Macroscopic models for fibroproliferative disorders: A review

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**Article info**

Article history:
Received 20 May 2009
Received in revised form 8 August 2009
Accepted 12 August 2009

Keywords:
Wound healing
Fibroproliferative disorders
Mathematical modelling
PDEs
Macroscopic models

**Abstract**

In this paper we review some mathematical modelling of organ reparative processes (wound healing) for both the physiological and pathological case. The natural process of healing consists in a series of overlapping phases involving cells, chemicals, extracellular matrix (ECM) and the environment surrounding the wound site. Sometimes the healing process fails and the reparative mechanism produces pathological conditions which are commonly termed fibrosis or fibroproliferative disorders. Biological insight into the pathogenesis, progression and possible regression of fibrosis is lacking and many issues are still open. Mathematical modelling can surely play its part in this field and this paper is aimed at showing what has been done so far and what has still to be done to achieve a unified framework for studying these kinds of problems. Due to the high complexity of this phenomenon, multi-scale modelling is certainly the appropriate approach that should be used for studying these kinds of problems. Unfortunately most of the mathematical literature on this topic consists of macroscopic continuous models which fail to investigate processes occurring at smaller length scales (cellular, sub-cellular). We present a review of some of the mathematical literature, showing the widely used approaches, focusing on the interpretation of results and indicating possible developments in the study of these highly complex systems.

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1. Introduction

The increasing importance that life science has gained in recent years has led a large community of mathematicians to face the challenge of studying and modelling complex biological systems. This interest is primarily motivated by the need of a multi-disciplinary approach which includes a mathematical formalization of problems, an approach which has been strongly recommended by top level biologists in past decades (see [1]).

Although living systems obey the same physical principle and laws of inert matter, the differences between the latter and the former are evident, especially if we consider the lack of background models to support a complete mathematical framework of the phenomena under analysis.

The classical heuristic methodology used to investigate complex biological systems is not sufficient to provide a complete tool apt to produce a full understanding of the processes investigated. An interdisciplinary approach is of crucial importance and, in light of this, mathematics can play a key role, not only for comprehending the phenomenon underlying the experimental observations and the data obtained from laboratory analysis, but also for providing predictive tools which may indicate and quantify possible strategies of intervention.

The role of mathematics in biological issues has been often seen with a too enthusiastic attitude or with excessive skepticism, producing researches that focussed only on mathematical aspects or others where mathematics was completely avoided. Many authors in journals dedicated to life science have stressed the importance of finding a balance where mathematicians can give their contribution, remarking the importance of a research that moves back and forth between experiment and theory (see [2,3]). Of course, some topics in biological science have attracted mathematicians more than others, but we can surely say that mathematics has been less intrusive in biological issues than in other natural sciences.

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doi:10.1016/j.mcm.2009.08.001
The investigation of the historical and scientific reasons for such a disparity is beyond the scope of this work, but we want to stress the fact that the many features one has to deal with when studying living matter are usually not considered in their whole complexity in the classical approach to modelling. Think for example of the concept of competition, cell cycles, reproduction and communications. Moreover, in biology, gross experimentally observed phenomena may be the result of processes which occur at cellular level and these, in turn, may be determined by gene expressions that alter some phenotype characteristics, activating the evolutionary selection. Of course, mathematics cannot definitely solve the problem, but it is undoubtedly necessary for developing the right framework in which a complete understanding of the topic can be obtained. Useful practical interventions necessitate the knowledge of “what is going on” and this can be surely achieved also by means of mathematical modelling.

A multi-scale approach, ranging from molecular to macroscopic level, is of capital importance when developing models for life sciences. Biological processes involve a large number of complex mechanical and biochemical mechanisms interacting in a highly nonlinear way. Depending on the scale at which these processes occur, different mathematical models can be used to provide a detailed description of the system, from the sub-cellular to the macroscopic scale.

When modelling biological systems one should be able to produce different mathematical models at different scales and provide a link between each model to get a complete description of the system. This is not certainly an easy task as it requires a deep understanding of the interactions of a series of complex inter-related processes occurring at different spatial and temporal scales. Unfortunately most mathematical models focus on a specific aspect of the problem at the selected scale with the aim of providing some particular answer, and usually a unified description of the system is lacking.

Most of the models in the literature are macroscopic, even though the recent literature on modelling biological tissues have initiated a systematic approach to multi-scale modelling (see [4,5]). Macroscopic models, usually based on sets of ordinary and partial differential equations, provide a qualitative and quantitative description of the average behaviour of cells and tissue. However, since this behaviour originates at cellular level and, more deeply, at molecular level, where genetic mutations occur (see [6] for a discussion on the multi-scale approach), such models necessarily miss the core of the problem. Therefore it is fundamental that models account for different phenomena that develop at different scales and that these scales are linked together to provide a coherent description of the entire system.

Further, once the reliability of the models is proved, numerical simulations should be used to predict outcomes and define possible strategies of intervention, drastically reducing the amount of experimentation that is usually needed for testing drug efficiency.

In this work we present a review of mathematical modelling of some wound healing and fibroproliferative disorders. This topic deals with the biological process of restoration of functionality of organs that has been damaged by some agents. We will focus also on the pathological aspects of the phenomenon, that is on the effects due to the so-called fibroproliferative diseases. From the mathematical point of view this subject has been widely studied at macroscopic level, but insight at cellular and sub-cellular level scale is missing.

We will not focus on a particular disease, but rather describe a generic class of mathematical models from which most of the models for fibroproliferative disorders can be derived, making suitable assumptions. Our aim is to look at the problem in a more general perspective, comprehending the features that seemingly different pathologies actually have in common. Further, we want to show that mathematical modelling, especially if multi-scale, offers a very powerful tool to understand these biomechanical processes, playing an important role by exploring the potential of various proposed mechanisms to account for clinical observations and by suggesting novel biological mechanisms which may lead to new experimental approach. Moreover, these models can be used not only to quantitatively describe the evolution of a disease but also to indicate how to operate to avoid a specific pathological condition.

In reviewing the mathematical literature on this subject we will focus on some approaches (continuous, discrete, etc), showing advantages and disadvantages depending on the phenomenon under analysis and on the length scale over which the system is analyzed. The vast majority of models in the literature are macroscopic, even though in recent years development of experimental techniques has shift the interest also on modelling at smaller scales (sub-cellular and cellular).

Macroscopic continuum mathematical models for fibroproliferative disorders usually consist of a set of PDEs for the main physiological parameters involved in the repair mechanism. They are set up to describe the normal evolution of the repair process and subsequently modified to account for the pathological case. Both the physiological and the pathological evolution of the system are studied by looking at the stable steady states of the systems, which represent, depending on the models considered, the normal healed state or the pathological chronic state of the fibrotic pathology.

The level of complexity of the mathematical formulation may vary depending on the numbers of parameters involved and on the geometry of the system. In most macroscopic models a simple plane geometry is used and the evolution is described by a set of balance equations for some concentrations and for the momentum of the tissue displacement. Numerical simulations and comparison with experimental data are frequently presented to validate the model.

Discrete models are often used when focusing on the evolution of individual cells, as well as their interactions with other cells and with the surrounding medium. In this approach cells are supposed to move on a lattice grid according to some rules which are established on the basis of experimental evidence. These models are usually solved in an iterative way, meaning that the state of the system, at a certain time step, is obtained from the preceding one. Some models may also be hybrid, in the sense that some biological quantities are treated as continuous and others as discrete. Models for multicellular systems are typically modelled by nonlinear integro-differential equations similar to kinetic theory or by partial differential systems with internal structure.
The paper is structured as follows: after a brief description of wound healing and fibroproliferative disorders (Section 2) we will present the state of the art of mathematical models for macroscopic case (Section 4). We will not dwell on technical details, preferring to present the general framework in which models are developed, rather than focusing on analytical issues such as existence, uniqueness etc. Nevertheless we will discuss the mathematical structures of the models, referring the interested reader to the bibliography for details and proofs.

The aim of the paper is to provide an indication of what has been done so far on this topic and to discuss possible developments for the future. Far from being exhaustive, it is intended to collect sufficient material for a critical analysis and to stimulate mathematicians to do a research activity on this very interesting topic.

2. Wound healing and fibroproliferative diseases

When we speak of “wound healing” we usually intend the formation of connective tissue as a result of injury or long term inflammation. In wound healing normal tissue is replaced by scar tissue, as the result of the body's physiological response in which specialized cells deposit layers of collagen, a ubiquitous protein that helps form scars. When the wound healing response goes out of control, the formation of scar occurs very fastly and production and deposition of collagen results in a pathological scarring, a process called fibrosis.

In the fibrotic process organs becomes stiff and cannot perform functions essential to life and health, leading to organ failure and death in the extreme cases. Fibrosis can be triggered by a variety of events including trauma, surgery, infection, environmental pollutants, alcohol, and other types of toxins and it can potentially involve most tissues and organs of the human body.

The fibrotic progression is characterized by the termination of the regular organ repair functionality and the development of fibroproliferative wound healing. This type of abnormal healing can be regarded as pathologically excessive responses to wounding in term of cells profiles and their inflammatory growth factor mediators.

In young people wound healing develops according a well–ordered sequence: inflammation, formation of new tissue (cell proliferation and production of extracellular matrix) and remodelling. The complex cellular events in which cells proliferate at the wound site, secrete growth factor and extracellular matrix proteins eventually leading to wound contraction are termed fibroplasia, a constitutive feature of a normal wound healing response.

In the ageing organism or in the presence of a specific pathology this process fails, at some stage. Phenomenologically, fibroproliferative diseases commonly exhibit increased healing responses and this abnormality results in a combination of chronic inflammation, fibroproliferative and non-regenerative repair.

Although its impact on the mathematical community has been far less striking than e.g. cancer modelling, the problem of abnormal organ repair is nevertheless a deeply important issue, in the framework of health care. It suffices to say that liver fibrosis (an abnormal wound healing response of the liver which can be due to multiple factors) is the 5th most common cause of death in the United Kingdom, with rising incidence. Fibroproliferative diseases – including pulmonary fibrosis, hypertrophic scars, scleroderma (thickening of the skin), diabetic retinopathy and age-related macular nephropathy, cardiomyopathy, cirrhosis and atresia (leading causes of liver fibrosis and failure), gglomerulosclerosis and IgA nephropathy (causes of kidney failure and need for dialysis and retransplant), congestive heart failure – are a leading cause of mortality and can affect all organs and tissues. Fibrotic tissue remodelling can also influence cancer metastasis and accelerate chronic graft rejection in transplant recipients. Despite increasing effort of medical research in the past 10–15 years, a complete understanding of the pathogenesis and dynamic nature of fibroproliferative disorders is still missing. Considering its enormous impact on human health, it is highly regrettable that there are no currently approved treatments that directly target the mechanisms of fibrosis, showing that the road is still long.

Detailed biological insight into the mechanisms of pathogenesis, progression, stabilization and possible regression of fibrosis is lacking. Existing clinical corrective methods are typically long term, unpredictable, often traumatic for the patient and prone to failure or recurrence. Unlike inflammation, for which anti-inflammatory therapies abound, there are no approved treatments that directly target the process of fibrosis, despite its preponderance and potentially fatal consequences in so many diseases. Current therapies for fibroproliferative disorders usually include anti-inflammatory drugs, which are palliative at best and fail to address the fibrotic process that causes disease progression. There is a large unmet need for a safe and effective anti-fibrotic therapy that delays disease progression and reduces mortality.

Four crucial events are characteristic of fibrosis: (i) inflammation and angiogenesis, (ii) migration and proliferation of cells, (iii) deposition of extracellular matrix, (iv) remodelling. These four phases are common to each type of fibrosis even if differences arise from organ to organ. Here below we have outlined some types of fibroproliferative diseases, briefly describing the evolution of the pathology. Of course it is not an exhaustive collection, but it gives an idea of the main features that should be taken into account when developing mathematical models for fibroproliferative pathologies.

2.1. Liver fibrosis

Liver fibrosis is a fibroproliferative disease where the pathological wound healing response results in hepatocytes apoptosis and necrosis. In liver fibrosis wound healing is mediated by some cells called myofibroblasts (see [7]). After injury, some resident hepatic stellate cells (HSC) undergo myofibroblasts-like phenotype conversion, which may mark the onset of fibrosis. This transformation is characterized by expressions of profibrotic genes like collagen 1, MMPs.
In the adjacent region fibroblasts form aggregates of cells known as granulation tissue (see [37x73]threeparts.

2.4. Bone wound healing

Bones, like other tissues, have the capability of self-repairing. The fracture healing process can be essentially divided into three parts.

**Phase (i) reactive phase:** after fracture, clotting take place at the wound site and blood vessels constrict to prevent bleeding. In the adjacent region fibroblasts form aggregates of cells known as granulation tissue (see [32]).
Phase (ii) reparative phase: after some days the cells of the periosteum (exterior part of the bone) near the bone gap develop in chondroblasts and form the so-called hyaline cartilage. Other periosteal cells distal to the fracture develop into osteoblasts and form woven bone (weak structure with high number of osteocytes). Also the fibroblasts in the granulation tissue help forming the hyaline cartilage. The hyaline cartilage and the woven bone grow in size until they unite to form the fracture callus ([33]). The subsequent step is the so-called endochondral ossification, where hyaline cartilage and the woven bone are substituted by lamellar bone. This process occurs after the collagen matrix of either tissue becomes mineralized. New lamellar bone, called trabecular bone, is then formed upon the recently exposed surface of the mineralized matrix. Eventually, all of the woven bone and cartilage of the original fracture callus is replaced by trabecular bone, restoring the bone's original strength.

Phase (iii) remodelling phase: this is the phase when trabecular bone is substituted with compact bone. The trabecular bone is first resorbed by osteoclasts, which subsequently deposit compact bone. Eventually, the fracture callus is remodelled into a new shape which closely duplicates the bone's original shape and strength.

In the healing process a key role is played by the growth factor secreted by the osteoblasts. Among these the one that affects bone growth is the bone morphogenetic protein (BMP). Some models take into account the so-called critical size defect (CSD), which is defined as the diameter of a bone wound beyond which complete calcification of the wound will not occur during lifetime.

We refer the reader to the Appendix for the meaning of some biological terms used in this section.

3. Multi-scale modelling

Wound healing is a multi-scale phenomenon involving cells. As for tumor growth, the implementation of models requires information on the dynamics at intracellular (molecular) scale, at cellular scale and at macroscopic scale. Phenomena occurring at these different scales are obviously linked together, with feedback down and feed-forward up mechanisms. Informations on the dynamics at molecular scales can be used as inputs for models at higher scales. The different levels of biological organization are defined whether they represent interactions between genes, cells, tissues and so on. The biological hierarchy is intuitively well defined, even though it is not easy to give the exact length values at which we switch from one level to the other. Any reasonable biological model have to include processes that vary on a wide range of time and length scales, where the latter are commonly defined in terms of level of biological organization. A multi-scale model is a model including two or more of these levels of organization in which some processes occur faster than others. A very interesting paper on multi-scale modelling in biology and physiology can be found in [34].

At molecular scale systems are commonly described through stochastic models that investigate the dynamics of gene regulatory network (see [35–38]). At higher scales through deterministic models. In stochastic processes computational issues arise because of the high number of particles involved and, in general, the time scales at which lower level processes occur are much faster than the ones at higher levels, so that most of the lower level processes are assumed to be instantaneous.

For what concerns wound healing and fibroproliferative disorders it is essential to develop multi-scale models which describe all the fundamental biological mechanisms involved in the process, from gene regulation to tissue damage.

Unfortunately most of the models in the literature are focussed on high level biological organization and few are devoted to the comprehension of mechanisms occurring at molecular level, such as production of proteins (as a result of gene expression). Protein synthesis is crucial in biological activity of an organ, since all biochemical reactions are catalyzed by enzymes and subunits (organelles) are made of proteins. In protein synthesis informations encoded in one strand of DNA flows to proteins through mRNA (transcription and translation, see [39]).

Cells activity is regulated by gene expression patterns and, for particular cellular functions, activation of genes are regulated by some feedback mechanism called gene and enzyme regulation. In the former protein synthesis is regulated by a particular region of DNA in such a way that if the synthesized quantity reaches a critical value, synthesis is inhibited by a negative feedback mechanism. In the latter the synthesized substance can deactivate the first enzyme necessary for the biochemical reaction. The knowledge of these complex mechanisms allows, in principle, to control proteins synthesis. In liver fibrosis, for instance, it allows to control collagen production.

It is clear the importance of modelling also at molecular scale, since the evolution of cells is regulated by interactions of genes contained in its nucleus that can result in temporary, or even permanent, alterations which can affect the cell’s state. The mathematical approach should be definitely multi-scale, even if we wish to model at a certain scale, since we do not have indications about how other phenomena occurring at other scales influence the process investigated. Of course the selection of particular scale is determined by what phenomenon we are trying to model and the availability of biological and experimental data.

In this review we will focus on some macroscopic models, that is we consider effects occurring at macroscopic scale. Macroscopic models are commonly based on a set of nonlinear partial differential equations. A variety of continuous models are formulated writing mass balance for components and reaction–diffusion systems for chemicals and extracellular matrix. These models describe the evolution of the system in terms of time and space averaged quantities representative of the behaviour of cell populations.

Due to the large amount of the available experimental observations at population scales [40], the vast majority of mathematical models for wound healing and fibroproliferative disorders fall in the class of macroscopic continuous
models, even though recent advances in microscopy, time-lapse imaging and magnetic resonance has allowed to perform observations and measurements over a wide range of scales (see [41]).

Cell invasion is central to normal and pathological wound healing and it is constituted essentially by cell migration and proliferation. The latter are typically modelled by the generalized Fisher’s equation which exhibits travelling wave solutions, in agreement with biological observations (see [42]). Models involving a large number of variables are usually reduced to caricature simplified models, because of the complexity of mathematical analysis.

4. Macroscopic continuous models

In this section we describe the approach commonly used to develop macroscopic mathematical models for biological processes involving the process of wound healing (both in the physiological and pathological case). The methodology presented can be applied to a large class of issues in which the repair of an organ tissue occurs. The idea is to present a general framework from which most of the models we find in the literature can be developed, giving the reader a unified perspective on a topic that covers a wide range of biological issues.

Mathematical modelling for biological complex systems, as already mentioned, should be based on a multi-scale approach that accounts for phenomena occurring at different temporal and spatial scales. Unfortunately, most of the models we found in the literature are macroscopic, either continuum or discrete.

Continuum models are based on the classical approach of writing PDEs for mass and momentum balance and closing the system by phenomenological models specifying some property of the system. In phenomenological models the intrinsic mechanics of the system is ignored and the issue of the motion is dealt with via specific simplifying assumptions. Systems where cells move as a result of diffusion, chemotaxis, haptotaxis, etc. are phenomenological.

A different way for closing the system is to use mechanical models where stress and strain responsible for cellular and tissue deformation are taken into account. In these mechanistic models an extra equation for force balance is used to determine how cells and tissue move as a result of forces action. Also for these kinds of models assumptions have to be made depending on the choice of how to model the tissue (as an elastic fluid, as a visco-elastic fluid, etc).

The equation representing the evolution of the system are coupled together to account for interactions between the biological variables used to describe the process. In most of the models we are going to consider these variables are cell population densities, chemical growth factors and extracellular matrix. For wound healing and fibroproliferative disorders, macroscopic models are usually based on the interactions between cells and extracellular matrix, as cells may synthesize and degrade extracellular matrix and extracellular matrix may affect cell properties and orientation (in dermal wound healing this inter-dependent relationship is called dynamic reciprocity, see [43]). The dynamics of both cells and extracellular matrix is mediated by some chemical growth factors, which regulate both cell proliferation and extracellular matrix reorganization. The evolution of each biological quantity is connected with the evolution of the others. The selection of the quantities representative of the system (cell types, growth factors, etc) has to be done according to experimental evidence.

4.0.1. Mathematical formulation

The biological quantities appearing in continuum models for wound healing and fibroproliferative diseases obey a generic conservation equation of the type

\[
\frac{\partial W}{\partial t} = -\nabla \cdot (\vec{J}_W) + f_W,
\]

where \( W \) is the observed quantity, \( \vec{J}_W \) represents the flux of \( W \) and \( f_W \) its production/degradation rate. The choice of \( \vec{J}_W \) and \( f_W \) has to be done on the basis of the experimental evidence. The complete mathematical formulation consists in a set of PDEs of type (1) for the various biological and physical ingredients of the process. The target is to provide a description of the averaged behaviour of cell populations, chemical growth factor, extracellular matrix and tissue displacement. The typical formulation from which most of macroscopic models are derived is outlined in the following differential system:

\[
\begin{align*}
\frac{\partial n_i}{\partial t} &= \nabla \cdot \left( D_i \nabla n_i - \chi(n, c) \nabla c - n_i a_i \nabla \rho - n_i \frac{\partial \vec{u}}{\partial t} \right) + \Gamma_i(n, c) \\
\frac{\partial c}{\partial t} &= \nabla \cdot \left( D_c \nabla c - c \frac{\partial \vec{u}}{\partial t} \right) + \Sigma(n, c) \\
\frac{\partial \rho}{\partial t} &= \nabla \cdot \left( -\rho \frac{\partial \vec{u}}{\partial t} \right) + \Phi(n, c, \rho) \\
\nabla \cdot \sigma &= \rho \dot{\varepsilon} (\vec{u})
\end{align*}
\]

where

(i) \( n_i(\vec{x}, t) \) represents the density of the \( i \)th species of cells involved in the model \( (n = (n_1, \ldots, n_m)) \); \( m \) is the total number of cell types;
(ii) \( D_i \) is the diffusion coefficient of the \( i \)th species, usually assumed to be constant. Some models also consider nonlinear diffusion;
(iii) \( c(\mathbf{x}, t) \) is the chemical (growth factor). The usual hypothesis is to consider a generic growth factor, in other words a chemical effectively summarizing the behaviour of a class of chemicals that take part in the system. If, on the contrary, there are other chemicals producing different effects, they have to be considered separately;

(iv) \( \chi(n, c) \) is the chemotactic sensitivity factor;

(v) \( \alpha_i \) is the haptotactic constant of the \( i \)th species;

(vi) \( \rho(\mathbf{x}, t) \) is the collagen, or extracellular matrix, density. Here too \( \rho \) is representative of the class of collagens forming the extracellular matrix;

(vii) \( \mathbf{u}(\mathbf{x}, t) \) is the tissue displacement;

(viii) \( \sigma \) is the stress tensor;

(ix) \( \Gamma, \Sigma, \Phi \) and \( \mathcal{O} \) are kinetic terms;

(x) \( \mathbf{x} \) is the spatial coordinate;

(xi) \( t \) is time;

Let us see in details the meaning of each equation. Eq. (2)_1 represents mass balance of the \( i \)th species. The contribution to the flux is given by linear Fickian diffusion, growth factor mediated chemotaxis (where \( \chi(n, c) \) is suitably chosen according to the cell surface receptor mechanism), linear haptotaxis, and passive convection due to tissue displacement. The kinetic term \( \Gamma(n, c) \) may include mitosis, phenotypic transformation between different cell species and natural cell death (apoptosis).

Eq. (2)_2 represents mass balance of the growth factor \( c \), whose flux is driven by linear diffusion and convection. The term \( \Sigma(n, c) \) accounts for production and consumption of chemical by cells and for natural chemical decay.

Eq. (2)_3 represents mass balance of the extracellular matrix. The flux is assumed to be due only to convection since collagen fibres are generally linked in a mesh-like structure so that the effects of diffusion is negligible (see [24,44]). The kinetic term \( \Phi(n, c, \rho) \) includes synthesis of collagen by cells, enhancement due to growth factor chemical and degradation.

The last equation represents tissue linear momentum balance, where \( \sigma \) is the stress tensor and \( \mathcal{O}(\rho, \mathbf{u}) \) accounts for external forces acting on the tissue. In (2)_4 inertia effects are neglected, an assumption motivated by the high viscosity of most of the tissue involved in these models. Due to the presence of (2)_4, system (2) is a mechanistic model.

The vast majority of biological continuum models describing wound healing and fibroproliferative disorders are based on a system of equations of type (2). These models can be used for a large variety of biological issues, such as dermal and epidermal wound healing, corneal wound healing, bone fracture, hypertrophic scarring, fibrosis and all those processes involving cell migration and cell proliferation in living tissues.

In the next section we will discuss the mathematical structure of the full system (2) and in Section 4.0.3 we will focus on cases in which some simplifications are applied. Most of the models we find in the literature are indeed simplified versions of (2), which prove to be sufficient for describing the main features of the biological system. We will motivate these simplifications and we will show how to analyze the evolution of the system along with the main mathematical tools used to analyze the evolution of these systems.

4.0.2. Mathematical analysis

The analysis of (2) may prove to be quite complex, analytically and numerically. In many cases one does not need to consider the full system, since the exclusion of some equation does not alter the general behaviour in a significant way. Depending on the specific case some terms can be neglected, excluding some effects that may not be relevant. Biological parameters in (2) are selected on the basis of the available experimental data. Moreover, to avoid some technical difficulties, the system is usually reduced to linear or axisymmetric geometries, as the mathematical analysis and numerical simulations become easier.

When setting up the model it is important to identify which class of cells, chemicals and other quantities are really decisive for the expected outcomes. The number of parameters and the number of variables must be kept in a reasonable range, since too complex models require often the introduction of parameters which simply cannot be measured.

Once the differential system is set up, boundary conditions and initial data must be specified. Also in this case the appropriate choice can be made exploiting experimental available data reflecting physiological and pathological conditions. The initial data, representing the wounded state, is usually given by a large perturbation of the uniform steady state of (2), representative of normal conditions.

The investigation of the evolution of the system is commonly performed by looking at the steady states of (2) and analyzing their stability. Due to the intrinsic complexity of (2), there is little hope to find useful analytical solutions. In any case, we know that much of the “wound healing potential” is predicted by linear analysis about uniform steady state solutions, which is also useful for guiding the numerical analysis.

For simplicity of notation we introduce the vector variable \( \mathbf{q} = (n_1, \ldots, n_m, c, \rho, u_1, u_2, u_3) \). In the full system (2) the unwounded spatially uniform steady state is given by the \( m+5 \)-ple \( \mathbf{q}_0 = (n_1, \ldots, n_m, 0, \rho, 0) \), since in the unwounded state no chemical production and no tissue displacement are present.

Restriction to spatially uniform steady states leads to the nonlinear system:

\[
\begin{align*}
\Gamma(n, c) &= 0, \\
\Sigma(n, c) &= 0, \\
\Phi(n, c, \rho) &= 0, \\
\mathcal{O}(\rho, \mathbf{u}) &= 0.
\end{align*}
\]
Under normal conditions $\hat{q}_c$ is a locally stable steady state solution (i.e. a solution of (3)) and the initial wounded state evolves back to $\hat{q}_c$, simulating the proliferative phase of non-pathological healing. In a more general framework, and depending on some parameters of the problem, there can be steady state solutions indicative of a pathological healing response. In this case steady solutions with $n_i > \hat{n}_i$, $c > 0$, i.e. solutions where the extracellular matrix is continuously produced, are found. These steady solutions, which may be locally stable to small perturbations, exhibit a permanent inflammatory state ($c > 0$), a characteristic of the vast majority of fibroproliferative pathologies. Therefore, it is crucial to determine those parameters that characterize the transition between normal and abnormal healing, as they may indicate how to intervene to avoid abnormal healing and emergence of pathologies.

### 4.0.3. Simplified models

Due to the high complexity of the full system most of the macroscopic models are usually reduced to caricature models which mimic the basic features of system. In this way explicit solutions, which may help to get further insight to the full system, are obtained. Of course simplifying assumptions have to be made in a careful manner, avoiding to discard the fundamental processes operating within the proliferative phase of healing. Simplified versions of (2), ranging from very simple models to quite complex ones, can be found in the literature for most healing processes.

The simplest models are the ones with only one cell species diffusing and proliferating (see [45,46]), or the ones where the system is simply described by the concentration of some growth factor responsible for the healing process (see [47–50]). The healed or non-healed state is represented by the concentration profile of cell population or chemical growth factor. In both cases the system is described by an equation of the type

$$\frac{\partial f}{\partial t} = \nabla \cdot [\alpha(f) \nabla f] + \beta(f),$$

where $\alpha$ and $\beta$ may be nonlinear functions and $f$ is cell density or chemical concentration. In [46], for instance, wound healing for the dermis is modelled by the one-dimensional Fisher’s equation

$$\frac{\partial n}{\partial t} = D \frac{\partial^2 n}{\partial x^2} + kn(n_0 - n),$$

(5)

for cell density $n(x, t)$, with a kinetics modelled as logistic growth ($x$ is the one-dimensional space variable and $t$ is time). Here the biochemical effects are assumed to be constant and $kn_o$ represents the maximum rate at which cells proliferate. Solutions of (5) are sought in the form of a travelling wave and it is proved that after a short transient, an invading front of cells move as a travelling wave at constant speed $2\sqrt{\hat{n}_i kD}$. Travelling wave solutions exist for a wide range of data corresponding to different propagation speed.

Some models are even simpler than (5). In [51], for instance, wound healing is studied for anterior cruciate and medial collateral ligament, assuming that the evolution of the cell is driven only by diffusion (Fisher’s equation without the proliferative term), and proliferation is not taken into account.

In [48] the problem for tissue regeneration in bones is considered and it is assumed that healing occurs depending on the growth factor concentration $c$. In circular geometry the governing equation is

$$\frac{\partial c}{\partial t} = \frac{D}{r} \frac{d}{dr} \left( r \frac{dc}{dr} \right) + \lambda c = P,$$

(6)

where $\lambda$ is the depletion coefficient and $P$ is the production rate ($r$ represents the radial coordinate). The model indicates that there exists a lower bound (critical size defect, CSD) for the growth factor region such that, if that region is smaller than this bound, healing cannot occur. In other words, if the region where the concentration of the chemical is wider than the critical size, then the wounded bone is healed.

In [52] a modified version of model (5) is proposed for modelling the healing process of severe burns. Here the cells involved in the repair mechanism are divided in two types: active and quiescent. The governing equations are

$$\frac{\partial n}{\partial t} = D \frac{\partial^2 n}{\partial x^2} + kn(n_0 - n - q) - \lambda u,$$

(7)

$$\frac{\partial q}{\partial t} = \lambda u,$$

(8)

where $n$ is the density of active cells, $q$ is the density of the quiescent cells and $-knq$ represents the contact inhibition (process of arresting cell growth when two or more cells come into contact with each other) of the proliferating active cells. The author proves the existence of a minimal speed $c_{\text{min}}$ such that for every speed $c \geq c_{\text{min}}$ there exists a unique physically meaningful travelling wave solution (no such a solution exists for $c < c_{\text{min}}$).

Switching to more complex models, a very common class is the one in which the problem for one species of cells is coupled with the one for the growth factor. As for the previous case, tissue displacement, chemotaxis and haptotaxis are not
taken into account and (2) reduces to
\[
\begin{align*}
\frac{\partial n}{\partial t} &= D_n \Delta n + \Gamma(n, c), \\
\frac{\partial c}{\partial t} &= D_c \Delta c + \Sigma(n, c),
\end{align*}
\tag{9}
\]
that, once integrated, allows to evaluate the ECM density through the integration of the nonlinear ODE
\[
\frac{\partial \rho}{\partial t} = \Phi(n, c, \rho).
\tag{10}
\]
System (9) is a two-component reaction–diffusion system whose solutions, in one dimension, can be sought in the form of travelling waves. Examples of biological applications to wound healing and fibroproliferative disorders can be found in [10, 53, 45, 54, 59, 56, 58].

The reaction–diffusion system (9) represents an appropriate choice for modelling fibroproliferative disorders, especially for a peculiar characteristic suggested by Turing in 1952 (see [57]). This characteristic consists in the fact that, under certain circumstances, \(n\) and \(c\) can diffuse producing steady spatially heterogeneous solutions, which, from the biological point of view, are highly representative of a pathological healing process (the physiological healed state is given by constant \(n\) and \(c = 0\)). This peculiarity of the reaction–diffusion system (9) is called diffusion-driven or Turing instability.

Sets of data for which the system evolves to such non-uniform steady states will be indicative of a pathological healing and has to be modified to obtain a normal healed state. In this optic, solutions of (9) provides also possible strategies of intervention, indicating which parameters has to be changed (for instance in the boundary conditions) in order to avoid the emergence of a pathology.

Turing observed that, if \(c\) and \(n\) tend to a linearly stable uniform steady state in the absence of diffusion (\(D_c = D_n = 0\)) then, under certain circumstances, they evolve to spatially heterogeneous steady states. The conditions for diffusion-driven instability can be found linearizing system (9) in the presence and in the absence of diffusion. Suppose \((n_o, c_o)\) is a homogeneous steady state. Linearizing (9) about \(\tilde{w} = (n - n_o, c - c_o)\) with \(D_c = D_n = 0\), we get \(\tilde{w}_t = A \tilde{w}\) where
\[
A = \begin{pmatrix} \Gamma(n_o, c_o) & \Sigma(n_o, c_o) \\ \Sigma(n_o, c_o) & \Sigma(n_o, c_o) \end{pmatrix}
\tag{11}
\]
is the Jacobian matrix of the vector field \((\Gamma, \Sigma)\). The solution \((n_o, c_o)\) is linearly stable if the roots \(\lambda_1, \lambda_2\) of det[\(\lambda I - A\)] = 0 have negative real parts, a condition guaranteed if
\[
\begin{align*}
\text{tr} A < 0, & \quad \det A > 0. 
\end{align*}
\tag{12}
\]
Then we consider the full reaction system (9) linearized about the steady state \(\tilde{w} = (n - n_o, c - c_o)\). We get
\[
\tilde{w}_t = A \tilde{w} + D \Delta \tilde{w},
\tag{13}
\]
where
\[
\Delta \tilde{w} = \begin{pmatrix} \Delta n \\ \Delta c \end{pmatrix}, \quad D = \begin{pmatrix} D_n & 0 \\ 0 & D_c \end{pmatrix}.
\tag{14}
\]
and we look for time-dependent solutions of the form
\[
\tilde{w}(\tilde{x}, t) = \sum_k c_k e^{k^2 t} \tilde{w}_k(\tilde{x}),
\tag{15}
\]
where \(c_k\) are determined by a Fourier expansion of the initial condition and \(\tilde{w}_k\) solves the eigenvalue problem
\[
\begin{align*}
\Delta \tilde{w} + k^2 \tilde{w} &= 0, \\
\text{B.C.},
\end{align*}
\tag{16}
\]
k being the eigenvalue. Problem (13) becomes
\[
\lambda \tilde{w}_k(\tilde{x}) = A \tilde{w}_k + D \Delta \tilde{w}_k,
\tag{17}
\]
and, by means of (16)\(_1\), we get
\[
(\lambda I - A + D k^2) \tilde{w}_k = 0.
\tag{18}
\]
Existence of non-trivial solutions of (18) requires
\[
\det (\lambda I - A + D k^2) = 0,
\tag{19}
\]
that is
\[
\begin{align*}
\lambda^2 + \lambda [k^2 \text{tr} D - \text{tr} A] + h(k^2) &= 0 \\
h(k^2) &= D_n D_c k^4 - (\Gamma n D_c + D_n \Sigma_c) k^2 + \det A.
\end{align*}
\tag{20}
\]
\(^1\) In other words system (9) may exhibit steady states which are stable in the local system and become unstable in the presence of diffusion.
The solution of (13) will be unstable if \( \text{Re}\lambda > 0 \) for some \( k \neq 0 \). This occurs if
\[
k'\text{tr } D < \text{tr } A, \quad \text{or } h(k^2) < 0, \tag{21}
\]
for some \( k \). The first of (21) is not compatible with the first of (12), since \( \text{tr } D > 0 \) and the only way to have \( \text{Re}\lambda > 0 \) is \( h(k^2) < 0 \). A necessary, but not sufficient, condition for \( h(k^2) < 0 \) is \( (F_nD_n + D_n\Sigma_c) > 0 \) in (20) (21). The sufficient condition is found differentiating \( h(k^2) \) w.r.t \( k^2 \) to find the minimum \( h_{\text{min}} = h(k_{\text{min}}^2) \)
\[
k_{\text{min}}^2 = \frac{(F_nD_n + D_n\Sigma_c)}{2D_cD_n}, \quad h_{\text{min}} = 4D_cD_n - (F_nD_n + D_n\Sigma_c)^2, \tag{22}
\]
and requiring
\[
det A < \frac{(F_nD_n + D_n\Sigma_c)^2}{4D_cD_n}, \tag{23}
\]
so that \( h(k^2) < 0 \) for some \( k \). Transition between stability and instability occurs at bifurcation, that is when the data are such that \( h_{\text{min}} = 0 \). Of course this depends on the parameters defining the system (diffusion coefficients, reaction kinetics, etc.). The expression \( \lambda(k^2) \) is called the dispersal relation. Its solutions determine the range of wavenumber \( k \) which are linearly unstable. The set of biological parameters for which such linearly unstable modes exist is called the Turing space.

When system (9) exhibits diffusion–driven instability the homogeneous steady state is unstable to small perturbations. In the nonlinear system, the linearly unstable eigenfunctions, which grows exponentially with time, can be bounded by the nonlinear terms and, depending on the specific reaction–diffusion model, a variety of spatially inhomogeneous solutions, representative of pathological situations, may emerge.

System (9) can be improved to account for other mechanisms. In [58], for instance, system (9) is rewritten replacing the dispersal coefficient \( D_n \) (which is constant in (9)), with a piece-wise constant function. Restricting to the one-dimensional case, the authors provide an analysis of the spatial pattern formation for two specific kinetics occurring in embriogenesis and ecology (see [59,60]). In [61–63] the coefficient \( D_n \) is replaced with \( D_n(c) \) taking into account dependence of the dispersal coefficient on the chemical growth factor. Other modifications can include the contribution of chemotaxis, as in [64], where the model for adult mammalian dermal wound healing is given by:
\[
\begin{align*}
\frac{\partial n}{\partial t} &= \frac{\partial}{\partial x} \left[ D_n \frac{\partial n}{\partial x} - f(n) \frac{\partial c}{\partial x} \right] + F(n, c), \\
\frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} + G(n, c),
\end{align*}
\tag{24}
\]
where \( n(x, t) \) is the fibroblast density (the only cell species in the model) and \( c(x, t) \) is the growth factor (assumed to simulate the combined action of platelet-derived growth factor and transforming growth factor \( \beta \)). The stability of the spatially uniform steady states of (24) is studied plotting the phase space diagrams and performing linear stability analysis for the equations \( F(n, c) = G(n, c) = 0 \). A key parameter \( k \) representing the maximal rate of the growth factor production (which appears in the expressions for \( F \) and \( G \)) then permits to plot the steady states \( n^* \) and \( c^* \) as functions of \( k \), obtaining bifurcations diagrams that allow to differentiate between normal and abnormal healing.

A more complex model accounting for chemotaxis is found in [65,66], where eukaryotic cell movement occurs in response to the chemical receptors distributed on the cell surface and to chemical concentration. In the one-dimensional case, the system is governed by the following set of PDEs
\[
\begin{align*}
\frac{\partial n}{\partial t} &= \frac{\partial}{\partial x} \left( D_n(\beta) \frac{\partial n}{\partial x} - f(n) \frac{\partial c}{\partial x} \right) , \\
\frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} + G(n, c), \\
\frac{\partial y}{\partial t} &= \frac{\partial}{\partial x} \left[ \beta \left( D_n(\beta) \frac{\partial n}{\partial x} - f(n) \frac{\partial c}{\partial x} \right) \right] + H(\gamma, c)
\end{align*}
\tag{25}
\]
where \( \gamma \) represents the density of receptors and \( \beta \) is the number of moles of receptors per cell. Differently from models based on the Keller–Segel approach (where transport coefficients are externally determined, see [67]), here the coefficients variations are determined on the basis of receptor kinetics.

In some other cases the number of cell types relevant for the model can be more than one (see [68]). In [69], for instance, the process of angiogenesis (which occurs in the early stage of wound healing) in soft tissues is described by the system:
\[
\begin{align*}
\frac{\partial n}{\partial t} &= D_n \frac{\partial^2 n}{\partial x^2} - \chi \frac{\partial}{\partial x} \left( n \frac{\partial c}{\partial x} \right) + F(n, m, c), \\
\frac{\partial m}{\partial t} &= D_m \frac{\partial^2 m}{\partial x^2} - \mu \frac{\partial n}{\partial x} + \chi \frac{\partial c}{\partial x}, \\
\frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} + \Sigma(n, c),
\end{align*}
\tag{26}
\]
where \( n(x, t), m(x, t), c(x, t) \) represent the capillary-tip density (number of tips per unit cross-sectional area), the blood vessel density and the chemoattractant concentration respectively. The model admits travelling wave solutions that exhibit many of the features characteristic of wound healing in soft tissue. Here insight in the balance between chemotaxis, tip proliferation, tip death and speed of the healing front is gained through the analysis of a simplified model, which allows to define a maximum wave-speed for the healing process.

Another important class of models is the one where the problem for the density of ECM cannot be solved autonomously as in (9) and (10). In [68] a model for wound healing angiogenesis is proposed, taking into account the contribution of haptotaxis in the migration of endothelial cells (the key constituent of newly-formed capillaries). The governing equations are

\[
\begin{align*}
\frac{\partial n}{\partial t} &= D(\rho) \frac{\partial n}{\partial x} - C(\rho) n \frac{\partial \rho}{\partial x} + \Gamma(n, \rho), \\
\frac{\partial \rho}{\partial t} &= \Gamma(n, \rho).
\end{align*}
\]

Here the problem for \( \rho \) (nonlinear ODE) is coupled with the one for the endothelial cell density \( n(x, t) \) and cannot be solved separately. The ECM is considered as formed by only one component which is, as we have said, a major simplification. More sophisticated models which assume that ECM is formed by different types of collagen can be found in the literature. In [70] a spatially homogeneous temporal model is proposed to determine the concentrations of collagen 1 and collagen 3 (whose ratio is known to regulate the diameter of the fibres forming the extracellular matrix).

In [71–73] systems with more than one cell species, more than one growth factor and more than one collagen type for fracture healing is presented. The set of PDEs can be outlined as

\[
\begin{align*}
\frac{\partial n_i}{\partial t} &= \nabla \cdot \left( D_{n_i} \nabla n_i - \sum_j f_i(n) \nabla c_j - \sum_k g_k(n) \nabla \rho_k \right) + \Sigma(n, c), & i = 1, \ldots, m, \\
\frac{\partial c_j}{\partial t} &= \nabla \cdot \left( D_{c_j} \nabla c_j \right) + h_j(c), & j = 1, \ldots, p, \\
\frac{\partial \rho_k}{\partial t} &= \gamma_k(\rho_k, n), & k = 1, \ldots, s,
\end{align*}
\]

where cell migration is modelled using haptotactic and chemotactic influences.

In some models the spatial dependence is not taken into account and system (2) reduces to a system of nonlinear ODE’s. In these models the healing process is only described by the temporal evolution of some components. In [74] the role of nitric oxide in hypertrophic scarring is studied through the system

\[
\begin{align*}
\frac{dn}{dt} &= f_1(n, \rho, o, p), \\
\frac{d\rho}{dt} &= f_2(n, \rho, o, p), \\
\frac{do}{dt} &= f_3(n, \rho, o, p), \\
\frac{dp}{dt} &= f_4(n, \rho, o, p),
\end{align*}
\]

where \( o \) is the concentration of oxygen and \( p \) is the concentration of nitric oxide. In [75] the action of transglutaminase in the ECM remodelling is studied through the system

\[
\begin{align*}
\frac{df}{dt} &= g_1(f, p), \\
\frac{dp}{dt} &= g_2(f, p),
\end{align*}
\]

where \( p \) and \( f \) represent the concentration of proteinase (an enzyme involved in matrix degradation) and transglutaminase (an enzyme involved in ECM remodelling). Various scenario, depending on the forms of \( g_1 \) and \( g_2 \) are obtained.

4.1. Mechanochemical models

So far we have not taken into account mechanochemical models, i.e. models where tissue displacement is modelled as a consequence of the cell–ECM traction forces, the intrinsic response of the tissue and the external resistance to tissue movements due to fibrous attachments to underlying tissues.

The basic ideas for including mechanistic effects in the system can be found in [76,77], in which a continuum mechanochemical model for cell traction driven tissue morphogenesis is presented. Most of the mechanochemical models for wound healing are developed within the framework of the model presented in [76,78,77]. A detailed review of mechanochemical models can also be found in [79].

Two facts are of crucial importance when considering mechanistic effects: (i) cells migrate on a substratum composed by fibrous ECM; (ii) cells may produce large traction forces which deform the ECM (possibly producing anisotropy in the ECM, which, in turn, affects cell motion).
In [78], beside the balance equation for the cell density \( n(\mathbf{x}, t) \) and the conservation law for the ECM density \( \rho(\mathbf{x}, t) \), a third equation for the tissue displacement \( \mathbf{u}(\mathbf{x}, t) \) is written. In this equation it is tacitly assumed that deformations are so small that, in first approximation, the continuum material formed by cells and ECM can be modelled as a linear, isotropic visco-elastic continuum with stress tensor \( \sigma(\mathbf{x}, t) \). Inertia effects can be safely ignored, since the system is in a very low Reynolds number regime (the time scale for cell motion is very long, while the spatial scale is very small). As a consequence, traction forces generated by cells are in mechanical equilibrium with restoring forces of the matrix and with external forces, so that we can write

\[
\nabla \cdot \sigma = \rho \mathbf{F},
\]

where \( \mathbf{F} \) is the resultant of the external forces acting on the matrix. The stress \( \sigma \) consists of the contribution from the ECM and the cells so that

\[
\sigma = \sigma_{\text{ECM}} + \sigma_{\text{cell}}.
\]

Depending on the specific case under consideration, constitutive assumptions have to be made for the stress exerted by the ECM. Usually, assuming isotropy for ECM fibres alignment and cell orientation, a simple visco-elastic constitutive relation, with stress/strain linear dependence (see [80]), is used for \( \sigma_{\text{ECM}} \). The stress exerted by the cells \( \sigma_{\text{cell}} \), on the other hand, has to take into account the enhancement of cell traction force due to high cell density and the inhibition due to high collagen density (see [81]). The expression for \( \sigma_{\text{ECM}} \) is found modelling the ECM as a linear visco-elastic fluid

\[
\sigma_{\text{ECM}} = [\mu_1 \varepsilon_1 + \mu_2 \theta] \mathbf{I} + \frac{E}{1 + \nu} \left[ \varepsilon + \frac{\nu}{1 - 2\nu} \theta \right],
\]

where \( 2\varepsilon = \nabla \mathbf{u} + \nabla \mathbf{u}^T \) is the strain tensor, \( \theta = \nabla \cdot \mathbf{u} \), \( E \) is the Young’s modulus and \( \nu \) is the Poisson’s ratio. The contribution from traction forces \( \sigma_{\text{cell}} \) must be modelled taking into account cell–cell contact inhibition and nonlocal effects due to the fact that cells attach to ECM through filopodia which extend beyond their immediate neighbourhood. In general we may write

\[
\sigma_{\text{cell}} = \sigma_{\text{cell}}(n, \rho).
\]

The external forces are dependent on the displacement, so that \( \mathbf{F} = \mathbf{F}(\mathbf{u}) \). One-dimensional mechanochemical models applied to normal and abnormal wound repair can be found in [82,83], where the system evolves according to

\[
\begin{align*}
\frac{\partial n}{\partial t} & = D_n \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x} \left[ n \frac{\partial u}{\partial t} \right] + \Gamma(n, \rho) \\
\frac{\partial \rho}{\partial t} & = -\frac{\partial}{\partial x} \left[ \rho \frac{\partial u}{\partial t} \right] + \Phi(n, \rho) \\
\mu \frac{\partial^3 u}{\partial x^3} & + \frac{\partial^2 u}{\partial x^2} + \frac{\partial \tau}{\partial x}(n, \rho) = \rho su
\end{align*}
\]

where it is assumed that external forces depend linearly on \( u (s > 0 \) is a positive constant). Since traction forces depend on the adhesion between cell surface receptors and binding sites on collagen fibres, it is reasonable to assume that \( \tau \) is proportional to \( n \rho \). Moreover, the capacity of cells to extend and protract protrusions to attach to the ECM is inhibited at high ECM densities. A typical choice for \( \tau \) is

\[
\tau(n, \rho) = \frac{\tau_0 n \rho}{R^2 + \rho^2},
\]

where \( R \) and \( \tau_0 \) are positive constants (see [83]). Extensions of model (33) can be found in [84,85].

An interesting problem arising in models of type (35) is the one of wound contraction. To investigate this phenomenon we assume that \( u \) and \( \rho \) are at spatially uniform steady states so that, from (35),

\[
\frac{d^2 u}{dx^2} = Ku,
\]

with boundary conditions

\[
u(0) = 0, \quad \frac{du}{dx}(\infty) = 0.
\]

Problem (37)–(38) admits the unique solution \( u \equiv 0 \), implying that there exists no non-trivial displacement when the species variables are spatially uniform. At the unwounded state the collagen density is found solving

\[
\frac{\partial \rho}{\partial t} = \Phi(\hat{n}, \rho),
\]
where $\hat{n}$ is cell density at the unwounded state. If the kinetics of $\rho$ is neglected (a reasonable approximation, see [82]), then $\rho$ may evolve to a spatially non-uniform inhomogeneous profile (Eq. (35) 2 does not fix $\rho$). Indeed, setting $\Phi \equiv 0$ and linearizing (35) about the initial profile
$$\rho(x, 0) = \rho_i + (1 - \rho_i)H(x - 1),$$
where $[0, 1]$ is the normalized initial wound space and $\rho$ has been normalized with its unwounded value, we get
$$\rho = \begin{cases} \rho_i \left(1 - \frac{\partial u}{\partial x}\right), & x \in [0, 1), \\ 1 - \frac{\partial u}{\partial x}, & x \geq 1. \end{cases}$$
(41)
The steady state force balance becomes
$$\frac{d^2 u}{dx^2} + v \frac{d}{dx} \left(\frac{\rho}{\phi^2 + \rho^2}\right) - s\rho u = 0,$$
(42)
$$u(0) = 0, \quad \frac{du}{dx}(\infty) = 0,$$
(43)
which differently from (37)–(38) admits non-zero spatially inhomogeneous solutions. In this case the collagen concentration remains close to its initial (wounded) value and the displacement does not relax to zero, a situation indicative of a permanent contracted state (scarring).

4.2. Initial and boundary conditions

Well posedness of macroscopic continuous models requires the necessary specification of initial and boundary conditions. For the latter the common idea is to consider that, at the boundary of the domain, the system (cell densities, chemicals, etc) are in the unwounded state. If $\Omega$ denotes the spatial domain of the generic system (2), boundary conditions are commonly chosen of Dirichlet type, i.e. $\bar{q} = \bar{q}_\sigma$ on $\partial \Omega$, where we recall that $\bar{q}$ is the vector whose components are the variables of (2) and $\bar{q}_\sigma$ represents the unwounded state of the system (characterized by no chemical concentration $c = 0$, and no tissue displacement $\bar{a} = 0$). Other boundary conditions are of Neumann or mixed type, meaning that fluxes at the wound edge are specified.

The initial conditions are usually taken as a large perturbation $\bar{q}_{ini}$ of the unwounded state $\bar{q}_\sigma$. From this condition the system may evolve through normal/abnormal healing to physiological/pathological steady states. Most of the models we find in the literature are one-dimensional and the initial wound is represented as a closed interval $[-a, a]$ outside which $\bar{q}_{ini}$ assumes unwounded levels. By symmetry reasons the system is solved in the semi-infinite domain $x \geq 0$, $t > 0$ with symmetric boundary conditions at $x = 0$.

In normal conditions the healed domain evolves as a level set in which the biological parameters assume unwounded values. When the system exhibits travelling wave solutions this set advances in the wound site through a wave front that invades the wounded area. In the abnormal process the level set is characterized by pathological healing values and the system evolves to a pathological steady state.

4.3. Travelling wave models

In the previous sections we have discussed some models in which solutions can be sought in the form of travelling waves. The study of travelling wave solutions provide useful information on the biology of wound healing or fibroproliferative diseases. In wound healing the process of cell invasion plays a fundamental role, since the healed state can be reached as the result of cell migration and proliferation. Migration occurs when an invading front of cells crawls along a substratum (e.g. ECM) and cells start to proliferate in the wounded area.

In vitro experiments have shown that, during cell invasion, a large variety of cells (human peritoneal mesothelial, endothelial, epithelial, fibroblasts, keratinocytes) exhibit a travelling wave-like behaviour. This means that, during invasion, a front of cells advance as a wave propagating in the wounded area. In wound healing cells migrates over different components of the ECM into the wound site, where they start to proliferate influencing segregation/degradation of the ECM.

Mathematical models must reproduce this wave-like behaviour, providing quantitative data of the speed of the invading front and on the wave shape. Several mathematical models have been proposed (see [52,86,87,46,88,42,89,90]), taking into account constant diffusive migration by random motility and proliferation described by logistic growth. All these models are based on Fisher’s equation which has travelling wave solutions that move at a constant speed dependent on diffusivity and on cell proliferation rate. Improvements accounting for diffusivity depending on chemicals (see [91]) or on local density (contact inhibition) (see [92]).

A typical example of this approach can be found in [46], where migration of human peritoneal mesothelial cells is studied during wound healing. The governing equation is (5), which is a Fisher’s equation with proliferation modelled using logistic

\[ \frac{\partial u}{\partial t} = \rho \frac{\partial^2 u}{\partial x^2} + v \frac{\partial u}{\partial x} \]
growth. A travelling wave solution is a solution of the form \( n(x, t) = n(x - ct) \), where \( c \) is the speed of the wave. Substituting into (5) yields

\[
-cn'(x - ct) = Dn''(x - ct) + kn(n_o - n),
\]

which is a second order nonlinear ODE \( n'(z) = d/dz \) that, under certain conditions, behaves as a wave of unchanging shape travelling at constant speed given by \( 2\sqrt{n_o k} \) (see [79]).

Travelling wave solutions may exist also for systems with more than one species. The spatiotemporal dynamics of system (24), for instance, can be investigated by means of travelling waves \( n(x - \xi t) \) and \( c(x - \xi t) \) which transform (24) to a system of coupled ordinary nonlinear differential equations, namely

\[
\begin{align*}
-\xi n'' &= D_n n'' - f(n)c' + F(n, c), \\
-\xi c' &= D_c c'' + G(n, c),
\end{align*}
\]

where \( ' = d/dz \) and \( z = x - \xi t \). The possible transition from the unwounded steady state to the pathological steady state is determined studying the stability of these states in the phase space.

### 4.4. Moving boundary problems

Most of continuous models for wound healing are based on reaction–diffusion equations in fixed domains. This is motivated by the fact that all the stimuli responsible for the wound healing process does not depend on the wound edge position. In some cases this condition does not hold and the wound edge evolution is modelled by a free or moving boundary problem. In general moving boundary problems have been widely used in many problems arising in applied mathematics, but scarcely in the case of biomathematical studies. This is despite the great relevance that free boundary models may have in invasive biological phenomena, such as wound healing.

An interesting example of a free boundary problem in wound healing is presented in [93], where corneal epithelial wound healing is modelled including the presence of a physiological electric field. Experimental investigations have indeed proved the presence of a physiological electric field at the wound edge influencing cell migration in the vicinity of the edge (see [94,95]). The problem is formulated in the one-dimensional case for the corneal epithelial cell density \( n(x, t) \) and the chemical stimulus concentration \( c(x, t) \)

\[
\begin{align*}
\frac{\partial n}{\partial t} &= \frac{\partial}{\partial x} \left( D_n(c) \frac{\partial n}{\partial x} \right) + \frac{\partial}{\partial x} \left( e(x, t)n \right) + f(n, c), \\
\frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} + g(c, n),
\end{align*}
\]

plus boundary (fixed) and initial conditions. The function \( e(x, t) \) is the electric field, which is assumed to be a given function depending on the free boundary \( x = s(t) \) (representing the wound edge). The free boundary conditions are given by

\[
\begin{align*}
n(s(t), t) &= n^*, \\
\left[ (\alpha + \beta c) \frac{\partial n}{\partial x} + e(x, t)n \right]_{x=s(t)} &= n^* \frac{ds}{dt}.
\end{align*}
\]

Results have shown that the model predicts a linear relation between the wound healing speed and the physiological electric field strength, this linear relation being robust to variations in critical parameters difficult to estimate. Well posedness of the mathematical problem has been proved in [96].

In [97] a mathematical model for the migration of enterocytes during experimental necrotizing enterocolitis (NEC) in one and two dimensions is studied. The model considers cell deformation including mobility promoting force due to lamellipod formation, mobility impeding adhesion to cell matrix and enterocyte proliferation. To model the wound closure by enterocytes migration, the boundary is modelled as a free boundary.

In this mechanistic model the system is modelled as a barotropic fluid with the stress tensor \( \sigma = -k \ln(n)I \). At the free boundary (the wound edge), it is assumed that lamellipodia exert a constant force \(-F \) (the negative sign means that the force is outward and cells are stretched). Therefore on the free boundary \( F = k \ln(n) \), which provides the free boundary condition

\[
n = \exp \left\{ \frac{F}{k} \right\}.
\]

Considering the balance of linear momentum (in which inertia effects are neglected)

\[
\vec{f} = \nabla \cdot \sigma,
\]

the author assumes that the body force is the result of total friction exerted by the substrate

\[
\vec{f} = -\frac{b}{n} \frac{\partial \vec{u}}{\partial t},
\]
where \( b \) is a positive parameter. On the moving boundary

\[
\frac{b}{\partial t} \frac{\partial \bar{u}}{\partial t} = -\nabla (k \ln(n)) = -k \frac{1}{n f_b} \nabla n = -k \exp \left\{ -\frac{F}{k} \right\} \nabla n,
\]

(52)

providing the other free boundary condition

\[
\bar{V} \cdot \bar{N} = -k \exp \left\{ -\frac{F}{k} \right\} \nabla n \cdot \bar{N},
\]

(53)

where \( \bar{V} \) is the velocity of the moving boundary and \( \bar{N} \) its normal unit vector.

### 4.4.1. Anisotropy

Some authors have pointed out (see [77,98,99]), the hypothesis of isotropy for the extracellular matrix in presence of cell force traction is definitely strong. For this reason some models take into account anisotropy. In particular, two alignment mechanisms have been proposed (see [100]): flux-induced alignment and stress-induced alignment. The first is caused by the remodelling of the extracellular matrix as cells move through the tissue, while the second results from mechanical forces acting at the wound site.

A simple way of considering anisotropy in a two-dimensional setting is presented in [101], where the authors split the ECM density as follows

\[
\rho(\vec{x}, t) = \rho_1(\vec{x}, t) + \rho_2(\vec{x}, t),
\]

(54)

where \( \rho_1(\vec{x}, t) \) defines the proportion of ECM aligned along one direction and \( \rho_2(\vec{x}, t) \) along the orthogonal direction. The matrix alignment is modelled as a dynamic reversible process

\[
\begin{align*}
\rho_1 &= \frac{R_1}{R_2} \rho_2
\end{align*}
\]

where \( R_1 \) and \( R_2 \) are the conversion rates. Assumptions on \( R_1 \) and \( R_2 \) are essential to distinguish between different mechanisms of alignment (cell-induced, stress-induced, etc.). In [101,100], for instance, the authors assume that the fibres are mutually orthogonal and that the transition rates are proportional to the respective cell flux components.

Modelling anisotropy as in (54) is nevertheless restrictive, as it does not permit to describe the case in which the vast majority of fibres are oriented in one of several discrete directions, or the one in which alignment is continuously distributed.

A typical flux-induced alignment model can be found in [100]

\[
\begin{align*}
\frac{\partial \rho_1}{\partial t} &= k_f (|F_2|\rho_1 + |F_1|\rho_2) + g(n, \rho), \\
\frac{\partial \rho_2}{\partial t} &= k_f (|F_2|\rho_1 - |F_1|\rho_2) + g(n, \rho), \\
\frac{\partial n}{\partial t} + \frac{\partial F_1}{\partial x} + \frac{\partial F_2}{\partial y} &= f(n, \rho),
\end{align*}
\]

(56)

where \( k_f > 0 \) is the flux-induced alignment parameter, \( n(\vec{x}, t) \) is cell density, \( g(n, \rho) \) is the production rate (assumed to be equal in both directions), \( f(n, \rho) \) is the rate of cell division and \( F_1, F_2 \) are the flux components in the \( x \) and \( y \) directions.

In [100] flux representation is based on random cell movement, haptotaxis and preferential movement in the direction of local ECM fibre orientation

\[
(F_1, F_2) = \left( \frac{\rho_1 / \rho}{\rho_2 / \rho} \right) \left[ \chi(\rho) n \frac{\partial \rho}{\partial x} - D(\rho) \frac{\partial n}{\partial x} \right],
\]

(57)

where it is tacitly assumed that the wound is one-dimensional, i.e. changes occur only in the \( x \) direction.

A stress-induced alignment model is also presented in [100]. In this case the conversion rates \( R_1 \) and \( R_2 \) are supposed to be functions of the stress tensor \( \sigma \) and, in particular, of the ratio \( \zeta = |\sigma_{11}/\sigma_{22}| \) (it is assumed that the principal stress axes are always parallel to the coordinate directions). The conservation equations for \( \rho_1, \rho_2 \) are

\[
\begin{align*}
\frac{\partial \rho_1}{\partial t} &= k_s \left( \frac{\zeta^p \rho_2 - \rho_1}{\zeta^p + 1} \right) + g(n, \rho), \\
\frac{\partial \rho_2}{\partial t} &= k_s \left( \frac{\rho_1 - \zeta^p \rho_2}{\zeta^p + 1} \right) + g(n, \rho),
\end{align*}
\]

(58)

where \( p > 0 \) represents the sensitivity of the ECM alignment response to variations in the stress field. Models combining flux-induced and stress-induced alignment are also found in [100].
4.5. Discrete models

In the continuum approach the healing process is modelled by a system of PDEs where the evolving components are represented by density variables. Although this way of proceeding is definitely more amenable to mathematical analysis, it is less realistic, since it does not consider the discrete nature of cells, which is fundamental when modelling the interactions between the extracellular matrix and the cells.

Discrete models are very useful when we are interested in the evolution of individual cells as well as the interactions occurring with other cells or with the surrounding medium. In the discrete approach cells are usually treated as points moving on a lattice according to certain rules that may vary from simple to very complex ones. Discrete models can be used also to describe the process of fibre alignment in the ECM reorientation, finding applications in ecology, pattern formation, tumor growth, angiogenesis among others. The main limitation of discrete models is the fact that they are very demanding from the computational point of view.

The choice between continuous and discrete models is essentially made depending on what scale we wish to investigate the phenomenon and on which particular biological mechanism we wish to describe. Clearly, having a continuous and discrete model for some phenomenon we must check that they give rise to similar solutions at scales in which their range of applicability overlaps. Moreover, discrete models can be used to derive biological parameters for continuous models, taking suitable limits in space and time (establishing a link between macroscopic quantities, such as diffusivity, and microscopic ones).

A first example of discrete model can be the one regarding ECM fibre orientation. The extracellular matrix, that has been modelled as a scalar quantity in the previous section, is actually composed by fibres which possess alignment that strongly influences the motion of cells (which, in turn, influence the production of ECM).

In continuum models a way of taking account ECM orientation can be the one presented in Section 4.4.1, where we discussed anisotropy at a macroscopic level. When focusing on anisotropy at microscopic levels (and this is the case of many connective tissues that are spatially homogeneous and isotropic at macroscopic scales, but have spatial structure at smaller scales), discrete models offer an efficient tool for describing the effects of ECM fibre alignment on cells.

In this framework cells are represented as discrete objects whose evolution is given by functions $\vec{f}_i(t)$, $i = 1,...,M$ ($M$ being the total number of cells) that keep track of the path followed by the cell. The evolution of each $\vec{f}_i$ is expressed by a set of ordinary differential equation whose expression depend on the orientation of the ECM fibres. In [100], for instance, the authors assume that cells have constant speed $s$ and that the ECM density does not vary with time. The system is governed by the following

$$\frac{df_i(t)}{dt} = s (\cos D_i, \sin D_i),$$

(59)

where

$$D_i(t) = \Theta(\vec{f}_i(t), t)$$

(60)

is the direction of cell motion and $\Theta$ is the orientation of the extracellular matrix$^2$ that evolves according to

$$\frac{\partial \Theta(x, t)}{\partial t} = \kappa \sum_{k=1}^{M} \Psi(\Theta(x, t), D_i(t-\tau), \vec{f}_i(t) - \vec{x}),$$

(61)

where $\tau$ represents a time lag (the time taken for the ECM reorientation towards the directions $D_i$ of the cells) and $\kappa$ measures the extent of cellular reorientation of the matrix. System (59)–(61) is solved numerically in a fixed square domain with periodic boundary conditions. The ECM orientation is represented plotting streamlines (curves whose tangents form an angle $\Theta$ with the reference direction) after a long time ($1000$ h), allowing the transient to dissipate. Results show that for low $\kappa$ the matrix tends to persist in a disorganized state, while for higher values patterns of alignment develop.

A slightly different orientation model is presented in [102], where the directional cues of the cells are no longer directed by the ECM orientation only, but by a weighted average of the previous direction of motion of the cells and the direction of the fibrous matrix at the current location. In practice the expression for $D_i$ is replaced by

$$D_i(t) = (1 - \rho)\Theta(\vec{f}_i(t), t) + \rho D_i(t - \tau),$$

(62)

where $\tau$ still represents the time lag. Numerical simulations of this model show the importance of the initial alignment of the ECM. In particular it is proved that cell density is less important than the initial orientation of the fibres and the variations in the cell flux. A small region of alignment in the initial state can greatly influence the final matrix alignment. The model is then extended (allowing for production and degradation of ECM by cells) to describe the case of dermal wound repair, where fibroblast cells move along the matrix fibres, eventually replaced with a collagen-based matrix that form the new tissue.

Other possible approaches consist in assuming that both cells and ECM have discrete orientations, a localized continuum of orientation or a continuous distribution of orientations with several maxima. In this case cells and ECM are represented

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$^2$ $D_i$ and $\Theta$ are angles measured with respect to some reference direction.
by continuous functions (expressing their density) taking non-zero values only along some discrete directions, a localized continuum of directions or a continuous distribution of directions with some maxima.

This is the spirit of [103], where a model for fibroblasts and collagen orientation – aimed to understand how fibroblasts for and remodel the ECM – is presented starting from a continuous setting. Here the system is described by the set of PDEs

$$\begin{align*}
\frac{\partial f}{\partial t} &= \frac{\partial}{\partial \theta} \left( D \frac{\partial f}{\partial \theta} - \alpha f \frac{\partial f}{\partial \theta} (W_1 * c) \right), \quad \theta \in [0, 2\pi], \\
\frac{\partial c}{\partial t} &= -\beta \frac{\partial}{\partial \theta} \left( c(W_2 * f) \frac{\partial f}{\partial \theta} (W_3 * f) \right), \quad \theta \in [0, 2\pi],
\end{align*}$$

(63)

where \(f(\theta, t), c(\theta, t)\) are the densities of fibroblasts and collagen fibres (assumed to be spatially homogeneous) oriented at angle \(\theta\) with respect to a reference configuration. The convolutions appearing in (63) are defined by

$$\langle W * u \rangle(\xi) = \int W(\xi - s)u(s)ds,$$

(64)

where the integral is over the domain of \(u\). The equation for the fibroblasts has a diffusion term (modeling random reorientation) and a flux term (modeling the tendency of fibroblasts to move up the gradient of collagen). This latter term is modeled with a convolution (a weighted average over all the orientations) which is empirically observed that even collagen which is far away in the angle space may influence fibroblasts. In the equation for collagen, the diffusion term is dropped because, in the ECM, collagen takes the form of a fibrous network with no random reorientation of the collagen. The forms of the kernels \(W_i\) are specified by the biological features of the system investigated.

Numerical implementation shows that, depending on the initial orientation of collagen and fibroblasts, solutions where collagen densities are concentrated at discrete, isolated orientations with fibroblasts densities localized around these discrete orientations can be obtained.

A different discrete model is found in [92], where cell migration in wound healing is studied. In this article the discrete model arises from a one-dimensional continuous model for cell migration and proliferation of type (4). Cell density evolves according to

$$\frac{\partial n_i}{\partial t} = D_o \left( \frac{\partial}{\partial x} \left( \frac{n_i}{N^*} \right) \frac{\partial n_i}{\partial x} \right) + an \left( 1 - \frac{n_i}{N^*} \right),$$

(65)

where \(D_o\) is the diffusivity of an isolated cell, \(D(n/N^*) \to 1 \text{ when } n \to 0\) and the proliferative term is modeled as logistic growth with carrying capacity \(N^*\) (\(\alpha\) represents the mitotic index). Solutions of (65) are found in travelling wave form.

Eq. (65) is then modified treating the individual cells as continuous-time nearest-neighbour random walkers, the main events taking place being transition between discrete sites (on the lattice \(x = i\Delta x\), birth and death. Denoting with \(n_i(t)\) the number of individuals at each lattice site \(i\) at time \(t\) over the maximum number of individuals for each lattice site, the equation governing the random walk process is

$$\frac{dn_i}{dt} = \frac{1}{\lambda_t} \left[ pn_{i+1} + qn_{i-1} - (p + q)n_i + \frac{\alpha}{\lambda_p} n_i (1 - n_i) \right],$$

(66)

where \(\lambda_t\) is the mean waiting time of a transition event (including the option of remaining at the current site), \(\lambda_p\) is the waiting time for birth and death event, \(p\) is the probability of making a transition to the left and \(q\) of making a transition to the right, \(1 - p - q\) is the probability of remaining at the current site). A similar approach, although discrete also in time, has been adopted in for modelling the response of neurons to a signaling molecule (see [104]), and the growth of blood vessels (see [105]).

In [106] cell migration, cell proliferation and contact inhibition in tissue growth are modelled through a discrete model based on cellular automata (see [107]). The domain consists of a 3D cubic grid with \(N_x \times N_y \times N_z = N\) computational sites, which can exist in (a) empty state, (b) occupied by a cell undergoing the mitotic process, moving to an adjacent site or occupied by a cell that is in a stationary state. Every site (automaton) is connected to its neighbours and evolves at discrete time step \(\Delta t\) because of the interactions with adjacent sites.

The state of each site is described by a vector function \(\tilde{X}_i(t \Delta t)\) whose components are the migration index \(m_i\), the division counter \(k_d\), and the persistent counter \(k_{ps}\). The evolution of the system is governed by a transition function \(F\) that must be specified on the basis of the probability of cells to migrate, proliferate, or stay at rest. The iterative process can be schematized as

$$\begin{align*}
\tilde{X}(t + 1) \Delta t &= F(\tilde{X}(t \Delta t)), \\
\tilde{X}(0) &= \tilde{X}_o,
\end{align*}$$

(67)

where \(\tilde{X}(t \Delta t) = (X_1(t \Delta t), \ldots, X_N(t \Delta t))\) represents the state of the cellular array at time step \(t\) and \(\tilde{X}_o\) represents the initial state of the array.

As we said at the beginning of this section, discrete models can be exploited to obtain macroscopic quantities on which continuous models are based, e.g. diffusivity, taking suitable limits in time and space. In [108], for instance, particles moving
on a one-dimensional lattice are modelled through
\[
\frac{\partial n_i}{\partial t} = \alpha \left[ n_{i-1} + n_{i+1} - 2n_i \right],
\]
where \( n_i(t) \) is the density of particles at point \( i \) and \( \alpha \) is the probability of the particle to move to the right \( (i+1) \) and left \( (i-1) \) position (transition to right and left are supposed to have the same probability). Writing \( n_{i+1} = n(x + \Delta x) \) and \( n_{i-1} = n(x - \Delta x) \), \( \Delta x \) being the space separating two adjacent lattice points, performing Taylor’s expansion, scaling time with \( t = \lambda \tau \) and taking the limit
\[
\lim_{h \to 0, \lambda \to \infty} \left( h^2 \lambda \right) = D
\]
transform Eq. (69) into
\[
\frac{\partial n}{\partial t} = \alpha D \frac{\partial^2 n}{\partial x^2},
\]
establishing a link between the transition probability and diffusivity \( D \). Of course, more complex equations can be used to derive macroscopic models, but the underlying idea remains the same, that is obtaining continuous models as the limit of discrete ones.

5. Conclusions

In this paper we have reviewed some mathematical models for wound healing and fibroproliferative disorders. The healing process has been considered in a generic framework, not focusing on any particular organ but indicating the main differences between the physiological and the pathological case.

Due to the intrinsic complexity of the phenomenon, we have stressed the importance of a multi-disciplinary approach which includes mathematical modelling. The latter can play a relevant role for the full comprehension of the problem, especially if performed in a multi-scale setting capable of studying phenomena occurring at different scales.

The mathematical literature on this subject is vast, even though it is mainly focussed on the macroscopic scale. Continuous models have been formulated for a large variety of tissues and organs and for different aspects such as angiogenesis, cell invasion, cell proliferation and wound contraction. They are formulated in terms of PDEs for biological quantities considered in an averaged sense.

Unfortunately few papers are devoted to multi-scale modelling, even though this approach could provide insight into the problem, since it allows not only to study a specific system at different levels but also to link together the models, showing consistency when shifting from one level to the other. In this framework the overall system can be viewed as a network of different interacting subsystems with interactions between contiguous subsystems satisfying compatibility conditions.

Acknowledgements

This work has been partially supported by RESOLVE, Health - 2007 - 2.2.2-2, Termination of developmental processes and their reactivation in adult life.

Appendix. Biological terminology

Angiogenesis: the process of developing new blood vessels.
Apoptosis: the process of programmed cell death that may occur in multicellular organisms.
Atresia: a condition in which a body orifice or passage in the body is abnormally closed or absent.
Cardiomyopathy: the deterioration of the function of the myocardium, i.e. the actual heart muscle.
Cell migration: the orchestrated movement of cells in particular directions to specific locations.
Cell proliferation: increase in cell number by division.
Chondroblast: a cell which originates from a mesenchymal stem cell and forms chondrocytes, commonly known as cartilage cells.
Cirrhosis: the consequence of chronic liver disease characterized by replacement of liver tissue by fibrous scar tissue.
Congestive heart failure: a condition in which a problem with the structure or function of the heart impairs its ability to supply sufficient blood flow to meet the body’s needs.
Dermis: the layer of skin between the epidermis and subcutaneous tissues.
Diabetic retinopathy: a common complication of diabetes affecting the blood vessels in the retina (the thin light-sensitive membrane that covers the back of the eye).
Endochondral ossification: one of the two processes during foetal development of the mammalian skeletal system resulting in the creation of bone tissue.
Epidermis: the outermost layer of the skin of vertebrates.
Epithelium: a tissue composed of cells that line the cavities and surfaces of structures throughout the body.
**Extracellular matrix (ECM):** the extracellular part of animal tissue that usually provides structural support to the animal cells in addition to performing various other important functions. The extracellular matrix is the defining feature of connective tissue in animals.

**Fibroblast:** a type of cell that synthesizes the extracellular matrix and collagen, the structural framework (stroma) for animal tissues.

**Fibronectin:** a high-molecular weight extracellular matrix glycoprotein that binds to membrane-spanning receptor proteins called integrins.

**Fibroplasia:** the formation of a scar during the fibroplastic repair phase of healing.

**Fibroproliferative disorders:** a disease characterized by the abnormal accumulation of fibrous tissue that can occur as a part of the wound healing process in damaged tissue.

**Fibrosis:** the formation or development of excess fibrous connective tissue in an organ or tissue as a reparative or reactive process, as opposed to a formation of fibrous tissue as a normal constituent of an organ or tissue.

**Graft rejection:** the rejection of a transplanted organ or tissue which is not accepted by the body of the transplant recipient.

**Glomerulonephropathy:** a progressive disease that affects the skin and connective tissue, including cartilage, bone, fat, and the tissue that supports the nerves and blood vessels throughout the body.

**References**


