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COMPUTATIONAL MODEL OF CIRRHOTIC PORTAL HYPERTENSION

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Abstract

Background & Aims: As liver disease progresses, scarring results in worsening hemodynamics ultimately culminate in portal hypertension. This process has classically been quantified via the Hepatic Venous Pressure Gradient (HVPG), however HVPG alone does not predict a given patient's clinical presentation with regards to Baveno stage of cirrhosis. In this study we propose that a patient's 'HVPG-sensitivity' to venous remodeling-could explain disparate disease trajectories.

Methods: We created a computational model of liver disease informed by actual physiologic measurements from the field of portal hypertension over the last four decades. We simulated progression of liver disease, clinical complications, and HVPG in the context of varying 'HVPG-sensitivity' to portal venous remodeling.

Results: Our results unify hemodynamics, venous remodeling, and the progression of liver disease. We demonstrate that in modifying the 'HVPG-sensitivity' to venous remodelingwe can explain multiple trajectories of liver disease.

Conclusion: This paper provides a basis for a future, whole-body computational model of decompensated liver disease and highlights the importance of venous remodeling in explaining patients' clinically presentation.

Keywords

portal hypertension, hemodynamics, cirrhosis

Introduction

The natural history of cirrhosis involves the progressive scarring of the liver and therefore increased resistance to blood flow across the organ. The end-result is portal hypertension which remodels the portal vasculature, alters systemic hemodynamics, and causes life-threatening cirrhosis decompensations such as ascites and variceal bleeding. Portal hypertension is graded in severity using the hepatic-venous pressure gradient (HVPG) which is the pressure difference between the portal vein and hepatic vein. The HVPG is a surrogate for hepatic resistance to blood flow[1]. This measure has been the cornerstone for the field of portal hypertension, with elevated HVPG a risk factor for variceal bleeding, decompensation, patient survival, peri-operative risk, and response to therapy[1–5].

Despite its importance, HVPG alone may not fully explain a patient's disease trajectory. For example, disease progression is conventionally modeled in stages: Stage 1 (no varices, no ascites), to Stage 2 (varices, no ascites) to Stage 3 and 4 (Ascites and/or bleeding).[6] However, patients may not follow this progression in a linear fashion[7–9]. Furthermore, chronically elevated portal pressure induces and enlarges portosystemic shunts, prevalent in up to 63.5% of patients with cirrhosis and correlated with poor outcomes[10]. These shunts circumvent portal flow to the liver and can lower HVPG by 5 to 15mmHg, interfering with the diagnostic utility of HVPG[11]. Thus, a more complete hemo-

dynamic understanding of the system could assist clinicians in understanding portal hypertension and its progression.

Herein, we develop a computational model of portal hypertension that can simulate the full spectrum of patients with cirrhosis encountered in clinical practice. We hypothesize the sensitivity of the portosystemic system to remodeling in the face of elevated HVPG represents a key driver of variability in trajectories of cirrhosis. Simulation results are shown to support the viability of this hypothesis. Thus the developed model provides a useful tool in illustrating and probing complex interactions between hepatic hemodynamics, ascites formation, and variceal status during the progression of cirrhosis. A web-based simulator for visualizing outcomes can be accessed at https://filip-jezek.github.io/Ascites/, while the model source codes in Modelica language can downloaded from https://github.com/filip-jezek/Ascites.

Methods

Objective and Hypothesis

In this study, we sought to simulate HVPGduring a consistently increasing amount of liver fibrosis ultimately culminating in the presence of portosystemic shunts and ascites. Simulation conditions are set based on parameter ranges from the literature with the goal of creating a meaningful, clinically relevant model of cirrhosis progression (see Appendix 1). In contrast to prior work, we hypothesize variability in the 'remodeling sensitivity' of portosystemic shunts in response to rising HVPG represents a key driver of differences intrajectories of cirrhosis progression. Specifically, patients 'sensitive' to HVPG will enlarge portosystemic shunts at a faster rate compared to 'insensitive' patients.

Steady State Simulation

For our simulated patient cases, we assumed that there are no other systemic diseases other than progressive liver fibrosis. We assumedthat progression of fibrosis occurs slow enough to allow for steady state of venous remodeling to be reached. In other words, our model is a simulation of the system at each time point after remodeling has been allowed to occur in response to a given level of fibrosis. This approach is reasonable because the progression of liver disease is known to occur on a much longer time scale than venous shunt formation. For instance, patients with portal vein thrombosis have been noted to form new venous systems within 3-5 weeks[13,14] while the median time from compensated cirrhosis diagnosis to decompensation ranging from 5 to more than 10 years in cohort studies[8,15,16]. In lieu of a time scale, the level of hepatic vascular resistance represents the degree of progression of disease. The simulation is designed in this way because 1) time to a given level of resistance is known to vary by cause of liver disease (e.g. viral, alcohol, metabolic etc), and 2) our model simulates steady state at each possible liver resistance. Utilizing an initial baseline value of 4 mmHg*min/L, (i.e. 4 mmHg HVPG at 1L/min portal flow, see Model Parameters), hepatic vascular resistance was gradually increased to 35 mmHg*min/L.

Model Parameters

We built our model assuming that portal vein inflow remains constant at approximately 1L/min, which matches flow rates seen in MRI studies of healthy and patients with cirrhosis[17,18]. Given that oxygen delivery is dependent on flow to tissues, proscribing a constant minimum outflow (i.e. portal vein inflow) from the mesentery is a necessity. Other parameter assumptions regarding generation of ascites were previously described

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in Levitt et al[19] and are delineated in Appendix 1. Our model represents an extension of this previously published model, which simulated ascites generationas it is related to portal hemodynamics but did not include shunts.

Novel Portosystemic Shunt Behavior

Most notably, our model incorporates shunt behavior as liver disease progresses. This is in comparison to past models which have omitted this major factor or maintained a fixed element to account for all cases[19–23]. In this study, we propose that the portosystemic shunting can change as liver disease progresses and that shunt diameter increases as HVPG increases. This relationship is well known clinically however has never before beensimulated in the context of hemodynamics[24]. We term the relationship between HVPG and fraction of shuntingas the're-modeling sensitivity' of each patient. In other words, with the same HVPG impetus, more 'sensitive' patients may form larger shunts while others who are less 'sensitive' may not. Of note, the 'sensitivity' of portosystemic shunts to remodeling should not be confused with minute-to-minute venous compliance, although they share the same units. We represent the behavior of all the portosystemic shunts in a single, lumped resistive compartment. As its luminal diameter increases, the resistance drops according to the Hagen-Poiseulle law:

$$\Delta P = R \cdot Q = \frac{8 \mu L}{\pi r^4} Q \tag{1}$$

where Q is blood flow, ΔP is pressure drop, μ is dynamic viscosity of the blood, L length of the shunt and r is the actual diameter. The shunt is characterized by its linear resistance R, given by Hagen-Poiseulle's law. The actual diameter is calculated from the actual volume:

$$V = Lr \tag{2}$$

The actual volume is then given by the shunt's pressure difference P_d (coincides with HVPG) and assumed vessel long-term susceptibility to pressure-dependent remodeling, expressed by the 'Remodeling sensitivity Constant' C_r

$$V = max(0, P_d - P_{nom})C_r + V_{nom} \tag{3}$$

V_{nom} is the normal volume, given by normal diameter r_{nom} as $V_{nom} = L\pi r^2_{nom}$, which in turn is calculated from assumed normal resistance R_{nom} (1000 mmHg.min/L) using the equation (1). The P_{nom} is assumed normal healthy pressure difference (8 mmHg). The 'Remodeling sensitivity Constant' C_r for the variceal and ascitic phenotypes has been arbitrarily set to represent the behaviour of distinct clinically observed cases. The parameters are listed in table 1.

Model Setup

A diagram of the setup can be seen in Figure 1. We employed 0-D steady state modelling of isolated splanchnic hemodynamics. We assumed constant flow and system free of transients (i.e. in steady state). As a basis, weused the model previously published by Levitt to calculate the steady state ascites pressure[19]. This model consists of resistive components in series (intestinal arteries, intestinal veins, liver, hepatic vein and assumed central venous pressure) and a model of the peritoneal compartment. When the hepatic vein pressure is lower than the peritoneal pressure, the hepatic vein collapses, increasing its resistance to flow.
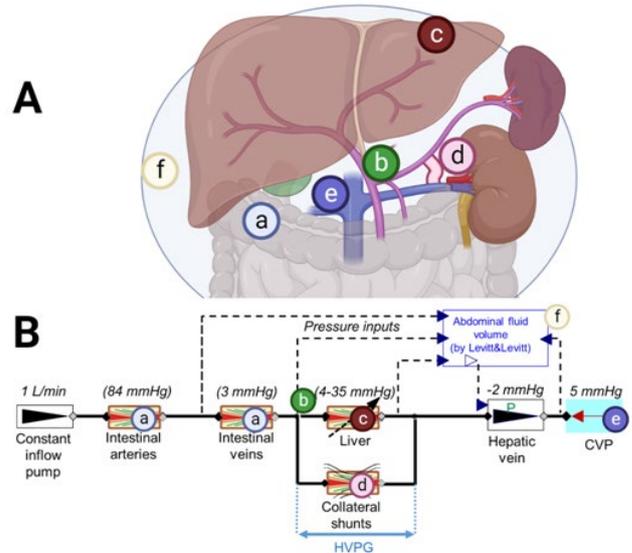
Figure 1 – Anatomy (A) and model setup (B) of the base model (a) intestines, (b) portal vein, (c) liver (d) shunt, (e) inf. vena cava (f) abdominal cavity with ascites. Nominal parameters are shown above each component. Created with BioRender.com.

The fixed pressure drops assumed by Levitt and Levitt for the liver (6 mmHg), intestine venules (3 mmHg) and intestinal arteries were replaced with appropriate resistances so that the pressure drop at the said components stays the same for selected normal inflow of 1 L/min[17,18]. Thus, we can observe the change of the pressure drop at different inflow rates.

Definitions for Stages of Cirrhosis

Following Baveno classification[5], we defined the stages as 1) no ascites present and no portosystemic shunt (varices), 2) varices present – the shunt receives > 10 % of the PV flow (100ml/min given set splanchnic inflow of 1 L/min), 3) clinically meaningful ascites (over 5L) and 4) variceal bleeding as varices present and Hepatic venous pressure gradient (HVPG) over 17 mmHg[3,4,25].

	Value	Unit	Description
P_{nom}	8	mmHg	Normal transmural pressure of the shunt
R_{nom}	1000	mmHg.min/L	Normal shunt resistance at Pnom
$C_{varices}$	1	ml/mmHg	Long-term pressure-volume remodeling sensitivity of the shunt of the variceal phenotype
$C_{ascites}$	0.5	ml/mmHg	Long-term pressure-volume remodeling sensitivity of the shunt of the ascitic phenotype
μ	4e-3	Pa.s	Blood dynamic viscosity
L	10	cm	Length of the portosystemic shunt

Table 1 – List of shunt model parameters

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Experimental setup

We initialized the model in steady state and then gradually increased liver resistance in increments of 2 mmHg.min/L, mimicking progression of fibrosis, while keeping the inflow constant at 1 L/min. The simulated outputs are HVPG, PPV, abdominal pressure, ascites volume, and Baveno stage of cirrhosis for a high and a low value of 'remodeling sensitivity' constant.

Simulations were designed and run in Dymola 2022x, using Modelica Standard Library 4.0 (https://github.com/modelica/ModelicaStandardLibrary) and Physiolibrary v2.5 (https://github.com/filip-jezek/physiolibrary). Source code including model documentation and usage instructions can be found at https://github.com/filip-jezek/ascites. Institutional Review Board approval was not applicable for this computational study.

Results

Portosystemic Shunt Remodeling Attenuates HVPG Rise

After simulation, HVPG varied significantly between patients who were HVPG-sensitive vs HVPG-insensitive remodelers. As liver disease progressed, HVPG response can be seen in Figure 2, with end simulation values labeled. Both shunt situationshave identical baseline initial conditions with near-zero flow through shunts until diameter rose (prescribed by equation (1)) at a sustained HVPG of 8mmHg per model starting conditions. HVPG-sensitive remodelers had lower HVPG and Pressure in the Portal Vein (PPV) as liver disease progressed compared to the insensitive and no-shunt cases. This is true at each simulated stage of liver disease and especially prominent in the final stages simulated. An example of a later stage of disease is denoted by the orange line in Figure 2, with HVPG decreased by 7 to 10 mmHg in insensitive and sensitive patients respectively. PPV followed a similar ratio, with insensitive and sensitive patients having significant decompression of venous pressure. Notably, HVPG of both shunted groups rise in a non-linear fashion, with a plateau of HVPG around 25 mmHg (and 23 mmHg in the HVPG sensitive group respectively) at later stages of liver disease despite progression of fibrosis.
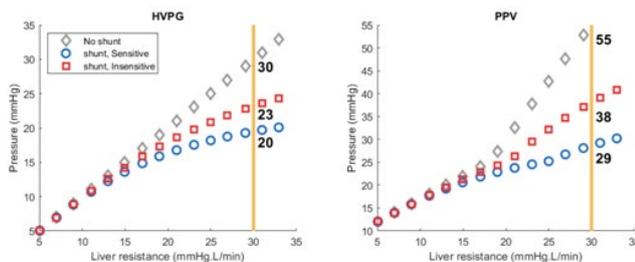
Figure 2 – With increasing liver resistance, increases in Hepatic-Venous Pressure Gradient (HVPG) and Pressure in the portal vein (PPV) are blunted by remodeled cases compared to 'No shunt' case. Patients with more remodeling achieved lower HVPG and PPV at all stages. The orange line shows an example of pressures simulated in an advanced disease case.
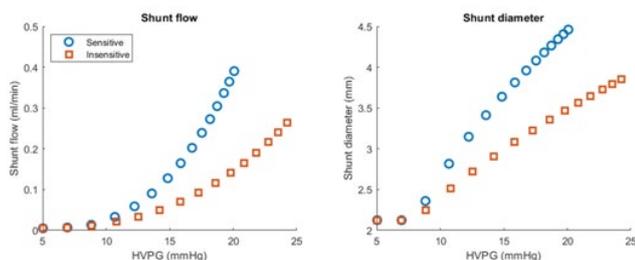
Figure 3 – With increasing HVPG, shunt flow and diameter are higher in 'HVPG-sensitive' vs 'insensitive' cases.

These differences in hemodynamics are further explored in Figure 3. Patients who were 'HVPG-sensitive' remodelers had higher shunt flow and diameter as HVPG rose, with 'sensitive' patients achieving more than 20% higher shunt diameter at HVPG of 15 and flow starting in earlier disease, in contrast to the 'insensitive' patient group who had smaller shunt diameter and required a much higher HVPG to begin flow through shunts.

Extent of Remodeling Predicts Clinical Course
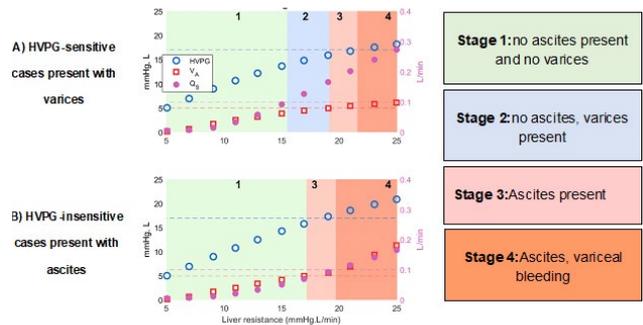
Figure 4 – Two representative cases. As liver disease progresses, HVPG increases non-linearly. After venous remodeling at each stage, 'HVPG-sensitive' (A) cases demonstrate early varices and bleeding compared to 'insensitive' (B) remodelers who present with ascites. At the end of simulation, both groups of patients achieved stage 4 through different trajectories.

HVPG= Hepatic venous pressure gradient (mmHg); Q_s = flow though shunts (L/min); V_A = Volume of ascites (L)

Figure 4 shows two representative simulations that demonstrate the differences in clinical presentation between 'HVPG-sensitive' remodelers (4A) and 'insensitive' remodelers (4B). Specifically, 'sensitive' remodelers displayed in 4A demonstrate a decompensation profile dominated by higher shunt flow (Q_s solid purple dots) and a lower rise in HVPG (Blue circles) compared to 'insensitive' patients seen in 4B. Accordingly, these patients experience earlier varices and developapscites (Red squares) later in disease progression. In contrast, the 'HVPG-insensitive' remodelers displayed in figure 4B experience ascites as a presenting symptom, with variceal bleeding occurring later in disease. For instance, at the same HVPG of 15mmHg 'HVPG-sensitive' patients would have >100mL/min of shunt flow, no significant ascites as compared to HVPG-insensitive patients who would have minimal shunt flow and clinically significant ascites. This is consistent with clinical observation in which HVPG alone is not sufficient to predict portal hypertensive complication type. Regardless of route, both 'sensitive' and 'insensitive' remodelers end at stage four disease with symptomatic ascites and variceal bleeding, however 'sensitive' remodelers have a predicted ascites volume of around 5-7L in this stage while 'insensitive' patients could potentially generate greater than 10L. Of course, these are two representative simulations, the true 'HVPG-sensitivity' factor C_r can be adjusted across a range of values and is likely somewhere around these two simulations for actual patients.

Demonstrational application

To allow experimentation with the model outside the two presented cases to general audience, we have developed a demonstrational web application employing on the Bodylight.js framework (https://bodylight.physiome.cz/). Making advantage of the model Modelica implementation, the model

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has been translated into JavaScript (using the Bodylight Virtual Machine from https://github.com/creative-connections/Bodylight-VirtualMachine) and further processed in the Bodylight.js Editor, running within the virtual machine. We encourage the reader to try out different values of 'sensitivity' to remodeling and splanchnic inflow using the simulator at https://filip-jezek.github.io/Ascites/. (Figure 5)
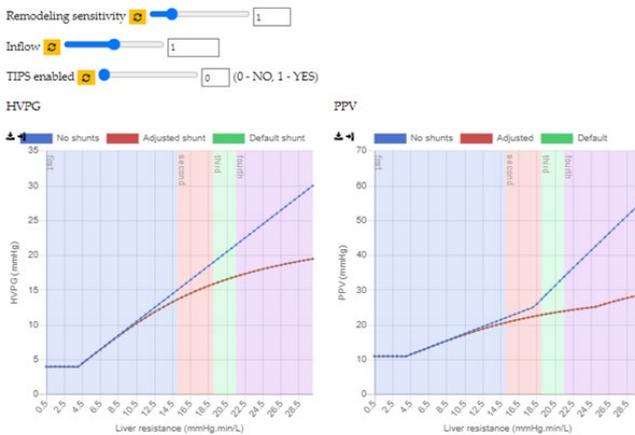
Figure 5 – Online web-based simulator. The reader is encouraged to manipulate the remodeling sensitivity and portal vein inflow at https://filip-jezek.github.io/Ascites/. Additionally, effects of transjugular intrahepatic portosystemic shunt (TIPS) can be simulated together.

Discussion

Our capacity to optimize and personalize the medical management of patients with cirrhosis requires an understanding of the pathophysiology that explains their heterogeneous phenotypes and clinical courses. While clinical guidelines for predicting and managing portal hypertensive events focus on the HVPG, this single parameteris insufficient to explain why different patients present differently. Our simulation elucidates the complex interactions between hepatic hemodynamics, ascites formation, and variceal status during the progression of cirrhosis, and demonstrates the viability and consequences of this hypothesis.

While computational modeling of cardiovascular dynamics has found numerous applications[29,30], previous application to liver disease have been limited. Golse et al predicted post-hepatectomy portal hypertension in non-decompensated patients using a 'digital twin', or a personalized computational model of the patient[21]. This application required intensive collection of CT and intraoperative hemodynamic data to inform parameters. Another study developed a model to simulate blood flow through the portal system and lobes of the liver[22], treating varices as static shunts. Other studies have modeled the formation of ascites at the level of the sinusoids[31] or portal system[19] but these studies primarily focused on the relationship between sinusoidal pressure and ascites generation. In this study, we demonstrate the critical role of portosystemic remodeling in the face of HVPG and link the aforementioned work together into a mathematically consistent, unified model. We show how our shunt dynamics could explain the heterogeneity of the disease course.

Implications of Shunt diameter and HVPG

We demonstrate that by altering portosystemic shunts so that their size grows with rising HVPG, we attenuate the rise in HVPG

in exchange for higher shunt (variceal) flow. Even a small variation in venous 'remodeling sensitivity' manifested as larger portosystemic shunt luminal diameter and significantly blunted HVPG rise. This is mainly due to the fourth power exponential relationship in the Hagen-Poiseuille law (Equation 1). In contrast to bleeding varices at later stages of liver disease, early portosystemic shunts may thus in fact serve as a useful adaptation to the rising resistance to flow through the diseased liver. This would help maintain venous drainage of the mesentery which must be perfused to avoid ischemia. This is seen in our simulation of HVPG-'sensitive' patients in that they remain compensated farther into liver disease progression, staving off significant ascites formation longer than their less remodeled counterparts.

Despite its importance in explaining clinical presentation, the exact mechanism of portal venous remodeling in response to HVPG is not known. Some animal studies suspect remodeling to be related to growth factor release[32,33]. Given the ongoing research in this area, we simplified the relationship between HVPG and shunt expansion to a sensitivity factor C_r which could allow simulation of various levels of HVPG-'sensitivity'.

Variations in HVPG-related remodeling explain disease progression

While the 'stages' of cirrhosis have been well documented by several longitudinal studies over the last forty years, the transition between stages have been less clear[7–9,16,34]. For instance, among patients with cirrhosis and varices, D'Amico finds an 8% annual rate of first decompensation with bleeding versus a 20% annual rate of other events (most commonly ascites) but it is not known why certain patients would present with one type of event or another[35]. Similar findings of ascites as a first decompensating event have been described in other large cohorts as well, but in some patients this is preceded by bleeding[9,34,36]. Our results provide insight into this pattern, showing that the relative severity of ascites as a presenting symptom suggests low HVPG remodeling 'sensitivity' while patients with larger shunts have natural relief from this complication at the potential cost of variceal bleeding and portosystemic encephalopathy.

This is most apparent in Figure 4B of our results, which demonstrates an absence of Baveno Stage two (varices without ascites). Namely, these patients transition from Stage one (no varices, no ascites) to Stage three (ascites) directly. In clinical practice, patients with portal hypertension manifested as ascites but with endoscopy negative for varices are common and may fall into this category. Importantly, our findings do not claim that patients with varices do not have ascites—as noted in figure 4 both trajectories of liver disease end with the combination of varices and ascites (Baveno stage four).

Limitations

Our study has several strengths and limitations. We do not use actual patient data in our study, however our goal was not to directly model a specific patient's data but to ensure that the assumptions and physiology accrued from decades of portal hypertension research were self consistent when integrated in a single model. Furthermore, creation of a 'digital twin' requires invasive measurement of physiologic parameters and acquiring this level of data on the timescale needed to observe the natural history of cirrhosis is impractical[20,21]. Despite this, utilizing previously published physiologic norms for healthy, cirrhotic, and decompensated cases we were able to explain the complex presentations of portal hypertension making our findings are more generalizable.

We do not model complications outside of the portal system, including hepatic encephalopathy, renal failure, hepatopulmo-

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nary syndrome, hyperdynamic circulation, etc. This first iteration of a model for portal hypertension was intended to enhance the 'stages' of cirrhosis as described in Baveno which also does not include these complications[1]. Furthermore, if we had attempted to draw parallels between quantity of portosystemic shunting and predict hepatic encephalopathy, we would not be able to account for the significant contributors of liver dysfunction and intestinal microbiome. We plan to connect our current model with an established model of the human circulatory system as a next step in order to examine the cardiorenal axis in the setting of progressive liver disease.

We assume that shunt remodeling and HVPG are linearly related. Some studies claim that shunt growth corresponds to shear stress and the wall thickness builds up with the transmural pressure[41]. We briefly explored this however the simulation does not support that shear stress alone would increase growth of shunts, rather caused them to close (results not shown). We also investigated remodeling strategy based on transmural pressure without a difference in clinical outcomes (results not shown).

In the current study we modeled the effect of all shunts 'lumped' into a single resistive component. In future work, a distinction between extra-abdominal (e.g. esophageal shunts) vs intraabdominal shunts will be made to determine if this influences outcomes. The Hagen-Poiseuelle equation for calculating resistance has some limitations when applied to the actual vessels in that the real resistance at given diameter might be significantly higher, as we omit possible turbulent effects. For simplicity, we implemented the generalized assumption that the vessel resistance decreases with larger diameter and due to lack of measurement data on pressure-resistance in branched shunts using the Hagen-Poiseulle law. Lastly, we make no assumptions of the rate of liver fibrosis, just that the time scale is much longer than venous remodeling. It is well known that the rate of scarring is anything but constant and can accelerate or stabilize depending on control of the underlying disease. This model is actually able to simulate a time-varying liver resistance, however actual data delineating the relative rates of liver resistance in various clinical scenarios does not exist and so we chose discrete fibrosis states to increase generalizability.

In future work, we hope to couple this model with existing whole body models to further simulate the changes of end stage liver disease[29,30]. Namely, we hope to show that the classic findings of hyperdynamic circulation and renal hypoperfusion due to effective arterial hypovolemia is a natural result of the findings within this paper[42]. Furthermore, future studies may employ more sophisticated personalized computational modeling, simulation of treatments (beta blockers, diuretics, paracentesis etc), TIPS, and transplant related hemodynamic changes, and to better understand the nuances of portal hypertension physiology.

Conclusion

This study reveals novel insights into the progression of liver disease by incorporating four decades of experimental measurements on portal flow, venous remodeling, and variceal bleeding into an interactive, unified physiological model. We demonstrate that while HVPG remains a crucial marker of portal hypertension, the full range of clinical presentations is determined only if sensitivity to venous remodeling is taken into account. Our hypothesized responsively remodeling shunt mechanism results in a plateau in HVPG around 23, consistent with HVPG measurements found in studies of advanced liver disease. This emergent result was not pre-tuned into our model, instead naturally arising from our baseline parameters, suggesting mathematical consistency of our literature-based model and actu-

al disease [3,4,40]. Altering this single parameter allows a consistent and flexible explanation for these phenotypes and in this way has an advantage over the 'stage of cirrhosis' models. We connect several domains of knowledge in portal hypertension to construct a working model of decompensation that augments the existing 'stage' based approaches. An interactive version of the model is available for experimentation at https://filip-jezek.github.io/Ascites/.

Appendix

For calculating ascites volume and pressure we use the model from Levitt and Levitt[19], as detailed below. All variables and parameters employed in the model are listed in Table 2.

The volume of ascites fluid in the abdominal cavity denoted A_v, is determined by the governing equation

$$A_v = V_{min} + \max\big(0, D(P_a - P_{min})\big) \tag{A1}$$

where V_{min} is minimal residual volume, P_{min} minimal abdominal pressure and D reflects linear abdominal compliance. The abdominal pressure Pa is calculated so that all lymph flows J_i (intestinal leak), J_l (liver leak) and J_y (leak from abdominal cavity) are in steady state balance. The leaks are defined as follows

$$Ji = Lt(P_c - P_a - A_p + A_a) \tag{A2}$$

where L_t is the intestinal leak constant, P_c is the intestinal capillary pressure (calculated from the resistances and flows), Pa is the abdominal ascites pressure and Ap and Aa are oncotic plasmatic and ascitic pressures. Between those two a relation holds:

$$A_a J_y = m A_p J_l \tag{A3}$$

where the m notes protein balance fraction constant. The liver leak is calculated as

$$J_l = L_l(P_l - P_a - P_{break}) \tag{A4}$$

where L_l is a liver leak constant, P_{break} notes a breaking pressure of liver sinuses, which cause greater leak and P_l is the liver pressure, taken as average pressure between portal vein and hepatic vein:

$$P_l = \frac{Pp + Phv}{2} \tag{A5}$$

The abdominal lymphatic leak J_y balances the lymph inflow so that $Jy=Jl+Ji$ and is given as:

$$Jy = \max\big(0, Ly(P_{min} + Pa - Pra)\big) \tag{A6}$$

where L_y is the leak constant and P_{ra} right atrial pressure parameter.

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Parameters	Unit	Value	Description
P_{ra}	mmHg	5	Right atrial pressure
A_p	mmHg	25	Blood colloid osmotic pressure
$P_{a.min}$	mmHg	2	Minimal ascites pressure. Must be less than Pra
P_{break}	mmHg	8	Breaking pressure of liver sinuses
L_v	ml/(mmHg.min)	0.131	Ascites outflow conductance
L_l	ml/(mmHg.min)	0.172	Liver to ascites conductance
L_t	ml/(mmHg.min)	0.104	Intestine to ascites conductance
D	L/mmHg	0.8	Abdominal compliance (ascites pressure-volume characteristics)
V_{min}	L	0.1	Residual abdominal fluid volume
m	*unitless*	0.8	Protein balance fraction
Variables			
P_l	mmHg	9.5[1]	Liver sinus pressure
A_a	mmHg	11.5[1]	Ascites oncotic pressure
P_a	mmHg	1.5[1]	Ascites pressure
P_{hv}	mmHg	7[1]	Hepatic vein pressure[2]
P_c	mmHg	15[1]	Intestinal capillary pressure[2]
P_p	mmHg	12[1]	Portal vein pressure[2]
A_v	L	0.1[1]	Ascites volume
J_l	ml/min	0[1]	Lymphatic flux from liver to ascites
J_i	ml/min	0[1]	Lymphatic flux from intestines to ascites
J_y	ml/min	0[1]	Lymphatic outflow

Table 2 – Model variables and parameters.
[1]*normal healthy value (at normal HVPG = 5 mmHg),* [2]*variable calculated from the resistances and flows (schematics on figure 1)*

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