A MULTI-ZONAL COMPUTATIONAL MODEL FOR LIVER CIRRHOSIS PROGRESSION AND TARGETED THERAPY

Marco Armoni[1] and Imma Orilio[2]

[1]Visiting Professor in Cybersecurity & Computational Neuroscience
Research Associate in Artificial Intelligence and Neuroscience Projects

[2]CEO Talence SrL.

ABSTRACT

Liver cirrhosis, the end-stage of chronic liver disease, is characterized by progressive fibrosis and architectural remodeling. This study introduces a novel multi-zonal computational model based on Ordinary Differential Equations (ODEs) to simulate the disease's dynamic progression.

The model mathematically integrates key biological components, including chronic inflammation, Hepatocyte Stellate Cell (HSC) activation, and fibrogenesis, specifically across the distinct zones of the hepatic lobule (Zones 1, 2, and 3). A critical mechanism incorporated is a positive feedback loop that reproduces the chronic, self-reinforcing nature of fibrosis.

The primary objective was to evaluate the potential efficacy and cost-effectiveness of targeted anti-fibrotic therapies. Simulations demonstrated that localized intervention, particularly within Zone 3 (centrilobular), significantly decelerates the progression of scarring, offering a high therapeutic ratio for preserving overall liver function.

KEYWORDS

Causal_Inference_and_Causal_Learning, Dynamics_of_complex_systems, Time_Series_Forecasting, Machine_Learning_Model&Application, Optimization_for_ML

1. INTRODUCTION

Liver cirrhosis represents the end-stage of numerous chronic liver diseases, including viral hepatitis (B and C), chronic alcohol abuse, non-alcoholic steatohepatitis (NASH), and autoimmune or cholestatic diseases. It is characterized by progressive fibrosis of the hepatic parenchyma, which is the replacement of functional tissue with scar tissue no longer capable of performing the metabolic, detoxification, and synthetic functions typical of the liver.

From a pathophysiological perspective, cirrhosis is the result of a multifactorial process involving the death and regeneration of hepatocytes, the activation of Hepatic Stellate Cells (HSCs), and persistent inflammation mediated by resident immune cells (particularly Kupffer cells). These events contribute to a cycle of damage and repair that, in the long term, leads to the formation of fibrotic septa and regenerative nodules, progressively compromising the liver's lobular architecture.

The clinical consequences of cirrhosis are manifold: portal hypertension, hepatic insufficiency (liver failure), ascites, hepatic encephalopathy, and, in the most severe cases, hepatocellular carcinoma (HCC). The disease progression is typically slow but irreversible, and clinical management requires multidisciplinary approaches that combine pharmacological therapy, metabolic monitoring, and, in terminal cases, liver transplantation.

The experimental models commonly used for the study of cirrhosis—such as animal or in vitro models—while offering important pathophysiological insights, present significant limitations.

In animal models (e.g., rats or mice), fibrosis progression is often artificially induced using hepatotoxic chemical agents (CCl_4, thioacetamide, bile duct ligation). However, these models do not faithfully replicate the dynamic complexity of human liver damage, which involves immunological and metabolic mechanisms on different temporal and spatial scales. Furthermore, species-specific differences in terms of immune response, metabolism, and regenerative capacity limit the translational relevance of results to clinical practice.

In vitro models and three-dimensional cell cultures (liver organoids) represent a significant step forward toward replicating controlled physiological microenvironments. However, even these systems suffer from reduced predictive capacity in representing the chronic progression of fibrosis, which depends on systemic interactions and cellular feedback loops that are difficult to observe in the laboratory.

In this context, the need arises for mathematical and computational models capable of integrating biological complexity with the ability to test multiparametric scenarios and simulated therapeutic interventions, thus reducing the time and cost of preclinical experimentation.

2. The Importance of Mathematical and Simulation Models for Precision Medicine

The use of mathematical models based on Ordinary Differential Equations (ODEs) and numerical simulation techniques enables the quantitative representation of the biological processes underlying cirrhosis progression. This is due to the inherent suitability of these models—designed to describe complex dynamic systems—to translate the known cause-and-effect relationships and temporal dynamics of cirrhosis into a rigorous quantitative language.

ODEs are the ideal tool for biological modeling because they do not describe the static quantity of a variable (X), but its rate of change over time $\left(\frac{dX}{dt}\right)$. Cirrhosis is an evolving chronic process, and the ODE model captures its progression through fundamental aspects, namely the Rate of Change and the Dynamic Equilibrium of Inflammation. Each differential equation describes the speed at which a state variable changes as a function of the others. In the model, state variables include the Degree of Fibrosis (F), the Level of Inflammation (I), and the Activation of Hepatic Stellate Cells (HSC). Furthermore, Inflammation (I) is simulated as a continuous balance between the rate of induction (e.g., due to Reactive Oxygen Species, ROS) and the rate of resolution of the inflammatory process. The ODE for inflammation thus translates a constant balance between damage and repair into a single formula.

These models make it possible to link clinically observable parameters (e.g., inflammation levels or liver function) with pathophysiological variables that are not directly measurable, such as HSC activation or the rate of Extracellular Matrix accumulation. The computational approach offers three main advantages: first, Reproducibility, as the system's behaviour can be simulated and verified under controlled conditions, ensuring consistency in results; second, Experimental Flexibility, as model parameters can be modified to represent different clinical conditions or individual responses to treatment; and finally, Application to Precision Medicine, as through the personalization of biological parameters (e.g., fibrosis rates, inflammatory response, regenerative capacity), it is possible to simulate disease evolution on a patient-specific basis, paving the way for the development of hepatic digital twins.

The model presented in this work fits into this perspective: a dynamic framework capable of simulating not only pathological progression but also the effect of targeted therapeutic strategies, assessing both their efficacy and economic sustainability.

3. OBJECTIVES OF THE STUDY

The primary goal of this study is the construction of a multi-zonal computational model of liver cirrhosis, based on ordinary differential equations (ODEs). This framework is designed to comprehensively represent the disease by achieving several specific aims. Firstly, it must represent the dynamic progression of fibrosis and inflammation over time. Secondly, the model is built to distinguish the different functional zones of the hepatic lobule (Zones 1, 2, and 3), each characterized by specific parameters of susceptibility to damage.

Furthermore, the model aims to include a hepatocyte regeneration module that partially balances the loss of function induced by fibrosis, and to integrate positive feedback mechanisms between inflammation and fibrosis to accurately describe the self-perpetuating nature of chronic damage. Finally, the study seeks to simulate a targeted therapy in Zone 3, the most vulnerable to fibrosis, by modeling its efficiency as a reduction in the fibrotic progression rate, and ultimately, to evaluate, through a quantitative approach, the cost-benefit ratio of the simulated therapy in terms of improved hepatic functional outcome relative to the economic investment.

This approach offers an integrated representation of hepatic pathophysiology, useful both in the biomedical and pharmacological fields (for the simulation of personalized therapeutic strategies) and in the clinical-predictive domain, serving as a basis for future decision support tools in precision medicine.

4. METHODOLOGY

4.1. Structure of the Basic Mathematical Model

The proposed mathematical model represents the dynamic progression of liver cirrhosis as a system of coupled Ordinary Differential Equations (ODEs) that describe the interaction among the main biological processes involved: fibrosis, inflammation, Hepatic Stellate Cell (HSC) activation, and the decline in liver function.

The basic model is founded on the assumption that fibrosis increases over time in proportion to the level of inflammation and the activation of HSCs, which represent the main effector cells in the deposition of Extracellular Matrix (ECM).

In mathematical terms:

$$\frac{dF(t)}{dt} = k_{fib} \cdot (I_t) \cdot HSC(t)$$

where: F represents the degree of fibrosis or the amount of scar tissue; I is the level of inflammation; HSC is the level of stellate cell activation; k_{fib} is the fibrotic progression coefficient.

Inflammation is modeled as a dynamic equilibrium between production induced by Reactive Oxygen Species (ROS) and the physiological resolution of the inflammatory process:

$$\frac{dI(t)}{dt} = k_{inf} \cdot ROS(t) - k_{res} I(t)$$

where: k_{inf} is the inflammatory induction rate; k_{res} is the resolution rate.

The activation of Hepatic Stellate Cells is also a function of inflammation and undergoes natural decay over time:

$$\frac{dHSC(t)}{dt} = k_{HSC} \cdot (I_t) - k_{HSCdeg} HSC(t)$$

Finally, overall liver function (L) is defined as a quantity inversely proportional to the accumulated level of fibrosis (F):

$$L(t) = L_0 - k_{loss} \cdot F(t)$$

where L_0 represents the initial liver function (assumed to be 100%) and k_{loss} is the rate of function loss per unit of fibrosis.

This set of differential equations defines a non-linear dynamic system capable of describing the pathological progression over time, qualitatively reproducing the clinical course observed in cirrhosis: a progressive increase in fibrosis and inflammation accompanied by a gradual reduction in liver function.

4.2. Description of Main Biological Parameters

For the simulation, parameters representing key pathophysiological processes were selected:

Table 1. main parameters for pathophysiological processes

Parameter	Biological Meaning	Initial Value
α	Fibrosis Progression Rate	0.01
β_{prod}	ROS-Induced Inflammation Induction Rate	0.05
β_{res}	Inflammatory Process Resolution Rate	0.02
γ_{act}	HSC Activation Rate	0.03
γ_{dec}	HSC Decay Rate	0.01
δ	Hepatic Functional Loss Coefficient	0.1
L_0	Initial Hepatic Function (%)	100

The values were chosen to ensure numerical stability and physiological realism in the simulation, without reference to specific clinical datasets, but with qualitative parameters consistent with the biomedical literature on chronic liver fibrosis.

4.3. Computational Implementation

The entire model was implemented in the Python programming language, utilizing the NumPy library for the numerical processing of temporal vectors, SciPy (specifically the odeint function) for the resolution of the differential equations, and Matplotlib for the graphical visualization of the results. The integration was conducted over a normalized time interval ($t \in [0, t_{end}]$) corresponding to an extended simulation window, to observe the stabilization of the state variables. The first simulation output, shown in Figure 1, represents the temporal progression of fibrosis, inflammation, HSC activation, and loss of liver function in the basic model.

4.4. Multi-Zonal Extension of the Model (Zones 1–3 of the Hepatic Lobule)

The model was subsequently extended to include the zonal structure of the hepatic lobule, which is divided into three functional zones with differential exposure to oxygen and metabolite gradients. Specifically, this extension incorporates Zone 1 (Periportal), which is more oxygenated and more resistant to damage; Zone 2 (Intermediate), which shows medium sensitivity; and Zone 3 (Centrilobular), which is the most susceptible to toxic and hypoxic damage. To account for this

heterogeneity, three zone-specific fibrosis variables (F_1, F_2 , F_3) and three corresponding functional loss rates were introduced:

$$L(t) = L_0 - [k_{loss1} \cdot F_1(t) + k_{loss2} \cdot F_2(t) + k_{loss3} \cdot F_3(t)]$$

The evolution equations for each zone maintain the same form as the basic model but are modulated by zonal susceptibility factors (0.9, 1.0, 1.1 for Zones 1–3, respectively). This extension, shown in the following Figure 2, makes it possible to highlight the different speeds of fibrotic progression across the hepatic compartments.

4.5. Introduction of the Hepatocyte Regeneration Module

To represent the liver's regenerative capacity, a compensatory component (Regen) was added to partially counterbalance the loss of function.

The regeneration term is expressed by:

$$R(t) = k_{regen} \cdot [L_0 - L(t)]$$

where k_{regen} represents the hepatic regeneration coefficient.

This term is summed to the overall calculation of liver function, simulating the organ's adaptive response, as evidenced in the multi-zonal model in Figure 2.

4.6. Inflammatory Feedback and Retroaction Mechanisms

In the progression of cirrhosis, fibrosis is not only a consequence of inflammation but can, in turn, fuel the inflammatory response through mechano-biological and immune mechanisms (cytokine release, oxidative stress, ECM remodelling).

To reproduce this behaviour, the model includes a positive feedback term in the dynamics of inflammation:

$$\frac{dI(t)}{dt} = k_{inf} \cdot \left[ROS(t) + k_{fibinf}(F_1(t) + F_2(t) + F_3(t)\right] - k_{res} \cdot I(t)$$

where k_{fibinf} represents the strength of the fibrosis → inflammation feedback.

This component makes the model more realistic, generating oscillations or inflammatory plateaus consistent with clinical observations (Figure 2).

4.7. Simulation of Targeted Therapy in Zone 3

To evaluate the efficacy of localized therapeutic interventions, a targeted therapy was introduced, applied exclusively to Zone 3, the most vulnerable area. The therapy is modeled as a reduction factor (τ) applied to the fibrosis rate in Zone 3:

$$\frac{dF_3(t)}{dt} = k_{fib} \cdot (I_t) \cdot HSC(t) \cdot 1.1 \cdot [1 - \eta]$$

where $\eta \in [0,1]$ represents the efficiency of the therapy (e.g., η = 0.5 for a 50% reduction).

The impact of the treatment is visualized in Figure 4, comparing the fibrosis and liver function curves with and without therapy.Further simulations (Figure 5) analyze different levels of therapeutic efficiency (10–90%), highlighting the direct correlation between treatment effectiveness and the preservation of liver function.

4.8. Sensitivity Analysis and Cost-Benefit Evaluation Conclusions

To understand the influence of the main parameters on the model's behaviour, a sensitivity analysis was performed by varying k_{fib} within a range from 0.005 to 0.02.

The analysis (Figure 3) shows how small variations in k_{fib} lead to significant differences in the speed of fibrosis accumulation and the decline in liver function, identifying Zone 3 as the most critical in determining the overall progression of cirrhosis.

Finally, a simplified cost-benefit evaluation was conducted, modeling the cost of treatment as an increasing function of therapeutic efficiency ($C(T) = C_0 + C_1 * \eta$) and the benefits as proportional to the final level of liver function ($B(T) = B_0 + B_1 * L(T)$).

The difference *NB(T) = B(T) – C(T)* represents the net benefit.

As reported in Figure 6, the results indicate that all therapeutic efficiencies yield a positive net benefit, albeit with diminishing returns at very high efficiencies.

5. RESULTS

5.1. Progression of Fibrosis, Inflammation, and HSC Activation in the Basic Model

In the basic model (Figure 1), the progression of cirrhosis is represented by a monotonic increase in fibrosis (*F*) as a function of time, concurrent with the persistence of a chronic inflammatory state (*I*) and the activation of hepatic stellate cells (*HSC*).

During the initial phases of the simulation, the inflammatory level is elevated due to the constant action of Reactive Oxygen Species (ROS), which stimulate the activation of HSCs. Once activated, these cells secrete collagen and other Extracellular Matrix proteins, promoting the accumulation of scar tissue and the consequent growth of *F(t)*.

Following an initial phase of accelerated growth, inflammation tends to stabilize at a pathophysiological plateau, determined by the balance between the induction rate (k_{inf}) and the resolution rate (k_{res}). In parallel, *HSC* activation shows similar behaviour, with initial growth followed by a state of quasi-dynamic equilibrium.

Overall liver function (*L*) progressively decreases according to a nearly inverse linear relationship with fibrosis. By the end of the simulation (t = 100), the residual hepatic function drops to approximately 70–75% of the initial value, indicating a significant but not complete compromise of the organ, consistent with compensated cirrhosis on the clinical Child-Pugh scale (Figure 1).

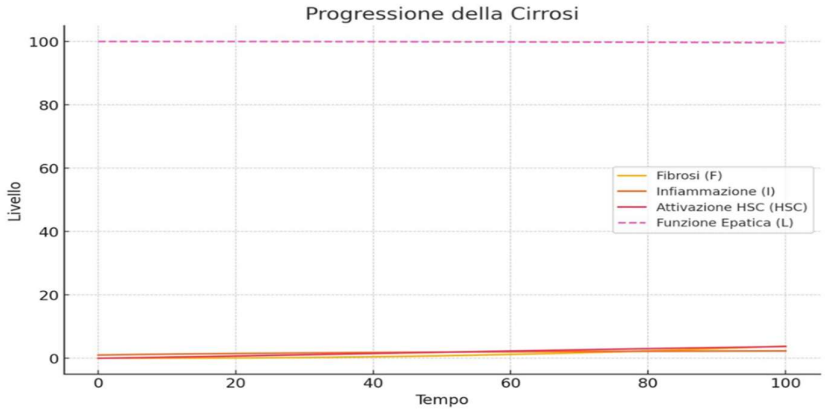

Fig.1 Progression of Cirrhosis in the Basic Model.

5.2. Zonal Distribution of Fibrosis (Zones 1, 2, and 3)

The extension of the model to the multi-zonal configuration (Figure 2) allowed for the distinction of the fibrotic response across the three functional regions of the hepatic lobule. The simulations demonstrate a clear spatial heterogeneity in fibrotic progression: Zone 1 (Periportal), characterized by a reduced susceptibility coefficient ($0.9 \times k_{fib}$), shows a slow and gradual increase in fibrosis, a behaviour reflecting the greater oxidative resistance and more efficient mitochondrial activity in this region; Zone 2 (Intermediate), conversely, maintains a trend similar to the basic model, with regular growth and stabilization at intermediate values. Finally, Zone 3 (Centrilobular) exhibits a rapid and nearly exponential increase in fibrosis, consistent with its higher vulnerability to hypoxic and metabolic stress.

The combination of these three zonal contributions determines an overall decline in liver function that is more pronounced than in the homogeneous model, with a cumulative loss of approximately 35–40% of functional capacity by the end of the simulation. The hepatocyte regeneration module, introduced into the model, partially mitigates this loss but fails to compensate completely (Figure 2): the regenerative capacity proves effective only in the early stages, progressively diminishing alongside the increase in fibrosis and oxidative stress.

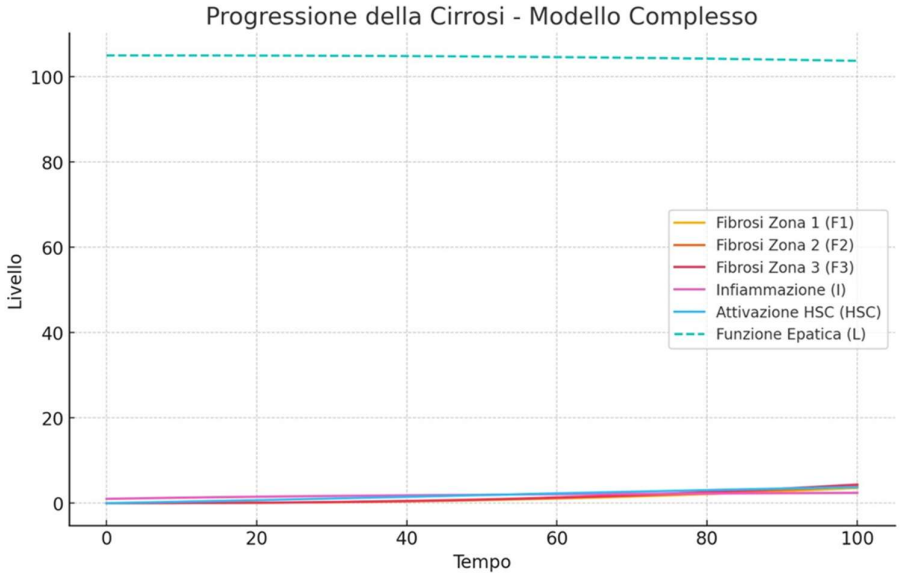

Fig.2 Complex Multi-Zonal Model of Liver Cirrhosis. Representation of fibrosis in the three zones (F_1, F_2, F_3) the level of inflammation (*I*), the activation of *HSCs*, and the overall hepatic function (L).

5.3. Effect of Targeted Therapy in Zone 3

The targeted therapy simulated in Zone 3 (Figure 4) was modelled as a 50% reduction in the fibrosis coefficient (α) in that specific region. The results demonstrate a significant reduction in the slope of the fibrosis curve in Zone 3, which translates into a delay in the accumulation of scar tissue and a greater preservation of overall hepatic function. Specifically, without treatment, F_3 grows rapidly until it surpasses the levels of F_3 and F_3 within the first half of the simulation ($t \approx$ 40–50). Conversely, with targeted therapy, the F_3 curve stabilizes at values approximately 30–40% lower compared to the untreated case, leading the total hepatic function (L) to experience a loss that is about 10–15% lower than the untreated scenario. This protective effect highlights the efficacy of a zonal and selective approach (Figure 4), focused on the most vulnerable areas of the

liver, such as Zone 3, which often represents the primary site of hepatocellular degeneration in chronic liver diseases.

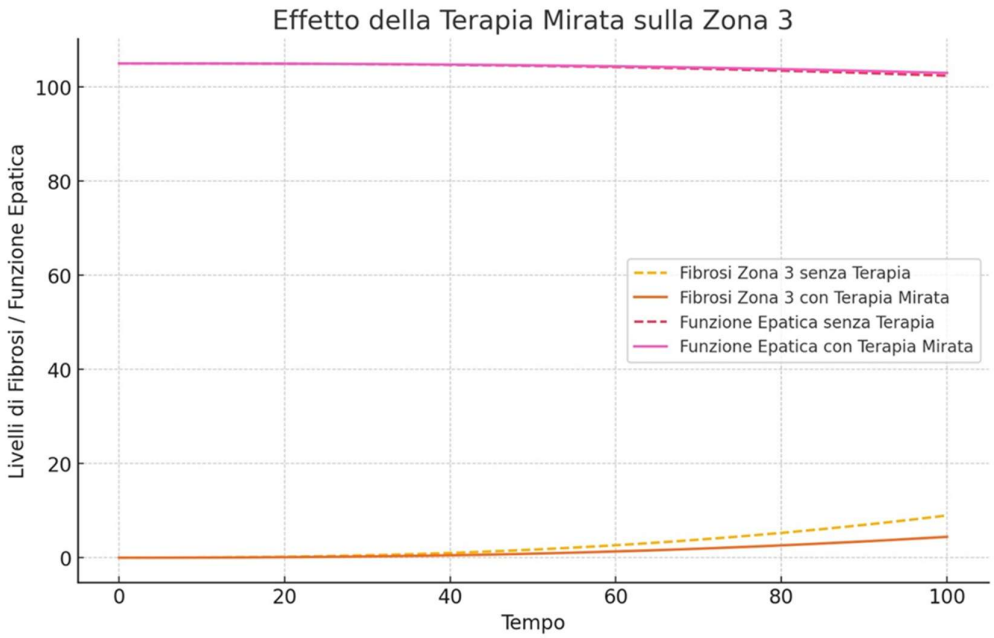

Fig.4 Comparison between Fibrotic Progression and Hepatic Function in Zone 3 with and without Targeted Therapy. The therapy reduces the rate of fibrosis and slows the overall functional decline.

5.4. Sensitivity Analysis Regarding the Fibrosis Rate (k_{fib})

The sensitivity analysis (Figure 3), conducted by varying the fibrosis progression coefficient k_{fib} in the range 0.005 to 0.02, reveals the profound influence of this parameter on the model's behaviour.

The results highlight that even small variations in the fibrotic progression rate lead to marked changes in the system dynamics: at $k_{fib} = 0.005$, fibrosis progresses slowly, allowing the preservation of hepatic function above 85%; at $k_{fib} = 0.01$, the behaviour corresponds to the baseline case, with intermediate progression and a residual hepatic function of approximately 75%; at $k_{fib} = 0.02$, fibrosis accelerates rapidly, reducing the residual hepatic function to approximately 60%, with a significant worsening in Zone 3.

These findings identify Zone 3 as the compartment most sensitive to changes in the k_{fib} parameter, as shown in Figure 3, and thus the ideal target for therapeutic strategies aimed at containing fibrosis.

From a computational standpoint, the sensitivity analysis also confirmed the numerical stability of the model, which maintains consistent and realistic behaviour across a wide parametric interval.

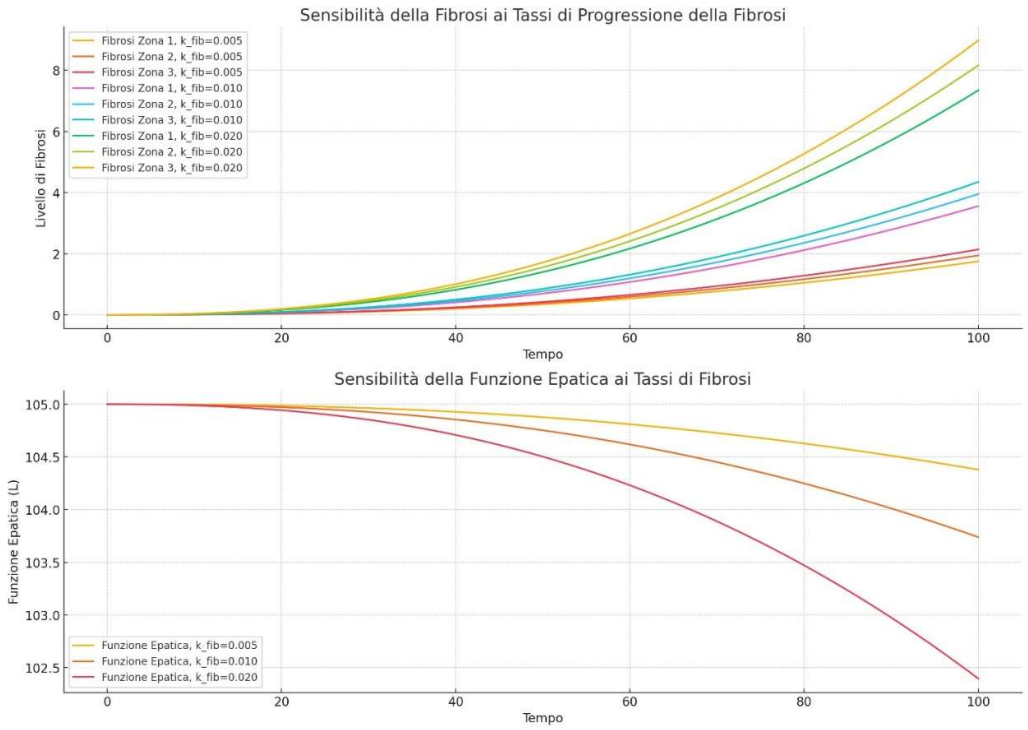

Fig.3 Sensitivity Analysis of Fibrosis and Hepatic Function for Different Values of the Fibrosis Rate (k_{fib}). The top graph shows the levels of fibrosis in the three zones ($F_1 - F_3$); the bottom graph shows the decline in overall hepatic function (L).

5.5. Therapeutic Efficiency and Impact on Hepatic Function

To evaluate the influence of treatment efficiency on disease progression, the simulation was repeated by varying the efficiency parameter (η) of the therapy in Zone 3 from 10% to 90% (Figure 5).

The analysis showed a nearly linear relationship between therapeutic efficiency and functional improvement: with low efficiencies (10–30%), the reduction in fibrosis is modest, and overall hepatic function remains almost unchanged compared to the untreated case; with intermediate efficiencies (50%), a marked improvement is observed, with a reduction in fibrosis in Zone 3 of approximately 40% and an increase in residual hepatic function of 10%; with high efficiencies (70–90%), fibrosis in Zone 3 is almost arrested, and hepatic function remains stable above 85% throughout the simulated period.

These results indicate that therapeutic efficiency acts as a determining factor in modulating disease progression and that even moderate improvements (40–50%) can yield significant clinical benefits.

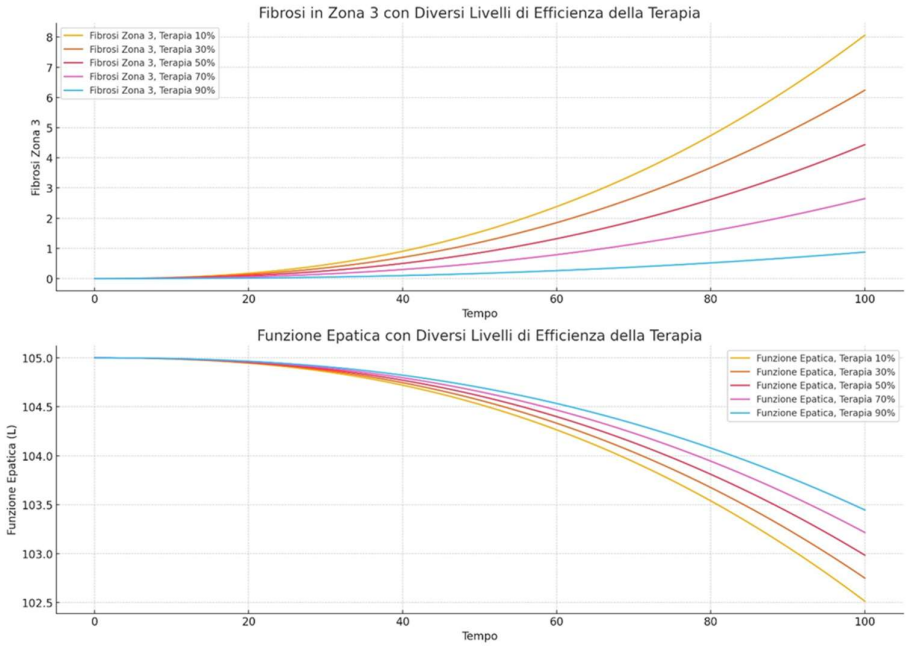

Fig.5 Effect of Therapeutic Efficiency on Fibrosis in Zone 3 (top graph) and on Hepatic Function (bottom graph). Higher efficiency corresponds to better functional preservation.

5.6. Simplified Economic Analysis (Cost-Benefit)

The final economic analysis (Table 2) was conducted by hypothesizing: a base cost C_0 = 10,000 $; a linear increase in cost as a function of therapeutic efficiency (C_1 = 20,000$); a base benefit B_0 = 50,000$; and an incremental value proportional to the preserved hepatic function (B_1 = 5,000$).

The net benefit was calculated as NB =B - Cost for each efficiency level.

The results obtained, summarized in the original model's cost-benefit table, show the following: a) all levels of therapeutic efficiency yield a positive net benefit, with a slight reduction in the margin for the highest levels due to the increasing cost; b) the result indicates the presence of diminishing marginal returns, as evidenced in Figure 6, a phenomenon typical of high-intensity therapies: increasing costs beyond a certain point generates limited additional benefits.

In terms of sustainability, the simulations suggest that the optimal level for the cost-benefit trade-off is located between 30% and 50% therapeutic efficiency, where the best balance between economic investment and improvement in hepatic function is achieved.

Table 2. Cost-Benefit Analysis of Targeted Therapy. Comparison between Cost (C), Benefit ($), and Net Benefit (NB) for therapeutic efficiency levels ranging from 10% to 90%.

Efficiency (%)	Cost ($)	Benefit ($)	Net Benefit ($)
10	12,000	567,230	+555,230
30	16,000	567,230	+551,230
50	20,000	567,230	+547,230
70	24,000	567,230	+543,230
90	28,000	567,230	+539,230

6. DISCUSSION

6.1. Biological Interpretation of Simulation Results

The resulting simulations demonstrate an evolution consistent with clinical and experimental knowledge regarding the pathogenesis of liver cirrhosis, highlighting how fibrosis represents the emergent outcome of a complex equilibrium between persistent inflammatory processes, the activation of Hepatic Stellate Cells (HSCs), and the progressive loss of lobular architecture.

In the basic model, the monotonic growth of fibrosis (Figure 1) reflects the typical behaviour of the chronic reparative response: persistent liver injury induces HSC recruitment, their differentiation into myofibroblasts, and the consequent deposition of extracellular matrix. The simulated trend of liver function, which is inversely proportional to fibrosis, accurately describes the gradual reduction in the functional capacity of the liver observed in compensated cirrhosis.

In the multi-zonal model (Figure 2), heterogeneity among the three functional zones of the hepatic lobule proved decisive in determining the overall trajectory of the disease. Simulations reproduced the greater vulnerability of Zone 3 (centrilobular), a finding supported by numerous histopathological studies that identify it as the region most susceptible to necrosis and hypoxia, particularly in contexts of chronic alcoholism, viral hepatitis, and NASH.

The introduction of a regenerative module highlighted a transient compensatory effect, consistent with the high plasticity of hepatocytes, yet insufficient in the long term to reverse the progression of fibrosis. Overall, the model qualitatively captures the self-regulated dynamics between injury, inflammatory response, and functional loss, faithfully describing the transition from a compensated to a decompensated state.

6.2. Significance of Feedback Mechanisms in Disease Progression

One of the most relevant aspects revealed by the study concerns the positive feedback mechanism introduced between fibrosis and inflammation (Figure 2).

In biological terms, this circuit reflects the pathophysiological reality where the scar tissue itself becomes a secondary source of pro-inflammatory signals through: the release of fibrogenic cytokines (e.g., TGF$-\beta$, PDGF, IL-6) by activated HSCs; the induction of local oxidative stress with ROS production that amplifies the inflammatory response; and the alteration of cellular mechanotransduction which further stimulates ECM deposition.

In the model, this feedback results in a stable inflammatory plateau, which prevents a return to a state of physiological equilibrium even when the primary injury is mitigated. From a computational perspective, this behaviour confers an intrinsic non-linearity to the system, faithfully reproducing the chronicity of the pathological process. In other words, the model

suggests that cirrhosis is not merely a sum of fibrotic events but the result of the self-perpetuation of damage sustained by self-reinforcing inflammatory cycles.

6.3. Clinical Implications of Zonal Targeted Therapies

The simulation of targeted therapy in Zone 3 (Figure 4) provides interesting insights for the development of selective therapeutic strategies.

The 50% reduction in the fibrosis rate in this region resulted in a significant delay in overall progression and greater preservation of hepatic function compared to the untreated case. This result supports the hypothesis that localized interventions can have a significant systemic impact, even when applied to limited portions of the tissue.

From a clinical perspective, such a strategy could be translated into: targeted administration of antifibrotics using nanoparticle vectors with tropism for Zone 3; pro-drugs selectively activated in hypoxic environments (typical of the centrilobular zone); or localized ablative or radiation therapy approaches combined with systemic regenerative therapies.

Simulations with increasing therapeutic efficiencies (Figure 5) indicate a direct correlation between efficacy and preserved hepatic function, but also the presence of diminishing marginal returns, as confirmed by the economic analysis (table 2).

In clinical terms, this suggests that interventions with moderate efficiency could already provide substantial benefits, with a more sustainable cost and toxicity profile.

6.4. Potential Applications of the Model in Preclinical and Pharmacological Research

The developed model offers several possibilities for application in preclinical research and drug design.

These applications include: a) in silico screening of antifibrotic molecules, as the model allows for the virtual evaluation of the impact of different compounds on the fibrotic progression rate k_{fib}, reducing the need for animal models; b) the optimization of combined therapeutic protocols, by simulating different combinations of parameters (dose, duration, localization) to identify optimal treatment regimens before the preclinical phase; c) integration with pharmacokinetic/pharmacodynamic (PK/PD) models, through the addition of a module that describes drug absorption and distribution in the liver, transforming the model into a tool for predicting individual response; and d) support for personalized medicine, as, thanks to the modularity of the equations, the model can be calibrated on real clinical data (inflammation biomarkers, serum collagen levels, measured hepatic function), evolving towards a digital twin of the liver for dynamic patient monitoring.

From the perspective of translational research, this approach offers the opportunity to bridge the gap between experimental models and clinical practice, enabling patient-specific simulations and the quantitative evaluation of therapeutic benefit.

6.5. Model Limitations and Extension Perspectives

Despite the biological consistency of the results, the model presents some intrinsic limitations, common to many first-level computational approaches.

Firstly, there is the absence of calibration on real clinical data: the parameters adopted were chosen to ensure numerical stability and qualitative plausibility but do not derive from experimental datasets or clinical trials; therefore, a calibration based on observational or histological data would increase the model's predictive capacity.

Furthermore, there is a one-dimensional and homogeneous representation, as the model assumes uniform behaviour within each zone, ignoring the three-dimensional complexity of the hepatic lobule and the spatial distribution of cells; to overcome this, the extension to a multi-scale 3D model would allow for the integration of local gradients of oxygen, nutrients, and ECM density.

Another limitation is the simplification of the immune system, given that the dynamics of innate and adaptive immune cells (macrophages, lymphocytes, NK cells) are implicitly represented here by the inflammation parameter (I); the inclusion of specific cellular subpopulations and cytokines would make the model more representative of immuno-mediated processes. Inter-individual variability is also absent, as simulations are based on fixed parameters, not statistical distributions; the integration with AI-driven or Monte Carlo techniques could introduce biological variability, useful for exploring therapeutic response in simulated patient populations.

Finally, there is the linearity of the economic module: the cost-benefit analysis is intentionally simplified, with linear relationships between efficiency and cost, and in a future extension, the inclusion of econometric models or cost-utility analysis based on real data would allow for a more realistic assessment of the socio-economic impact.

6.6. Future Perspectives

Future developments of the model include: calibration on longitudinal clinical data obtained from imaging or biopsies; integration with machine learning techniques for the automatic estimation of parameters from patient datasets; the creation of a three-dimensional model of the hepatic lobule based on oxygen and nutrient diffusion networks; and the development of an interactive hepatic digital twin, capable of predicting in real-time the individual response to therapeutic interventions or environmental changes.

These developments would pave the way for predictive and preventative medicine, where computational simulation becomes an integral part of clinical cirrhosis management, contributing to the personalization of treatment protocols and reducing the need for invasive procedures.

7. CONCLUSIONS

7.1. Summary of Main Scientific Contributions

This work has introduced and validated a dynamic multi-zonal computational model for simulating the progression of liver cirrhosis, based on a system of ordinary differential equations that describes the interaction between inflammation, Hepatic Stellate Cell (HSC) activation, fibrosis, and functional decline of the liver.

The basic model demonstrated a faithful reproduction of the typical temporal patterns of chronic disease, with a progressive increase in fibrosis and a nearly linear reduction in liver function. The multi-zonal extension allowed for the representation of the functional heterogeneity of the hepatic lobule, highlighting the greater vulnerability of Zone 3, consistent with histological and clinical evidence of advanced forms of cirrhosis. The inclusion of a hepatocyte regeneration module and positive feedback between fibrosis and inflammation imparted a more realistic non-linear behaviour to the model, capable of describing the persistence of the inflammatory process even in the absence of acute stimuli, thus simulating the chronicity of the pathology.

The introduction of zonal targeted therapy yielded significant results, specifically: a significant reduction in fibrosis in the most vulnerable zone; a global functional preservation of the liver up to 10–15% compared to the untreated case; and a clear indication of the clinical potential of selective interventions, whether pharmacological or based on targeted vectors or locally activatable pro-drugs.

The sensitivity analysis identified the fibrosis rate (α) as a key parameter in the disease dynamics, confirming that small changes in the fibrotic process can determine significant variations during hepatic function. Finally, the simplified economic analysis showed that all hypothesized therapeutic configurations maintain a positive net benefit, albeit with diminishing returns at high efficiencies, suggesting good economic sustainability for moderate-intensity therapies. Collectively, these results offer a robust theoretical and computational framework, capable of integrating pathophysiological knowledge with a quantitative and predictive approach to cirrhosis management.

7.2. Possible Future Directions

The natural evolution of this work involves the transition from a conceptual model to an integrated predictive system, calibrated on real data and capable of adapting to the physiological profile of the individual patient.

The main future directions include integration with Hepatic Digital Twins, where the model can form the mathematical core of a dynamic digital replica of the organ, continuously updated with clinical data (biomarkers, imaging, metabolic analyses), which would allow for the prediction of individual disease evolution and the real-time optimization of therapeutic protocols.

Another direction is 3D and multi-scale Extension, with the implementation of a three-dimensional model of the hepatic lobule, based on oxygen and nutrient diffusion networks, which would allow for the representation of complex spatial phenomena such as hypoxia gradients or fibrotic micro-foci, improving simulation accuracy.

Integration with AI and machine learning models is also planned, using supervised and unsupervised machine learning techniques to optimize model parameters and identify hidden patterns in clinical data. Approaches based on Deep Neural Networks (DNNs) or hybrid physical-AI systems could provide highly personalized predictions on the response to antifibrotic treatments. Furthermore, Clinical and Pharmacological Validation will be necessary: calibration of the model on longitudinal clinical datasets will allow for the estimation of its predictive capacity in real patients and the experimental validation of the hypotheses arising from the simulations, in collaboration with hepatology centres and translational pharmacology laboratories.

Finally, the Economic and Health Extension is targeted, integrating the model with modules for health technology assessment and cost-utility analysis to support strategic decisions at the health policy level, estimating the economic impact of different therapeutic strategies based on realistic population scenarios.

7.3. General Conclusion

The proposed model represents a starting point for the predictive modeling of liver cirrhosis and for defining targeted and personalized therapeutic strategies. It combines mathematical rigor, biological consistency, and a translational perspective, laying the foundation for the integration of computational models, precision medicine, and artificial intelligence. Looking ahead, the fusion of these tools into a single clinical simulation ecosystem—powered by real data and continuously updated—can substantially contribute to transforming cirrhosis management from reactive to predictive and preventative, opening the way for a new generation of digital models of the human liver in service of research and medical practice.

8. Acknowledgements, Author Contributions, and Bibliography

8.1. Acknowledgements

The authors wish to express their gratitude to the Department of Research and Development in Artificial Intelligence and Computational Sciences at Studio Armoni & Associati for the technical and methodological support provided during the development of this work.

Special thanks are extended to the professionals and researchers in the fields of computational biomedicine, clinical hepatology, and predictive modeling who contributed to the conceptual validation of the model and the critical review of the results.

We also thank colleagues from partner academic centres for their scientific contributions and interdisciplinary discussion on the mathematical models of liver damage and simulation in translational medicine.

8.2. Author Contributions

The work was developed with a multidisciplinary approach that integrated expertise in computational biology, translational medicine, mathematical modeling, and artificial intelligence.

Marco Armoni contributed to the model conceptualization, scientific coordination, technical supervision, and manuscript drafting.

The Research Unit of Studio Armoni & Associati was responsible for the computational implementation in Python, analysis of simulation data, graphical visualization, and technical writing support.

External Collaborators and Clinical Reviewers provided consultation in hepatology and pathophysiological validation of the model.

All authors have read and approved the final version of the manuscript.

8.3. Conflict of Interest Statement

The authors declare that they have no financial or personal conflicts of interest that may have influenced the work reported in this study.

8.4. Funding

The research was conducted as part of the internal activities of Studio Armoni & Associati – Department of Research and Development in AI and Computational Sciences, without direct external funding.

The project is part of a broader research program on predictive computational models applied to life sciences and the integration between AI and precision medicine.

References

[1] Bataller, R., & Brenner, D. A. (2005). Liver fibrosis. Journal of Clinical Investigation, 115(2), 209–218.

[2] Friedman, S. L. (2008). Mechanisms of hepatic fibrogenesis. Gastroenterology, 134(6), 1655–1669.

AUTHORS

Marco Armoni, PhD

Visiting Professor in many International University and Professor of the Artificial Intelligence Faculty at MUSA Formazione. With over thirty years of experience in cybersecurity, artificial intelligence, and digital health, his research focuses on the intersection between advanced AI systems and medical diagnostics, as well as cloud security and data protection. Throughout his career has collaborated with institutions such as MIT, Johns Hopkins University Medical Center, University of Tennessee Medical Center, and CERN, contributing to projects on network systems, brain simulation, and applied AI in healthcare. He has published numerous books, manuals, and research articles on topics including AI in healthcare, cybersecurity, cloud security, and computational neuroscience. Recent work includes Digital Healthcare. Practical Guide to Managing Identities, Data and Documents (Themis, 2023) and studies on EDR systems, deep learning models for neurodegenerative diseases, and NLP transformers. Member of IEEE, ACM, ISSA, CLUSIT, IAPP and several scientific committees, he received awards for excellence in research and leadership, including the Le Fonti Award (2020). In 2023, was nominated for the Nobel Prize in Physics for the research on “The Photon Non Linear Motion".

Imma Orilio, eng.

The professional career of Imma Orilio is marked by a distinctive evolution from scientific research to technological leadership. She started, in 1990, as a researcher at the Italian Center for Aerospace Research (CIRA), graduating “cum laude” in Aeronautical Engineering. After a decade of research, she moved to executive management in the aviation sector (DEMA Spa) before moving on to public health. For ten years she worked as Executive Engineer and CIO at ASL Napoli 2 Nord, where she pioneered the digital transition to the cloud and interoperability. In 2016 she founded CREMETE Srl, a strategic and technological consulting company for both the healthcare and industrial sectors. In 2023, she launched Talence Srl, an innovative startup focused on the development of XAI and NLP platforms. Today she collaborates with prof. Armoni for the introduction of BNNs in healthcare and in the aerospace sector. Through its companies, Cremete and Talence, it is currently part of the Mechatronics Valley Cluster.