Department of Chemical Engineering & Technology

Mathematical Modelling of Corneal Wound Healing

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Introduction

- Corneal epithelial wound healing is a critical physiological process involving coordinated **cell migration**, **adhesion**, and **mitosis.**
- **EGF(Epidermal Growth Factor)**,a protein that stimulates cell growth and differentiation. It's produced by many cells in the body , is believed to be crucial for epithelial repair.
- In this study, we develop and analyze a reaction-diffusion model to investigate the dynamics of corneal epithelial repair, with a focus on the role of Epidermal Growth Factor (EGF) as a key .

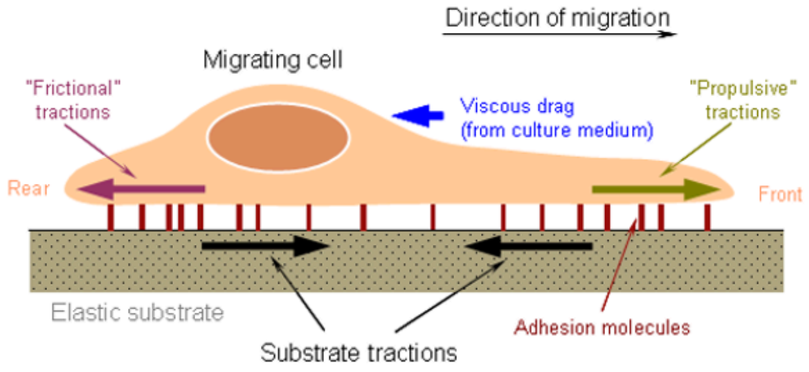
Objectives

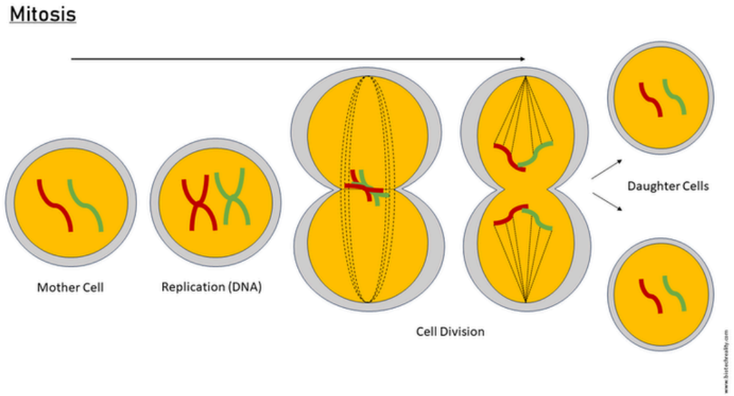
1) Our **goal** is to study a **predictive model** that captures the key elements of **healing kinetics** in response to EGF and offer insight into optimal therapeutic strategies.

2) **To utilize COMSOL Multiphysics**—for solving coupled differential equations via a multiphysics workflow (weak form setup, mesh generation, and time-dependent solver with parameter sweeps).

How EGF works

- EGF binds to its receptor, the epidermal growth factor receptor (EGFR)
- This binding activates the EGFR, which initiates intracellular signaling
- The signaling controls cell division and survival





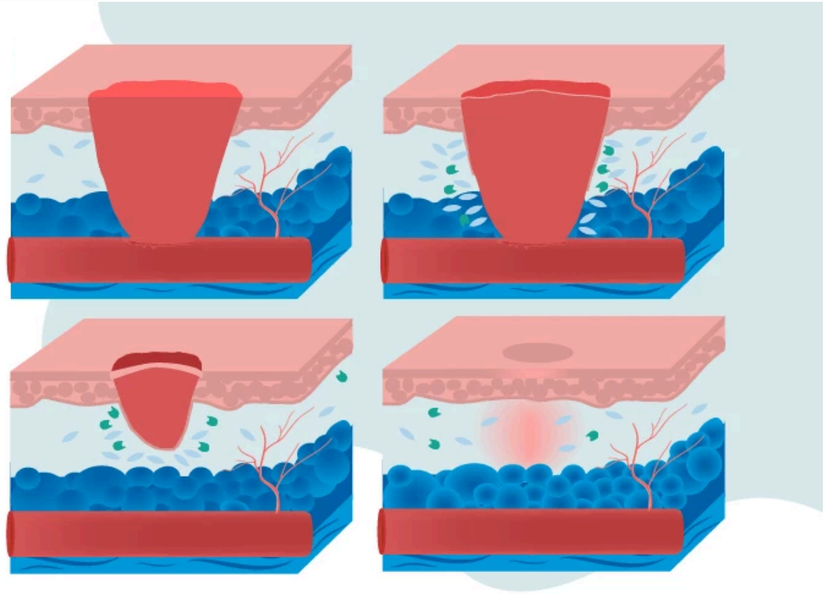


Fig: Wound healing over time

Model Equations

A reaction-diffusion model is used, where:

- **Cell movement** follows **Fickian diffusion**.
- **Cell mitosis** follows a **logistic growth model.**
- **EGF diffusion**, decay, and production are included.
- The system is modeled in one dimension, **simplifying a wound as a strip**.

Key Governing Equations:

- Change in cell density(n) = Migration + Mitosis - Natural loss.
- Change in EGF concentration(c) = Diffusion + Production - Decay.

$$\frac{\partial n}{\partial t} = \nabla\cdot\left(D_n(c)\nabla n\right) + s(c)n\left(\nu - \frac{n}{n_0}\right) - kn$$

$$\frac{\partial c}{\partial t} = D_c\nabla^2 c + f(n) - h(c)n - \delta c,$$

Where,

- **C(r,t)** is the EGF concentration at a position r at time t.
- **n(r,t)** is the cell density at a position r at time t.
- **f(n**) is the function representing the production of EGF by the cell.
- **s(c)** is an increasing function that represents the chemical control of mitosis.
- **h(c**) is a function that represents degradation of EGF due to decay of cell.

Linear Healing Rate ~ 60 μm/h (independent of wound size)

Models Used

1) Tear Film Model (Initial Model)

- Assumes **EGF is only supplied by the tear film**.
- Much slower healing rate.
- Conclusion: Tear film EGF alone is insufficient.
- Assumes f(n)= A, constant value of EGF conc.

2) Adding EGF externally (Final Model)

- **Introduces an additional EGF source.**
- The new source increases mitosis near the wound edge, leading to faster cell migration.
- This model is used for further simulations.

For our amended form of $f(n)$, we look for a function which is constant for low cell densities and decreases linearly to zero for larger cell densities, motivated by the above experimental results. We thus take $f(n) = A + B(n)$, where

$$B(n) = \begin{cases} \sigma & \text{if } n < 0.2 \\ \sigma(2-5n) & \text{if } 0.2 \le n \le 0.4 \\ 0 & \text{if } n > 0.4 \end{cases}$$

Where, sigma= 4000

Simulation Methods

Understanding Equations

1) Cell Density Equation

$$\frac{dn}{dt} = \nabla\left(D_n(c)\nabla n\right) + s(c)n\left(v - \frac{n}{n_0}\right) - kn$$

This equation accounts for:

- ·**Cell migration**:Modeled by a diffusion term where Dn(c)is the EGF-dependent cell diffusivity.
- ·**Mitosis:** Described by a logistic term s(c)n(ν−n/n0),
- **ν**: Maximum proliferation capacity,
- **n/n**0: Reference cell density.
- **Natural cell loss**: Represented by the decay term −kn, where k is the cell loss rate

2) EGF Concentration Equation

$$\frac{dc}{dt} = D_c\nabla^2 c + f(n) - h(c)n - \delta c$$

This equation represents:

- **EGF diffusion**: Modeled by the constant term.
- **Production of EGF**:Through a source term f(n).
- **EGF consumption**: By epithelial cells, modeled as h(c),where h(c) represents how EGF uptake depends on its local concentration.
- **Degradation:** Modeled by the first-order decay term −δc.

Parameter Estimation

To simplify numerical solutions, the model is non-dimensionalised using

$$n^* = n/n_0, \quad c^* = c/c_0, \quad x^* = x/L$$
$$t^* = kt, \quad \hat{c}^* = \hat{c}/c_0, \quad s^*(c_0c^*) = s(c)/k$$
$$D_c^* = D_c/kL^2, \quad f^*(n_0n^*) = f(n)/kc_0, \quad \mu^* = \mu n_0/kc_0$$
$$\delta^* = \delta/k, \quad D_n^*(c_0c^*) = D_n(c)/kL^2.$$

Asterisks were dropped for algebraic convenience

This results in the dimensionless PDEs

$$\frac{\partial n}{\partial t} = \frac{\partial}{\partial x}\left((\alpha c + \beta)\frac{\partial n}{\partial x}\right) + (\alpha_1 c + \beta_1)n(2-n) - n$$

$$\frac{\partial c}{\partial t} = D_c\frac{\partial^2 c}{\partial x^2} + f(n) - \frac{\mu nc}{(\hat{c}+c)} - \delta c.$$

Assumptions and Simplifications

- 1D spatial simplification (**linear wound**).
- Constant or linearly dependent diffusion coefficients.
- **EGF** and **mitosis** exhibit **saturation behavior** at high concentrations.
- The **cell cycle time** is approx **6.6 days** and its degradation follows first order kinetics.
- The wound length is assumed to be 4mm and it spans from x=2 mm to x=6 mm.
- The **wound healing is symmetric about the wound center**, so we solve only for the left half plane i.e. **for x= 2 mm(left wound edge) to 4 mm(wound center).**

Understanding Cell density Equation:

1. **Cell Migration :**

- Driving force : cell number density gradient
- Represented by non-classical Fick's 2nd Law (reason : diffusion coefficient is not constant)
- $D_n(c)$: Cell diffusion coefficient

↳ $D_n(c)$

- Order of magnitude ~ 10-9 $cm^2 s^{-1}$ (from previous modelling experience)
- Assume, Cellular diffusion coefficient increases linearly with EGF concentration (first approximation)

$$D_n(c) = \alpha c + \beta$$

- Also, $\alpha c_0 + \beta \approx 10^{-9}\, cm^2\, s^{-1}$
- α = 0.01 and β= 0.1 (by matching model solutions with experimental data) (*these value are of non-dimensional form*)

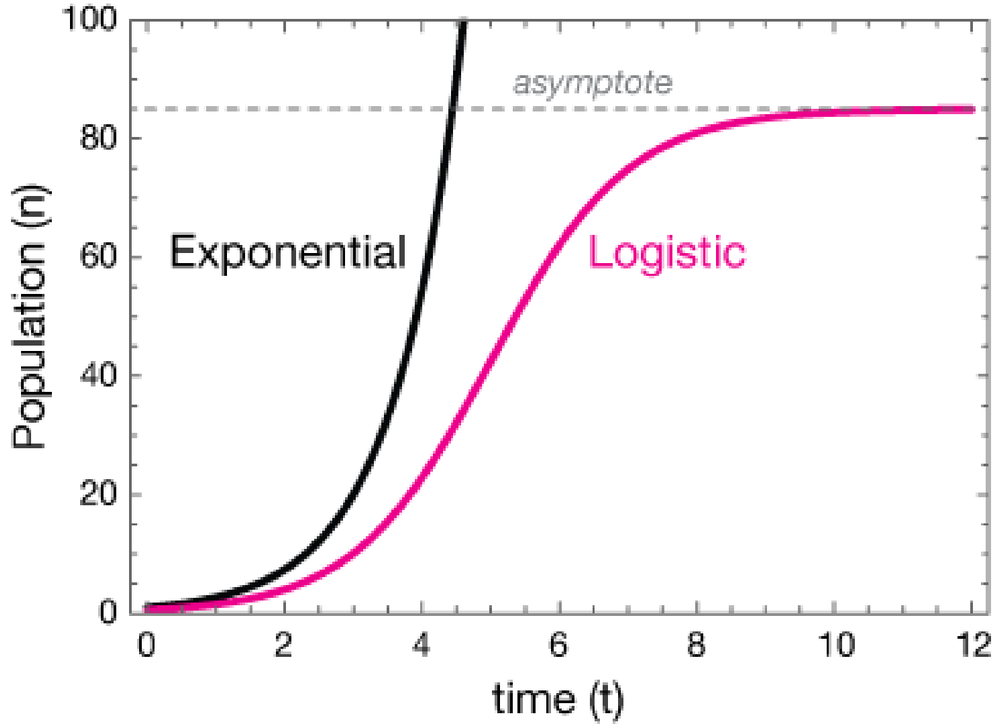
2. **Cell Mitosis** : $s(c)n\left(v - \frac{n}{n_0}\right)$

- Logistic Growth :(*density dependent mitosis*) ensures that mitosis decreases when the cell density (n) approaches n_0 preventing overproliferation (*Proliferation refers to the regulated process of cell division that increases cell numbers through controlled growth and replication.*)
- Logistic Growth avoids unphysical predictions of infinite cell density.
- Resources (or space) become limited and slow growth as the population nears a maximum sustainable value.

Understanding Cell density Equation:

↳ **General model of LOGISTIC GROWTH :** $\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right)$

- In the classical form, the growth factor is *r* ; here, however, it is replaced by s(c) so that growth is dependent on the chemical environment.
- *Why do we need a function like s(c) instead of a fixed growth rate?* Because experiments show that EGF dynamically enhances mitosis; its effect is dose dependent rather than constant.



**The above plot illustrates the general shape of logistic growth and is not an exact solution of the model equations used in this study.*

Understanding Cell density Equation:

- Estimation of v (assuming ideal condition i.e. $c=c_0$)
- At the unwounded steady state, we expect the net growth (mitosis minus loss) to match a standard logistic growth

$$s\left(c_0\right)n\left(v-\frac{n}{n_0}\right)-kn=kn\left(1-\frac{n}{n_0}\right)$$

  - *v = 2*
  - *By comparison : $s(c_0)=k$*
  - *s(c) is a linear function*

2. **Natural Loss** : kn

- Natural loss represents the constant shedding of outermost epithelial cells (sloughing) under normal conditions.
- *Assumption : first order process*
- Cell cycle time ~ 6.6 days

$$k=\left(\frac{\log_e 2}{6.6\times 24}\right)hr^{-1}=6.31\times 10^{-3}\,hr^{-1}$$

Understanding EGF concentration Equation:

1. **EGF Diffusion** :
- Represented by *Fick's 2nd Law* (driving force : EGF concentration gradient)
- $D_n(c)$: Cell diffusion coefficient
- c : EGF concentration

2. **EGF production** :
  - Tear film supplies a constant source of EGF independent of cell number.
  - Simplest model : $f(n) = A$, where A is a constant
  - more complex form of *f(n)* will be considered later

3. **Natural Decay**:
  - EGF naturally breaks down over time due to enzymatic activity or environmental instability.
  - Assumed to be first order process
  - EGF has a half life of ~ 1hr
  - δ = log 2 hr^{-1}

4. **EGF degradation by cells**:
  - h(c) = μĉ /(ĉ + c), where μ and ĉ are positive constants
  - ĉ ≈ 2 x 10^{-9} M
  - μ ≈ 5.75 x 10-20 mol $cell^{-1}$ h^{-1}

Key Model Parameters & Their Roles

Symbol	Meaning	Value Used	Role in Model
$D_n(c)$	**Cell diffusion coefficient**	$D_n(c) = \alpha c + \beta$	Controls **cell migration rate**, increasing with EGF.
D_c	**EGF diffusion coefficient**	25	Governs **EGF spread** in tissue.
$s(c)$	**Mitosis stimulation function**	$s(c) = \frac{135c}{134+c}$	Models **EGF-stimulated mitosis**, saturates at high EGF.
$f(n)$	**EGF production by cells**	$f(n) = A + B(n)$	Captures **EGF release** by epithelial cells.
$h(c)$	**EGF degradation function**	$h(c) = \frac{pc}{\hat{c}+c}$	Models **cellular uptake** of EGF.
δ	**Natural EGF decay rate**	$\log 2$ (half-life = 1 hour)	Governs **EGF breakdown over time**.
k	**Mitotic rate constant**	$\frac{\log 2}{6.6\times 24} \approx 6.31 \times 10^{-3}$ h^{-1}	Sets **baseline cell division rate**.
n_0	**Unwounded cell density**	10^9 cells/L	Reference for **normal epithelial density**.
c_0	**Baseline EGF concentration**	6.6×10^{-10} M	Normal **tear film EGF level**.

Reference

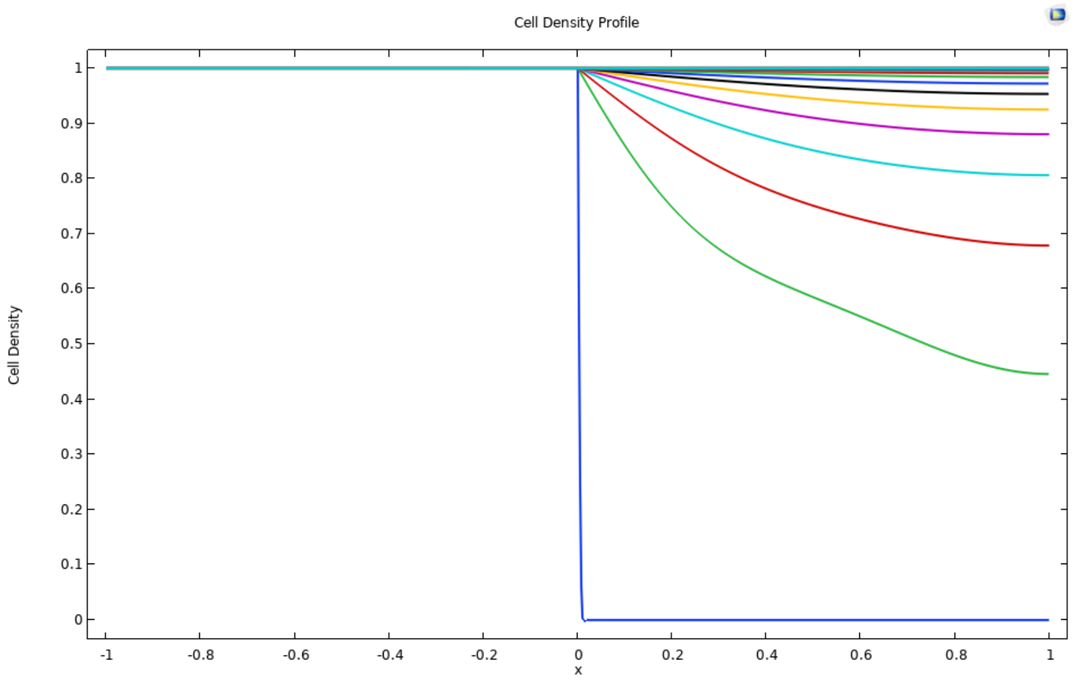
Parameters

S.No	Parameter	Value (Dimensional)	Value(Dimensionless)
1.	α	0.38242	0.01
2.	β	2.524×10^{-9}	0.1
3.	α_1	8.6045×10^{6}	0.9
4.	β_1	6.31×10^{-4}	0.1
5.	δ	0.693	110
6.	μ	5.75×10^{-20}	1.37×10^{4}
7.	D_c	6.31×10^{-7}	25
8.	$\hat{c}$	2×10^{-9}	3.02

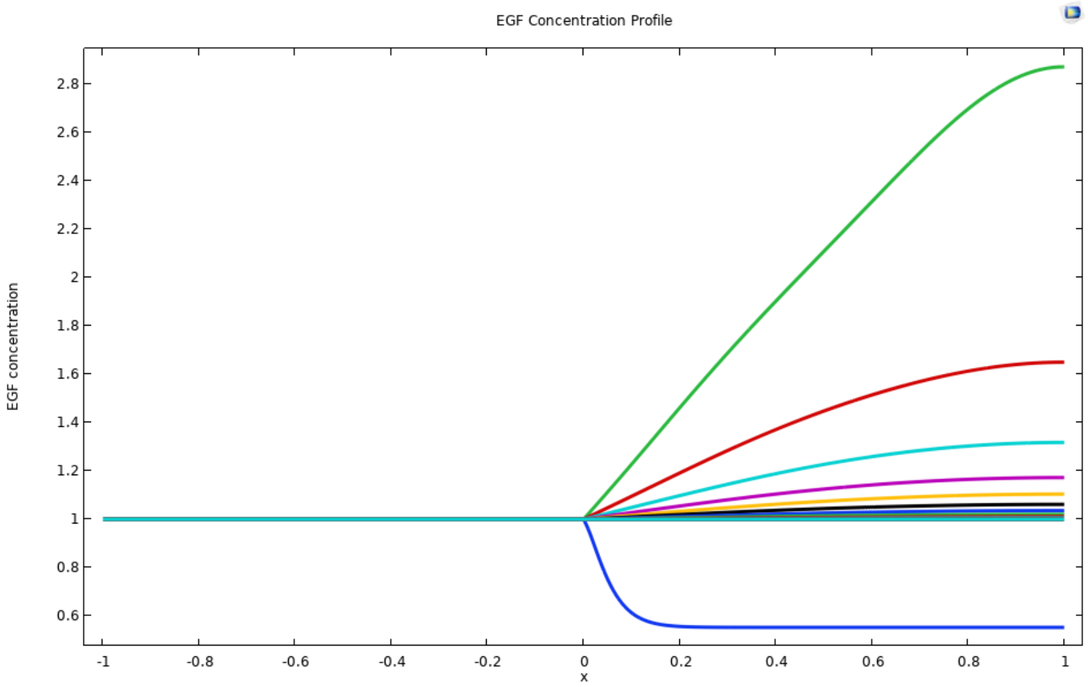
Definition of *f(n)*

Dimensional	Dimensionless
• $n < 0.2n_0$: $f(n) = A + B$	• $n^* < 0.2$: $f(n^*) = A^* + 4000$
• $0.2n_0 \leq n < 0.4n_0$: $f(n) = A + B(2 - 5n/n_0)$	• $0.2 \leq n^* < 0.4$: $f(n^*) = A^* + 4000(2 - 5n^*)$
• $0.4n_0 < n$: $f(n) = A$ $A = 1.47 \times 10^{-8}$ $B = 1.666 \times 10^{-8}$	• $0.4 < n^*$: $f(n^*) = A^*$ $A^* = 3518$

Results



Profile for cell density



Profile for EGF concentration

Conclusion & Future Work

While this study has focused on modeling corneal epithelial wound healing, the underlying reaction- diffusion approach provides a generalizable framework that can be extended to study regeneration in other tissues.

Next Focus: Liver Regeneration

- Explore liver regeneration, especially **under fatty liver disease** (steatosis).
- Unlike the cornea, liver regeneration is driven by **Hepatocyte Growth Factor** (HGF).

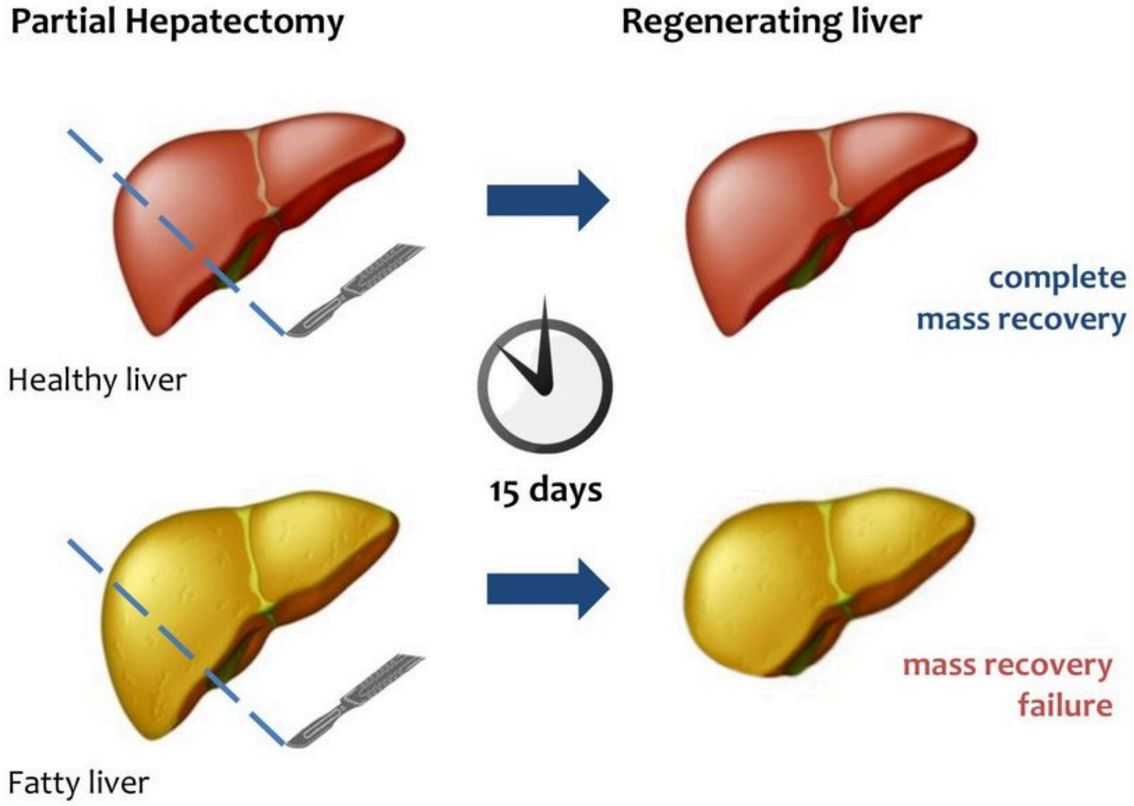
Model Adaptation

- Replace EGF with HGF in the model.
- Use liver-specific data for reparameterization.
- HGF production/degradation rates
- Hepatocyte proliferation and migration responses

Potential Insights

- Quantify how fatty liver disease impairs regeneration.
- Identify **fat accumulation** thresholds **affecting liver healing**.
- Find potential treatment to restore regenration ability.

Hepatectomy or liver resection is a surgical operation to remove part or all of your liver. If you have part of your liver removed, it can grow back to its former size.



Liver Regeneration affected due to fat accumulation (fatty liver disease).

References

Key references from the study include:

1. Dale, Paul D., Philip K. Maini, and Jonathan A. Sherratt. "Mathematical modeling of corneal epithelial wound healing." Mathematical biosciences 124.2 (1994): 127-147.
2. Periwal, V., et al. "Mathematical model of liver regeneration in human live donors." Journal of cellular physiology 229.5 (2014): 599-606.
3. Furchtgott, Leon A., Carson C. Chow, and Vipul Periwal. "A model of liver regeneration." Biophysical journal 96.10 (2009): 3926-3935.

Thank You