods. The distribution of $n$ and $c$ are qualitatively similar, however, there are differences in $c$ and $v$.

The time cells (each timestep represents 2 days) spend in the live and dead states (if we take $x^* = 2.2$ and $x_0 = 0.2$) can be given using

$$T_{\text{live}} \approx \int_{x_0}^{x^*} \frac{1}{v} \, dx = 6 \text{ days},$$

$$T_{\text{dead}} \approx \int_{2.2}^{6.2} \frac{1}{v} \, dx = 18 \text{ days}.$$  

The whole process takes $\approx 24$ days, which falls into the time period expected from normal skin activity. It is relatively simple to adjust the thickness of the layers as required, by changing $c_c$ and $\beta$ as with the model of Chapter 3.

The signals (see right simulation of Figure 4.2) and birth rate (see right simulation of Figure 4.4) decline monotonically in the live layer and reaches a low level near constant solution thereafter, as the dependency on signals diminishes with cell death. This correlates well with the binding material available (see Figure 4.3) which also decline in the desquamation period; cell death inhibits production levels and velocity (see right of Figure 4.3) also becomes constant as a result.

IGF-1 levels subside monotonically as illustrated in Figure 4.4, decreasing as cells die towards the surface. The immune cells can only penetrate to $x \approx 1$ so production of $A$ is very limited to the basal membrane region. The inflammatory response is modelled simply by reducing the death rate, as this will initiate immune cell infiltration. IGFBP-3 expression amplifies from initial onset reaching high concentrations where $B \approx 3.2$, in the dead cell region shown in Figure 4.4. Because cell division requires IGF-1 to be at sufficient quantities, this only occurs in the basal region. Here, the binding levels are reduced, but moving away from $x = 0$, cells are less inclined to reproduce and binding strengthens, hence the initial rise. As cells die, the
Figure 4.2: Evolution of the (left) live cell fraction \( n \) and (right) signal concentration \( c \) using values in Table 4.4 at steps of \( t = 20 \).

Figure 4.3: Evolution of (left) cell-cell binding protein concentration \( b \) (middle) immune cell fraction \( I \) and (right) velocity \( v \) using values in Table 4.4 at steps of \( t = 20 \).
binding strength is reduced and declines towards the surface.

The results present normal activities and highlights the promoter-inhibitor relationship between IGF-1 and IGFBP-3, which work together to regulate the proliferative and apoptotic cell activity systematically in this maturation phase. Immune cells are only visible in the lower epidermal layers in agreement with literature [49, 56].

4.3.3 Psoriatic Epidermis

The psoriatic involved epidermis is characterised by overabundant IGF-1 and low levels of IGFBP-3 concentrations causing an inflammatory response, where immune cell production increases and may penetrate further into the upper epidermal layers. Here the same parameters in Table 4.4 apply, except for the natural loss of immune cells is reduced, hence $\rho = 0.5$ (reduced from $\rho = 2$) to simulate the initiation of the inflammatory response. The simulations are given in Figures 4.5-4.7 which could resemble the common psoriatic case discussed in Chapter 1, and the arrows point to $H_{\infty} \approx 8$.

Immediately we notice that epidermal activities of the live cells (refer to Figure 4.2) takes place on an larger domain going from $x \in (0, 6.2)$ to $x \in (0, 8)$, which is almost a third increase from the normal case and suggests that skin thickness has elevated and exceeds the surface (see left simulation of Figure 4.5 to compare). The cell birth rate does not decline instantly (see right simulation of Figure 4.4 to compare), as there is a phase when $x \in (0, 2)$ where birth remains unchanged and diminishes very rapidly thereafter.
The steady state times for live and dead cells (if $x^* = 6.2$ and $x_0 = 0.6$) are $T_{live} = 4$ days and $T_{dead} = 5$ days, where live cell region is thinner than the dead cell area and a total of 9 days to complete the maturation process suggests that psoriatic involved cell turnover rate is considerably quicker, when compared to the standard case seen in Figure 4.2. This results in the coexistence of live and dead cells at the surface ($n \approx 0.2$) affecting the skin homeostasis, where we observe a greater production of binding proteins ($b \approx 0.3$) also (see left simulation of Figure 4.3 to compare).

IGF-1 levels increase initially then declines to constant unit concentration level of $A \approx 1$, and remains unaffected as an outcome of inadequate IGFBP-3 concentrations (under expressed) in the suprabasal layers (see Figure 4.7); unable to exceed $B \approx 0.6$ in the keratinisation phase and is reduced towards the skin surface, hence $B \approx 0.2$. This stimulates the inflammatory response where immune cell distribution (see Figure 4.7) penetrate a little further than the normal case (see Figure 4.3). This highlights the promoter-inhibitor relationship between the two proteins, and how change in production levels can affect live cell distribution, (see Figure 4.5). Consequently the velocity increases substantially (by 3 fold) reaching a maximum of $v \approx 3.4$, which could be due to incomplete desquamation and increased live cell activity near the skin surface.

The results are consistent with biological literature that supports under-expression of IGFBP-3, overabundant IGF-1, shorter turnover rate (7-10 days [75]) and small penetration of immune cells into suprabasal layers could result in hyperproliferation and some parakeratosis [49]. There are treatments available to regulate inflamed skin behaviour in psoriasis and treatments

![Figure 4.5: Evolution of (left) signals (c) (middle) birth rate $\Theta(c, A)$ and (right) live cell fraction ($n$) at steps of $t = 20$, using values in Table 4.4 except for $\rho = 0.5$.]
Figure 4.6: Evolution of (left) velocity $v$ (middle) cell-cell binding protein concentration ($b$) and (right) immune cell fraction ($n$) at steps of $t = 20$, using values in Table 4.4 except for $\rho = 0.5$.

Figure 4.7: Evolution of (left) IGF concentration ($A$) and (right) IGFBP-3 concentration ($B$) at steps of $t = 20$, using values in Table 4.4 except for $\rho = 0.5$. 

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will be considered next.

**Treatment of IGFBP-3**

As we have identified a relationship between IGF-1 and IGFBP-3, we can introduce a topical application of IGFBP-3 to regulate the excess IGF-1 concentrations that exist in a psoriatic domain to inhibit its proliferative activity. The treatment takes the form of a dressing which releases IGFBP-3 into the wound at a flux $dB(H,t)/dt = 3$. The simulations for IGF-1, IGFBP-3, cell binding and live cell distribution are given in Figures 4.8-4.10.

![Figure 4.8: Evolution of (left) live cell fraction (n) (right) cell-cell binding protein production (b) at steps of $t = 20$, using values in Table 4.4 except for $p = 0.5$, when $B_x(H,t) = 3$ is imposed.](image)

The results suggest that increasing IGFBP-3 at the boundary elevates its concentration by 5 fold ($B \approx 3$) and penetrates beyond the lower epidermal layers with sufficient concentrations. This impacts on cell proliferation and lowers IGF levels considerably ($A \approx 0.1$) and inhibits the extent of immature keratinisation. The combined effects of the proteins stimulates cell death at the surface ($n \approx 0.1$) and the live cell region increases ($x \in (0,3)$). Although not all the cells are able to desquamate in response to treatment it certainly helps regulate abnormal activities, and lower binding protein concentrations at the surface supports this (see right of Figure 4.8). Consequently the inflammation visible at the skin’s surface lessens, and domain changes from $x \in (0,8)$ in the psoriatic involved case to $x \in (0,7.1)$ with treatment.

The topical application of IGFBP-3 applied to a psoriatic involved epidermis can help stabilise hyperproliferation, which in reality could lead to reduced inflammation and allow the skin to
Figure 4.9: Evolution of (left) IGF-1 (A) and (right) IGFBP-3 (B) at steps of $t = 20$, using values in Table 4.4 except for $\rho = 0.5$, when $B_\mu(H, t) = 3$ is imposed.

return to a normal homeostatic state, by forcing IGF-1 concentrations to decline and help the keratinisation process. There is noticeably less live cells and binding proteins at the skin surface in response increase in IGFBP-3. This is just a temporary solution in managing psoriatic involved skin, and one that requires further investigation to remove the full extent of the inflamed skin.

4.3.4 Overabundant IGFBP-3 Expression

Up to now we have considered the normal and overabundant IGF-1 cases, in this section we will investigate over expression of IGFBP-3 to see how this contributes to the re-epithelisation, as this scenario will promote inhibition of cell proliferation at all stages. The parameters values in Table 4.4 are applied except for $\kappa_1 = 10$. and the simulations for live cells, IGF-1 and IGFBP-3 are given in Figure 4.10.

We can observe from the results that cells die very quickly, and their behaviour is supported by rapid monotonic decline in IGF levels which is localised in the lower epidermal layers, inhibiting proliferative ability of these cells, in response to great quantities of IGFBP-3 present in the epidermis. This will result in a less substantial membrane as the desquamation phase is lengthened.

In general the results suggest that overabundant IGFBP-3 may create a thinner epidermal membrane than in the healthy case, or the behaviour observed in psoriasis where there is inflammation beyond the skin’s surface [99].
4.4 Summary

Psoriasis is a chronic inflammatory disease that impedes the keratinisation process and cell turnover is more irregular, although many factors contribute to the onset of this disease, it is not clear what the causal processes are. This chapter provided a model extension to that already seen in Chapter 3, to investigate the role of immune cells, IGF-1 and IGFBP-3 concentrations in both normal and psoriatic epidermal situations. It is generally believed that irregular immune cell activity is involved and it has been reported that the imbalance of IGF-1 and IGFBP-3 is an important consequence, leading to the symptoms.

The results obtained from 1D reaction-advection-diffusion model suggest that we can reproduce epithelial recovery for normal epidermis with the additional components and psoriatic behaviour when IGF-1 concentrations are plentiful, causing inflammation and coexistence of live and dead cells at the skin's surface. The condition can be managed by introducing IGFBP-3 via the skin surface in the form of a dressing; although this improves the complete keratinisation process and reduces inflammation it is unable to return to the normal skin margin after treatment, and may suggest an overactive functional membrane.

The model was aimed at providing details and comparisons between the normal and abnormal epidermal behaviour, where we highlighted a relationship between IGF-1 and IGFBP-3. For purposes of simplicity we excluded many components such as,

- Dermal and epidermal cell interaction.
• Other treatments available that target the inflammation at the surface.
• Size and frequency of psoriatic plaques.
• Factors such as infections that may trigger its onset.

The limitations in the model provides scope for further investigation, as it is still a relatively a new research area and one that requires further developments.
Chapter 5

Deep Tissue Wounds: Normal and Compromised Healing

5.1 Introduction

The normal wound healing process is disrupted greatly in chronic wounds as discussed in Chapter 1. These long term wounds exhibit protracted periods in the inflamed state, and are commonly aggravated by intrinsic factors including excess inflammatory cytokines and poor vascularisation. Such wounds require clinical intervention to restore or aid normal repair, where the wound bed is prepared by means of debridement or alternative treatments [17, 56].

Superficial partial, deep partial and full thickness wounds affect both the epidermal and dermal membranes, and healing is dependent on the extent of injury and tissue lost. The epidermal and dermal membranes communicate via the cross talk of cells, however the dermis also provides essential nutrients and GFs to the epidermis, which is not equipped with its own vasculature [8, 11, 25, 26].

To investigate more challenging wounds the dermal functions are considered. The dermis consists of an intricate structure and is the skin's thickest functional membrane as shown in Figure 5.1. In this chapter we will explore the healing between the proliferative and re-modelling stages of deep tissue wounds as shown in Figure 5.2, and key activities that occur include angiogenesis, tissue growth replacing the initial clot, cell migration, collagen deposition, immune response and wound closure. Acquiring a greater knowledge of the primary processes and their interactive mechanisms during normal wound healing will help identify relative differences that develop in abnormal healing patterns; where key characteristics can be examined in more detail.
Figure 5.1: Functional layers of the skin highlighting the intricate structure of the dermis.

Figure 5.2: Stages of wound healing and the transition from one phase to the next [63].
Aims

Deep tissue recovery will be considered in this chapter and the main aims of the modelling to come are

- Obtain insight into normal and abnormal healing.
- Identify key parameters responsible for impeding normal healing.
- Assess variable behaviour, interaction and its significance to healing and repair.

5.2 Model Development

To develop the mathematical model and understanding of dermal healing, the functions and activities need to be considered in order of significance. We should note that dermal factors interact and work collectively to maintain skin homeostasis and tissue integrity. The schematic diagram in Figure 5.3, provides a simplified overview of key events initiated upon dermal injury and the transition to repair, emphasising the significance of cell behaviour. We will assume we have gone beyond the inflammatory phase, as our interest lies in modelling proliferation, which comprises of tissue generation and deposits to occupy the wound domain.

Numerous studies discussed in Chapter 2 (such as [11, 17, 22, 29, 34, 40, 92]) have highlighted many important wound components. Given the extensive literature in the area, research only exposes independent dermal processes such as angiogenesis. In our model we will consider a general overview of the proliferative phase, and focus on key events from preparing the injured domain to wound closure.

Our aim in this chapter is to key factors that contribute to the healing process and incorporate this into the mathematical modelling to come. This will hopefully provide greater insight into healing progression, migratory behaviour and impact on re-epithelisation. Note that granulation tissue defined in this chapter is distinct from the “granular layer” discussed in Chapters 3 and 4, which is confined to the epidermal membrane defining cell appearance (“granules”) in the maturation process.

5.2.1 Dermal Components

To include all the dermal functions discussed in Chapter 1 would lead to a very complicated system of equations. It is clear that fibroblasts, keratinocytes, damaged dermis, healthy dermal ECM, signals (GFs and cytokines), nutrients and granulation tissue formation are key elements, that together impact greatly on normal skin development during wound healing.
Figure 5.3: Schematic flow diagram of dermal healing highlighting cellular activities that enable wound repair.

The proposed model aims to include all the key features, although some simplifications will be made. The following assumptions are applied.

- Dead wound material and clotting components (fibrin, fibrinogen, fibronectin and ECM) will be combined into one variable. This will be a source of GFs and will be removed during healing. Platelet activity can also be accounted for by the damaged tissue, as their functionality is largely dependent on the extent of injury and repair processes stimulated.

- Both fibroblasts and immune cells are present in the wound throughout the healing phase of interest. They are both activated by GFs and chemotactically migrate towards the wound (Figure 5.5). Their combined effects allow the normal healing course as immune cells remove foreign material and allow debridement, whereas fibroblasts help restore a blood supply and replace lost tissue. For simplicity, these densities will be accounted for by a single variable that will be involved in laying down granulation tissue, removal of dead material and further GF secretion.

- Elastin and collagen forms the component of the granulation tissue and the effects will be accounted for by fibroblast activities.

- Blood supply and wound perfusion will be incorporated into a function of dermal and granulation levels. This reflects dermal health status to support a vasculature and angiogenesis, as healthy tissue growth will perfuse the wound environment.
• Birth and death of tissues and cells are nutrient dependent.
• Wound healing is considered complete when keratinocytes migrate over the entire wound domain, representing complete re-epithelisation.
• Fibroblasts/immune cells and keratinocytes move chemotactically in response to GF gradients at speeds that are enhanced by the health of dermal and epidermal tissue.
• GFs will be combined into one variable which will exhibit the generic characteristics of the healing process. Some of the most important GFs and cytokines actively involved in the wound healing process can be summarised below as a reminder [3, 11, 32].
  - PDGF - Promotes chemotaxis and proliferation of fibroblasts and granulation tissue production.
  - TGF-β - Promotes chemotaxis and proliferation of fibroblasts and cytokine production, although it inhibits keratinocyte proliferation.
  - EGF - Promotes keratinocyte migration and is significant for re-epithelisation.
  - IGF - Promotes cell growth in dermis and tissue generation.

The wound environment is of course a 3-D structure, which can be made 2-D \((x, z)\) as an initial approximation (see Figure 5.4). To simplify further we will consider the model's components in terms of total or mean cross sectional densities/thickness. Let \(P(x, z, t)\) denote the local volume fraction of either (1) dermal, (2) epidermal, (3) granulation tissue or (4) damaged dermal tissue and the quantity of interest \(p(x, t)\) is defined as follows

\[
p(x, t) = \int_0^H P(x, z, t) \, dz
\]

i.e. the quantity \(p(x, t)\) is the cross sectional thickness of a certain component of the skin. Thus the thickness \(z = H(x, t)\) will be the sum of thickness of these four components. Let \(Q(x, z, t)\) be the local density/concentration of either fibroblasts/immune cells, nutrients or growth factors then

\[
q(x, t) = \frac{1}{H} \int_0^H Q(x, z, t) \, dz,
\]

\(q(x, t)\) is the mean concentration of these components. Using these ideas we avoid the complications of analysing a model in high dimensions and the explicit treatment of the moving boundary \(z = H(x, t)\), as this drops out naturally from the model. The model variables are listed in Table 5.1.

Using these as the leading dermal constituents of healing the model will consider the interaction of
• Birth and death processes of cells and granulation tissue.
Variables | Description
--- | ---
\(n(x,t)\) | Keratinocyte cross sectional thickness
\(m(x,t)\) | Damaged dermis cross sectional thickness
\(d(x,t)\) | Normal (healthy) dermis cross sectional thickness
\(g(x,t)\) | Granulation tissue cross sectional thickness
\(f(x,t)\) | Fibroblast and immune cell cross sectional density
\(c(x,t)\) | Nutrient cross sectional concentration
\(s(x,t)\) | Signals (GFs and cytokines) cross sectional concentration

Table 5.1: Variables considered in the mathematical model

- Transport and diffusion of nutrients, signals and motile cells.
- Degradation of eschar/dead material.

The one dimensional system proposed in Section 5.3.2, will investigate the relative importance of signals and nutrients, on cell migration of fibroblasts and keratinocytes, granulation tissue formation and vasculature of the skin, with the intention to gain insight about the integrated dermal functions and problems that may arise in deep tissue injuries.

## 5.3 Mathematical Modelling

### 5.3.1 Model Derivation

In healthy skin we have \((n,d,g,m) = (n_0,d_0,0,0)\), where \(n_0\) and \(d_0\) are the cross sectional thickness of the epidermal and dermal layers. Consequently we expect a wound to have \(d < d_0\) and \(n < n_0\) which reflects the tissue mass lost. Figure 5.4 shows a schematic of an idealised wound, showing a typical set-up of the model with the initial and boundary conditions imposed in the simulation to come, where we will assume symmetry at \(x = 0\) for modelling convenience which will simplify data output.

The main modelling assumptions are:

- \(c(x,t)\) and \(s(x,t)\) mediate the repair process.
- \(g(x,t)\) deposited at the wound site indicates normal healing hence repair.
- \(f(x,t)\) is responsible for \(g(x,t)\) production.
- Generic immune response has been incorporated into \(f(x,t)\).
- Cell motility of \(f(x,t)\) and \(n(x,t)\) governed by diffusion and up \(s(x,t)\) gradients.
- Birth and death processes of all variables are regulated by \(c(x,t)\).
Figure 5.4: Schematic of the wound domain used in the simulation. This is an idealised situation, but we can adjust the initial conditions to represent general initial damage.

- $c(x,t)$ has dependency on $d(x,t)$ and $g(x,t)$ which reflects the extent of existing and new vasculature.
- $d(x,t)$ and $g(x,t)$ are responsible for providing a perfused and functional medium allowing for $f(x,t)$ and $n(x,t)$ to enter the repairing domain as they provide a scaffold for migration.

Figure 5.5: Schematic diagram illustrates migration of fibroblasts and immune cells into a wound medium to remove eschar and foreign bodies present.
5.3.2 Governing Equations

The system of equations are derived below. As expected with a problem of this complexity, there are many parameters. To assist in the interpretation, parameters of the form \( \beta \), represent birth rates, \( \delta \), denote the death/removal rates and \( \gamma \), are inhibitor threshold parameters, the subscripts indicate the model variables involved in the corresponding expressions in the equation.

**Heaviside Functions**

Heaviside functions are introduced to incorporate wound behaviour of signals and nutrients where

\[
H(s - \tilde{s}) = \begin{cases} 
1 & \text{if } s > \tilde{s} \text{ (active)} \\
0 & \text{if } s < \tilde{s} \text{ (inactive)} 
\end{cases}
\]

\[
H(\tilde{c} - c) = \begin{cases} 
1 & \text{if } c < \tilde{c} \text{ (unhealthy)} \\
0 & \text{if } c > \tilde{c} \text{ (healthy)} 
\end{cases}
\]

and will be applied appropriately to the governing equations described below.

**Dermis \( d(x,t) \)**

Upon injury we assume there is damage to the dermis, which results in removal of skin mass. We suppose that some healthy dermal ECM \( d \) is retained and not compromised, as it remains in a perfused state maintaining uniformity during wound healing, as degradation is assumed absent \([11, 70]\). Whereby in the proliferative phase there is no new "healthy" dermis being created. We further assume that it is non-diffusible so that

\[
\text{Rate of change of } d(x,t) \quad = \quad 0,
\]

hence a general equation

\[
\frac{\partial d}{\partial t} = 0, \quad (5.1)
\]

implying \( d(x,t) = d(x,0) = d_t(x) \) so the healthy "dermal bed" in the wound remains intact during healing (this will not apply to the next chapter as dermal removal will be an issue).
**Damaged dermis \( m(x, t) \)**

The damaged dermis \( m(x, t) \), comprises of dead material, fibrin clot and eschar where nutrients and GFs may be "trapped" in this domain. The necrotic tissue that accumulates will release panic messages (neciscption) to inform the local area of change, promoting repair processes. The main role of this component in the model is as a source of GFs and the general expression for \( m(x, t) \) in word terms is

\[
\text{Rate of change of } m(x, t) = - \text{ Loss/degredation},
\]

hence

\[
\frac{\partial m}{\partial t} = - \lambda_m(m, f, s), \tag{5.2}
\]

where \( \lambda_m \) denotes the removal and natural loss via sloughing. Damaged tissue is removed by the immune cells (component of density \( f(x, t) \)) in response to chemokines and GFs [11, 40]. Hence, we expect

\[
\frac{\partial \lambda_m}{\partial f} > 0 \quad \frac{\partial \lambda_m}{\partial s} > 0 \quad \text{and} \quad \frac{\partial \lambda_m}{\partial m} > 0,
\]

where \( f \) removes dead tissue/eschar \( m \), which is enhanced by \( s \) and will prepare the wound bed for repair [46, 32]. The simplest functional form describing this is given by

\[
\lambda_m = -mf(\delta_m + s_m) - \delta_mm.
\]

**Signals (Growth Factors & Cytokines) \( s(x, t) \)**

Signals \( s \) represent the GFs, cytokines and chemokines produced by all living cells (including macrophages) and have the ability to diffuse through the ECM. These chemical stimuli mediate many healing processes by allowing cells to communicate, and respond accordingly by recruiting repair cells into the wound medium [53, 56].

There are many GFs released in a wound environment some which have been mentioned in Table 1.2. The two most important ones are TGF-\( \beta \) and PDGF, which remain actively involved throughout the entire process, exhibiting both promoting and inhibitory actions. We assume one generic signal for purposes of simplicity, acting as a chemoattractant for both fibroblasts and keratinocytes.
We propose

\[
\frac{\partial s}{\partial t} = \frac{\partial}{\partial x} \left( D_s \frac{\partial s}{\partial x} \right) + k_s(n, m, f, c, s) - \lambda_s(n, f, s),
\]

(5.3)

where \( k_s \) denotes rate of signal secretion by platelets in the wound/clot, fibroblasts and keratinocytes. \( \lambda_s \) represents natural loss, usage by cells and granulation tissue production.

For the rate of production \( k_s(n, c, f, m, s) \), we expect

\[
\frac{\partial k_s}{\partial n} > 0, \quad \frac{\partial k_s}{\partial c} < 0, \quad \frac{\partial k_s}{\partial f} > 0, \quad \frac{\partial k_s}{\partial m} > 0, \quad \text{and} \quad \frac{\partial k_s}{\partial s} > 0
\]

so that signal production by keratinocytes and fibroblasts is enhanced in the presence of endogenous signals and reduced when nutrient supply is sufficient. We adopt

\[
k_s = (n(\beta_{sn} + \beta_{sn} s) + f(\beta_{sf} + \beta_{sf} s))(1 + \beta_{sc} H(\varepsilon - c)) + \theta_p \beta_{sm} m.
\]

For the degradation rate \( \lambda_s(n, f, s) \) and we expect,

\[
\frac{\partial \lambda_s}{\partial n} < 0, \quad \frac{\partial \lambda_s}{\partial f} < 0, \quad \text{and} \quad \frac{\partial \lambda_s}{\partial s} < 0.
\]

as cell usage and granulation tissue production will cause decline or removal of signals as they are "sensed" by such cells. Hence

\[
\lambda_s = s(\delta_s + \delta_{sn} n + \delta_{sf} f).
\]

**Fibroblasts/Immune System \( f(x, t) \)**

Fibroblasts and immune cells are pivotal to the wound healing process, responsible for synthesis of ECM components, collagen production, wound bed preparation, removal of foreign material and wound contraction. These cells migrate to the wound bed from the surrounding tissue by means of diffusion and chemotaxis (directed cell movement) in response to signals.
(PDGF and TGF-β) [11, 29, 68, 92, 111]. We assume

\[
\begin{align*}
\text{Rate of change of } f(x, t) & = \text{Birth} \\
& + \text{Migration via diffusion} \\
& - \text{Migration via chemotaxis} \\
& - \text{Loss/degredation}
\end{align*}
\]

and this can be written as

\[
\frac{\partial f}{\partial t} = \frac{\partial}{\partial x} \left( D_f \frac{\partial f}{\partial x} \right) - \frac{\partial}{\partial x} \left( f \chi_f (d + \sigma_f g) \frac{\partial s}{\partial x} \right) + k_f (f, c) - \lambda_f (f, c, s). \tag{5.4}
\]

From (5.4), the constant \( \chi_f \) denotes the chemotaxis coefficient, which is prominent in the presence of dermal or granulation tissue and mediated by signals \( s \). Here \( k_f \) is the cell birth by fibroblasts (logistic growth) and vasculature activities in response to nutrients and signals (particularly GFs), and \( \lambda_f \) is removal rate of \( f \) which is lost via inadequate nutrient supply or apoptosis, as healing progresses.

These cells become activated in the elevated presence of various GFs, in that they increase cell division and reduce their turnover rates [53]. For the rate of cell birth \( k_f (c, d, f, g, s) \), we expect

\[
\begin{align*}
\frac{\partial k_f}{\partial c} > 0, & \quad \frac{\partial k_f}{\partial d} < 0, \\
\frac{\partial k_f}{\partial g} > 0, & \quad \frac{\partial k_f}{\partial s} > 0 \quad \text{and} \quad \frac{\partial k_f}{\partial f} > 0
\end{align*}
\]

their production is enhanced by nutrients (first term) and growth factors (fourth term) sourced from vasculature (second & third terms) [37, 38]. Hence

\[
k_f = f c \left( \beta_f c \left( 1 - \frac{f}{\kappa_f} \right) + \beta_f c s H(s - s) \right) + \beta_f b (d, g).
\]

For the death rate parameter \( \lambda_f (f, c, s) \) we expect

\[
\begin{align*}
\frac{\partial \lambda_f}{\partial f} > 0, & \quad \frac{\partial \lambda_f}{\partial c} < 0 \quad \text{and} \quad \frac{\partial \lambda_f}{\partial s} < 0
\end{align*}
\]

which means the cell death rate is reduced in the presence of high GFs and inadequate i.e low nutrient levels [32, 56]. Hence,

\[
\lambda_f = \frac{\delta_{fc} f}{1 + (c + \rho_f s)/\gamma_{fc}}.
\]

The nutrient source function is key to the model, and defined as

\[
k_b = \frac{(d + \rho_s g)^\theta}{\gamma_b + (d + \rho_s g)^\theta} \tag{5.5}
\]
which describes the health of the vasculature as a function of dermal and granulation tissue. This term assumes that angiogenesis occurs in concert with dermal repair. The constant \( \rho_b \) governs efficiency of granulation tissue relative to dermal tissue in supporting vasculature, and \( \gamma_b \) is the "critical" level of \( (d + \rho_b g) \) between poor and adequate vascular perfusion.

**Granulation Tissue** \( g(x,t) \)

Granulation tissue formation contributes to the reinstatement of the blood supply of a wound, being a prerequisite for the angiogenesis process that takes place in the provisional matrix. The two processes occur simultaneously after wound bed preparation occurs. A well perfused medium is needed for this to occur effectively. In impaired wounds granulation tissue formation is inhibited and may contribute to the vascular insufficiency typical in such wounds [32, 40, 53, 79]. We assume it remains static once laid down. We suggest

\[
\text{Rate of change of } g(x,t) = \text{Natural birth} - \text{Natural loss/degredation},
\]

and in mathematical form

\[
\frac{\partial g}{\partial t} = k_g(c,f,s) - \lambda_g(g,c), \quad (5.6)
\]

where \( k_g \) signifies granulation tissue production in response to fibroblasts, signals and nutrients and \( \lambda_g \) is the natural loss as nutrient supply declines.

For rate of granulation tissue formation \( k_g(c,f,s) \), it is assumed that

\[
\frac{\partial k_g}{\partial c} > 0, \quad \frac{\partial k_g}{\partial f} > 0 \quad \text{and} \quad \frac{\partial k_g}{\partial s} > 0
\]

where fibroblasts produce new tissue and this depends on supplies of nutrients and signals [67, 70]. We also assume that no more granulation tissue is laid down when nutrients have reached a "good" level \( \bar{c} \) or when GFs are below a level \( \bar{s} \). Hence

\[
k_g = c f(\beta_{gsf} + \beta_{gs} c) H(s - \bar{s}) H(\bar{c} - c).
\]

Here we have assumed granulation tissue is activated only when GFs are high \( s > \bar{s} \) and nutrient levels are low \( c < \bar{c} \). Thus granulation tissue production will subside once normal healing and repair is noticeable [56].

For the rate of natural decay \( \lambda_g(g,c) \) we expect that

\[
\frac{\partial \lambda_g}{\partial g} > 0 \quad \text{and} \quad \frac{\partial \lambda_g}{\partial c} < 0,
\]
reflects lower granulation tissue and limited nutrient supply will promote decay and natural loss [58, 79], hence we write
\[
\lambda_g = g \left( \frac{\delta_p c}{1 + c/c_g} \right).
\]

**Nutrients \( c(x, t) \)**

The nutrient supply is essential for normal repair and development and we suggest a generic nutrient oxygen or carbon source for purposes of modelling. Nutrients are consumed by all living material and diffuse into the dermal ECM. They are transported through plasma or blood which itself consists of other essential nutrients, required for cell functionality and development. The nutritional composition in a skin medium especially after injury is very important, as it sustains cellular growth and repair towards homeostasis. Limited oxygen supply referred to as hypoxia, can result in abnormal healing with chronic characteristics, leading to vascular insufficiency which is common in diabetic sufferers, where the circulatory actions are impeded [11, 40, 112]. We assume

\[
\text{Rate of change of } c(x, t) = \text{Natural birth} + \text{Dispersion via diffusion} - \text{Cell consumption & natural loss}
\]

and we write
\[
\frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left( D_c \frac{\partial c}{\partial x} \right) + k_c(d, g) - \lambda_c(n, f, c, d, g)
\]

(5.7)

where \( k_c \) are the nutrients obtained from skin vasculature and \( \lambda_c \) are the nutrients supplied to keratinocytes and fibroblasts, allowing the production of granulation tissue and restoring healthy skin characteristics.

The only nutrient source is from the vasculature, which we assume is a function of \( d \) and \( g \), reflecting the health status of the tissue supported by the healing structure. The function \( k_b(d, g) \) discussed above describes this, and in general we expect the source of nutrient to satisfy \( k_c(d, g) = k_c(k_b) \) where

\[
\frac{\partial k_c}{\partial k_b} > 0,
\]

and we assume the simplest concentration

\[
k_c = \beta k_b(d, g).
\]

Nutrients are consumed by keratinocytes and fibroblasts. For the death rate function \( \lambda_c(c, n, f) \),

83
we expect
\[ \frac{\partial \lambda_c}{\partial c} > 0, \quad \frac{\partial \lambda_c}{\partial n} > 0 \quad \text{and} \quad \frac{\partial \lambda_c}{\partial f} > 0. \]

The simplest form being
\[ \lambda_c = c(\delta_{en}n + \delta_{ef}f). \]

**Keratinocytes \( n(x, t) \)**

Keratinocyte density is affected by many factors which include signal concentration, cell death, migration and proliferation. They are important as we are modelling the partial thickness and deep partial wounds where both the epidermal and dermal membranes are affected. Keratinocytes play a significant and versatile role in wound healing, but primarily involved in re-epithelisation which protects the underlying wound area. These cells migrate from surrounding healthy tissue at the wound edges via diffusion and chemotaxis when prompted, although they require granulation tissue as a scaffold/matrix in deep tissue wounds [40, 53].

We assume

\[
\text{Rate of change of } n(x, t) = \text{Birth} + \text{Migration via diffusion} + \text{Migration via chemotaxis} - \text{Death},
\]

and write

\[
\frac{\partial n}{\partial t} = D \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x} \left( n \chi_n (d + \sigma_n g) \frac{\partial s}{\partial x} \right) + k_n(n, c, s) - \lambda_n(n, c).
\]

(5.8)

The assumed main role of keratinocytes is to cover the wound site, which will allow the succession of healing provided the entire wound is concealed by these epidermal cells. From (5.8), \( k_n \) is the growth rate of keratinocytes in response to nutrients and signals (GFs and cytokines), and \( \lambda_n \) denotes natural loss via apoptosis as nutrient supply diminishes and wound recovery is observed.

For the birth rate function \( k_n(n, c, s) \) we expect

\[ \frac{\partial k_n}{\partial c} > 0, \quad \text{and} \quad \frac{\partial k_n}{\partial s} < 0, \]

which means that \( c \) enhances production and \( s \) inhibits birth [56, 43].

The function has to be limiting in \( n(x, t) \) to reflect keratinisation and sloughing, for simplicity
we use a logistic type crowding term to describe this. Hence, we write

\[ k_n = \frac{\beta_n r c}{1 + s/\gamma_{ncs}} \left( 1 - \frac{n}{\kappa_n} \right). \]

For the death rate function \( \lambda_n(c_n, n) \), we expect

\[ \frac{\partial \lambda_n}{\partial c} < 0 \quad \text{and} \quad \frac{\partial \lambda_n}{\partial n} > 0, \]

as nutrients help to maintain cell numbers, reducing their death rate [11, 40]. The functional form is given by

\[ \lambda_n = \left( \frac{\delta_{nc}}{(1 + c/\gamma_{nc})} \right) n. \]

### 5.3.3 Full System of Equations

For reasons of clarity we present the system in full

\[
\frac{\partial n}{\partial t} = \frac{\partial}{\partial x} \left( D_n \frac{\partial n}{\partial x} \right) - \frac{\partial}{\partial x} \left( n \lambda_n (d + \sigma_n g) \frac{\partial s}{\partial x} \right) + \frac{\beta_n r c}{1 + s/\gamma_{ncs}} \left( 1 - \frac{n}{\kappa_n} \right) - \frac{\delta_{nc} n}{1 + c/\gamma_{nc}}
\]

\[
\frac{\partial m}{\partial t} = - m f (\delta_{mf} + \delta_{ms} s) - \delta_{m} m
\]

\[
\frac{\partial d}{\partial t} = 0
\]

\[
\frac{\partial g}{\partial t} = c f (\beta_{gf} + \beta_{g} s) H(s - \bar{s}) H(c - c) - \frac{g \delta_{gc}}{1 + c/\gamma_{gf}}
\]

\[
\frac{\partial f}{\partial t} = \frac{\partial}{\partial x} \left( D_f \frac{\partial f}{\partial x} \right) - \frac{\partial}{\partial x} \left( f \chi_f (d + \sigma_f g) \frac{\partial s}{\partial x} \right)
\]

\[
+ \beta_{f} k_{b}(d, g) + f c \left( \beta_{fc} \left( 1 - \frac{f}{\kappa_f} \right) + \beta_{fc} H(s - \bar{s}) \right)
\]

\[
- \frac{\delta_{fc} f}{1 + (c + \rho_{fs})/\gamma_{fc}}
\]

\[
\frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left( D_c \frac{\partial c}{\partial x} \right) + \beta_{cb} k_{b}(d, g) - c (\delta_{cn} n + \delta_{cf} f)
\]

\[
\frac{\partial s}{\partial t} = \frac{\partial}{\partial x} \left( D_s \frac{\partial s}{\partial x} \right) + \left( n (\beta_{sn} + \beta_{sm} s) + f (\beta_{sf} + \beta_{ssf} s) \right) (1 + \beta_{sc} H(c - c))
\]

\[
+ \theta_{p} \beta_{sm} m - s (\delta_{s} + \delta_{cn} n + \delta_{sf} f)
\]

where vasculature is defined by the hill function

\[ k_{b}(d, g) = \frac{(d + \rho_{g})^{\eta}}{\gamma_{b}^{\eta} + (d + \rho_{g})^{\eta}}. \]
This is a highly nonlinear coupled system of PDEs of mixed type, defined on the fixed domain \((0, L)\). The initial and boundary conditions defined below present a closed system.

**Initial and Boundary Conditions**

Figure 5.4 illustrates a typical domain of interest. It is important that the domain is large enough so that the solutions change regularly from the perfectly healthy state in the vicinity of \(x = L\).

- At \(t = 0\) we assume a partial-deep thickness wound which affects the first two functional membranes (epidermis and dermis) and suggest that \(n = n_I(x)\), \(m = m_I(x)\), \(g = 0\), \(d = d_I(x)\), \(c = c_I(x)\), \(f = f_I(x)\) and \(s = s_I(x)\).

- At \(x = 0\) we will assume symmetry and impose zero flux conditions which become

\[
\frac{\partial n}{\partial x} = 0, \quad \frac{\partial c}{\partial x} = 0, \quad \frac{\partial f}{\partial x} = 0 \quad \text{and} \quad \frac{\partial s}{\partial x} = 0,
\]

noting that there is no chemotactic contribution due to \(\frac{\partial g}{\partial x} = 0\) as the initial wound occurs.

- At \(x = L\) we assume healthy skin where \(n = n_0\), \(f = f_0\), \(c = c_0\), \(s = s_0\), \(d = d_0\), \(m = 0\) and \(g = 0\).

**5.3.4 Model Parameters**

Table 5.2 lists the model parameters, giving their biological interpretation and where possible, an estimate from literature which closely resemble those used. The experimental values are highly dependent on control conditions imposed and purposes of research, which can result in great variation across studies. In many cases, especially for the diffusion coefficients we can obtain multiple values. In addition to those stated in Table 5.2, other values for \(D_n\), \(D_c\), \(D_f\) and \(D_s\) [60, 82, 92] are,

- \(D_n = 1.9 \times 10^{-12} \text{ mm}^2 \text{ h}^{-1}\) vs. \(1.26 \times 10^{-3} \text{ mm}^2 \text{ h}^{-1}\) in Table 5.2.
- \(D_c = 7.2 \text{ mm}^2 \text{ h}^{-1}\) vs. \(0.18 \text{ mm}^2 \text{ h}^{-1}\) in Table 5.2.
- \(D_f = 6.12 \times 10^{-5} \text{ mm}^2 \text{ h}^{-1}\) vs. \(3 \times 10^{-4}\) in Table 5.2.
- \(D_s = 0.44 \text{ mm}^2 \text{ h}^{-1}\) vs. \(0.01 \text{ mm}^2 \text{ h}^{-1}\) in Table 5.2.
<table>
<thead>
<tr>
<th>Parameters</th>
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<tr>
<td>$L$</td>
<td>Wound size</td>
<td>mm</td>
<td>Varies</td>
</tr>
<tr>
<td>$D_n$</td>
<td>Diffusion coefficient of $n$</td>
<td>$\text{mm}^2 \text{h}^{-1}$</td>
<td>$1.26 \times 10^{-3}$ [92]</td>
</tr>
<tr>
<td>$\chi_n$</td>
<td>Chemotaxis coefficient of $n$</td>
<td>$\text{mm}^3 (\text{gh})^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\sigma_n$</td>
<td>Chemotaxis ratio of $n$ for $g$</td>
<td>$\text{mm}^2 (\text{gh})^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_n$</td>
<td>$n$ birth rate</td>
<td>$\text{mm}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\gamma_{nc}$</td>
<td>Keratinocyte birth constant</td>
<td>$\text{g mm}^{-2} \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\gamma_{nc}$</td>
<td>$n$ inhibited by nutrient availability</td>
<td>$\text{mm}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\delta_{nc}$</td>
<td>$n$ cell death rate from lack of nutrients</td>
<td>$\text{h}^{-1}$</td>
<td>$8.75 \times 10^{-3}$ [39]</td>
</tr>
<tr>
<td>$\delta_m$</td>
<td>$m$ removed by fibroblasts</td>
<td>$\text{mm}^2 \text{(gh)}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\delta_m$</td>
<td>Enhanced removal constant of $m$ due to $s$</td>
<td>$\text{h}^{-1}$</td>
<td>$8.3 \times 10^{-4}$ [111]</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>Enhanced $g$ production rate due to $s$</td>
<td>$\text{mm}^5 \text{g}^{-2} \text{cells} \text{(gh)}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\delta_{sf}$</td>
<td>$g$ loss rate due to lack of $c$</td>
<td>$\text{mm}^3 (\text{gh})^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>$g$ production rate by $f$</td>
<td>$\text{mm}^2 \text{g}^{-2} \text{cells} \text{(gh)}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>$f$ infiltration rate from vasculature</td>
<td>$\text{g mm}^{-2}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>Vascular nutrient source constant</td>
<td>$\text{cells mm}^{-2} \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>Critical vascular nutrient source constant</td>
<td>$\text{mm}$</td>
<td>Varies *</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>Nutrient source function exponent</td>
<td>Dimensionless</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>Fibroblast birth rate</td>
<td>$\text{mm}^2 (\text{gh})^{-1}$</td>
<td>$1 \times 10^{-3}$ [12]</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>Fibroblast threshold</td>
<td>$\text{g mm}^{-2}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>Enhanced $f$ birth rate due to signal</td>
<td>$\text{mm}^2 (\text{g h})^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>$f$ production rate by signals</td>
<td>$\text{cells mm}^{-2} \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>Fibroblast death rate</td>
<td>$\text{cells mm}^{-2} \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>Fibroblast death rate constant</td>
<td>Dimensionless</td>
<td>-</td>
</tr>
<tr>
<td>$D_c$</td>
<td>Diffusion coefficient of $c$</td>
<td>$\text{mm}^2 \text{h}^{-1}$</td>
<td>$0.18$ [111]</td>
</tr>
<tr>
<td>$\beta_{cf}$</td>
<td>Nutrients source rate from vasculature</td>
<td>$\text{g mm}^{-3}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{cf}$</td>
<td>Nutrients consumption rate by $n$</td>
<td>$\text{g mm}^{-3} \text{h}^{-1}$</td>
<td>$0.5$ [13]</td>
</tr>
<tr>
<td>$\beta_{cf}$</td>
<td>Nutrients consumption rate by $f$</td>
<td>$\text{g mm}^{-3} \text{cells} \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$D_s$</td>
<td>Diffusion coefficient of $s$</td>
<td>$\text{mm}^2 \text{h}^{-1}$</td>
<td>$0.01$ [92]</td>
</tr>
<tr>
<td>$\beta_{sn}$</td>
<td>Signals production rate by $n$</td>
<td>$\text{g mm}^{-2} \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sn}$</td>
<td>Further signal secretion rate by $n$</td>
<td>$\text{g \ ((mm) h)}^{-1}$</td>
<td>$4.2 \times 10^{-9}$ [136]</td>
</tr>
<tr>
<td>$\beta_{sn}$</td>
<td>Signals produced by $f$</td>
<td>$\text{mm}^2 \text{g}^{-2} \text{cells} \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sn}$</td>
<td>Further signal secretion by $f$</td>
<td>$\text{mm}^2 \text{g}^{-2} \text{cells} \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sn}$</td>
<td>Signal production rate due to lack of $c$</td>
<td>Dimensionless</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{sn}$</td>
<td>Signals release rate from $m$</td>
<td>$\text{g mm}^{-2} \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$g$</td>
<td>Critical granulation tissue density</td>
<td>$\text{g mm}^{-2}$</td>
<td>-</td>
</tr>
<tr>
<td>$\delta_s$</td>
<td>Decay rate of signals</td>
<td>$\text{h}^{-1}$</td>
<td>$0.1$ [60]</td>
</tr>
<tr>
<td>$\delta_{sn}$</td>
<td>Signal consumption rate by $n$</td>
<td>$\text{mm}^2 \text{h}^{-1}$</td>
<td>-</td>
</tr>
<tr>
<td>$\delta_{sn}$</td>
<td>Signal consumption rate by $f$</td>
<td>$\text{mm}^2 \text{cells} \text{h}^{-1}$</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5.2: For illustrative purposes, the units are taken to be time (hours), distance (mm), mass (g) and "cells"; hence the units of $n$, $d$, $m$ and $g$ are mm, s and g and c are g/mm$^2$ ad $f$ is cells/mm$^2$. $\gamma_b$ will depend on various factors including location of wound and other chronic illnesses such as diabetes. $\beta_{sn}$ is variable and depends on extent and quality of clot.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Experimental Value</th>
<th>Equivalent Dimensionless Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_0$</td>
<td>24 hours</td>
<td>1</td>
</tr>
<tr>
<td>$x_0$</td>
<td>50 mm</td>
<td>1</td>
</tr>
<tr>
<td>$n_0$</td>
<td>0.01-2 mm [40]</td>
<td>1</td>
</tr>
<tr>
<td>$m_0$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$d_0$</td>
<td>1-5 mm [11]</td>
<td>1</td>
</tr>
<tr>
<td>$g_0$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$f_0$</td>
<td>$10^{-11}$ g mm$^{-3}$ [111]</td>
<td>1</td>
</tr>
<tr>
<td>$c_0$</td>
<td>$5.4 \times 10^{-12}$ g mm$^{-3}$ [111]</td>
<td>1</td>
</tr>
<tr>
<td>$s_0$</td>
<td>$10^{-11}$ g mm$^{-3}$</td>
<td>1 [111]</td>
</tr>
</tbody>
</table>

Table 5.3: Dimensionless parameters values for the healthy skin state.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Dimensionless Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_n$</td>
<td>1</td>
</tr>
<tr>
<td>$\delta_{nc}$</td>
<td>0.21</td>
</tr>
<tr>
<td>$\delta_m$</td>
<td>$1.9 \times 10^{-2}$</td>
</tr>
<tr>
<td>$D_f$</td>
<td>0.238</td>
</tr>
<tr>
<td>$\kappa_f$</td>
<td>$10^3$</td>
</tr>
<tr>
<td>$\delta_{fc}$</td>
<td>$4.8 \times 10^{-3}$</td>
</tr>
<tr>
<td>$D_c$</td>
<td>142.9</td>
</tr>
<tr>
<td>$\delta_{cn}$</td>
<td>9</td>
</tr>
<tr>
<td>$D_s$</td>
<td>7.9</td>
</tr>
<tr>
<td>$\beta_{sf}$</td>
<td>0.01</td>
</tr>
<tr>
<td>$\delta_s$</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Table 5.4: Dimensionless parameters values for the experimental data obtained.
5.3.5 Nondimensionalisation

We nondimensionalised the model based on the keratinocyte birth rate ($\sim 1/\beta_n c_0$) for the timescale and the distance these cells diffuse during this period ($\approx D_n/\beta_n c_0$).

We rescale using

\[ \{ \hat{x}, \hat{t} \} = \left\{ \frac{x}{D_n / \beta_n c_0} \right\} \]

\[ \{ \hat{n}, \hat{m}, \hat{d}, \hat{g}, \hat{f}, \hat{c}, \hat{s} \} = \left\{ \frac{n}{n_0}, \frac{m}{d_0}, \frac{d}{d_0}, \frac{g}{f_0}, \frac{f}{c_0}, \frac{c}{s_0} \right\} \]

\[ \{ \hat{D}_f, \hat{D}_c, \hat{D}_s \} = \frac{1}{D_n} \{ D_f, D_c, D_s \} \]

\[ \{ \hat{x}_n, \hat{x}_f \} = \left\{ \frac{x_n}{D_n}, \frac{x_f}{D_n} \right\} \]

\[ \{ \hat{\gamma}_ncs, \hat{\gamma}_nc, \hat{\gamma}_gf, \hat{\gamma}_fcs, \hat{\gamma}_f \} = \left\{ \frac{\gamma_n \gamma_n \gamma_n \gamma_n \gamma_n \gamma_n}{\gamma_n \gamma_n \gamma_n \gamma_n \gamma_n \gamma_n} \right\} \]

\[ \{ \hat{\delta}_ncs, \hat{\delta}_nc, \hat{\delta}_mr, \hat{\delta}_m, \hat{\delta}_g, \hat{\delta}_d \} = \left\{ \frac{\delta_n \delta_n \delta_n \delta_n \delta_n \delta_n}{\delta_n \delta_n \delta_n \delta_n \delta_n \delta_n} \right\} \]

\[ \{ \hat{\delta}_nc, \hat{\delta}_m, \hat{\delta}_m, \hat{\delta}_m, \hat{\delta}_f, \hat{\delta}_f \} = \left\{ \frac{\delta_n \delta_n \delta_n \delta_n \delta_n \delta_n}{\delta_n \delta_n \delta_n \delta_n \delta_n \delta_n} \right\} \]

\[ \{ \hat{\beta}_n, \hat{\beta}_f \} = \left\{ \frac{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n}{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n} \right\} \]

\[ \{ \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_f, \hat{\beta}_f \} = \left\{ \frac{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n}{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n} \right\} \]

\[ \{ \hat{\beta}_n, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_f, \hat{\beta}_f \} = \left\{ \frac{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n}{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n} \right\} \]

\[ \{ \hat{\beta}_n, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_f, \hat{\beta}_f \} = \left\{ \frac{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n}{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n} \right\} \]

\[ \{ \hat{\beta}_n, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_f, \hat{\beta}_f \} = \left\{ \frac{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n}{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n} \right\} \]

\[ \{ \hat{\beta}_n, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_m, \hat{\beta}_f, \hat{\beta}_f \} = \left\{ \frac{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n}{\beta_n \beta_n \beta_n \beta_n \beta_n \beta_n} \right\} \]

The nondimensionalisation of a system forces the steady states for the healthy skin conditions, and the variables $n$, $f$, $c$, and $s$ are normalised so that they are equal to unity; this implies the following parameter relationships

\[ \hat{\delta}_{nc} = \frac{1}{1/\gamma_{ncs}} \left( 1 - \frac{1}{\hat{\gamma}_{ncs}} \right) \left( 1 + \frac{1}{\hat{\gamma}_{ncs}} \right), \]

\[ \hat{\delta}_{fc} = \left( \hat{\beta}_p \hat{\gamma}_p(1,0) + \hat{\beta}_f \left( 1 - \frac{1}{\hat{\gamma}_p} \right) \right) \left( 1 + (1 + \hat{\beta}_f) \gamma_{fcs} \right), \]

\[ \hat{\beta}_{cb} = \frac{\beta_{cb}}{c_0 \beta_n} = \frac{\hat{\delta}_{nc} + \hat{\delta}_{cf}}{\gamma_p(1,0)}, \]

\[ \hat{\delta}_s = \frac{\hat{\delta}_s}{c_0 \beta_n} = \hat{\beta}_n + \hat{\beta}_{n\gamma} \hat{\beta}_f + \hat{\beta}_{sf} - \hat{\delta}_{nc} - \hat{\delta}_{sf}, \]

and the dimensionless parameters are given in Table 5.5.
Dropping the hats for clarity, the nondimensionalised system is given below

\[
\frac{\partial n}{\partial t} = \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x} \left( n \chi_n (d + \sigma_n s) \frac{\partial s}{\partial x} \right) - \frac{\nu c}{1 + s/\gamma_{ncx}} \left( 1 - \frac{n}{\kappa_n} \right) - \frac{\delta_{nc} n}{1 + c/\gamma_{nc}} \tag{5.30}
\]

\[
\frac{\partial m}{\partial t} = -m f(\delta_{mf} + \delta_{ms}s) - \delta_{m} m \tag{5.31}
\]

\[
\frac{\partial d}{\partial t} = 0 \tag{5.32}
\]

\[
\frac{\partial g}{\partial t} = c f(\beta_{gs} g + \beta_{ss}s)H(s - \bar{s})H(\bar{c} - c) - \frac{g \delta_{sec}}{1 + c/\gamma_{gf}} \tag{5.33}
\]

\[
\frac{\partial f}{\partial t} = D_f \frac{\partial^2 f}{\partial x^2} - \frac{\partial}{\partial x} \left( f x_f (d + \sigma_f g) \frac{\partial s}{\partial x} \right) + \beta_{fs} k_b(d, g) + f c \left( \beta_{fc} \left( 1 - \frac{f}{\kappa_f} \right) + \beta_{fcs} H(s - \bar{s}) \right) - \frac{\delta_{ff}}{1 + (c + \rho_f s)/\gamma_{fcs}} \tag{5.34}
\]

\[
\frac{\partial \epsilon}{\partial t} = D_c \frac{\partial^2 \epsilon}{\partial x^2} + \beta_{ec} k_b(d, g) - c(\delta_{en} n + \delta_{ef}) \tag{5.35}
\]

\[
\frac{\partial s}{\partial t} = D_s \frac{\partial^2 s}{\partial x^2} + (n(\beta_{sn} + \beta_{ss} s) + f(\beta_{sf} + \beta_{ss} s))(1 + \beta_{sc} H(\bar{c} - c)) + \beta_{sm} m - s(\delta_s + \delta_{sn} n + \delta_{sf}) \tag{5.36}
\]

The corresponding initial and boundary conditions are

\[
t = 0: \quad n = n_f(x), f = f_f(x), d = d_f(x), s = s_f(x), c = c_f(x), m = g = 0.
\]

\[
x = 0: \quad \frac{\partial n}{\partial x} = 0, \frac{\partial f}{\partial x} = 0, \frac{\partial s}{\partial x} = 0, \frac{\partial d}{\partial x} = 0.
\]

\[
x = L: \quad n = f = c = s = d = 1, m = g = 0.
\]

The nondimensionalised system given by equations (5.30), (5.31), (5.32), (5.33), (5.34), (5.35) and (5.36), with corresponding initial and boundary conditions will be investigated numerically in Section 5.4.2.

5.4 Model Analysis

5.4.1 Numerical Methods

To solve the nonlinear PDE system we used finite difference schemes, in particular central differencing in space and standard explicit forward Euler time-step in time. The methods were encoded using Fortran. Refer to Appendix A.3 for more details on the schemes applied. We will consider different scenarios by highlighting important parameters that will change healing behaviour which will be compared to the normal and expected repair process.
5.4.2 Results

Table 5.5 presents the standard set of parameter values applied for the "normal healing case" and will be discussed below. Following this, the main parameters we investigate the effects of are

- \( \gamma_b \) - which determines the nutrient delivery to the wound hence describes the extent and efficiency of the vascularisation.
- \( \beta_{sm} \) - which describes quality and extent of clot formation.

Table 5.5: Standard set of parameter values used in simulation for normal healing.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Parameters</th>
<th>Values</th>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( L )</td>
<td>40</td>
<td>( D_f )</td>
<td>0.5</td>
<td>( \kappa_f )</td>
<td>1.1</td>
</tr>
<tr>
<td>( \chi_n )</td>
<td>0.001</td>
<td>( \chi_f )</td>
<td>0.01</td>
<td>( \beta_{fsa} )</td>
<td>3.0</td>
</tr>
<tr>
<td>( \sigma_n )</td>
<td>1.0</td>
<td>( \sigma_f )</td>
<td>1.0</td>
<td>( \gamma_{fsa} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \gamma_{acs} )</td>
<td>1.0</td>
<td>( \rho_b )</td>
<td>0.6</td>
<td>( \delta_{fsa} )</td>
<td>0.4</td>
</tr>
<tr>
<td>( \kappa_n )</td>
<td>1.2</td>
<td>( \beta_{jb} )</td>
<td>0.04</td>
<td>( \beta_f )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \gamma_{ac} )</td>
<td>1.0</td>
<td>( \gamma_{b} )</td>
<td>0.6</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \delta_{ns} )</td>
<td>0.2</td>
<td>( \delta_{sf} )</td>
<td>0.4</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \delta_{nf} )</td>
<td>0.2</td>
<td>( \delta_{sn} )</td>
<td>0.4</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \delta_{nas} )</td>
<td>0.05</td>
<td>( \delta_{sm} )</td>
<td>0.4</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \delta_{m} )</td>
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<td>( \delta_{m} )</td>
<td>0.4</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \beta_{ps} )</td>
<td>0.4</td>
<td>( \delta_{s} )</td>
<td>0.4</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \delta_{ps} )</td>
<td>0.0</td>
<td>( \delta_{ps} )</td>
<td>0.4</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \beta_{gf} )</td>
<td>0.3</td>
<td>( \beta_{gf} )</td>
<td>0.4</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \delta )</td>
<td>3.0</td>
<td>( \beta_{asf} )</td>
<td>0.4</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
<tr>
<td>( \beta_{sc} )</td>
<td>0.4</td>
<td>( \beta_{asf} )</td>
<td>0.4</td>
<td>( \beta_{ob} )</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Normal Healing

Figures 5.6 - 5.12 shows model solutions for a successfully healed wound using the standard parameter set given in Table 5.5. The results show that the profiles form into travelling wave (TW) fronts, moving right to left from healthy (repaired/uninjured) denoted by \( x = 40 \) to unhealthy (injured) skin at \( x = 0 \) as indicated by the arrows.

The injured wound corresponds to \( x \in (0,32) \) and the initial conditions are as follows

\[
0 < x < 32 : \quad n = 0, c = 0, f = 0, s = 1, m = 1, d = 0.1 \quad \text{and} \quad g = 0.
\]
\[
32 \leq x \leq L : \quad n = d = c = s = 1, g = m = 0.
\]

Figure 5.6 shows the distribution of GF at equal time steps, demonstrating a retreating front towards \( x = 0 \) of elevated \( s \) within the wound. The increase in GF levels exceeds the threshold seen in normal skin, and initiates the wound healing cascade of events by recruiting
Figure 5.6: Evolution of signal concentration \((s)\) in steps of \(t = 6\) using parameters given in Table 5.5.

repair/immune cells to the affected area (Figure 5.7), which in turn lays down granulation tissue (Figure 5.8). In this simulation the recruitment of \(f\) is from the healthy surrounding tissue, which generates a chemotactic peak at the edge of the wound. Because \(n \approx 0\) and \(f \approx 0\) in the wound domain, the maximum signal concentration can be found from (5.36) to be

\[
s = \frac{\beta_{erm} m}{\delta_s},
\]

which approximates to \(s \approx 9.4\) using the values in Table 5.5.

From Figure 5.8 we observe granulation tissue produced by \(f\) is consistent in the wound medium and fills the wound space but is raised at the wound edge (which is common is any wound), where \(x = 32\). We expect the wound edge to harden during and after repair in a "real" wound, which will eventually contract and return to normal skin level with time. The non-uniformity of the granulation tissue is interesting, and perhaps one of the reason as to why the remodelling process in the maturation phase can lead to scar tissue formation. This behaviour was not incorporated into the model, but is predicted naturally as a model solution.

From Figure 5.9 wound recovery is obtained with vasculature providing 80% of the nutrients of healthy tissue, and the wound domain \((d + \rho_d g) > \gamma_c = 0.6\); indicating successful revascularisation as granulation and dermal tissue, are adequate to support successful angiogenesis to reapply nutrients for healing to take place (see Figures 5.8 and 5.12). It should be noted that there is a noticeable gap at \(x \approx 32\) (see Figure 5.9 compared to excess \(g\) in Figure 5.8), where a small amount of granulation tissue is laid down and suggests nutrients sources from
Figure 5.7: Evolution of fibroblasts/immune cell density \( (f) \) in steps of \( t = 6 \) using parameters given in Table 5.5.

Figure 5.8: Evolution of granulation tissue thickness \( (g) \) in steps of \( t = 6 \) using parameters given in Table 5.5.
Figure 5.9: Evolution of vasculature \((k)\) in steps of \(t = 6\) using parameters given in Table 5.5.

vasculature are adequate here.

Keratinocytes are responsible for re-epithelisation and cells migrate from the wound edges, as shown in Figure 5.10 over a perfused domain defined by adequate nutrient and granulation tissue levels. Consequently the whole wound is eventually covered by the epidermis, enabling the wound to progress to the maturation phase and restore the skin's barrier.

As normal healing persists, we see from Figure 5.12 that the damaged dermis retreats, being replaced by granulation tissue and eventually the epidermis as shown in Figures 5.8 and 5.10. In this simulation the revascularisation and nutrient supply within the healed domain are slightly lower than that of the healthy skin. There is paucity of quantitative data in the literature, regarding whether the levels in a healing wound should be above or below that of healthy skin. Though it is straightforward to change the predicted nutrient supply by appropriately adjusting parameters \(\gamma_0\) and \(\rho_0\).

We observe from the results that dermal recovery and wound closure are obtained, with a healing speed of \(\approx 3.2\) and is completed within \(t \approx 16\) days. This accounts for repair from initial damage to wound coverage, replacing dermal and epidermal tissue in the normal healing domain, for a partial/deep thickness wound. The healed wound is close to homeostatic levels of keratinocytes, nutrients, fibroblasts/immune cells and signal levels. Adequate nutrient supply is obviously a key factor and effective to ensure skin homeostasis and complete wound repair. The effects of a less efficient blood supply is explored next.
Figure 5.10: Evolution of keratinocytes thickness ($n$) in steps of $t = 6$ using parameters given in Table 5.5.

Figure 5.11: Evolution of nutrient concentration ($c$) in steps of $t = 6$ using parameters given in Table 5.5.
Figure 5.12: *Evolution of damaged dermis thickness (d) in steps of t = 6 using parameters given in Table 5.5.*

**Effects of Poor Vasculature**

The importance of vascular efficiency of transporting nutrient to the wound is highlighted in Figures 5.6-5.12. Here the same parameters in Table 5.5 apply, except for the vascular hill function parameter being $\gamma_b = 0.85$ instead of $\gamma_b = 0.6$; this represents a reduction in vascular effectiveness in delivering nutrients. These simulations could reflect the circumstances of chronic conditions such as diabetes, where nutrient supply is severely impaired as a result of poor circulation. Figures 5.13-5.15 presents abnormal/non-healing wounds due to the increase in $\gamma_b$ and the initial and boundary conditions remain unchanged.

The figures show the healing process starting as normal i.e. similar to the previous simulation, but slows down and eventually tends to steady state. The lack of wound closure (right simulation of Figure 5.15) indicates a failure of wound healing in this simulation. Despite signal levels (see left simulation of Figure 5.13) approximately the same within the wound as in Figure 5.6, produced by the “dead material” (see right of Figure 5.14) and dispersing into a large proportion of the injured medium; and other dermal components are unable to sustain this supply. Fibroblast/immune cell levels at the edge of the wound are initially high (right simulation in Figure 5.13), however insufficient granulation tissue is being laid down to support a functioning vasculature (Figures 5.14). Consequently inadequate nutrients infiltrate the wound (Figure 5.15), which disallows cell activity, migration, tissue growth and signal usage beyond the localised wound edge within the region of $x \in (20,32)$, as they are unable to function normally or recruit further reinforcements to the wound area (Figures 5.13, 5.14 and 5.15).

We note, in this simulation that eschar material does not decay naturally, and hence remains
Figure 5.13: Evolution of the (left) signals concentration \((s)\) and (right) fibroblasts/immune cell density \((f)\) in steps of \(t = 6\), using values in Table 5.5 except for \(\gamma_b = 0.85\).

Figure 5.14: Evolution of the (left) granulation tissue thickness \((g)\) (middle) Vasculature \((k)\) and (right) damaged dermis thickness \((m)\) in steps of \(t = 6\), using values in Table 5.5 except for \(\gamma_b = 0.85\).
in the unhealed part of the wound; there being insufficient nutrients for fibroblasts/immune
cells to penetrate and degrade it (see right simulation in Figure 5.14).

Figure 5.15: Evolution for (left) nutrient concentration (c) and (right) keratinocyte thickness
n in steps of t = 6, using values in Table 5.5 except for γb = 0.85.

The results here shows the crucial role of supplying nutrients to the wound area to drive the
healing components. A small shift (γb = 0.6 to γb = 0.85) of vascular effectiveness due to
for example, poor circulation can lead to significant differences in the wound healing process,
resulting in non-healing profiles and wound closure failure.

Bolus Treatments to Promote Healing

We can attempt to restore normal wound recovery or promote vascularisation to the non­
healing wounds presented in Figures 5.13-5.15 by focusing on key components, namely fibro­
blasts, signals and nutrients both independently and/or combined to see the effects on tissue
production, vasculature and re-epithelisation. We will retain γb = 0.85 from the previous
simulation, but to emphasise the features, the simulation here are performed on a domain size
of L = 20 and a wound domain of size x ∈ (0, 16). change to the wound environment, by ma­
nipulating initial concentrations in the wound site. In this section we simulate the treatments
detailed below.

1. Introduce bolus of fibroblasts/immune cells f(x, 0) = 10 into the wound site as shown
   in Figures 5.16-5.21 (left simulations).

2. Introduce bolus of GF's s(x, 0) = 10 into the wound site, shown in Figures 5.16-5.21
   (middle simulations).
3. Combined therapy of (1) and (2) into the wound site and simulations are given in Figures 5.16-5.21 (right simulations).

4. Introduce bolus of nutrients $c(x,0) = 0.01$ to the wound site and simulations are given in Figures 5.22-5.24.

We note from the left simulations in Figures 5.16-5.21 that the healing distance is about 5 - 10 significantly less than 20, so wound closure will not occur. We can interpret from the results that a poorly vascularised wound ($\gamma_b = 0.85$) responds better to $s(x,0) = 10$ when compared to $f(x,0) = 10$. Imposing equal densities/concentrations we assume GFs have a greater impact in the initial wound, which can be supported by the standard set of simulations (Figures 5.6 and 5.7).

GFs enhance repair through greater infiltration of fibroblasts/immune cells and secrete further signals to the wound domain, which helps remove debris although decays too quickly to allow wound closure. Treatment (2) demonstrates $f$ "leaking" into the wound area, but they are not sustained hence impact little on the overall healing profiles. Other dermal components are inhibited as a result of treatments (1) and (2), where nutrient delivery to the wound domain is limited and is defined by the vascularised regions which work in conjunction with one another; enhanced by granulation tissue growth and the retreat of the damaged dermis. The results of treatment (3) explores combined applications of fibroblasts and signals at the initial wound site, as presented in (right simulations) Figures 5.16-5.21.

![Figure 5.16](image-url)  
*Figure 5.16: Evolution for fibroblasts/immune cell density ($f$) in steps of $t = 2$ using values in Table 5.5 except for $\gamma_b = 0.85$ and applying the following treatments (left) $f(x,0) = 10$ (middle) $s(x,0) = 10$ and (right) $f(x,0) = 10$ and $s(x,0) = 10$.  

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Figure 5.17: Evolution for signal concentration ($s$) in steps of $t = 2$ using values in Table 5.5 except for $\gamma_b = 0.85$ and applying the following treatments (left) $f(x,0) = 10$ (middle) $s(x,0) = 10$ and (right) $f(x,0) = 10$ and $s(x,0) = 10$.

Figure 5.18: Evolution for nutrient concentration ($c$) in steps of $t = 2$ using values in Table 5.5 except for $\gamma_b = 0.85$ and applying the following treatments (left) $f(x,0) = 10$ (middle) $s(x,0) = 10$ and (right) $f(x,0) = 10$ and $s(x,0) = 10$.

Introducing treatment (3) shows improvement to the wound domain, as cells (right simulation of Figures 5.17 and 5.20) are able to infiltrate deeper into the wound and coverage is greater than $s$ and $f$ applied independently. Granulation tissue within the vascularised region is deposited in great quantities, increasing the thickness which peaks immensely at the wound.
Figure 5.19: Evolution for granulation tissue thickness \( g \) in steps of \( t = 2 \) using values in Table 5.5 except for \( \gamma_b = 0.85 \) and applying the following treatments (left) \( f(x,0) = 10 \) (middle) \( s(x,0) = 10 \) and (right) \( f(x,0) = 10 \) and \( s(x,0) = 10 \).

edge and declines thereafter which is directly reflected by high signal concentrations within the healing domain, also the nutrient delivery and fibroblasts/immune cells made available (Figures 5.17 and 5.18).

Figure 5.20: Evolution for vasculature \( k \) in steps of \( t = 2 \) using values in Table 5.5 except for \( \gamma_b = 0.85 \) and applying the following treatments (left) \( f(x,0) = 10 \) (middle) \( s(x,0) = 10 \) and (right) \( f(x,0) = 10 \) and \( s(x,0) = 10 \).
Figure 5.21: Evolution for keratinocyte thickness $(n)$ in steps of $t = 2$ using values in Table 5.5 except for $\gamma_0 = 0.85$ and applying the following treatments (left) $f(x,0) = 10$ (middle) $s(x,0) = 10$ and (right) $f(x,0)$ and $s(x,0) = 10$.

The fibroblasts/immune cells available cannot be sustained by the wound environment, and increase in both $f$ and $s$ limits distribution within the injured domain, resulting in insufficient granulation tissue deposition, vasculature and nutrient supplies (Figures 5.18), as we can observe from Figure 5.21 (right simulation) where wound closure has failed. These results do not differ much from inputting $f$ alone, although it penetrates further as shown in Figure 5.16 (left simulation). The nutrient distribution and vasculature prevents complete wound recovery, and cannot support the damaged region incurred from injury.

In treatment (4) we introduce a relatively small bolus of nutrients into the wound (from $c = 0$ to $c = 0.01$). We can see from Figures 5.22-5.24 that this has a remarkable effect on healing, as it re-establishes the collective behaviour of dermal components, where the wound domain transposes from a hypoxic to a hyperoxic medium (see Figure 5.23) and improvement in vasculature (see Figure 5.24) reflects this. This treatment expresses importance of perfusion to a compromised wound domain.

We can conclude that a small supply of nutrients at the wound site sufficiently supplements that from vasculature, and provides impetus to the repair process at the edges. These results are comparable with standard healing seen in Figures 5.7-5.10. Applying signals or fibroblasts both combined or independently, are unable to provide the appropriate levels that remain consistent throughout the wound medium to stimulate repair. The time for healing is $t \approx 21$ days with a healing speed of $\approx 0.8$, and is slower than the standard case (see Figures 5.6-5.10). The simulations in this section emphasises the vital role of nutrients in wound healing, which
Figure 5.22: Evolution for (left) signal concentration $s$ (right) fibroblasts/immune cell density ($f$) in steps of $t = 2$ using values in Table 5.5 except for $\gamma_0 = 0.85$ and applying treatment $c(x, 0) = 0.01$.

Figure 5.23: Evolution for (left) nutrient concentration ($c$) and (right) granulation tissue thickness ($g$) in steps of $t = 2$ using values in Table 5.5 except for $\gamma_0 = 0.85$ and applying treatment $c(x, 0) = 0.01$. 

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Figure 5.24: Evolution for (left) vasculature (k) (right) keratinocyte thickness (n) in steps of $t = 2$ using values in Table 5.5 except for $\gamma_h = 0.85$ and applying treatment $c(x, 0) = 0.01$.

can be supported by literature [2, 25, 34, 47, 111].

Effects of Poor Clotting

The clotting mechanism is important for the initial stages of injury, providing a barrier of protection preventing further damage and allows healing to take place underneath. Wound healing can be perturbed if the clotting matrix is not efficient, providing a poor foundation for wound bed preparation and may inhibit the onset of essential dermal and epidermal activities in the proliferative stage. Abnormalities in clotting can develop in chronic wounds and investigation may also provide insight into platelet disorders (such as von Willebrand disease) where haemorrhaging and thrombosis are common, although our interest lies in wound repair aspect of healing.

In this section the standard parameter values in Table 5.5 apply ($\gamma_h = 0.6$), apart from $\beta_{sm}$ which is reduced to $\beta_{sm} = 4$ (from $\beta_{sm} = 6$), and implies that signal secretion from the dead material region is reduced. Figures 5.25-5.27 present the effects of initial clot insufficiency and how this reflects on the overall healing process.

The signal levels (left simulation in Figure 5.25) are approximately two thirds (here $s \approx 6.2$) of that seen in the normal healing case (refer to Figure 5.6), and cannot suffuse the whole wound to sufficient levels for successful cell recruitment (fibroblasts/immune cells), or initiate clotting processes (right of Figure 5.25) beyond $x \approx 20$ adequately (Figures 5.27).

The low signal concentrations are reflected in the fibroblast/immune cell distribution, levels
Figure 5.25: Evolution of (left) signal concentration ($s$) (right) fibroblast/immune cell density in steps of $t = 6$ using values in Table 5.5 except for $\beta_{am} = 4$.

Figure 5.26: Evolution of (left) granulation tissue thickness ($g$) (middle) vasculature ($k$) and (right) damaged dermis thickness ($m$) in steps of $t = 6$ using values in Table 5.5 except for $\beta_{am} = 4$. 

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that are lower than the normal density seen in Figure 5.7 ($f \approx 2.5$ here). The limitation on $f$ implies that granulation tissue formation is restricted, and the removal of the unhealthy tissue will be delayed (see right simulation in Figure 5.26), inhibiting angiogenesis and nutrient availability (left simulations of Figures 5.26 and 5.27).

It can be interpreted that the profiles resemble those observed when nutrient delivery was reduced ($\gamma_n = 0.85$) in Figures 5.13-5.15, although they are even more localised to the wound edge and variable activities are bounded, particularly noticeable in the signals and damaged dermis distribution (Figures 5.25 and 5.27). Figures 5.26 and 5.27 demonstrate failure of wound closure of granulation tissue and recovery of the epidermis, the former leading to inadequate revascularisation and deficient nutrient supply (Figures 5.26 and 5.27).

This simulation emphasises the crucial role of the clotting scaffold within the eschar, during the process of healing via the release of GFs. The small reduction of GF production rate by $m$, from $\beta_{sm} = 6$ to $\beta_{sm} = 4$ can result in wound healing failure. We can conclude that an inefficient clotting scaffold only allows partial repair at the wound edges as $s$ levels are insufficient with the inability the cover the wound, when proliferation processes are stimulated.

**Nutrient Bolus Treatments for Poor Clots**

To investigate a means of restoring defects in healing as a result of poor clotting quality we focus on adding an initial bolus of nutrients of $c(x, 0) = 0.01$ as before. It was found from the
Figure 5.28: Evolution of (left) fibroblasts/immune cell density \( f \) and (right) signal concentration \( s \) in steps of \( t \) = 2 using values in Table 5.5 except for \( \beta_{sm} = 4 \) and applying treatment \( c(x,0) = 0.01 \).

previous simulations when \( \gamma_b = 0.85 \) that applying \( s \) and \( f \) independently or combined, did not retrieve the normal healing path and we will only consider the nutrient treatment. The results are shown in Figures 5.28-5.30.

Figure 5.29: Evolution of (left) granulation tissue density \( g \) and (right) vasculature \( k \) in steps of \( t = 2 \) (using values in Table 5.5 except for \( \beta_{sm} = 4 \) and applying treatment \( c(x,0) = 0.01 \).
Applying \( c \) to the wound site, immediately improves the wound domain as \( f \) migrates into the region, and encourages cell secretion as presented in Figures 5.28 and 5.30. This allows new tissue growth once eschar/clot has been replaced. This reinstates vascular ability of the wound area enabling efficient nutrient delivery to the whole wound area, as shown in Figures 5.29 and 5.30. The integrated variable efforts to restore healing ensures that a suitable scaffold is provided for keratinocyte to migrate over and allow wound closure, presented in Figure 5.30 (left simulation).

We can conclude from the above results that an inefficient clotting matrix created by a small reduction in \( \beta_{sm} \) (\( \beta_{sm} = 6 \) to \( \beta_{sm} = 4 \)) can disrupt the healing process, and provides similar behaviour to those seen in a poorly vascularised wound when \( \gamma_b = 0.85 \) (Figures 5.13-5.15). We found that healing was restored with additional nutrients at the wound site, which compares well with the healing traits in a poorly vascularised wound as it provides the stimulus for complete recovery.

**Varying Wound Geometry**

So far we have only considered the rather ideal rectangular shaped wounds and to attain greater insight into healing behaviour, more irregular wound shapes can be examined. In this section a more rounded wound bed presented in Figure 5.31, will be investigated in the same domain as before (Figure 5.31) by varying \( d(x,0) \) which defines the wound edge at the initial
injury, given by

\[ d(x, 0) = d_{\min} + (1 - d_{\min}) \left( \frac{z}{L} \right)^\zeta, \]

(5.38)
to see how this alters the healing behaviour. In (5.32), \( d_{\min} \) is the lowest point in the wound and the exponent \( \zeta \) governs the steepness of the damaged area. We apply \( \zeta = 1 \) and \( d_{\min} = 0.1 \), for the following simulations presented in Figures 5.32-5.34. The standard parameters in Table 5.5 apply and we manipulate \( \gamma_b \) to determine a relationship, if any between wound shape and vascularisation and we compare the standard (\( \gamma_b = 0.6 \)) and poorly vascularised cases (\( \gamma_b = 0.85 \)).

The healing process differs little from the standard simulation, presented in Figures 5.6-5.11 for the rectangular wound case. The major disparities appear in the deposition of granulation tissue at the wound site (Figure 5.34), where the "raised" tissue (which peaks) can be seen across the wound domain (\( x \in (0, 10) \)), and is not localised at the edges (Figure 5.8). Fibroblast/immune cell levels peaks to \( f \approx 5 \) (see Figure 5.33) at the wound edge, which is greater than the standard simulation in Figure 5.7. This supports and furthers the stimulation of vasculature, which "dips" at \( x = 10 \) although retains high levels thereafter and resembles the rectangular wound bed in the region of \( 0 \leq x < 10 \). The components allow re-epithelisation hence wound closure (see Figures 5.32).

A wound of this shape retains healthy tissue underneath the damaged area for \( x \in (0, 32) \) (Figure 5.32) and could contribute the healing process especially in a poorly vascularised wound. By changing \( \gamma_b \) from normal to the poorly vascularised case, where \( \gamma_b = 0.85 \) as given in Figures 5.35-5.36, we can compare the simulations to the rectangular wound case (Figures

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**Figure 5.31:** Schematic of the wound domain after change is imposed to the wound bed and imposing the idealised conditions from the standard simulation.
Figure 5.32: Evolution of (left) keratinocyte thickness ($T_t$) (middle) normal dermis thickness ($d$) and (right) damaged dermis thickness ($m$) in steps of $t = 6$ using values in Table 5.5 and we apply $\zeta = 1$.

Figure 5.33: Evolution of (left) signal concentration ($s$) and (right) fibroblast/immune cell density in steps of $t = 6$ using values in Table 5.5 and we apply $\zeta = 1$. 
Figure 5.34: Evolution of (left) granulation tissue thickness ($g$) and (right) vasculature ($k$) in steps of $t = 6$ using values in Table 5.5 and we apply $\zeta = 1$.

Figure 5.35: Evolution of (left) signal concentration ($s$) (middle) fibroblast/immune cell density and (right) damaged dermis thickness ($m$) in steps of $t = 6$ using values in Table 5.5 except for $\gamma_0 = 0.85$ and we apply $\zeta = 1$. 

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Figure 5.36: Evolution of (left) granulation tissue thickness \( g \) (middle) vasculature \( k \) and (right) keratinocyte thickness \( n \) in steps of \( t = 6 \) using values in Table 5.5 except for \( \gamma_b = 0.85 \) and we apply \( \zeta = 1 \).

5.6-5.11). We observe that reducing vascular efficiency in a wound of this shape has the ability to successfully heal (see Figure 5.36). Appropriate signal and fibroblasts levels (see Figures 5.35) are available to the wound domain, although granulation tissue formation is slightly lower \( (g \approx 0.75) \) when compared to the normal simulation in Figure 5.34. In both cases using the exponent \( \zeta = 1, (\gamma_b = 0.6 \text{ and } \gamma_b = 0.85) \) the damaged dermis retreats and re-epithelisation takes place, indicating a relationship between wound shape and healing.

To investigate further the healing dependency on the wound bed shape, we increase the exponent to \( \zeta = 2 \) which reduces steepness of the damaged region hence healthy tissue surrounding the wound. The simulations are given in Figures 5.37-5.38 for the poorly vascularised case, hence when \( \gamma_b = 0.85 \).

Healing fails when we increase the exponent \( (\zeta = 2) \), although wound coverage is greater than the rectangular non-healing case (Figures 5.13-5.15) and the appropriate signals levels and supporting vasculature are observed (Figures 5.37 and 5.38). The fibroblasts/immune cell density peaks to \( f \approx 4.5 \) and declines steadily to the non-healing steady state near the wound centre \( (x = 0) \). This allows granulation tissue formation in the vascularised region (Figures 5.37 and 5.38). Wound closure is not achieved, however, and only a small region remains unhealed for \( x \in (0, 10) \).

The simulations in this section suggest that varying wound geometry has a significant impact on the wound healing behaviour, and we have shown that wound closure is successful in a poorly vascularised domain of a shallow wound where \( \zeta = 1 \), as the healthy tissue underneath...
stimulates healing of localised deep tissue areas. Reducing the steepness of the damaged area impedes wound closure by leaving a small area unhealed.

Figure 5.37: Evolution of (left) signal concentration (s) (middle) fibroblast/immune cell density and (right) granulation tissue thickness (g) in steps of t = 6 using values in Table 5.5 except for \( \gamma_b = 0.85 \) and we apply \( c = 2 \).

Figure 5.38: Evolution of (left) vasculature (k) (middle) keratinocyte thickness (n) and (right) normal dermis thickness (d) in steps of t = 6 using values in Table 5.5 except for \( \gamma_b = 0.85 \) and we apply \( c = 2 \).
Topical Application of GF

Up to now, the model predicts that the crucial elements in healing are the nutrient supply and GFs from the clot as seen in Figures 5.13-5.15 and Figures 5.25-5.27, where non-healing occurs. Bolus treatments of GFs and fibroblasts are relatively unsuccessful, when applied to the initial wound site. In practice it may not be favourable to maintain the eschar, as wound debridement may be necessary to keep the area clean and free from infection. In this section we investigate the topical application of GFs to a poorly vascularised wound defined by $\gamma_b = 0.85$, e.g. from a specially designed wound dressing. This will compensate for loss of signal source from the blood clotted material, and secrete further signals to the injured area.

We extend the signal equation to describe the additional infusion of GFs with the introduction of a source term

$$\beta_s H(\bar{n} - n),$$

so that the $s$ equation becomes

$$\frac{\partial s}{\partial t} = D_s \frac{\partial^2 s}{\partial x^2} + (\alpha(\beta_{sn} + \beta_{snn}) + f(\beta_{sf} + \beta_{ saf}))((1 + \beta_{se} H(\bar{c} - c))$$

$$+ \beta_{snn} m + \beta_s H(n - \bar{n}) - s(\delta_s + \delta_{snn} + \delta_{sf})),$$

where $\beta_s$ represents the signal infusion rate so that the additional term provides a "drip-feed" of GFs in a wound defined as $n < \bar{n}$. We have assumed that infusion is only possible if the keratinised layer is relatively thin i.e. $n < \bar{n}$; the Heaviside function here implying

$$H(\bar{n} - n) = \begin{cases} 
1 & \text{if } n < \bar{n} \text{ (GF application needed)} \\
0 & \text{if } n \geq \bar{n} \text{ (GF does not penetrate)}. 
\end{cases}$$

In this simulation we assume wound debridement removes the dead material in preparation for GF application, which is denoted by $m(x,0) = 0$ and that signals present at the wound domain are also removed during this process hence $\beta_{sn} = 0$. Parameters in Table 5.5 apply and we use "modest" infusion rate of $\beta_s = 2$ and let $\bar{n} = 0.3$. The simulations for signals, fibroblasts, granulation tissue and keratinocytes are presented in Figures 5.39-5.42.

The simulations show a successfully healed wound as keratinocytes are able to migrate over the wound area to ensure closure, enabled by adequate signal presence in the wound (Figure 5.39), to recruit fibroblasts/immune cells to the damaged area (Figure 5.40). We note that signal levels here ($s \approx 3 - 5$), are somewhat lower that in the normal healed case where $s \approx 9$ (Figure 5.6). Granulation tissue production is apparently over stimulated as a result (Figure 5.41) and larger deposits are observed with $g \approx 1.7$ as opposed to $g \approx 1$ in the normal case (compare to Figure 5.8). With $\gamma_b = 0.85$ and $\rho_b = 0.6$, more granulation tissue is needed to provide the adequate dermal tissue for an effective blood supply, which may offer an explanation to
Figure 5.39: Evolution of signal concentration ($s$) in steps of $t = 6$ after GF application where $\beta_s = 2$ and we use values in Table 5.5 except for $\gamma_b = 0.85$.

Figure 5.40: Evolution of fibroblasts/immune cell density($f$) in steps of $t = 6$ after GF application where $\beta_s = 2$ and we use values in Table 5.5 except for $\gamma_b = 0.85$. 
Figure 5.41: Evolution of granulation tissue density ($g$) in steps of $t = 6$ after GF application where $\beta_6 = 2$ and we use values in Table 5.5 except for $\gamma_6 = 0.85$.

Figure 5.42: Evolution of keratinocytes thickness ($n$) in steps of $t = 6$ after GF application where $\beta_6 = 2$ and we use values in Table 5.5 except for $\gamma_6 = 0.85$. 
increased levels observed above.

We can conclude that clinical application of GFs in a non-healing wound can activate the healing components, to restore the normal healing processes and successful re-epithelisation.

**Surface Nutrients**

The bolus nutrients have been successful in the compromised healing scenarios considered and presented in Figures 5.28-5.30, although up until now atmospheric nutrients present at the wound surface (imposed as a boundary condition) have not been investigated. Continuous oxygen ($O_2$) consumption in the wound tissue allows healing to progress, and encourages the wound to become resistant to infections. Therapy based on $O_2$ treatments, applied either locally or through a hyperbaric chamber improves epithelial recovery and polymorphonuclear functions in removing necrotic tissue [46, 48].

If we extend the nutrient equation to include surface nutrients (resembling hyperbaric chambers) with the introduction of the source term

$$Q(\bar{c}_0 - c)H(\bar{n} - n),$$

and we write

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + \beta \delta k_0(d, g) + Q(\bar{c}_0 - c)H(\bar{n} - n) - c(\delta_{cn} n + \delta_{cf}),$$

where $Q$ represents transfer coefficient of nutrients into the wound domain and $\bar{c}_0$ are the critical nutrient concentration at the wound surface. Infiltration into the wound domain will depend on the thickness of the keratinised layer ($n < \bar{n}$) defined by the heaviside function given in (5.39). Parameters in Table 5.5 apply and we impose $\bar{n} = 0.3$ and the critical nutrient concentration $\bar{c}_0 = 1.0$. The simulations presented in Figures 5.43 and 5.44 illustrate the different healing profiles for both nutrients and keratinocytes, when the transfer coefficient differs and $Q = 0.0001$ and $Q = 0.1$ are investigated.

It can be interpreted from Figures 5.43 and 5.44 (left simulations) that an inadequate atmospheric nutrient supply ($Q = 0.0001$) results in a retarded wound, which is deprived of essential oxygen concentration and may be unable to reach the deeper wound area. This could be explained by debris or necrotic tissue that accumulates on the wound surface and may prevent oxygen entering the damaged domain. Increasing the transfer coefficient to $Q = 0.1$ (as presented in right simulations of Figures 5.43 and 5.44) helps restore the healing profiles as we would expect in a normally healed wound. This additional supply or ability to enter the wound may help remove debris and initiate many of the key healing processes, as the wound is highly perfused and encourages processes such as vasculature and wound coverage (right simulation
Figure 5.43: Evolution of keratinocyte thickness ($n$) in steps of $t = 6$ using values in Table 5.5 and (left) $Q = 0.0001$ and (right) $Q = 0.1$.

Figure 5.44: Evolution of nutrient concentration ($c$) in steps of $t = 6$ using values in Table 5.5 and (left) $Q = 0.0001$ and (right) $Q = 0.1$. 

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in Figure 5.44).

The delayed healing profiles presented in Figures 5.43 and 5.44 (left simulations), can be compared to previous results presented in earlier sections when vasculature (refer to Figures 5.25-5.27) and the clotting matrix (refer to Figures 5.13-5.15) were impeded and healing was greatly affected. In these compromised healing cases, we found that bolus nutrients helped retrieve the normal healing course and enabled full wound recovery and essentially highlights the importance of this variable in the wound healing phenomena. Our findings from this section suggests that atmospheric nutrient delivery in the host tissue, contributes to the healing process provided the transfer nutrient is of a sufficient quantity to allow wound debridement and the keratinised layer supports the nutrient delivery within the damaged region.

Overall we can conclude that nutrients play a vital role in the wound healing process whether it is obtained atmospherically or as a bolus treatment to a severely impaired/delayed wound and can restore normal healing profiles, provided debridement is effective minimising the necrotic tissue that may accumulate.

5.5 Summary

This chapter explored the loss of deep skin tissue referred to as partial/full thickness wounds, where both the epidermal and dermal membranes are removed. A simple model was proposed describing dermal behaviour during the proliferative and repair stages of wound healing and the overall healing process was key to this model. The model investigated collective and interactive behaviour of fibroblasts, keratinocytes, granulation tissue, signals, nutrients, healthy and unhealthy wound area as healing persists. Influx of cells, nutrients and signals was accounted for by diffusion and chemotaxis terms; consequently a large number of parameters (approximately 45 parameters in the standard simulation) are inputted into the model to accommodate for the key healing components.

The resulting 1D reaction-diffusion model was solved numerically in Fortran, and simulations presented in this chapter illustrate normal (refer to Figures 5.6-5.12) and abnormal healing scenarios (delayed or arrested healing). The key parameters

- $\gamma_b$ defines the nutrient delivery to the wound domain and determines vascular efficiency and
- $\beta_{sm}$ describes the quality and extent of clotting,

were investigated to highlight the normal and delayed cases. It was found that small reduction ($\gamma_b = 0.6$ to $\gamma_b = 0.85$) in nutrient delivery had detrimental effects on the vascular effectiveness, inhibiting granulation tissue growth, cell migration and causing healing arrest (refer to Figures 5.13-5.15). Similar behaviour was observed after reduction in clotting ability hence $\beta_{sm} = 4$
(refer to Figures 5.25-5.27), where lower signal concentration available to the wound domain and localised cell migration near the wound edge also delayed wound healing.

Retrieving the delayed/arrested healing using bolus treatments was the most successful with nutrients in both cases. The simulations suggest the role of nutrients are critical and even small amounts available in bolus form can make the difference between healing and non-healing (refer to Figures 5.22-5.24 and 5.28-5.30). This is supported further by atmospheric nutrients which improve the healing ability when the transfer coefficient is adequate, enabling tissue perfusion and promote wound closure (refer to Figure 5.43 and 5.44). In contrast, a bolus of GFs is less effective, but a continuous influx provided naturally by the clot components of the eschar or artificially from a special dressing can restore the normal healing course. In reality a single nutrient or GF is unlikely to have such a notable effect as nucleated by the model simulations, however a suitable mix of nutrients and GFs planted in the wound could significantly enhance healing and revert a chronic wound scenario. However, the modelling of multiple nutrients and GFs is beyond the scope of this study and we present this as a hypothesis based on the results of the model.

Wound shape was also shown to be an important factor when considering nutrient delivery \( \gamma \), where shallower, healthier tissue surrounding the wound can help promote the healing of neighbouring deeper parts of the injured areas, even when vascular efficiency is compromised as illustrated in Figures 5.35-5.36.

The results obtained provide awareness into realistic behaviour and reproduce dermal healing scenarios, during the proliferative and repair stages to maintain skin homeostasis, emphasising the significant role of nutrients. To simplify the modelling we concentrated on the most significant components to demonstrate normal healing characteristics and excluded a number of factors believed to be important, such as

- Bacterial invasion and infections.
- PH levels and toxicity of wound fluid.
- Body temperature.
- Independent GFs and their influence on healing processes.
- Individual nutrient constituents.

The first of these is probably the most significant and bacterial infection will be considered in the next chapter.
Chapter 6

Bacterial Infections

6.1 Introduction

Once damaged skin is exposed to the external environment, it will naturally come into contact with micro-organisms such as the bacteria. Examples include *Staphylococcus Aureus*, *Streptococcus* spp and *Pseudomonas Aeruginosa*. They are routinely removed by the immune system to allow complete wound recovery, as discussed in Chapter 1. Figure 6.1 presents the normal stages of healing from injury to wound closure and successful removal of foreign bodies entering the damaged area. Deep wound tissue provides an ideal habitat for bacterial invasion. This may impair wound bed preparation and contribute to chronic wound development, if unattended or with insufficient wound management. The severity and spread of infections is often dependent on the wound size and anatomical location [2, 8, 18, 53, 71, 116].

Many species of infecting bacteria metabolise nutrients both aerobically and anaerobically, with the ability to adapt to hypoxic conditions resulting in overabundant bacterial burden or critical colonisation in the affected area. Invasion can delay the healing process and in some cases patients become unresponsive to antibiotic or other available treatments. Microbial infections are an important part of the wound healing process, and can be the major cause of chronic wounds [25, 26, 34, 71]. The dermal model seen in Chapter 5 is extended here with the introduction of bacteria into the system, to investigate their role in the wound healing process.
Figure 6.1: Normal wound healing in the presence of bacteria. (a) Inflammation - a fibrin clot is formed and an abundance of bacteria, neutrophils and platelets. (b) Fibroblast migration stimulates granulation tissue formation and angiogenesis. (c) Re-epithelisation and wound is contracted although remodelling underneath will continue. This diagram has been reproduced with the permission of Sabine Werner [53].
6.2 Mathematical Modelling

6.2.1 Model Background

The addition of bacteria changes the model slightly, as wound debridement and removal of necrotic tissue is essential to prevent infections and provide a clean wound bed for tissue growth and wound closure. A simple schematic diagram is presented in Figure 6.2 illustrating the key dermal events and immune cell activities become more prominent in response to bacterial infections.

Figure 6.4 presents a schematic representation of the wound domain and the cross sectional quantities considered and listed in Table 6.1. This is the same set up as the model discussed in Chapter 5, except bacteria will inhabit the wound region.

The main aims of the modelling in addition to those mentioned in 5.3.1 are

- Investigate the role of bacteria in normal and abnormal healing.
- Identify parameters key to the onset of infections.

Bacteria can infiltrate where there is broken skin, although the eschar region can act as a barrier, see Figure 6.3. The host responds by recruiting immune cells to the wound site

![Schematic of dermal wound healing with bacteria](image-url)

Figure 6.2: Schematic of dermal wound healing with bacteria.
Figure 6.3: Schematic diagram illustrates migration of fibroblasts and immune cells in response to bacteria invasion into the wound medium.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n(x,t)$</td>
<td>Keratinocyte cross sectional thickness</td>
</tr>
<tr>
<td>$m(x,t)$</td>
<td>Damaged dermis cross sectional thickness</td>
</tr>
<tr>
<td>$d(x,t)$</td>
<td>Normal (healthy) dermis cross sectional thickness</td>
</tr>
<tr>
<td>$g(x,t)$</td>
<td>Granulation tissue cross sectional thickness</td>
</tr>
<tr>
<td>$f(x,t)$</td>
<td>Fibroblast and immune cell cross sectional density</td>
</tr>
<tr>
<td>$c(x,t)$</td>
<td>Nutrient cross sectional concentration</td>
</tr>
<tr>
<td>$s(x,t)$</td>
<td>Signals (GFs and cytokines) cross sectional concentration</td>
</tr>
<tr>
<td>$w(x,t)$</td>
<td>Bacteria cross sectional density</td>
</tr>
</tbody>
</table>

Table 6.1: Variables considered in the bacteria-dermal model

To remove the bacteria, the assumptions of Chapter 5 are carried through and we add to these,

- We assume a single “generic” species of bacteria.
- $n(x,t)$ prevents $w(x,t)$ entering wound as it provides a barrier to external stimuli.
- Bacteria are removed by $f(x,t)$ and decay due to natural death from sloughed material.
- Presence of bacteria will induce further secretion of $s(x,t)$ by fibroblasts and keratinocytes.
- Birth rate of bacteria is dependent on nutrients and dead cell material.
- Living tissue is broken down by bacteria to create more $m(x,t)$.

The latter assumption is relevant in the severe of cases of bacterial infections, as they destroy healthy tissue, which could lead to an expanding wound.
6.2.2 Governing Equations

Amendments will be made to the equations seen in 5.3.2, by incorporating the influence of bacteria to the model. As before parameters of the form \( \beta \) will describe birth rates, \( \delta \) will refer to death/removal rates and \( \gamma \) represents inhibitor threshold parameters of model variables involved. We introduce \( \alpha \) which describes ratio of selective terms \( (\delta_{n_0}, \delta_{a_n}, \delta_{m_p}, \beta_{md}, \delta_{u}, \delta_{gw}, \delta_{fu}, \delta_{ew} \) and \( \delta_{uf} \) as stated in Chapter 5), to the maximum eschar/dead material produced by bacteria.

**Bacteria** \( w(x, t) \)

Microbial presence can be observed immediately after injury and in most cases the immune response ensures removal, hence wound closure under normal healing conditions [11, 14]. The rate of change is given by

\[
\text{Rate of change of } w(x, t) = \text{Infiltration from environment} + \text{Birth} - \text{Loss/degredation}
\]

hence

\[
\frac{\partial w}{\partial t} = k_w(w, c, m) - \lambda_w(w, f) \tag{6.1}
\]

where \( k_w \) is bacteria production rate promoted by poorly keratinised presence and the expected proportion of \( k_w \) are nutrients and damaged dermis. We expect

\[
\frac{\partial k_w}{\partial w} > 0, \quad \frac{\partial k_w}{\partial c} < 0, \quad \frac{\partial k_w}{\partial m} > 0 \quad \text{and} \quad \frac{\partial k_w}{\partial n} < 0.
\]

We assume that keratinocytes form an effective barrier when \( n > \bar{n} \) (where \( \bar{n} < n_0 \)), and infiltration occurs when \( n < \bar{n} \), and the corresponding rate of infiltration is taken as \( \beta_{wn}H(\bar{n} - n) \), where

\[
H(\bar{n} - n) = \begin{cases} 
1 & \text{if } n < \bar{n} \text{ (open wound)} \\
0 & \text{if } n > \bar{n} \text{ (closed wound)}
\end{cases}
\]

we also assume a linear dependence on \( c \) and \( m \) on the birth rate. Hence

\[
k_w = w(\beta_{wc}c + \beta_{wm}m) + \beta_{wn}H(\bar{n} - n).
\]

However microbial movement relies on \( n \), as they are responsible for re-epithelisation and progressive wound closure will prevent influx of microbes [32, 53].
The bacterial removal rate $\lambda_w$ depends on fibroblasts, immune cells and natural loss. It has the expected properties

$$\frac{\partial \lambda_w}{\partial w} < 0 \quad \text{and} \quad \frac{\partial \lambda_w}{\partial f} < 0,$$

hence we assume

$$\lambda_w = w(\delta_w + \delta_w f).$$

**Dermis $d(x, t)$**

The normal dermis can become damaged by bacteria. In the model of the previous chapter there was no dermal removal, hence $\lambda_d = 0$. However the presence of bacteria will modify these properties, and we expect

$$\frac{\partial \lambda_d}{\partial d} < 0 \quad \text{and} \quad \frac{\partial \lambda_d}{\partial w} < 0,$$

and write

$$\lambda_d = -\alpha_d m w d.$$  

**Damaged Dermis $m(x, t)$**

The destruction of living cells by bacteria generates more damaged/necrotic material, which changes the production rate $k_m$ with the following properties,

$$\frac{\partial k_m}{\partial w} > 0 \quad \frac{\partial k_m}{\partial n} < 0 \quad \frac{\partial k_m}{\partial g} < 0 \quad \text{and} \quad \frac{\partial k_m}{\partial d} < 0.$$

Although bacteria consumes dead/damaged material, it is assumed that the volumes concerned are negligible compared to the total volume of material so that

$$\frac{\partial \lambda_m}{\partial m} \approx 0,$$

we write

$$k_m = w(\alpha_m w^n + \alpha_g m g + \alpha_d m d).$$

**Nutrients $c(x, t)$**

In addition to 5.3.2 we extend the consumption rate function $\lambda_c$ by introducing a bacterial depletion term, and we expect

$$\frac{\partial \lambda_c}{\partial w} > 0,$$
hence

\[ \lambda_c = c(\delta_{cn} n + \delta_{cf} f + \alpha_{cw} w). \]

**Signals \( s(x, t) \)**

Bacteria present at the wound domain will initiate immune cell migration and secrete further \( s(x, t) \) and we expect an additional property of \( k_s \) to be

\[ \frac{\partial k_s}{\partial w} > 0, \]

and write

\[ k_s = (n(\beta_{sn} + \beta_{sfn}) + f(\beta_{sf} + \beta_{sff}))((1 + \beta_c H(\tilde{c} - c)) + \theta_p \beta_{smm} + \beta_{sw} f w \]

where the last term being the most recent addition. Although it should be noted that signals secreted in response to fibroblasts and immune cells are dependent on the level of bacterial levels.

**Fibroblasts \( f(x, t) \)**

Immune cells help remove foreign bodies from the wound area, though fibroblasts are likely to be vulnerable and we expect

\[ \frac{\partial \lambda_f}{\partial w} > 0, \]

we write

\[ \lambda_f = f \left( \frac{\delta_{fc}}{1 + (c + \rho_f s)/\gamma_{fc}} + \alpha_{fmu} w \right). \]

**Granulation Tissue \( g(x, t) \)**

The granulation tissue production can be inhibited by bacterial infiltration, which largely depends on the severity of the deep tissue colonisation [24]. Both birth \( k_g(c, f, s, w) \) and death \( \lambda_g(g, c, w) \) functions are extended from that seen in 5.3.2.

For birth rate \( k_g(c, f, s, w) \) in addition to what is already known, we expect some suppression in this production, hence

\[ \frac{\partial k_g}{\partial w} < 0, \]

and we assume

\[ k_g = \frac{cf(\beta_{gef} + \beta_{gss})}{1 + w/\gamma_{gw}} H(s - \tilde{s})H(\tilde{c} - c). \]
Like the dermis, granulation tissue may also be removed by bacteria, hence we expect

\[ \frac{\partial \lambda_g}{\partial w} < 0. \]

We write

\[ \lambda_g = g \left( \frac{\delta_{gc}}{1 + c/\gamma_{gc}} + \alpha_{gmw}w \right). \]

**Keratinocytes \( n(x,t) \)**

Though keratinised skin tissue is an effective barrier, non-keratinised epithelial cells are likely to be vulnerable to bacteria, hence we expect

\[ \frac{\partial \lambda_n}{\partial w} > 0 \]

and write

\[ \lambda_n = n \left( \frac{\delta_{nc}}{1 + c/\gamma_{nc}} + \alpha_{nmw}w \right). \]

**6.2.3 Full System of Equations**

For purposes of clarity we present the full extended system

\[
\begin{align*}
\frac{\partial n}{\partial t} &= \frac{\partial}{\partial x} \left( \frac{D_n}{\partial x} \right) - \frac{\partial}{\partial x} \left( n \chi_n (d + \sigma_n g) \frac{\partial s}{\partial x} \right) + \beta_{an} \frac{n}{\sigma_n} \left( 1 - \frac{\delta_{nc}}{1 + c/\gamma_{nc}} + \alpha_{nmw}w \right) \\
\frac{\partial m}{\partial t} &= w (\alpha_{nmw} n + \alpha_{gmw} g + \alpha_{omw} d) - m f (\delta_{mf} + \delta_{ms} d) - \delta_{m} m \\
\frac{\partial g}{\partial t} &= \frac{\partial}{\partial x} \left( J \chi f (d + \sigma f g) \frac{\partial s}{\partial x} \right) + \beta_{fg} k_0 (d, g) + f c \left( \beta_{fc} \left( 1 - \frac{J}{\nu_f} \right) + \beta_{fcs} (s - \bar{s}) \right) \\
\frac{\partial c}{\partial t} &= \frac{\partial}{\partial x} \left( D_c \frac{\partial c}{\partial x} \right) + \beta_{cb} k_0 (d, g) - c (\delta_{cn} n + \epsilon_{wf} f + \alpha_{cmw} w) \\
\frac{\partial w}{\partial t} &= w (\alpha_{omw} c + \beta_{wm} m) + \beta_{wm} H (n - n) - w (\delta_w + \delta_{w} f) \\
\frac{\partial s}{\partial t} &= \frac{\partial}{\partial x} \left( D_s \frac{\partial s}{\partial x} \right) + (n (\beta_{sm} + \beta_{s} m) + f (\beta_{sf} + \beta_{s} s)) (1 + \beta_{sc} H (\bar{c} - c)) + \epsilon_{sf} f \frac{\partial s}{\partial x} + \delta_{sf} f
\end{align*}
\]
where the vasculature function is defined as before by

$$k_b(d, g) = \left(\frac{(d + \rho_b g)^n}{\gamma_b^n + (d + \rho_b g)^n}\right)^{\frac{1}{n}}.$$

The system is defined on the fixed domain $(0, L)$ and the initial and boundary conditions are provided below and define a closed system.

**Initial and Boundary Conditions**

To close the system the following conditions are imposed and Figure 6.4 presents the typical wound domain considered

- At $x = 0$ signifies the centre of the wound and the initial damaged domain. We apply the zero-flux conditions

  $$\frac{\partial n}{\partial x} = 0, \quad \frac{\partial f}{\partial x} = 0, \quad \frac{\partial c}{\partial x} = 0, \quad \text{and} \quad \frac{\partial s}{\partial x} = 0.$$

- At $x = L$ this is the healthy skin state provided normal repair has occurred and the transition to wound closure is observed then $n = n_0$, $f = f_0$, $c = c_0$, $s = s_0$, $m = 0$, $d = d_0$, $g = 0$ and $w = 0$.

- At $t = 0$ as skin mass is lost we assume $n = n_1(x)$, $d = d_1(x)$, $m = m_1(x)$, $c = c_1(x)$, $f = f_1(x)$, $s = s_1(x)$, $w = w_1(x)$ and $g = 0$.  


<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Units</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_{nmw} )</td>
<td>Death rate of ( n ) by ( w )</td>
<td>( \text{mm}^2 \text{(cells h)}^{-1} )</td>
<td>-</td>
</tr>
<tr>
<td>( \alpha_{gmw} )</td>
<td>Death rate of ( g ) by ( w )</td>
<td>( \text{mm}^2 \text{(cells h)}^{-1} )</td>
<td>-</td>
</tr>
<tr>
<td>( \alpha_{dvw} )</td>
<td>Death rate of ( d ) by ( w )</td>
<td>( \text{mm}^2 \text{(cells h)}^{-1} )</td>
<td>-</td>
</tr>
<tr>
<td>( \gamma_{gw} )</td>
<td>( g ) inhibited by ( w ) presence</td>
<td>( \text{cells mm}^{-2} )</td>
<td>10^4 [74]</td>
</tr>
<tr>
<td>( \alpha_{fmu} )</td>
<td>Death rate of ( f ) by ( w )</td>
<td>( \text{mm}^2 \text{(cells h)}^{-1} )</td>
<td>-</td>
</tr>
<tr>
<td>( \alpha_{uw} )</td>
<td>Bacteria production rate due to nutrients</td>
<td>( \text{mm}^2 \text{(gh)}^{-1} )</td>
<td>-</td>
</tr>
<tr>
<td>( \beta_{uw} )</td>
<td>Enhanced bacteria production rate due to ( m )</td>
<td>( \text{cells (mm}^2 \text{h)}^{-1} )</td>
<td>-</td>
</tr>
<tr>
<td>( \beta_{wn} )</td>
<td>Bacteria seeding rate from environment</td>
<td>( \text{mm} )</td>
<td>-</td>
</tr>
<tr>
<td>( \bar{n} )</td>
<td>Critical keratinocyte level</td>
<td>( \text{h}^{-1} )</td>
<td>10 [74]</td>
</tr>
<tr>
<td>( \delta_{w} )</td>
<td>Natural loss of bacteria</td>
<td>( \text{mm} )</td>
<td>-</td>
</tr>
<tr>
<td>( \delta_{wf} )</td>
<td>Removal rate of bacteria by fibroblasts</td>
<td>( \text{mm}^2 \text{(cells h)}^{-1} )</td>
<td>-</td>
</tr>
<tr>
<td>( \alpha_{cemw} )</td>
<td>Nutrients consumption by bacteria</td>
<td>( \text{mm}^2 \text{(cells h)}^{-1} )</td>
<td>-</td>
</tr>
<tr>
<td>( \beta_{sw} )</td>
<td>Signal production in response to ( w )</td>
<td>( \text{g mm}^2 \text{(cells}^2 \text{h)}^{-1} )</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.2: Additional parameters considered in the bacteria-dermal model using the units set \( h, g/\text{mm} \) and "cells", as with Table 5.5 where the units of \( w \) is taken to be cell/\( \text{mm}^2 \).

Model Parameters

The model parameters from the extended model are given in Table 6.2, with their biological interpretation. We also include corresponding experimental values where possible.

6.2.4 Nondimensionalisation

We nondimensionalise the model based on the keratinocyte birth rate and in the timescale where cells travel given by,

\[
\{\tilde{x}, \tilde{t}\} = \left\{ \frac{x}{\beta_n c_0}, t \frac{c_0}{\beta_n} \right\}.
\]

Refer to Appendix B.4 for more details.

As before the rescalings for common parameters stated in Chapter 5 apply, in which the healthy states corresponds to \( n = 1, f = 1, c = 1, s = 1, d = 1, m = 0, g = 0 \) and \( w = 0 \). The additional rescalings are

\[
\{\tilde{\phi}, \tilde{\gamma}_{gw}\} = \frac{1}{\beta_n c_0} \left\{ \frac{n_0}{d_0}, \gamma_{gw} \alpha_{nmw} \right\}
\]

\[
\{\tilde{\alpha}_{gmw}, \tilde{\alpha}_{dvw}, \tilde{\alpha}_{fmu}, \tilde{\alpha}_{sw}, \tilde{\alpha}_{cemw}\} = \frac{1}{\alpha_{nmw}} \left\{ \alpha_{gmw}, \alpha_{dvw}, \alpha_{fmu}, \alpha_{sw}, \alpha_{cemw} \right\}
\]

\[
\{\tilde{\delta}_{w}, \tilde{\delta}_{wf}\} = \frac{1}{c_0 \beta_n} \left\{ \delta_{w}, \delta_{wf}\right\}
\]

\[
\{\tilde{\beta}_{wn}, \tilde{\beta}_{uw}, \tilde{\beta}_{sw}\} = \frac{1}{c_0 \beta_n} \left\{ \beta_{wn}, \beta_{uw}, \beta_{sw}\right\}
\]

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\( \{ \hat{\beta}_{uv} \} = \left\{ \frac{\beta_{uv} f_0}{\hat{\delta}_0 \alpha_{nmw}} \right\}, \) 

and the parameter relationships remain unchanged from that given in Section 5.3.2.

Dropping the hats for clarity, the nondimensionalised system is given below

\[
\begin{align*}
\frac{\partial n}{\partial t} = & \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x} \left( n \chi_n (d + \sigma_n g) \frac{\partial g}{\partial x} \right) + \frac{nc}{1 + \sigma / \gamma_{nc}} \left( 1 - \frac{n}{\kappa_n} \right) - n \left( \frac{\delta_{nc}}{1 + c / \gamma_{nc}} + w \right) \\
\frac{\partial m}{\partial t} = & q (\phi n + \alpha_{gmu} g + \alpha_{dmw} d) - m f (\delta_{mf} + \delta_{m} s) - \delta_{m} m n \\
\frac{\partial d}{\partial t} = & - \alpha_{dmw} w d \\
\frac{\partial g}{\partial t} = & c f (\beta_{fg} + \beta_{gg} H(s - \bar{s}) H(c - \bar{c}) - \gamma \left( 1 + c / \gamma_{fg} \right) + \alpha_{gmu} w) \\
\frac{\partial f}{\partial t} = & D_f \frac{\partial^2 f}{\partial x^2} - \frac{\partial}{\partial x} \left( f x f (d + \sigma_f g) \frac{\partial g}{\partial x} \right) + \beta_{f} k_0 (d, g) \\
& + c f \left( \beta_{fc} \left( 1 - \frac{f}{\kappa_f} \right) + \beta_{fc} H(s - \bar{s}) \right) - f \left( \frac{\delta_{fg}}{1 + (a + \rho_f) / \gamma_f} + \alpha_{fmu} w \right) \\
\frac{\partial c}{\partial t} = & D_c \frac{\partial^2 c}{\partial x^2} + \beta_{bc} k_0 (d, g) - c (\delta_{cm} n + \delta_{cf} f + \alpha_{cnu} w) \\
\frac{\partial w}{\partial t} = & w (\beta_{wc} c + \beta_{wn} m) + \beta_{wn} H(n - n) - w (\delta_{wn} + \delta_{w} f) \\
\frac{\partial s}{\partial t} = & D_s \frac{\partial^2 s}{\partial x^2} + (n (\beta_{sv} + \beta_{sm} s) + f (\beta_{sf} + \beta_{sff} s)) (1 + \beta_{s} H(c - \bar{c})) \\
& \beta_{sm} m + \beta_{sv} f w - s (\delta_{s} + \delta_{sm} n + \delta_{sf} f) \\
\end{align*}
\]

The nondimensionalisation implies that the initial and boundary conditions become

\[
\begin{align*}
t = 0 : & \quad n = n_1 (x), f = f_1 (x), d = d_1 (x), s = s_1 (x), c = c_1 (x), m = g = w = 0. \\
x = 0 : & \quad \frac{\partial n}{\partial x} = 0, \frac{\partial f}{\partial x} = 0, \frac{\partial c}{\partial x} = 0, \frac{\partial s}{\partial x} = 0. \\
x = L : & \quad n = f = c = s = d = 1, m = g = w = 0.
\end{align*}
\]

We are looking at a 1D nonlinear PDE system as presented by the equations (6.11)-(6.18). The additional parameters introduced to the extended model are given in Table 6.3, note that the standard parameter values given in Tables 5.3, 5.4 and 5.5 still hold.
6.3 Model Analysis

6.3.1 Numerical Methods

The nonlinear system is solved using finite difference schemes and we apply central differencing to the spatial domain and Euler time-step in the temporal domain. Refer to Appendices A.3 and B.4 for more details.

6.3.2 Results

The simulations presented in the following subsections will investigate the normal and delayed healing course, with the exploration of key parameters that may perturb wound closure and lead to the onset of infections, we have identified as

- \( \alpha_{dmw} \), determines the healthy ECM removed by bacterial "attack".
- \( \beta_{wn} \), describes the infiltration of bacteria hence the "seeding" rate into the wound.

Tables 5.5 and 6.3 provide the standard set of parameters values used to simulate normal healing of the extended model.

Effects of an Initial Bacteria Inoculum

Figures 6.5-6.8 presents standard simulations under normal healing conditions. We assume that there is no loss of healthy ECM post wounding and bacteria cannot infiltrate beyond the superficial membrane, hence \( \alpha_{dmw} \) and \( \beta_{wn} \) are inactive here. The initial conditions are as follows and the injured area corresponds to \( x \in (0, 32) \):

\[
0 < x < 32 : \quad n = 0, c = 0, f = 1, s = 1, m = 1, d = 0.1, w = 0.1 \text{ and } g = 0.
\]

\[
32 \leq x \leq 40 : \quad n = d = c = s = 1, g = m = w = 0.
\]

We consider small bacterial innoculums of \( w(x, 0) = 0.1 \) and \( w(x, 0) = 0.5 \) respectively at the initial wound site, to assess the healing dynamics.

In the first case we can observe that healing is successful as bacteria retreats (see left simulation of Figure 6.5), where re-epithelisation takes places to prevent further microbial presence, and forms a barrier of protection as shown in Figure 6.8 (left simulation).

A higher inoculum of bacteria \( (w(x, 0) = 0.5) \) begins to proliferate at the wound site, where a greater density can be observed \( (w \approx 7.5) \) as seen in Figure 6.5 (right simulation). This leads to an increased secretion of signals, and granulation tissue deposited and indicates that the immune response has been effective in removing a large proportion of the contamination present in the wound. Wound closure to an adequate level is observed for \( x \in (5, 32) \), as


Table 6.3: Standard set of parameter values for normal healing with bacteria.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_{mn}$</td>
<td>0.004</td>
<td>$\beta_{wc}$</td>
<td>0.2</td>
</tr>
<tr>
<td>$\beta_{mg}$</td>
<td>0.004</td>
<td>$\beta_{wm}$</td>
<td>0.2</td>
</tr>
<tr>
<td>$\beta_{md}$</td>
<td>0.004</td>
<td>$\beta_{wn}$</td>
<td>0.0</td>
</tr>
<tr>
<td>$\alpha_{dmw}$</td>
<td>0.0</td>
<td>$\gamma_w$</td>
<td>0.004</td>
</tr>
<tr>
<td>$\gamma_w$</td>
<td>0.004</td>
<td>$\delta_w$</td>
<td>0.2</td>
</tr>
<tr>
<td>$\alpha_{gmw}$</td>
<td>0.04</td>
<td>$\delta_{wj}$</td>
<td>0.2</td>
</tr>
<tr>
<td>$\alpha_{fmw}$</td>
<td>0.04</td>
<td>$\alpha_{cmw}$</td>
<td>0.4</td>
</tr>
</tbody>
</table>

keratinocytes (vary in thickness from wound edge to wound centre) are unable to migrate appropriately in the absence of a suitable matrix; hence re-epithelisation is incomplete near the wound centre ($x < 5$).

A contaminated wound will heal successfully provided the initial innoculum are at low levels, and compares well with results in Chapter 5 to resemble normal repair. Increase in initial $w(x, 0)$, impacts on the healing path and can delay or prevent complete wound recovery.

Figure 6.5: Evolution of bacteria ($w$) in steps of $t = 6$ using values in Table 6.3 when initial $w$ innoculum is (left) $w(x, 0) = 0.1$ and (right) $w(x, 0) = 0.5$. 

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Figure 6.6: Evolution of signal concentration (s) in steps of $t = 6$ using values in Table 6.3 when initial $w$ inoculum is (left) $w(x, 0) = 0.1$ and (right) $w(x, 0) = 0.5$.

Figure 6.7: Evolution of granulation tissue thickness ($g$) in steps of $t = 6$ using values in Table 6.3 when initial $w$ inoculum is (left) $w(x, 0) = 0.1$ and (right) $w(x, 0) = 0.5$. 
Figure 6.8: Evolution of keratinocytes thickness \((n)\) in steps of \(t = 6\) using values in Table 6.3 when initial inoculum is (left) \(w(x, 0) = 0.1\) and (right) \(w(x, 0) = 0.5\).

**Effects of Bacterial Seeding- \(\beta_{wn} > 0\)**

Perturbations in the healing process are likely to occur the longer a wound remains open, posing a greater risk of bacterial colonisation as they invade the skin and penetrate further into the dermis leading to long term infections. Here the same parameters apply as in Tables 5.5 and 6.3, except for the “seeding” of bacteria into the wound modelled when \(\beta_{wn} > 0\), where infiltration occurs when \(n < n_f\).

Figures 6.9-6.13 compares the wound activities for three different “seeding rates” of \(\beta_{wn} = 0.001\), \(\beta_{wn} = 0.01\) and \(\beta_{wn} = 0.1\) respectively, to show the transition from a normal healing to an infected/non-healing wound as seeding increases.

From the simulations we can observe normal healing when \(\beta_{wn} = 0.001\) (left simulations of Figures 6.9-6.13) as the contaminated wound heals successfully. Although there are dramatic difference in healing profiles when infiltration reaches deep tissue between \(\beta_{wn} = 0.01\) to \(\beta_{wn} = 0.1\), where bacterial density increases rapidly (Figure 6.9) at the wound site for \(x \in (0, 20)\) in the extreme case, using the damaged dermis as a breeding domain (Figure 6.12). This could potentially inhibit the actions of signals, preventing perfusion and the immune response (see middle and right simulations of Figures 6.10).

The immune response is triggered to combat microbial invasion, and recruits the repair cells which peaks at the wound edge (right simulation of Figure 6.10). Although activity is suppressed with the growing number of wound pathogens between \(\beta_{wn} = 0.01\) and \(\beta_{wn} = 0.1\) (see left and right hand simulations of Figures 6.10), and \(f\) allocation is unable to cover the entire...
wound area or prevent the spread of infection in the damaged region.

Eshcar/dead material \( m \) (see right simulation of Figure 6.12) cannot withdraw from the wound domain as bacterial invasion becomes more prominent in the dermal and epidermal tissue, due to lack of satisfactory signals, nutrients and the immune response (right simulations of Figure 6.10). The dead material in the case of \( \beta_{wn} = 0.1 \), has somewhat elevated values which in reality will be sloughed off or leaked away. Note the corresponding parameter \( \delta_m = 0 \) is used for comparison with previous simulations, having \( \delta_m > 0 \) would resolve this issue.

For \( \beta_{wn} = 0.01 \), granulation tissue deposition is relative covering large proportion of the wound domain, although reaches its steady state before the wound centre (see right simulation of Figure 6.13). The knock on effect of inadequate fibroblasts/immune cell distribution can be observed in Figure 6.11 (right simulation), where new tissue growth is severely obstructed and struggles under the hostile conditions, disrupting vasculature and the perfused environment which become limited and unable to fulfill their obligations for normal developments which can be seen from the unhealed damaged domain (see Figure 6.12). The low quantities enable inconsequential repair at the wound edge.

When \( \beta_{wn} = 0.1 \), wound closure is unlikely considering the activities of the dermal components seen in Figures 6.9-6.12, as this region becomes greatly disturbed by microbial activity. Note that we have increased the domain size for the case of \( \beta_{wn} = 0.01 \) from \((x \in (0,40))\) to \((x \in (0,50))\) to emphasise the non-healing profile (see middle simulation of Figure 6.13). Re-epithelisation is subdued as there is a "weak" scaffold for migration to take place, as \( g \) is

![Figure 6.9: Evolution of bacteria density \( (\omega) \) in steps \( t = 6 \) using values in Table 6.3, except for \( \beta_{wn} \) where we consider (left) \( \beta_{wn} = 0.001 \), (middle) \( \beta_{wn} = 0.01 \) and (right) \( \beta_{wn} = 0.1 \)]
Figure 6.10: Evolution of fibroblasts/immune cell density ($f$) in steps $t = 6$ using values in Table 6.3, except for $\beta$ where we consider (left) $\beta = 0.001$, (middle) $\beta = 0.01$ and (right) $\beta = 0.1$.

Figure 6.11: Evolution of granulation tissue thickness ($g$) in steps $t = 6$ using values in Table 6.3, except for $\beta$ where we consider (left) $\beta = 0.001$, (middle) $\beta = 0.01$ and (right) $\beta = 0.1$. 

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Figure 6.12: Evolution of damaged dermis thickness (m) in steps $t = 6$ using values in Table 6.3, except for $\beta_{wn}$ where we consider (left) $\beta_{wn} = 0.001$, (middle) $\beta_{wn} = 0.01$ and (right) $\beta_{wn} = 0.1$.

Figure 6.13: Evolution of keratinocyte thickness (n) in steps $t = 6$ using values in Table 6.3, except for $\beta_{wn}$ where we consider (left) $\beta_{wn} = 0.001$, (middle) $\beta_{wn} = 0.01$ and (right) $\beta_{wn} = 0.1$. 
localised to the wound edge at low levels (see Figure 6.13).

The simulations presented demonstrate that the model can predict healing, partial healing and chronic wound scenarios depending on bacteria levels. As infiltration of $w$ increases, accessing dermal tissue the healing path is greatly disrupted, and will begin to "attack" other surrounding healthy tissue if left unmanaged. The observations suggest that we can identify three clinical classifications [56] of behaviour, namely contamination (e.g. the case with $\beta_{wn} = 0.001$), colonisation (e.g. the case with $\beta_{wn} = 0.01$) and infection (e.g. when $\beta_{wn} = 0.1$).

**Bolus Nutrient Treatment**

We can attempt to restore healing in an infected wound as shown in Figures 6.9-6.13 by incorporating an initial bolus of nutrients at $c(x,0) = 0.01$ for $\beta_{wn} = 0.01$ and $\beta_{wn} = 0.1$ scenarios, similar to Chapter 5. We focus on the behaviour of bacteria, fibroblasts/immune cells and keratinocytes to differentiate between the healing states and determine the likelihood of repair. The simulations are presented in Figures 6.14-6.16 for the two non-healing cases of $\beta_{wn}$ (see middle and right simulations of Figures 6.9-6.13 to compare).

![Figure 6.14: Evolution of bacteria density ($w$) in steps of $t = 3$ after bolus of $c(x,0) = 0.01$ is applied, using values in Table 6.3, except for $\beta_{wn}$ where we consider (left) $\beta_{wn} = 0.01$ and (right) $\beta_{wn} = 0.1$.](image)

From the simulations we can observe that normal healing resumes for the first case when $\beta_{wn} = 0.01$, enabling complete wound recovery although there is slight delay in re-epithelisation and is reflected by the the increase in bacteria concentrations to $w \approx 0.7$ (see Figures 6.14 and 6.16). However it has a contradictory effect when the infection is more widespread for a greater
Figure 6.15: Evolution of fibroblast/immune cell density ($f$) in steps of $t = 3$ after bolus of $c(x, 0) = 0.01$ is applied, using values in Table 6.3, except for $\beta_{\text{wn}}$ where we consider (left) $\beta_{\text{wn}} = 0.01$ and (right) $\beta_{\text{wn}} = 0.1$.

Figure 6.16: Evolution of keratinocyte thickness ($n$) in steps of $t = 3$ after bolus of $c(x, 0) = 0.01$ is applied, using values in Table 6.3, except for $\beta_{\text{wn}}$ where we consider (left) $\beta_{\text{wn}} = 0.01$ and (right) $\beta_{\text{wn}} = 0.1$. 
Figure 6.17: Evolution of bacteria density ($w$) in steps $t = 6$ using parameters given in Table 6.3 except for $\beta_{ewn} = 0.001$ when considering (left) $\alpha_{dmw} = \alpha_{gmw} = 20$ (middle) $\alpha_{dmw} = \alpha_{gmw} = 100$ and (right) $\alpha_{dmw} = \alpha_{gmw} = 500$.

infiltration rate, as seen in the right simulations of Figures 6.14-6.16, where the small nutrient concentration initiates the activity of fibroblasts, (see Figures 6.15) penetrating further into the wound domain, although insufficient to cover the whole injury. Consequently the bacteria benefit (see right of Figure 6.14) from the treatment as their density increases dramatically reaching $w \approx 450$ by $t = 20$, seemingly well beyond the levels that can be managed by the immune system.

It appears in this simulation that a bolus of nutrient in a severely infected wound, would provide a stimulus for both bacteria and healing components; however wound healing could fail if the bacterial density becomes unmanageable allowing infections to persist. This suggests that the "golden bullet" of adding nutrient could have detrimental effects by benefiting the bacteria more than the host tissue.

Loss of Healthy ECM - $\alpha_{dmw} > 0$

So far we have considered bacterial invasion in the wound domain for selected infiltration rates. In this section we investigate bacteria "attacking" healthy ECM (dermal) that remains intact post injury, which can result as infections persist. The parameters for the above simulations (Figures 6.9-6.13) apply here for a small infiltration rate of $\beta_{ewn} = 0.001$, except we consider the cases where $\alpha_{dmw} > 0$.

We can observe from the simulations that $w$ consumption of the dermis has a significant impact.
on the healing processes, where small loss allows complete repair (see left simulation of Figures 6.19) and wound closure (see left simulations of Figures 6.17-6.21). Complete dermal removal occurs when bacterial movement in deep tissue intensifies and this impairs recovery (when \( \alpha_{dmw} = 100 \)) by producing non-healing profiles. This interferes with adequate granulation tissue deposition which supports the wound matrix and an inconsequential quantity is present at the wound edge. This reflects the fibroblasts/immune cell density that is less sufficient (\( f \approx 2.5 \)-compare left and middle simulations of Figure 6.20) in this case and cannot penetrate into the entire wound domain, hence wound closure fails (see middle simulation of Figure 6.21). We should note that the small infiltration of bacteria introduced does not grow rapidly (see Figure 6.17), and could indicate that presence at the wound bed may be problematic, irrespective of the original population.

In the worse case, we observe some regressive behaviour in fibroblasts/immune cells (further reduction in density at the wound edge \( f \approx 2 \) here) and keratinocytes (see right simulations of Figures 6.20 and 6.21), even though bacteria density does not exceed \( w \approx 0.25 \) (they are at low levels). The surrounding healthy tissue in consumed in addition to dermal tissue present in the damaged region (see right simulation of Figure 6.19) leading to an expanding wound domain. This stalls the re-epithelisation process (see Figure 6.21), as the immune response is perturbed causing insignificant contribution to granulation tissue formation (see Figures 6.18 and 6.20).

**Figure 6.18:** Evolution of granulation tissue thickness \( (g) \) in steps of \( t = 6 \) using parameters given in Table 6.3 except for \( \beta_{wn} = 0.001 \) when considering (left) \( \alpha_{dmw} = \alpha_{gmw} = 20 \) (middle) \( \alpha_{dmw} = \alpha_{gmw} = 100 \) and (right) \( \alpha_{dmw} = \alpha_{gmw} = 500 \).
Figure 6.19: Evolution of normal dermis thickness (d) in steps of t = 6 using parameters given in Table 6.3 except for $\beta_{wm} = 0.001$ when considering (left) $\alpha_{dmw} = \alpha_{gmw} = 20$ (middle) $\alpha_{dmw} = \alpha_{gmw} = 100$ and (right) $\alpha_{dmw} = \alpha_{gmw} = 500$.

Figure 6.20: Evolution of fibroblasts/immune cell density (f) in steps of t = 6 using parameters given in Table 6.3 except for $\beta_{wm} = 0.001$ when considering (left) $\alpha_{dmw} = \alpha_{gmw} = 20$ (middle) $\alpha_{dmw} = \alpha_{gmw} = 100$ and (right) $\alpha_{dmw} = \alpha_{gmw} = 500$. 
Figure 6.21: Evolution of keratinocyte thickness \( n \) in steps of \( t = 6 \) using parameters given in Table 6.3 except for \( \beta_{\text{un}} = 0.001 \) when considering (left) \( \alpha_{\text{dmw}} = \alpha_{\text{gmw}} = 20 \) (middle) \( \alpha_{\text{dmw}} = \alpha_{\text{gmw}} = 100 \) and (right) \( \alpha_{\text{dmw}} = \alpha_{\text{gmw}} = 500 \).

From the simulations in this section, we can conclude that bacterial infections that reach the dermis and completely remove the remaining tissue after wounding, severely suspends the healing course, preventing recovery and wound closure. They "attack" surrounding healthy skin if invasion persists determined by consumption rate of bacteria into a weak superficial membrane, resulting in an enlarging wound area. The characteristics exhibited by the infections of the deep damaged tissue in this section are common in chronic wounds, as granulation tissue is almost absent due to incomplete wound bed preparation and re-epithelisation is delayed as a result \([32, 71, 129] \).

**Varying Wound Geometry**

It was found in Chapter 5 (see Figures 5.35-5.36) that altering the wound shape had a significant impact on healing, whereby wound closure could occur in a sloping wound when vasculature was considered poor, using \( \gamma_0 = 0.85 \). In this section we will consider the expanding wound case as presented in Figure 5.31 (see left simulations of Figures 6.17-6.21), to investigate whether the domain shape has any significance in a poorly vascularised wound and modestly contaminated with bacteria, hence \( \beta_{\text{un}} = 0.001 \) and \( \alpha_{\text{dmw}} = 20 \). \( d(x,0) \) function remains unchanged from that seen in Chapter 5, and we also use the exponent \( \zeta = 1 \). The simulations are given in Figure 6.22-6.23.

The results suggest that although signal concentrations (see Figure 6.23) are adequate and consistent throughout the wound domain, the small infiltration of bacteria have the ability
Figure 6.22: Evolution in steps of $t = 6$ for (left) granulation tissue thickness ($g$) and (right) bacteria density $w$ using the parameter values in Table 6.3 except for $\alpha_{d,w} = 20$, $\beta_{w,n} = 0.001$ and $\gamma_b = 0.85$.

Figure 6.23: Evolution in steps of $t = 6$ for (left) signal concentration ($s$) and (right) keratinocyte thickness ($n$), when $\zeta = 1$ using the parameter values in Table 6.3 except for, $\alpha_{d,w} = 20$, $\beta_{w,n} = 0.001$ and $\gamma_b = 0.85$. 

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to "attack" tissue surrounding the wound, disrupting granulation tissue depositions near the wound centre (see left simulation of Figure 6.22), which prevents complete wound healing as re-epithelisation is impaired (see Figure 6.23). Note, if $\alpha_{dmw} = 0$ i.e no dermal damage by bacteria, the wound will heal normally. The simulations demonstrates that in a poorly vascularised wound, a low level presence of bacteria can contribute to significantly impairing the healing process.

**Topical Application of GFs**

In this section we will consider the topical application of GFs seen in chapter 5, to observe whether this would retrieve the normal healing path for $\beta_{wn} = 0.001$ (vascularised wound where $\gamma_{b} = 0.6$), in the cases when $\alpha_{dmw} = 100$ and $\alpha_{dmw} = 500$ seen in Figures 6.17-6.21 (middle and right simulations). Debridement of necrotic tissue is key to reducing the risks of worsening infection where $m(x, 0) = 0$ and $\beta_{wn} = 0$ are consequently removed. As a reminder the treatment is given by

$$\beta_{s}H(\bar{n} - n),$$

and the $s$ equation becomes

$$\frac{\partial s}{\partial t} = D_{s} \frac{\partial s}{\partial x} + (n(\beta_{sm} + \beta_{sm}s) + f(\beta_{sf} + \beta_{sf}s))(1 + \beta_{sc}H(\bar{c} - c))$$

$$\beta_{sm}m + \beta_{sm}f w - s(\delta_{s} + \delta_{sn}n + \delta_{sf}f) + \beta_{s}H(\bar{n} - n).$$

Using $\beta_{s} = 4$ and $\bar{n} = 0.3$, the simulations for bacteria, signals, granulation tissue, fibroblasts and keratinocytes are presented in Figures 6.26-6.28.

From the results we can observe wound closure is successful when topical application of signals are administrated, for the first non-healing case as re-epithelisation takes place, after adequate signals, fibroblast/immune cells and granulation tissue (see Figures 6.26, 6.25 and 6.27) are available in the wound domain. We expect travelling waves solutions, guaranteeing eventual wound closure, from Figures 6.27 (left simulation), as the wavefront appears flat which is clearly not the case without treatment (see Figure 6.7 to make comparisons). Bacteria behaviour appears insubstantial (see Figure 6.24), when comparing the two cases after debridement and signals have been topically applied; densities may have become more manageable with treatment and less able to reach deep tissue.

However, this treatment is unable to fully revive the abnormal behaviour for the expanding wound case ($\alpha_{dmw} = 500$). The signals secreted "leak" into the wound and provide the stimulus, allowing sufficient granulation tissue deposition ($g \approx 2.5$ here), although keratinocyte migration is severely inhibited; it may need further intervention of a combination of
Figure 6.24: Evolution of bacteria density ($w$) in steps of $t = 6$ using parameter values in Table 6.3, except for $\beta_w = 0.001$, $\beta_s = 4$ when considering (left) $\alpha_{dmw} = 100$ and (right) $\alpha_{dmw} = 500$.

Figure 6.25: Evolution of fibroblasts/immune cell density ($f$) in steps of $t = 6$ using parameter values in Table 6.3, except for $\beta_w = 0.001$, $\beta_s = 4$ when considering (left) $\alpha_{dmw} = 100$ and (right) $\alpha_{dmw} = 500$. 

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Figure 6.26: Evolution of signal concentration ($s$) in steps of $t = 6$ using parameter values in Table 6.3, except for $\beta_{wm} = 0.001$, $\beta_s = 4$ when considering (left) $\alpha_{draw} = 100$ and (right) $\alpha_{draw} = 500$.

Figure 6.27: Evolution of granulation tissue thickness ($g$) in steps of $t = 6$ using parameter values in Table 6.3, except for $\beta_{wm} = 0.001$, $\beta_s = 4$ when considering (left) $\alpha_{draw} = 100$ and (right) $\alpha_{draw} = 500$. 
Figure 6.28: Evolution of keratinocyte thickness (n) in steps of t = 6 using parameter values in Table 6.3, except for $\beta_{wm} = 0.001$, $\beta_s = 4$ when considering (left) $\alpha_{dmw} = 100$ and (right) $\alpha_{dmw} = 500$.

treatments. It also suggests that there may be a relationship as large deposits of granulation tissue exceeding the skin's surface known as hypergranulation, could be responsible for stalling the re-epithelisation process; preventing wound contraction and are common characteristics described in chronic wounds [11, 31, 56, 65]. This can lead to tissue “rolling” over the wound edges (also known as epiboly) [65] and excess tissue deposits with unequal distribution in the region $x \in (30, 35)$ as keratinocytes retreat (see Figure 6.27). The process of hypergranulation is likely to involve a number of processes outside the scope of the current modelling; however, the results here may provide an indication to its initiation. This type of application may have encouraged immature angiogenesis and cause the wound area to become swollen due to unrelieved pressure [65].

We can conclude that topical application of signals could be effective and this treatment succeeds in enabling the laying down of the ECM bed, but is unable to be effective against epidermal vulnerability against bacteria. Although fibroblast/immune cells and granulation tissue levels seem appropriate, it is unfavourable for re-epithelisation to take place. Further intervention methods are likely to be needed to prevent progressive bacterial invasion and allow recruitment of repair cells able to cover the entire domain.

1Rapid cell division in the vicinity of slow dividing cell groups
Topical Application of Fibroblasts

The expanding wound domain requires intervention in attempts to restore tissue lost via infections, as application of signals is unsuccessful for $\alpha_{dnu} = 500$ case. In this section we will consider the application of fibroblasts, which could describe the skin substitutes such as Dermagraft. Again, we will assume that debridement has taken place $m(x,0) = 0$ and signals are lost as a result hence $\beta_{im} = 0$. Although $f$ activity subsides in the delayed/non-healing wound, we assume they become inactive and are not lost through intervention methods.

Topical application of fibroblasts should essentially stimulate wound fibroblasts/immune cells, granulation tissue production and prevent further invasion which are inhibited in chronic wounds, and works symbiotically with the other dermal components. An additional birth rate term will be applied to the fibroblast equation given by

$$\beta_{fw} H(\bar{n} - n), \quad (6.20)$$

so that the $f$ equation becomes,

$$\frac{\partial f}{\partial t} = D_f \frac{\partial^2 f}{\partial x^2} - \frac{\partial}{\partial x} \left( f x_f (d + \sigma_f g) \frac{\partial \alpha}{\partial x} ight) + \beta_{fs} k_u (d, g) + f c \left( \beta_{fc} \left( 1 - \frac{f}{\kappa_f} \right) + \beta_{fcs} H(s - \bar{s}) \right) + \beta_{fw} H(\bar{n} - n) - f \left( \frac{\delta_f}{1 + (c + \rho_f s)/\gamma_{fcs}} + \alpha_{fmu} w \right),$$

where $\beta_{fw}$ describes the fibroblasts/immune cell introduction in a hypoxic wound bed to combat bacterial invasion, hence $n < \bar{n}$

$$H(\bar{n} - n) = \begin{cases} 1 & \text{if } n < \bar{n} \text{ (Treatment required)} \\ 0 & \text{if } n \geq \bar{n} \text{ (Treatment not necessary)}. \end{cases}$$

We use the parameter values of $\beta_{fw} = 0.3$ and $\bar{n} = 0.3$ and the corresponding simulations are presented in Figures 6.29-6.30.

From the results we can observe that healing is restored in the expanding wound domain, as signal levels increase, further recruiting more fibroblasts to the damaged region, where normal levels of granulation tissue formation occurs and peaks at the wound edge (see Figures 6.29, 6.30).

It appears that topical application of fibroblasts is an effective strategy, that can retrieve normal healing patterns in a severely infected wound characterised by surrounding tissue damage. This treatment prevents further bacterial invasion entering the wound and is able to stimulate the healing components such as granulation tissue growth, at appropriate levels to allow wound repair to take place. This simulation gives results that qualitatively agree with
Figure 6.29: Evolution of (left) signal concentration \( s \) and (right) fibroblast/immune cell density \( f \) in steps of \( t = 6 \) using parameters in Table 6.3, except for \( \beta_{wn} = 0.001, \alpha_{mdw} = 500 \) and \( \beta_{fw} = 0.3 \).

Figure 6.30: Evolution of (left) granulation tissue thickness \( g \) and (right) keratinocyte thickness \( n \) in steps of \( t = 6 \) except for \( \beta_{wn} = 0.001, \alpha_{mdw} = 500 \) and \( \beta_{fw} = 0.3 \).
the frequently successful application of skin substitutes, such as Dermagraft, on advancing the healing process when infection is problematic [44, 63, 90, 100, 136].

6.4 Summary

This chapter explores the healing behaviour of deep tissue wounds exhibiting microbial activity common in chronic wounds; to resemble a more realistic wound scenario. The severity of bacterial activity defined by the three states contamination, colonisation and infection can severely impair the normal healing path and provide a retarded wound that may require clinical intervention. A simple model was proposed, which extended ideas presented in Chapter 5; exploiting the proliferation process and investigating the two key parameters

- $\beta_{\text{in}}$ which is responsible for bacterial infiltration into the wound domain,
- $\alpha_{\text{dmw}}$ which represents the loss of healthy ECM as bacterial infections can expand and attack surrounding healthy tissue,

to highlight normal (refer to Figures 6.5-6.8) and abnormal (refer to Figures 6.9-6.13 and 6.17-6.21) healing scenarios as they impact greatly to the wound environment, and contribute to invasion of bacteria in deep tissue wounds.

It is evident from the simulations that bacterial growth and contamination are key factors that govern healing profiles; although low level contamination can be detrimental to a poorly vascularised wound (refer to Figures 6.5-6.8). In severe cases especially when $\alpha_{\text{dmw}} > 0$ (refer to Figures 6.17-6.21), reflecting cases of very poor wound management, infection can impact on the healthy tissue bordering the wound causing spread of the damage and increasing the initial wound domain. It is interesting to note that whilst enhancing the nutrient supply can be very effective in retrieving normal healing in contaminated wounds (refer to Figure 6.14-6.16 left simulations); this may benefit the bacteria more in the other two cases of infections (colonised and infected) causing greater complications and wound recovery is prevented (refer to Figures 6.14-6.16 middle and right simulations). In such circumstances, the results suggest that an additional supply of growth factors and fibroblasts will provide a better outcome. Although topical application of growth factors leads to hypergranulation and stalls the re-epithelisation in the infected (extreme) wound case (refer to Figures 6.24-6.28) and full recovery is only possible when fibroblasts are applied (refer to Figures 6.29-6.30). This implies that fibroblast substitutes such as dermagraft are less sensitive to the severity of infections when compared to growth factor treatment.

The standard practice of wound debridement and replacement of fresh dressings to remove and restrict infection is very important as the simulations demonstrate that bacteria presence, even in small amounts, can prevent complete healing leading to chronic wounds.
For purposes of modelling many factors were ignored as listed below:

- Delivery of antibiotic treatments.
- Individual bacteria species.
- Polymicrobial infections.
- Differentiating between anaerobic and aerobic bacteria
- Anatomical location of wounds which may affect healing rates and spread of infections.

and could be the focus of further investigation in this area.
Chapter 7

Concluding Remarks & Future Work

7.1 Key Findings

The thesis incorporates many biological activities and functions, important to dermatological disease and recovery which are described by the new mathematical PDE models given in Chapters 3-6. They provide a realistic account of skin activity after damage or disease and the nonlinear systems were solved using analytical and numerical methods. There are two broad areas

1. Epidermal growth and recovery investigated in Chapters 3 and 4

2. Dermal and epidermal healing between the proliferative and repaired stages of healing investigated in Chapters 5 and 6

where wound healing was the main research area in both superficial and partial/full thickness wounds. One of the fundamental aims of the research was to obtain a greater understanding behind the wound healing phenomenon in normal and abnormal cases, which was obtained by manipulating key parameters and extending model concepts. Details of individual models will be discussed below accompanied by the key findings.

7.1.1 Models

The self-renewal property of the epidermal membrane is governed by the keratinisation process where fundamental epidermal cells namely keratinocytes undergo a maturation process and slough at the skin's surface. When considering the superficial wounds in Chapter 3, the
keratinisation process was key to demonstrate the re-epithelisation process and the model devised of cell binding, signal distribution, cell velocity and cell growth. The model was able to reproduce the re-epithelisation process where the live and dead cell states were highlighted. The key findings predicted by our model are as follows:

- During the re-epithelisation process signals (GFs) dominate the reformation of the live cell region and once completed the keratinisation develops.
- We can quantitatively describe epithelial recovery and development within a reasonable time scale that agrees with literature and is confirmed by medical observations.
- We can assess in terms of individual model parameters (such as $\lambda$) epithelial thickness, thickness of live and dead cells and timescale for growth.
- The signal molecules obtained from the dermis and binding protein production are sufficient to regulate the thickness and structure of the epidermis.
- The effect of growth factors on recovery rate and skin structure provides scope to look more closely at impaired epithelial healing. It was found that increasing $\lambda$ would restrict growth factor delivery causing premature cell death and result in a thinner live cell region.
- Elevated signal (GF) levels in the skin may occur due to a reduced domain obtained from superficial injury, where signal levels in healthy skin will be more evenly distributed.

The model was extended and applied to the skin disease psoriasis presented in Chapter 4, which is an incurable condition that exhibits hyperproliferation and parakeratosis (live and dead cells coexist). The symptoms occur in the form of psoriatic plaques (resulting from the inflammatory response), which are most visible at the skin's surface and explains why the epidermal membrane was considered. We introduced immune cells, IGFBP-3 and IGF-1 to accommodate for the onset of abnormal keratinocyte cell behaviour and investigate the normal and abnormal cases. The key findings predicted by our model are as follows:

- The normal re-epithelisation process can be reproduced with the introduction of the new components, provided the promoter and inhibitor relationship between IGF-1 and IGFBP-3 are balanced.
- Psoriatic behaviour results from overabundant IGF-1 and low levels of IGFBP-3 initiating the inflammatory response, as immune cell production increases and penetrates further into the upper epidermal layers (which would not normally exist).
- Skin thickness exceeds the surface of normal unaffected areas, and cell death rate is impeded allowing live and dead cells to coexist at the surface resembling psoriatic behaviour.
- Topical application of IGFBP-3 applied as a dressing can regulate excess IGF-1 levels.
by inhibiting the proliferative activity and reduce the skin domain although some live cells still appear at the surface and requires further investigation.

- Overabundant IGFBP-3 severely inhibits the the proliferative activity resulting in a thinner epidermal membrane.

Deep tissue wounds affecting the dermal and epidermal membranes are problematic when they become chronic, compromising and delaying the healing process. Many components are involved in the general wound healing process, although surprisingly the entire process has not been modelled before due to the complexity, which results in the generation of numerous variables. In Chapter 5 a dermal wound healing model is presented, which comprise of key variables (fibroblasts, keratinocytes, GFs, healthy dermis, damaged dermis, granulation tissue and nutrients) selected after reviewing many sources of literature, where vasculature and blood clotting ability were important measures to determine the healing progress. Many scenarios were investigated to highlight the change in wound recovery and most important parameters contributing to impaired healing. Bolus and topical applications were reviewed to observe their ability to retrieve a delayed/arrested wound. The key findings predicted by our model are as follows

- Expected normal dermal healing profiles are achieved by cell and signal interaction in the form of travelling wave solutions and wound recovery is observed.

- Lowering the vasculature parameter $\gamma$ and clotting ability $\beta_{fm}$ results in a poorly vascularised wound with an inefficient clotting matrix, resulting in healing arrest and resembling poor circulation common in diabetes. Both cases illustrate lack of adequate nutrients to the entire wound domain, which prevents signal distribution, cell migration, tissue formation and wound closure. Bolus nutrients was the most effective in retrieving the normal wound healing in such both cases.

- Topical application of GFs is enough to retrieve the severely retarded wounds by allowing signal infusion allowing cell migration, tissue growth and wound coverage.

- Varying the wound geometry from rectangular to a semicircle shape, allows healthy tissue to be retained underneath the damaged area. The effects of poor vascularisation are less dramatic, as wound coverage is greater than the rectangular wounds, although complete wound recovery still fails.

A common problem in chronic wounds are recurrent bacterial infections resulting from the hostile necrotic wound environment, inhibiting normal growth and development. We introduced bacteria and extended the model in Chapter 5, to investigate the impact on the healing process in terms of bacterial seeding rate $\beta_{bm}$ and loss of healthy ECM $\alpha_{dew}$ as presented in Chapter 6. The key findings predicted by our model are as follows

- Small inoculum of bacteria resembles a contaminated wound that can impair complete
wound healing however one that can be retrieved quite easily.

- Contamination, colonisation and infection can be illustrated by different seeding rates as bacteria penetrates further into the dermal tissue, severely perturbing the healing ability. In the severe case, the widespread bacterial activity obstructs new tissue growth, vasculature, perfusion and re-epithelisation of the wound area.

- Bolus nutrients are only effective for the colonised wound as bacteria can be removed to restore normal repair. However there is a contradictory effect in the severely infected wound scenario as a greater infiltration rate results in bacteria competing for nutrients, and we see a dramatic increase in bacterial density which exceeds the realm of the immune system. This implies that nutrient applied can benefit the bacteria more than the host tissue.

- Unmanageable infections can result in the loss of healthy ECM tissue, as they ‘attack’ surrounding tissue and expand the wound domain. This results in regressive cell behaviour which is unable to initiate the immune response to its full capacity, allow adequate signal or nutrient distribution and stalls the re-epithelisation process.

- Topical application of GFs applied to the expanding case, is only effective when a wound is colonised as full wound recovery is observed. However in the severely infected case this results in large deposition of granulation tissue known as hypergranulation which may be responsible for hindering the re-epithelisation activities.

- Dermal substitutes presented in the form of topical fibroblasts is successful in reinstating complete wound recovery in the infected case, as fibroblast activities are enhanced allowing debridement and sufficient new tissue growth to complete wound healing.

7.1.2 Thesis Summary

In this thesis, we focus on dermatological activity with particular interest given to the wound healing phenomenon, defined by mathematical models formulated and simulated using non-linear PDE systems to describe epidermal and dermal skin growth and recovery. One of the principal aims of the research was to gain insight into healing behaviour of normal injuries particularly of deep tissue wounds, then translate these findings to delayed/non-healing wounds and highlight key parameters involved which refer to biological components or functions. A more in depth overview was obtained and the transformation from an acute to chronic wound state, was made clearer once we established the most influential parameters as it was clearer to envisage why such behaviour occurred. The investigations of non-healing/delayed scenarios which resembles characteristics common to chronic wounds, suggests that abnormality should be attended to immediately, to prompt reinstatement of healing the components. Conventional therapies are important, however our results imply that management of nutrients, GFs
and fibroblasts and prevention of infection all enhance the healing process by reducing the chance of the wound becoming chronic. Many of the management strategies are now possible and the current modelling framework enables a theoretical analysis to investigate and optimise these treatments.

7.2 Future Work

The thesis investigated many interesting scenarios that demonstrate dermatological growth and repair of chronic conditions, which includes deep tissue wounds and the skin disease psoriasis. From the superficial healing aspect we can make further investigations into the following areas

- Many growth factors aid the epidermal healing process such as EGF, FGF and TGF-β; further investigation could study the role of specific GFs in the wound and the characteristics they exhibit to ensure repair and re-epithelisation.

- Psoriatic model provides a foundation for skin diseases that exceed the wound margins. This concept and modelling can be improved and applied to the study of keloids and hypertrophic scars for insight into their behaviour, to determine whether there are perturbations in the keratinisation process. This would require a more in depth understanding of the conditions.

- The role of calcium signalling on the regulation of the keratinisation process.

- Examine the similarities of skin diseases mentioned to see if a generic model can be imposed, which will deduce the effectiveness of modern treatment and their effects on managing the signs and symptoms.

The dermal model which was key to the research in the report has many areas that can be investigated further, some of which are mentioned below

- The model has considered simple wound shapes so far in 1D and future work can investigate radially symmetric wounds, which will offer more details regarding healing profiles and the problems faced by chronicity.

- Nutrients were considered as a generic variable, and further studies could look more closely at specific types such as glucose and/or oxygen to obtain information on concentrations in healthy and unhealthy skin.

- Platelet disorders such as von Willebrand disease could be investigated by extending the model and looking closely at the clotting mechanism, which could provide greater insight into healing defects and possible intervention methods.
• Literature suggests presence of two specific GFs, namely TGF-β and PDGF that influence wound repair by exhibiting positive and negative characteristics. The way in which these interact in a wound environment from the beginning to the final stages, could be insightful when considering topical applications.

• Wound closure was modelled between the proliferative and repair stages of healing, this can be extended to account for wound contraction and maturation to highlight transitional period from granulation tissue growth to scar formation.

• Hypergranulation observed after topical application of signals in an infected wound can be investigated further. Excess tissue in wounds can make them more prone to bleeding as the presence of immature capillaries cause swelling of the wound, and special dressings could absorb moisture stimulating re-epithelisation. Research is limited in this area and could contribute greatly, to understanding chronic wounds further.

• It is common to find low quantities of granulation tissue in chronic wounds when vasculature is inadequate, it would be interesting to find a common element responsible for the under or over-abundant deposition at the wound. There may exist a fibroblast threshold and variation in granulation tissue behaviour as a response.

• We considered chronic wounds, and further work could extend the model in Chapter 6 and look more closely at certain wound type e.g foot ulcers and try to compare healing pathology.

• Loss of the hypodermis from deep injury could also be another avenue for research, as it seems such wounds heal even slower and are prone to infections. Research into this area may need to consider interaction between bacteria and adipose tissue, and other appendages that are found in the membrane.

• A more in depth investigation of wound healing processes in circulatory problems e.g. diabetes would benefit advancing treatments available and may prevent severe strategies such as amputations.

• Bifurcation analysis between healing and non-healing domains and parameter sensitivity analysis will provide details regarding the models introduced to the thesis. Travelling wave analysis will also benefit further understanding of the models.

Many of the suggested investigations should only require small modifications and/or extensions to the models studied in this thesis. It is hoped that the work described in this thesis has offered many insights into key processes of normal and impaired wound healing, and forms a basis for advanced studies and perhaps development of new and effective treatments.
Appendix A

Finite Difference Schemes

The mathematical modelling of the wound healing of epidermal and dermal membranes and skin conditions, involves coupled nonlinear system of first order and second order PDE systems. Finite difference schemes are used to produce numerical results [118]. In this appendix we will summarise the schemes that will be applied to Chapters 3, 4, 5 and 6. We want to find solutions of the PDEs at the mesh points \((x, t) = (i\Delta x, j\Delta t)\) for \(i \in (0, I)\) and \(j \in (0, K)\). The general form of the PDEs are as follows

\[
\frac{\partial u}{\partial t} = -\frac{\partial J}{\partial x} + f
\]

where \(J\) is the flux.

1. In Chapters 3 and 4 we have \(J = vu\). Defined \(\tilde{f} = f - u \frac{\partial f}{\partial x}\) the problem of the form

\[
\frac{\partial u}{\partial t} = v \frac{\partial u}{\partial x} + \tilde{f},
\]

Figure A.1: Mesh grid for finite schemes highlighting the initial point \(u_{i,j}\), where \(i\) is the spatial and \(j\) the temporal index of the mesh point [118].
was described using an explicit Euler time step and upwinding for space so that

\[
\frac{\partial u}{\partial t} \approx \frac{U_{i,j+1} - U_{i,j}}{\Delta t},
\]

\[
\frac{\partial u}{\partial x} \approx \begin{cases} 
\frac{U_{i+1,j} - U_{i,j}}{\Delta x} & u_{i,j} < 0 \\
\frac{U_{i,j} - U_{i-1,j}}{\Delta x} & u_{i,j} > 0 
\end{cases}
\]

and \( f \) was approximate by \( f_{i,j} \). This is \( O(\Delta x) \) and \( O(\Delta t) \) accurate in

\[
\left| \frac{u_{i,j} \Delta t}{\Delta x} \right| \leq 1,
\]

which is the so called Courant-Friedrichs and Levy (CFL) condition.

2. Diffusion terms \( J = -D \frac{\partial u}{\partial x} \) in Chapter 5 and 6 were solved using the standard central difference schemes, namely

\[
D \frac{\partial^2 u}{\partial x^2} \approx \frac{U_{i+1,j} - 2U_{i,j} + U_{i-1,j}}{\Delta x^2},
\]

and \( \partial u / \partial t \) as above. This is \( O(\Delta x^2) \) and \( O(\Delta t) \) accurate and numerically stable if

\[
\left| \frac{ D \Delta t }{ \Delta x^2 } \right| \leq \frac{1}{2} .
\]

3. Chemotactic coefficients used in Chapter 5 and 6 given by \( J = \chi \frac{\partial}{\partial x} \) are solved using the central difference in the following manner

\[
- \frac{\partial J}{\partial x} \approx - \frac{J_{i+1/2} - J_{i-1/2}}{\Delta x} \approx - \frac{1}{\Delta x} \left( \chi \left( U_{i+1/2} \right) \frac{\partial u}{\partial x} \right)_{i+1/2} \\
\approx - \frac{1}{\Delta x} \left( \chi \left( \frac{U_{i+1} + U_{i}}{2} \right) S_{i+1} - S_i - \chi \left( \frac{U_{i} + U_{i-1}}{2} \right) S_i - S_{i-1} \right) ,
\]

and \( \partial u / \partial x \) as above. This is \( O(\Delta x^2) \) approximation of the chemotactic terms, with more complicated stability criteria requiring a contribution from the diffusion term. We found in our simulation that (A.1) was generally sufficient.

The quasi-steady equations are of the form

\[
\frac{\partial v}{\partial x} = f, \tag{A.3}
\]

and

\[
\frac{\partial^2 c}{\partial x^2} = f. \tag{A.4}
\]
The first of these was solved using the trapezium method, namely

$$\frac{V_{i+1,j} - V_{i,j}}{\Delta x} = \frac{f_{i+1} + f_i}{2} \implies V_{i,j} = V_{i,j} + \frac{\Delta x}{2} (f_{i+1} - f_i),$$  \hspace{1cm} (A.5)

$$V_{i,j} = V_{i,j} + \frac{\Delta x}{2} (f_{i+1} - f_i),$$  \hspace{1cm} (A.6)

which is $O(\Delta x^2)$ accurate.

The non-linear 2nd order quasi-steady equation is solved using the Numerical Algorithm Group (NAG) boundary value solver D03RAF.

For the co-ordinate of the moving boundary, $H(t)$ in Chapters 3 and 4, the simple Euler method is used, hence

$$\frac{dH}{dt} = u - \frac{\beta}{b}$$

is rewritten as

$$\frac{H_{j+1} - H_j}{\Delta t} = V_{i,j} - \frac{\beta}{b_{i,j}} \implies \quad H_{j+1} = H_j + \Delta \left(V_{i,j} - \frac{\beta}{b_{i,j}}\right).$$  \hspace{1cm} (A.7)

A.1 Numerical Schemes: Chapter 3

We solve the rescaled system given in Chapter 3 using FDM, and compute in Fortran. The NAG routine D03RAF solves the $c(x,t)$ and its corresponding boundary condition. (3.71) is discretised on

$$N_{i,j+1} = N_{i,j} - \Delta T \left( N_{i,j} \left\{ \left( 1 - \frac{\sigma c_i^j}{c_i^e + c_i^j} \right) - \frac{V_{i,j} - V_{i-1,j}}{H_j \Delta Z} \right\} + \frac{(V_{i,j} - ZH_j) \Delta N}{H_j} \right),$$  \hspace{1cm} (A.9)

(3.73) is discretised on

$$B_{i,j+1} = B_{i,j} + \Delta T \left( N_{i,j} - B_{i,j} \left\{ \delta - \frac{(V_{i,j} - V_{i-1,j})}{H_j \Delta Z} \right\} + \frac{(V_{i,j} - ZH_j) \Delta B}{H_j} \right),$$  \hspace{1cm} (A.10)

and (3.72) becomes

$$V_{i,j+1} = N_{i,j} H_j \Delta Z \left( 1 - \frac{\sigma c_i^j}{c_i^e + c_i^j} \right) \left( \frac{\phi}{n_{mox}} - \frac{1}{n_{mox}} \right) + V_{i,j}.$$  \hspace{1cm} (A.11)
A.2 Numerical Schemes: Chapter 4

The rescaled system from Chapter 4, also solved in Fortran where the NAG routine D03RAF is applied to \( A(x, t) \), \( B(x, t) \) and \( c(x, t) \) and the corresponding boundary conditions. As seen in Appendix A.1, the modified equations for \( n, b \) and \( v \) become

\[
N_{i,j+1} = N_{i,j} + \Delta T \left( N_{i,j} \left( k_d(C_{i,j}) + \Theta(C_{i,j}, A_{i,j}) \left( 1 + \frac{1}{n_{\text{max}}} \right) \right) - \frac{V_{i,j} - Z H_{i,j}}{H_j \Delta Z} \right),
\]

(A.12)

\[
B_{i,j+1} = B_{i,j} + \Delta T \left( \frac{\mu N_{i,j}}{1 + \gamma \Theta(C_{i,j}, A_{i,j})} - \delta B_{i,j} + k_d(C_{i,j} N_{i,j} \gamma) - \frac{V_{i,j} - Z H_{i,j}}{H_j \Delta Z} \right),
\]

(A.13)

\[
V_{i,j+1} = V_{i-1,j} + \frac{H_j \Delta Z}{2} \left( k_d(C_{i,j}) N_{i,j} + \Theta(C_{i,j}, A_{i,j}) \frac{N_{i,j}}{n_{\text{max}}} - k_d(C_{i-1,j}) N_{i-1,j} + \Theta(C_{i-1,j}, A_{i-1,j}) \frac{N_{i-1,j}}{n_{\text{max}}} \right).
\]

(A.14)

The analytical solution for immune cells can be written as

\[
U_{i,j+1} = \frac{\cosh \left( \frac{\sqrt{\beta H^2}}{D_i(1-z)} \right)}{\cosh(\sqrt{\beta H^2})}.
\]

(A.15)

A.3 Numerical Schemes: Chapter 5

If \( \phi(a) = \frac{a_i + a_{i+1}}{2} \) and \( \varphi(b) = \frac{b_i + b_{i+1}}{2} \) where \( a = n, f, d, g \) and \( b = n, f, c, s \) then using central differencing, “Euler” and forward schemes the system becomes

\[
N_{i,j+1} = N_{i,j} + \Delta T \left( \frac{\varphi(n) - \varphi(n)(n_d g(n) + \sigma_n g(g)) + \frac{N_{i,j} C_{i,j}}{1 + S_{i,j} / \gamma_{\text{cs}}} \left( 1 - \frac{N_{i,j}}{n_n} \right) - \frac{\delta_n N_{i,j}}{1 + C_{i,j} / \gamma_{\text{cs}}} \right)
\]

(A.16)

\[
F_{i,j+1} = F_{i,j} + \Delta T \left( \frac{\varphi(f) - \varphi(f)(n_f g(n) + \sigma_f g(g)) + \frac{F_{i,j} C_{i,j}}{1 + S_{i,j} / \gamma_{\text{cs}}} \left( 1 - \frac{F_{i,j}}{f_n} \right) - \frac{\delta_f F_{i,j}}{1 + C_{i,j} / \gamma_{\text{cs}}} \right)
\]

(A.17)

\[
C_{i,j+1} = C_{i,j} + \Delta T \left( \frac{\varphi(c)}{\Delta_x} + \beta_{cb} k_b(D_{i,j}, G_{i,j}) - C_{i,j} (\delta_{cn} N_{i,j} + \delta_{cf} F_{i,j}) \right)
\]

(A.18)

\[
S_{i,j+1} = S_{i,j} + \Delta T \left( \frac{\varphi(s)}{\Delta_x} + (N_{i,j} (\beta_s + \beta_{sn} S_{i,j}) + F_{i,j} (\beta_f + \beta_{sf} S_{i,j})) \right)
\]

(A.19)
\begin{align}
M_{i,j+1} &= M_{i,j} + \Delta t \left( N_{i,j} F_{i,j} \left( \delta_f \beta_{ef} + \beta_{es} S_{i,j} \right) H(S_{i,j} - \bar{s}) H(\bar{c} - C_{i,j}) - \frac{G_{i,j} \delta_m}{1 + G_{i,j} / \gamma_m} \right) \\
G_{i,j+1} &= G_{i,j} + \Delta t \left( C_{i,j} F_{i,j} \left( \delta_m \beta_{mf} + \delta_m \delta_f \right) H(S_{i,j} - \bar{s}) H(\bar{c} - C_{i,j}) - \frac{G_{i,j} \delta_m}{1 + G_{i,j} / \gamma_m} \right)
\end{align}

(A.20)

(A.21)

**A.4 Numerical Schemes: Chapter 6**

The additional components have been imposed to give

\begin{align}
N_{i,j+1} &= N_{i,j} + \Delta t \left( \phi(n) - \phi(n)(\gamma_n \phi(d) + \sigma_n \phi(g)) \phi(s) \right) + \frac{N_{i,j} C_{i,j}}{1 + S_{i,j} / \gamma_n \kappa_n} \left( 1 - \frac{N_{i,j}}{\kappa_n} \right) \\
F_{i,j+1} &= F_{i,j} + \Delta t \left( \phi(f) - \phi(f)(\gamma_n \phi(d) + \sigma_n \phi(g)) \phi(s) \right) + \beta_f k_b (D_{i,j}; C_{i,j}) + F_{i,j} C_{i,j} \beta_{fc} H(S_{i,j} - \bar{s}) \\
C_{i,j+1} &= C_{i,j} + \Delta t \left( \phi(c) \frac{D_{i,j}}{\kappa_c} \right) - \frac{\delta_c}{1 + (C_{i,j} + \beta f S_{i,j}) / \gamma f} - \alpha_{f c} W_{i,j} \\
S_{i,j+1} &= S_{i,j} + \Delta t \left( N_{i,j} (\phi_n + \phi_{sm} S_{i,j}) + F_{i,j} (\beta_n + \beta_{ef} S_{i,j}) \right) (1 + \beta_s H(\bar{c} - C_{i,j})) \\
M_{i,j+1} &= M_{i,j} + \Delta t \left( \phi_m \beta_{sm} M_{i,j} + \beta_{bw} F_{i,j} W_{i,j} - \delta_s + \delta_m N_{i,j} + \delta_{ef} F_{i,j} \right) \\
D_{i,j+1} &= D_{i,j} - \Delta t \alpha_{dm} W_{i,j} D_{i,j} \\
G_{i,j+1} &= G_{i,j} + \Delta t \left( C_{i,j} F_{i,j} \left( \beta_n \phi_c + \beta_{sm} S_{i,j} \right) H(S_{i,j} - \bar{s}) H(\bar{c} - C_{i,j}) - \frac{G_{i,j} \delta_m}{1 + G_{i,j} / \gamma_m} \right) \\
W_{i,j+1} &= W_{i,j} - \Delta t \left( W_{i,j} (\beta_{wc} C_{i,j} + \beta_{sm} M_{i,j}) + \beta_{uw} H(n - N_{i,j}) - W_{i,j} (\delta_u + \delta_{wf} F_{i,j}) \right)
\end{align}

(A.22)

(A.23)

(A.24)

(A.25)

(A.26)

(A.27)

(A.28)

(A.29)
Appendix B

Nondimensionalisation

B.1 Re-epithelisation Model

We introduce the nondimensional quantities \( t = t_0 \hat{t}, \quad x = x_0 \hat{x}, \quad H = x_0 \hat{H}, \quad v = v_0 \hat{v}, \quad b = b_0 \hat{b}, \)
\( c = c_0 \hat{c} \) and \( u_w = v_0 \hat{v}_w \). We note that \( V(t) = v(1 - w) + u_w w \) so that \( \dot{V}(t) = v_0 \dot{V}(t) \) and \( n \) and \( m \) are dimensionless. On substitution the system given in Chapter 3,

\[
\begin{align*}
\frac{1}{t_0} \frac{\partial n}{\partial \hat{t}} + \left( \frac{v_0}{x_0} \frac{\partial}{\partial \hat{x}} (\hat{v}n) \right) &= -\Omega \left( 1 - \frac{\sigma (c_0 \hat{c})^\eta}{c_0^2 + (c_0 \hat{c})^2} \right) n, \\
\frac{v_0}{x_0} \frac{\partial \hat{c}}{\partial \hat{x}} &= \Omega \left( 1 - \frac{\sigma (c_0 \hat{c})^\eta}{c_0^2 + (c_0 \hat{c})^2} \right) n \left( \frac{\phi}{n_{max}} - \frac{1}{n_{max}} \right), \\
\frac{b_0}{t_0} \frac{\partial \hat{b}}{\partial \hat{t}} + \left( \frac{v_0 b_0}{x_0} \frac{\partial}{\partial \hat{x}} (\hat{v} \hat{b}) \right) &= \mu n - \delta \hat{b}, \\
c_0 \frac{\partial \hat{c}}{t_0} + \frac{v_0 V(t) c_0 \partial \hat{c}}{x_0} = \frac{D_c c_0}{x_0} \frac{\partial^2 \hat{c}}{\partial \hat{x}^2} - \ln \left( \frac{\sigma (c_0 \hat{c})^\eta}{c_0^2 + (c_0 \hat{c})^2} \right),
\end{align*}
\]

and the initial and boundary conditions become

\[
\begin{align*}
\frac{b_0 \hat{b} - \mu n_{max}}{\delta} \\
\frac{x_0}{t_0} \frac{\partial H}{\partial \hat{t}} &= \frac{v_0 \hat{b}}{b_0} - \frac{F_0}{b_0} \\
0 &= c_0 \hat{c} \left( \frac{x_0}{t_0} \frac{dH}{dt} - v_0 V(t) \right) + \frac{D_c c_0}{x_0} \frac{\partial \hat{c}}{\partial \hat{x}}.
\end{align*}
\]

We can multiply the system by \( t_0, \frac{x_0}{t_0}, \frac{b_0}{c_0} \) and \( \frac{b_0}{c_0} \) respectively and this gives

\[
\begin{align*}
\frac{\partial \hat{n}}{\partial \hat{t}} + \frac{v_0 t_0}{x_0} \frac{\partial}{\partial \hat{x}} (\hat{v} \hat{n}) &= -\Omega t_0 \left( 1 - \frac{\sigma (c_0 \hat{c})^\eta}{c_0^2 + (c_0 \hat{c})^2} \right) n, \\
\frac{\partial \hat{b}}{\partial \hat{x}} &= \frac{\Omega x_0}{v_0} \left( 1 - \frac{\sigma (c_0 \hat{c})^\eta}{c_0^2 + (c_0 \hat{c})^2} \right) n \left( \frac{\phi}{n_{max}} - \frac{1}{n_{max}} \right).
\end{align*}
\]
\[
\begin{align*}
\frac{\partial \tilde{b}}{\partial t} + \frac{v_0 t_0}{x_0} \frac{\partial}{\partial x} (\tilde{v} \tilde{b}) &= \frac{\mu t_0}{t_0} \frac{\partial}{\partial x} (\tilde{v} t_0) - \delta t_0 \tilde{b} \\
\frac{\partial \tilde{c}}{\partial t} + \frac{V(t) v_0 t_0}{x_0} \frac{\partial}{\partial x} = \frac{D c_0 t_0}{x_0^2} \frac{\partial^2 \tilde{c}}{\partial x^2} - \lambda t_0 \frac{\partial}{\partial x} n \left( \frac{\sigma (c_0 \tilde{c})}{c_0^\alpha + (c_0 \tilde{c})^\alpha} \right)
\end{align*}
\]  
(B.10)
(B.11)

and multiply the initial and boundary conditions by \( \frac{1}{t_0} \), \( \frac{\mu t_0}{x_0} \) and \( \frac{D c_0}{x_0} \) so the initial and boundary conditions become
\[
\begin{align*}
\tilde{b}_0 &= \frac{\mu t_{0,\text{max}}}{t_0} \\
\frac{\partial H}{\partial t} &= \frac{v_0 t_0}{x_0} \tilde{b}_0 - \frac{F_0 t_0}{x_0} \tilde{b}_0 \\
\frac{\partial \tilde{c}}{\partial x} &= \frac{x_0^2}{t_0 D_c} \tilde{c} \left( \frac{v_0 t_0}{x_0} V(t) - \frac{dH}{dt} \right).
\end{align*}
\]  
(B.12)
(B.13)
(B.14)

Using the rescalings \( t_0 = \frac{1}{\delta} \), \( x_0 = \frac{x}{\delta} \), \( b_0 = \frac{b}{\delta} \), \( \tilde{b} = \frac{\tilde{b}}{\delta} \), \( c_0 = \frac{c}{\delta} \), \( \lambda = \frac{\lambda_0}{\delta} \) and \( \beta = \frac{\beta_0}{\delta} \) and dropping the hats we can derive the full nondimensionalised system and corresponding initial and boundary conditions, presented in Chapter 3.

### B.2 Psoriatic Model

We introduce the nondimensional quantities \( b = b_0 \tilde{b} \), \( t = t_0 \tilde{t} \), \( x = x_0 \tilde{x} \), \( c = c_0 \tilde{c} \), \( V(t) = v_0 \tilde{V}(t) \), \( H = x_0 \tilde{H} \), \( v = v_0 \tilde{v} \), \( v_w = v_0 \tilde{v}_w \), \( A = A_0 \tilde{A} \), \( B = B_0 \tilde{B} \) and \( I = I_0 \tilde{I} \). On substitution

\[
\frac{1}{t_0} \frac{\partial n}{\partial t} + \frac{v_0}{x_0} \frac{\partial}{\partial x} (v_0 \tilde{v} t_0 \tilde{n}) = \Omega \frac{(c_0 \tilde{c}) \tilde{n}}{(c_0 \tilde{c})^\alpha + (c_0 \tilde{c})^\alpha} \left( \frac{(A_0 \tilde{A}) \tilde{n}}{(A_0 \tilde{A})^\alpha + (A_0 \tilde{A})^\alpha} \right)^n - \Omega \left( 1 - \frac{(c_0 \tilde{c}) \tilde{n}}{(c_0 \tilde{c})^\alpha + (c_0 \tilde{c})^\alpha} \right)^n
\]  
(B.15)
(B.16)

\[
\frac{\gamma}{t_0} \frac{\partial n}{\partial t} + \frac{v_0 V(t) c_0}{x_0} \frac{\partial}{\partial x} = \frac{D c_0}{x_0^2} \frac{\partial^2 \tilde{c}}{\partial x^2} = \lambda n \left( \frac{(c_0 \tilde{c}) \tilde{n}}{(c_0 \tilde{c})^\alpha + (c_0 \tilde{c})^\alpha} \right)^n + \Omega \left( 1 - \frac{(c_0 \tilde{c}) \tilde{n}}{(c_0 \tilde{c})^\alpha + (c_0 \tilde{c})^\alpha} \right)^n
\]  
(B.16)

\[
\frac{b_0}{t_0} \frac{\partial \tilde{b}}{\partial t} + \frac{v_0 b_0}{x_0} \frac{\partial}{\partial x} (v_0 \tilde{v} b_0 \tilde{t} \tilde{b}) = \frac{\mu n}{1 + \frac{\gamma (c_0 \tilde{c}) \tilde{n}}{(c_0 \tilde{c})^\alpha + (c_0 \tilde{c})^\alpha} \left( \frac{(A_0 \tilde{A}) \tilde{n}}{(A_0 \tilde{A})^\alpha + (A_0 \tilde{A})^\alpha} \right)^n} - \delta b_0 \tilde{b}
\]  
(B.18)

\[
\frac{c_0}{t_0} \frac{\partial \tilde{c}}{\partial t} + \frac{v_0 V(t) c_0}{x_0} \frac{\partial}{\partial x} = \frac{D c_0}{x_0^2} \frac{\partial^2 \tilde{c}}{\partial x^2} + \lambda n \left( \frac{(c_0 \tilde{c}) \tilde{n}}{(c_0 \tilde{c})^\alpha + (c_0 \tilde{c})^\alpha} \right)^n - \zeta_1 A_0 \tilde{A} B_0 \tilde{B} + \zeta_2 A_0 \tilde{A} I_0 \tilde{I}
\]  
(B.19)

\[
\frac{B_0}{t_0} \frac{\partial \tilde{B}}{\partial t} + \frac{v_0 V(t) B_0}{x_0} \frac{\partial}{\partial x} = \frac{D B_0}{x_0^2} \frac{\partial^2 \tilde{B}}{\partial x^2} + \kappa_1 n - \kappa_2 A_0 \tilde{A} B_0 \tilde{B} - \kappa_3 B_0 \tilde{B} I_0 \tilde{I}
\]  
(B.20)

\[
\frac{I_0}{t_0} \frac{\partial \tilde{I}}{\partial t} + \frac{v_0 V(t) I_0}{x_0} \frac{\partial}{\partial x} = \frac{D I_0}{x_0^2} \frac{\partial^2 \tilde{I}}{\partial x^2} - \rho I_0 \tilde{I}
\]  
(B.21)

\[
\frac{\partial \tilde{I}}{\partial t} + \frac{v_0 V(t) I_0}{x_0} \frac{\partial}{\partial x} = \frac{D I_0}{x_0^2} \frac{\partial^2 \tilde{I}}{\partial x^2} - \rho I_0 \tilde{I}
\]  
(B.22)
subject to the initial and boundary conditions

\[ b_0 \dot{\theta} = \frac{\mu n_{\text{max}}}{\delta (1 + \gamma \beta (c, A))}, \]

\[ \frac{x_0 \partial \dot{H}}{t_0} = v_0 \dot{\theta} - F_0 \]

\[ 0 = \delta c_0 \left( \frac{x_0}{t_0} \frac{dH}{dt} - V(t) \right) + \frac{D_c c_0}{x_0} \frac{\partial \dot{c}}{\partial x}, \]

\[ 0 = \dot{A} A_0 \left( \frac{x_0}{t_0} \frac{dH}{dt} - V(t) \right) + \frac{D_A A_0}{x_0} \frac{\partial \dot{A}}{\partial x}, \]

\[ 0 = \dot{B} B_0 \left( \frac{x_0}{t_0} \frac{dH}{dt} - V(t) \right) + \frac{D_B B_0}{x_0} \frac{\partial \dot{B}}{\partial x}, \]

\[ 0 = \dot{I} I_0 \left( \frac{x_0}{t_0} \frac{dH}{dt} - V(t) \right) + \frac{D_I I_0}{x_0} \frac{\partial \dot{I}}{\partial x}. \]

We can multiply by \( t_0, \frac{x_0}{t_0}, \frac{x_0}{t_0} \), \( \frac{x_0}{t_0} \), \( \frac{x_0}{t_0} \), \( \frac{x_0}{t_0} \) respectively.

\[ \frac{\partial n}{\partial t} + \frac{v_0 t_0}{x_0} \frac{\partial n}{\partial x} = \left( c_0 \right)^n \frac{(c_0 \dot{c})^n}{\left( (c_0 \dot{c})^n + (c_0 \dot{c})^n + (A_0 \dot{A})^n \right)} - \Omega n_0 \left( 1 - \frac{\sigma (c_0 \dot{c})^n}{(c_0 \dot{c})^n + (c_0 \dot{c})^n} \right) n \]

\[ \frac{\partial \dot{c}}{\partial t} = \frac{\partial^2 \dot{c}}{\partial x^2} = \frac{c_0}{x_0} \frac{v_0}{(c_0 \dot{c})^n + (c_0 \dot{c})^n} \left( \frac{\sigma (c_0 \dot{c})^n}{(c_0 \dot{c})^n + (c_0 \dot{c})^n} \right) \]

\[ \frac{\partial \dot{A}}{\partial t} + \frac{V(t)}{x_0} \frac{\partial \dot{A}}{\partial x} = \frac{D_A A_0}{x_0} \frac{\partial^2 \dot{A}}{\partial x^2} = \frac{\lambda A_0}{x_0} \left( \frac{\sigma (c_0 \dot{c})^n}{(c_0 \dot{c})^n + (c_0 \dot{c})^n} \right) \]

\[ \frac{\partial \dot{B}}{\partial t} + \frac{V(t)}{x_0} \frac{\partial \dot{B}}{\partial x} = \frac{D_B B_0}{x_0} \frac{\partial^2 \dot{B}}{\partial x^2} = \frac{\lambda_B B_0}{x_0} \left( \frac{\sigma (c_0 \dot{c})^n}{(c_0 \dot{c})^n + (c_0 \dot{c})^n} \right) \]

and multiply the initial and boundary conditions using \( \frac{1}{b_0}, \frac{x_0}{t_0}, \frac{x_0}{t_0}, \frac{x_0}{t_0} \), \( D_c c_0, A_0, B_0, I_0 \) and \( \frac{x_0}{t_0} \)

\[ \dot{b} = \frac{\mu n_{\text{max}}}{\delta b_0 (1 + \gamma \beta (c, A))} \]

\[ \frac{\partial \dot{H}}{\partial t} = \frac{v_0 t_0}{x_0} \frac{F_0}{x_0 b_0} + \frac{\partial \dot{c}}{\partial x} = \frac{x_0^2}{t_0 D_c} \frac{(v_0 t_0 V(t) - \frac{dH}{dt})}{x_0} \]

\[ \frac{\partial \dot{A}}{\partial x} = \frac{x_0^2}{t_0 D_A} \frac{(v_0 t_0 V(t) - \frac{dH}{dt})}{x_0}, \]

\[ \frac{\partial \dot{B}}{\partial x} = \frac{x_0^2}{t_0 D_B} \frac{(v_0 t_0 V(t) - \frac{dH}{dt})}{x_0}, \]

\[ \frac{\partial \dot{I}}{\partial x} = \frac{x_0^2}{t_0 D_I} \frac{(v_0 t_0 V(t) - \frac{dH}{dt})}{x_0}. \]
The additional rescalings to are $\epsilon_A = \frac{2\delta u}{\delta A}$, $\chi_1 = \frac{2\delta u}\epsilon_A$, $\chi_2 = \frac{2\delta u}{\delta B}$, $\epsilon_B = \frac{2\delta u}{\delta B}$, $\chi_1 = \frac{2\delta u}{\delta B}$, $\chi_3 = \frac{2\delta u}{\delta B}$, $\epsilon_1 = \frac{2\delta u}{\delta B}$, and $\hat{p} = \frac{\epsilon B}{\epsilon B}$. The nondimensionalised system is given in Chapter 4.

**B.2.1 Zero Flux Boundary Condition**

We are aware of the moving boundary and to overcome this issue, a conservation argument is used to obtain the correct boundary condition. The zero flux condition for the growth factor concentration at $x = H(t)$ will be deduced here and applies to Chapter 3 and 4. The total amount of $c$ in the spatial domain ($x \in (0, H)$) is given by (using conservation law)

$$\frac{\partial}{\partial t} \int_0^H c \, dx = J_c(0, t) - \lambda \int_0^H \frac{c^n}{c_2^n + c^n} \, dx,$$

equivalent to

$$\frac{\partial}{\partial t} \int_0^H c \, dx = -D_c \frac{\partial c}{\partial x}(0, t) + V(t)c(0, t) - \lambda \int_0^H \frac{c^n}{c_2^n + c^n} \, dx,$$

as $\delta x \to 0$. Recalling the growth factor concentration equation

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} - V(t) \frac{\partial c}{\partial x} - \lambda n \frac{c^n}{c_2^n + c^n},$$

and integrating between the spatial domain gives

$$\int_0^H \frac{\partial c}{\partial t} \, dx = \int_0^H \left( D_c \frac{\partial^2 c}{\partial x^2} - V(t) \frac{\partial c}{\partial x} - \lambda n \frac{c^n}{c_2^n + c^n} \right) \, dx.$$

Reversing the normal differentiation process inside the integral argument we obtain

$$\frac{\partial}{\partial t} \int_0^H c \, dx = c(H, t) \frac{\partial H}{\partial t} + \int_0^H \left( D_c \frac{\partial^2 c}{\partial x^2} - V(t) \frac{\partial c}{\partial x} - \lambda n \frac{c^n}{c_2^n + c^n} \right) \, dx,$$

and integration yields

$$\frac{\partial}{\partial t} \int_0^H c \, dx = c(H, t) \frac{\partial H}{\partial t} + \left[ D_c \frac{\partial c}{\partial x} \right]_0^H - \left[ V(t)c \right]_0^H - \int_0^H \lambda n c \, dx.$$

Subtracting (B.37) from (B.40)

$$c(H, t) \frac{\partial H}{\partial t} + \left[ D_c \frac{\partial c}{\partial x} \right]_0^H - \left[ V(t)c \right]_0^H - \lambda \int_0^H \frac{c^n}{c_2^n + c^n} \, dx = \int_0^H c^n \, dx = \int_0^H c^n \, dx.$$
simplifying to

\[ c(H, t) \frac{\partial H}{\partial t} + D_c \frac{\partial c}{\partial t}(H, t) - V(t)c(H, t) = 0 \]  

(B.42)

and substituting (3.18) gives the zero flux condition for \( c \). Similarly we can derive the zero flux conditions for \( A, B \) and \( I \) for the extended model in Chapter 4.

### B.3 Dermal Model

Substituting the rescalings \( x = x_0 \delta, t = t_0 \delta, n = n_0 \delta, m = d_0 \delta, d = d_0 \delta, g = d_0 \delta, f = f_0 \delta, \) \( c = c_0 \delta \) and \( s = s_0 \delta \), the dermal system in Chapter 5 becomes

\[ \frac{n_0 \delta \partial n}{t_0 \delta} = \frac{D_n n_0}{x_0^2} \frac{\partial^2 n}{\partial x^2} - \frac{s_0 n_0}{x_0^2} \frac{\partial}{\partial x} \left( \frac{n_x n(d_0 \delta + \sigma_d d_0 \delta)}{\partial \delta} \right) \]  

(B.43)

\[ \frac{m_0 \delta \partial m}{t_0 \delta} = -m_0 f_0 m \left( \delta_{mf} + \delta_{ms} s_0 \delta \right) - \delta_m m_0 \delta \]  

(B.44)

\[ \frac{d_0 \delta d}{t_0 \delta} = 0 \]  

(B.45)

\[ \frac{d_0 \delta d}{t_0 \delta} = c_0 f_0 \delta \left( \delta_{sf} + \delta_{sf} s_0 \delta \right) H(s_0 \delta - \delta) H(c - c_0 \delta) - \frac{d_0 \delta d}{1 + c_0 \delta / \gamma_{df}} \]  

(B.46)

\[ \frac{f_0 \delta f}{t_0 \delta} = \frac{D_f f_0}{x_0^2} \frac{\partial^2 f}{\partial x^2} - \frac{s_0 f_0}{x_0^2} \frac{\partial}{\partial x} \left( f_x f(d_0 \delta + \sigma_f d_0 \delta) \frac{\partial \delta}{\partial \delta} \right) \]  

(B.47)

\[ + \beta_{fe} \delta \left( \delta_{fe} \left( 1 - \frac{f_0 \delta}{f_f^*} \right) + \beta_{fe} H(s_0 \delta - \delta) \right) \]  

\[ - \delta f_0 \delta \]  

(B.48)

\[ \frac{c_0 \delta c}{t_0 \delta} = \frac{D_c c_0}{x_0^2} \frac{\partial^2 c}{\partial x^2} + \beta_{ce} \delta \left( c_0 \delta + \delta_{ce} \right) \]  

(B.49)

Multiplying the system by \( t_0 / n_0, t_0 / m_0, t_0 / d_0, t_0 / d_0, t_0 / f_0, t_0 / c_0 \) and \( t_0 / s_0 \) respectively to give

\[ \frac{\partial n}{\partial t} = \frac{D_n t_0}{x_0^2} \frac{\partial^2 n}{\partial x^2} - \frac{s_0 t_0}{x_0^2} \frac{\partial}{\partial x} \left( n_x n(d_0 \delta + \sigma_n d_0 \delta) \frac{\partial \delta}{\partial \delta} \right) \]  

(B.51)

\[ + \frac{\delta_t t_0 c_0 \delta c}{1 + s_0 \delta / \gamma_{cs}} \left( 1 - \frac{n}{\delta} \right) - \frac{\delta_n t_0 \delta}{1 + c_0 \delta / \gamma_{nc}} \]  

\[ \frac{\partial m}{\partial t} = m_0 f_0 \delta \left( \delta_{mf} + \delta_{ms} s_0 \delta \right) - \delta_m t_0 \delta \]  

(B.52)
The system can be simplified further by applying appropriate nondimensional quantities which are presented in Section 5.3.5 as well as the full nondimensionalised system.

B.4 Bacteria Model

Substituting the rescalings \( x = x_0 \hat{x} \), \( t = t_0 \hat{t} \), \( n = n_0 \hat{n} \), \( m = m_0 \hat{m} \), \( d = d_0 \hat{d} \), \( g = g_0 \hat{g} \), \( f = f_0 \hat{f} \), \( c = c_0 \hat{c} \), \( w = w_0 \hat{w} \) and \( s = s_0 \hat{s} \), the dermal system in Chapter 6 becomes

\[
\begin{align*}
\frac{\partial \hat{d}}{\partial \hat{t}} &= 0 \quad \text{(B.53)} \\
\frac{\partial \hat{n}}{\partial \hat{t}} &= \frac{t_0}{d_0} c_0 f_0 \hat{f} (\beta_{sf} + \beta_{sf} s_0 \hat{s}) H(\hat{e} - c_0 \hat{c}) - \frac{\hat{d} \delta_{m0}}{1 + c_0 \hat{c} / \gamma_{sf}} \quad \text{(B.54)} \\
\frac{\partial \hat{f}}{\partial \hat{t}} &= \frac{D_f f_0}{x_0^2} \frac{\partial^2 \hat{f}}{\partial \hat{x}^2} - \frac{s_0 f_0}{x_0^3} \frac{\partial}{\partial \hat{x}} \left( f_X f(d_0 \hat{d} + \sigma_f d_0 \hat{d}) \frac{\partial \hat{d}}{\partial \hat{x}} \right) \\
&\quad + \frac{\beta_{fs} \delta_{s0}(d, g)}{f_0} + f_0 c_0 \hat{c} \left( \beta_{fc} \left( 1 - \frac{f_0 \hat{f}}{\kappa_f} + \beta_{fc} H(\hat{e} - c_0 \hat{c}) \right) \right) \\
&\quad - \frac{\delta_{f0} \hat{f}}{1 + (c_0 \hat{c} + \beta_{fs} s_0 \hat{s}) / \gamma_{fc}} \quad \text{(B.55)} \\
\frac{\partial \hat{e}}{\partial \hat{t}} &= \frac{D_e e_0}{x_0^2} \frac{\partial^2 \hat{e}}{\partial \hat{x}^2} + \frac{\beta_{es} \delta_{s0}(d, g)}{e_0} - \delta_{e0} (\delta_{en} n_0 \hat{n} + \delta_{ef} f_0 \hat{f}) \quad \text{(B.56)} \\
\frac{\partial \hat{s}}{\partial \hat{t}} &= \frac{D_s s_0}{x_0^2} \frac{\partial^2 \hat{s}}{\partial \hat{x}^2} + t_0 \left( \delta_{en} n_0 \hat{n} (\beta_{en} + \beta_{es} s_0 \hat{s}) + f_0 \hat{f} (\beta_{sf} + \beta_{sa} s_0 \hat{s}) \right) \left( 1 + \beta_{se} H(\hat{e} - c_0 \hat{c}) \right) \\
&\quad + \frac{\delta_{s0} \delta_{sm} d_0 \hat{m}}{s_0} - \delta_{s0} (\delta_{en} n_0 \hat{n} + \delta_{es} f_0 \hat{f}) \quad \text{(B.57)}
\end{align*}
\]

The system can be simplified further by applying appropriate nondimensional quantities which are presented in Section 5.3.5 as well as the full nondimensionalised system.
Multiplying the system by $t_0/n_0$, $t_0/m_0$, $t_0/d_0$, $t_0/f_0$, $t_0/c_0$, $t_0/w_0$ and $t_0/s_0$ respectively to give

\[ \frac{\partial \tilde{n}}{\partial \tilde{t}} = \frac{D_n t_0}{x_0^2} \frac{\partial^2 \tilde{n}}{\partial \tilde{x}^2} - \frac{s_{a t_0}}{x_0^3} \left( \tilde{\alpha} \chi_b (d_0 \tilde{d} + \sigma_0 \tilde{d} g) \right) \left( \frac{\partial \tilde{s}}{\partial \tilde{x}} \right) + \frac{\beta_{a t_0} \tilde{n} \tilde{c}_0}{1 + s_0 \gamma_{nc}} \left( \frac{1}{\kappa_n} \right) - \left( \frac{\alpha_{nm} t_0 \tilde{w}_{0 t_0}}{\gamma_{nc}} + \alpha_{nm w} \tilde{w}_{0 t_0} \right) \]  

(B.67)

\[ \frac{\partial \tilde{t}}{\partial \tilde{t}} = \frac{\alpha_{nm w} \tilde{w}_{0 t_0}}{d_0} \left( \alpha_{nm w} \tilde{t}_{0 t} + \alpha_{nm w} \tilde{t}_{0 s} \right) + \tilde{t}_0 \tilde{m} \tilde{f}_0 \tilde{f} \left( \delta_{m} + \delta_{m s} \tilde{d} \tilde{s} \right) - \delta_{m t_0} \tilde{m} \]  

(B.68)

\[ \frac{\partial \tilde{g}}{\partial \tilde{t}} = \frac{c_{a f} \tilde{f}_0 \tilde{f}_0 (\beta_{a s} + \beta_{a s s} \tilde{s} \tilde{d})}{d_0 (1 + \tilde{w}_{0 t} / \gamma_{gw})} \]  

(B.69)

\[ \frac{\partial \tilde{f}}{\partial \tilde{t}} = \frac{D_{f} t_0}{x_0^2} \frac{\partial^2 \tilde{f}}{\partial \tilde{x}^2} - \frac{s_{a f}}{x_0^3} \left( \tilde{f} \chi_b (d_0 \tilde{d} + \sigma_0 \tilde{d} g) \right) \left( \frac{\partial \tilde{s}}{\partial \tilde{x}} \right) + \frac{\beta_{f t_0} \tilde{n} \tilde{c}_0}{f_0} \left( \beta_{f c} \left( \frac{1}{\kappa_f} \right) + \beta_{f c a} H (\tilde{s}_0 \tilde{s} - \tilde{s}) \right) - \left( \frac{\delta_{f} \tilde{f}_0 \tilde{f}}{1 + (c + \rho \tilde{s}) / \gamma_{f c a}} + \alpha_{f m w} \tilde{w}_{0 t_0} \right) \]  

(B.70)

\[ \frac{\partial \tilde{c}}{\partial \tilde{t}} = \frac{D_{c} t_0}{x_0^2} \frac{\partial^2 \tilde{c}}{\partial \tilde{x}^2} + \frac{\beta_{c t_0} \tilde{n} \tilde{c}_0}{c_0} - \epsilon t_0 \left( \delta_{c m} \tilde{n}_0 \tilde{t} + \delta_{c f} \tilde{f}_0 \tilde{f} + \alpha_{c m w} \tilde{w}_{0 t_0} \right) \]  

(B.72)

\[ \frac{\partial \tilde{w}}{\partial \tilde{t}} = \tilde{t}_0 \tilde{w} (\beta_{w e c} \tilde{c}_0 + \beta_{w m} \tilde{m}_0 \tilde{n}) + \beta_{w m} H (\tilde{n} - \tilde{n}_0 \tilde{t}) - \tilde{t}_0 \tilde{w} (\delta_{w} + \delta_{w f} \tilde{f}_0 \tilde{f}) \]  

(B.73)

\[ \frac{\partial \tilde{s}}{\partial \tilde{t}} = \frac{D_{s} t_0}{x_0^2} \frac{\partial^2 \tilde{s}}{\partial \tilde{x}^2} + \frac{\tilde{t}_0}{s_0} \left( \tilde{n}_0 (\beta_{m} + \beta_{s e} \tilde{d} \tilde{s} + \tilde{f}_0 \tilde{f} (\beta_{s f} + \beta_{s e f} \tilde{s} \tilde{d})) (1 + \beta_{w e} H (\tilde{c} - \tilde{c}_0)) \right) \]  

(B.74)

\[ + \frac{\beta_{s t_0}}{s_0} \beta_{t m d} \tilde{m}_0 \tilde{n} \]  

(B.75)

The rescalings and full nondimensionalised system can be found in Section 6.2.4.
Bibliography


