CHAPTER 1
INTRODUCTION

1.1 Scope of Mathematical Biosciences

The approach of Mathematical Biosciences provides a general strategy or a set of theoretical concepts for designing mathematical models for quantitative description of a rather broad class of dynamical phenomena in biosciences. Quite often the term biomathematics is used for mathematical biosciences. It is an interdisciplinary subject with a vast and exponentially growing literature scattered over a large number of journals belonging to different disciplines. Contributions to it have been made by mathematicians, physicists, statisticians, computer scientists, botanists, demographers, medical scientists, and many others. A large number of mathematical models have been developed to get an insight into complex biological, ecological, and physiological situations. A variety of mathematical techniques have been employed to solve these models. These include techniques for solution of differential, difference, integral, and integro-differential equations as well as techniques of linear and nonlinear, dynamics and so on.

“I believe the day must come when the biologist, without being a mathematician, will not hesitate to use mathematical analysis when he requires it” said Karl Pearson. Biological science has long been advanced from purely descriptive to analytical science. Many analytical methods of physical science have been used successively in the study of biological sciences. Biofluid mechanics is the study of certain class of biological problems from fluid mechanics points of view. Biofluid mechanics does not involve any new development of general principles of fluid mechanics but it involves some new applications of the method of fluid mechanics. Complex movements of fluids in the biological system demand for their analysis professional fluid mechanics skills. The most common fluid mechanics problem in the biological system is the flow of blood. The upcoming area which is growing fast is the flow of bile in the human biliary system. Where the anatomical and physiological aspects of the human biliary system have been studied extensively, little is known about flow mechanics in the system. Still the mechanism of the pathogenesis of gallstones and pain production remain poorly
understood. However, despite the extensive literature in clinical studies, only limited work has been carried out to study the biliary system from the dynamical point of view. The modeling of flow of bile in the human biliary system has emerged as the demanding area.

1.2 Motivation

The human biliary system consists of an organ and ductal system. The role of human biliary system is to create, store, transport and release bile into the duodenum to aid digestion of fats. The anatomy comprises of liver, gallbladder and the biliary tract- cystic duct, hepatic duct and the common bile duct (Figure 1.1 and 1.2). The gallbladder is a small pear-shaped sac generally measuring 7-10 cm in length and about 3 cm in width and is located beneath the liver on the right side of the abdomen. Its primary function is to store, concentrate and secrete bile contents into the small intestine at the proper time to help digest food. The average storage capacity of the gallbladder is about 20-30 ml. Bile, the liquid that flows in the biliary system is a yellow-brown fluid produced by the liver and is composed of three main components – cholesterol, bile salts and bilirubin.

As food passes from the stomach into the small intestine, the gallbladder contracts and sends its stored bile into the small intestine through the common bile duct. Once in the small intestine, bile helps digest fats in food. Under normal circumstances most bile is recirculated in the digestive tract by being absorbed in the intestine and returning to the liver in the bloodstream. When the gallbladder is not functioning properly, components of bile are supersaturated leading to the formation of solid crystals called gallstones.

Most common biliary diseases are:

- Cholelithiasis - the presence of gallstones.
- Cholecystitis – the inflammation of gallbladder.
Figure 1.1 Gallbladder and the ducts

Figure 1.2 Human Biliary System
Figure 1.3 The Anatomy of the human biliary tree showing part of the gallbladder neck connected to the spiral valves in the cystic duct.
A detailed knowledge of the fluid mechanism in the biliary system will help in understanding of the etiology of cholelithiasis. The gallstones may be caused by a combination of factors including inherited body chemistry, body weight, gallbladder motility and diet.

In addition increased level of hormone estrogen as a result of pregnancy or hormone therapy may increase cholesterol level in bile and also decrease gallbladder movement resulting in gallstone formation.

The motivation behind the proposed study is to develop mathematical model of the flow of bile and influence of factors affecting it, and to understand the role of fluid dynamics in human biliary system. So that it can be used in prescribing preventive measures to patients at risk to gallstones.

In this research work, the new models addressing the bile flow problems in the human biliary system are formulated and solved using analytical and computational methods.

1.3 Survey of related literatures

Al-Atabi et al. [1] worked on cystic duct visual-based evaluation of gallstones formation risk factors. Gallstones are commonly related to the super-saturation of bile with cholesterol in the presence of nucleating agents. Clinical evidence showed that gallstones were frequent in healthy persons with complex cystic ducts geometry, an indication that fluid mechanics of the bile flow may play a role in the formation of gallstones. In order to evaluate this role, correlations between idealized cystic duct geometry and the pressure drop across it had been determined both experimentally and numerically simulated with computational fluid dynamics (CFD) techniques. The work forms part of a larger project to understand the functions of the human cystic duct, especially the influence of its various anatomical structures on the resistance to bile flow, to provide insight into the pathogenesis of gallstone formation and the origins of biliary pain. Al-Atabi et al. [2] presented a mathematical model accounting for the effects of geometry of the
baffle configurations. It predicted the pressure drop in circular pipe fitted with segmental baffles. The model was solved algebraically for flow in pipe with three baffle arrangements and the results were validated by experimental data. Al-Atabi et al. [3] assessed the role of the valves of Heister during both the filling and the emptying phases of the gallbladder. The result suggested that the existence of these valves helps both the filling and the emptying of the gallbladder by providing structural support and preventing the duct from total collapse. Bird et al. [4] described the variation in geometry of the cystic duct, obtained from acrylic resin casts of the neck and first part of the cystic duct in gallbladders removed for gallstones disease and obtained from patients undergoing partial hepatectomy for metastatic disease. The data obtained allowed the formation of number of standard terms for describing cystic duct morphology and demonstrates that the term ‘spiral valve’ is only partially correct when describing the duct anatomy. Also, the term valve implies active resistance to flow in one direction, whereas the internal baffles of the cystic duct would serve to regulate bile flow in both directions.

Dang et al. [5] presented the structural and mechanical re-modeling of the common bile duct. The net effect of the structural and mechanical remodeling was to restore the stress and strain to their homeostatic values. Furthermore, the strain recovered more rapidly and more completely than stress. Finally, the remodeling data were expressed mathematically in terms of indicial response functions (IRF), i.e. change of particular feature of a common bile duct (CBD) in response to a unit step change of the pressure. Duch et al. [6] quantified the structural and mechanical changes in the CBD at different time intervals after acute obstruction. Biliary obstruction in man, most often caused by cholelithiasis, induced remodeling of the bile ducts. The collagen area increased during obstruction but no correlation between the size of the collagen area and biomechanical parameters was found. A practical implication of the present study serves as a warning to surgeons. It was suggested that operative procedures such as suturing, anastomosis and procedures must be performed with special care to avoid damage to the CBD.
Holzbach et al. [7] described a direct method for measuring the maximum cholesterol solubility in bile. Application of this method to five large mammalian species, including man produced a micellar zone significantly smaller than that previously reported. Further, studies on in vitro model solution patterned after bile confirmed this new micellar zone. Thus, direct evidence demonstrated that the micellar zone boundary derived in vitro from model solutions was applicable to human gallbladder bile. Using the present criteria, normal human bile, in contrast to bile from other mammalian species, is commonly supersaturated with cholesterol. A male–female difference in bile composition is not demonstrable despite the well-established female preponderance of cholelithiasis. Bile from patients with cholesterol cholelithiasis has a micellar zone similar to normal but differs compositionally in that there is a greater excess of cholesterol above saturation. Thus, they concluded that cholesterol supersaturation may be a necessary but not solely sufficient cause for gallstones formation.

Jungst et al. [8] suggested that the supersaturation and rapid nucleation of cholesterol in bile were of key importance in the pathogenesis of cholesterol gallstones. While the effects of bile acids and phospholipids on cholesterol saturation of bile had been extensively studied, their influence on the cholesterol nucleation time has not been compared. Therefore, investigation was done to find whether increases of bile acid or phospholipid concentration in bile by in vitro supplementation affect the cholesterol nucleation time. The increase of phosphatidylcholine or bile acid concentration decreased the mean cholesterol saturation index to a similar extent. Supplementations of bile with increasing amount of synthetic or biliary PCs caused a marked prolongation of the nucleation time in bile. It was speculated that increasing phospholipid concentrations in bile might be more effective for the prevention of cholesterol gallstones than increasing bile acid concentrations.

Jungst et al. [9] found that the viscosity of gallbladder bile is markedly higher than that of hepatic bile in patients with gallstones. The concentration of mucin was the major determinant of biliary viscosity and may contribute by this
mechanism to the role of mucin in the pathogenesis of gallstones. Li et al. [10] developed a mechanical model for the human biliary system during the emptying phase, based on a clinical test in which gallbladder volume changes were measured in response to a standard stimulus and a recorded pain profile. The model described the bile emptying behavior, the flow resistance in the biliary ducts, the peak total stress, including the passive and active stresses experienced by the gallbladder during the emptying. Li et al. [11] worked on two one-dimensional models to estimate the pressure drop in the normal human biliary system for Reynolds number up to 20. Excessive pressure drop during bile emptying and refilling may result in incomplete bile emptying, leading to bile stasis and subsequent gallstones formation. The effects of biliary system geometry, elastic property of cystic duct and bile viscosity on pressure drop was studied. It was found that the maximum pressure drop occurs during bile emptying immediately after a meal, and was greatly influenced by the viscosity of bile and the geometric configuration of the cystic duct (i.e.) the patients with more viscous bile or with a cystic duct containing more baffles or a larger length had the greatest pressure drop. It was found that the most significant parameter was the diameter of the cystic duct.

Li et al. [12] extended their previous study of the human biliary system to include two new factors: the non–Newtonian properties of bile, and elastic deformation of the cystic duct. A one–dimensional (1D) model was analyzed and compared with three–dimensional fluid structure interaction simulations. It was found that non–Newtonian bile raises resistance to the flow of bile, which can be increased enormously by the elastic deformation(collapse) of the cystic duct. Luo et al. [13] researched to understand the physiological and pathological functions of the biliary system. It was believed that the mechanical factors play an important role in the mechanism of the gallstone formation and biliary diseases. In this paper, the state of art knowledge of the fluid dynamics of bile flow in the biliary tract, the solid mechanics of the gall bladder and bile ducts, recent mathematical and numerical modeling of the system, and finally the future challenges were discussed. Moreover, the paper has reviewed the current progress in understanding the mechanical
aspects of the biliary system, and covered the areas in bile fluid dynamics, bile rheology, gallbladder and duct tissue mechanics, mathematical and numerical modeling, and the correlation between the mechanical stresses and the gallbladder.

Master and Elman [14] observed that after feeding a dog, a forceful contractions of the gallbladder occurred. The pressure within the gallbladder of a healthy unanesthetized dog fasted 24 to 28 hours is usually about equal to a column of bile 100 mm high. After a few swallows of food there is a rapid increase in the pressure to more than 200 mm, with a gradual fall in it again, and repeated similar rises and falls occurred thereafter. The gallbladder contractions responsible for these alterations were accompanied by a lessening in the resistance to the passage of bile to the intestine, a resistance which is maintained by the muscles at the lower end of the common duct. There would appear to be a reciprocal response on the part of the two structures to the one stimulus.

Norman et al. [15] proposed a simple mathematical model to account for the coupling of secretion rates of bile salts, lecithin and cholesterol into bile. The model presented by them, described the quantitative relationship between BS (Bile Salts), L (Lecithin) and Ch (Cholesterol) secretion into bile and had applied this model to analyses a wide range of physiological and biochemical data from man and other species. Ooi et al.[16] discussed the simulation of the biliary system, that includes deformable feature of the cystic duct and investigate its role in cystic duct resistance using fluid–structure interaction technique. Ooi et al. [17] presented a numerical study of steady flow in human cystic duct models. Idealized models were constructed, first with staggered baffles in a channel to represent the valves of Heister and lumen. Numerical simulations of bile flow in cystic duct models was conducted to investigate the function of cystic duct in gallstone formation. It was found that the most vital geometric factor responsible for increasing cystic duct resistance is the baffle clearance, followed by the number of baffles, while the least important are the angle between the duct and gallbladder. It was hypothesized that patients with a small lumen and large number of valves of Heister are more likely to develop gallstones, since the higher resistance
through the duct will promote stasis of bile in the gallbladder. Pitt et al. [18] observed that cystic duct resistance increases while sphincter of oddi resistance is unchanged in the presence of lithogenic bile without gallstones. They tested the hypothesis that before gallstone formation, stasis results from increased cystic duct resistance and altered gallbladder compliance. Thus, cystic duct resistance increased but gallbladder compliance was unchanged before gallstone formation. Finally, they concluded that increased resistance to flow across the cystic duct, and not altered gallbladder compliance is etiologically related to bile stasis, an important event in gallstone formation. Rodkiewicz et al. [19] conducted experiments showing that bile flowing in a rigid tube, behaves like a Newtonian fluid. The immediate result of this development was that the analytical and experimental finding available from fluid mechanics and heat transfer principle which are applicable to the laminar flow of Newtonian fluid, may be used to understand the flow phenomena of bile in the human biliary tree, in both qualitative and quantitative manner. Rodkiewicz et al. [20] developed a mathematical model of the mechanical factors affecting the flow of bile. It was found that the rate of flow of bile in a duct of extrahepatic biliary tree is related to the associated pressure drop by the power law. Taylor and Armstrong [21] observed the factors influencing the migration of gall stones on patients undergoing cholecystectomy.

1.4 Organization

Thesis comprises of nine chapters. Chapter 1 entitled ‘Introduction’ starts with the scope of biosciences, motivation to the work undertaken, survey of related literatures and organization of the thesis. Chapter 2 entitled ‘Preliminaries’ discusses a brief explanation of the biological terms used. It gives the general introduction about the human biliary system, liver, gallbladder, gallstones and others. It also introduces to the basics of the field of fluid dynamics.

Chapter 3 entitled ‘Effect on the resistance to the flow of bile in the cystic duct’ discusses the effect of cystic duct geometry on the flow characteristics of bile in the cystic duct. The two types of geometry have been taken into account namely cosine shaped and composite shaped. It is assumed that the rheology of bile is characterized by Newtonian
fluid. The flowing bile is incompressible, homogeneous, laminar and steady. The role of valves of heister is assumed to be negligible, therefore not contributing in the geometrical configuration of the cystic duct. Moreover, stone formation is assumed to be symmetrical. Thereafter, Chapter 4 entitled ‘Effect on the resistance to flow of bile in the gallbladder and the cystic duct’ is presented. In this chapter, an idealized model of the gallbladder and the cystic duct is considered. The pressure in the gallbladder exceeds the pressure in the common bile duct. During this time sphincter of Oddi relaxes which lowers the pressure in the common bile duct further. The combined effect of gallbladder and the cystic duct on the flow resistance is studied. It is assumed that the rheology of bile is characterized by Newtonian fluid. The flowing bile is incompressible, homogeneous, laminar and quasi-steady. The combined effect of gallbladder and the cystic duct geometry on the flow characteristics like resistance to flow is analyzed.

Chapter 5 entitled ‘Effect of the plug flow on the flow characteristics of bile through diseased cystic duct’ focuses on the effect of the plug flow characteristics on the flow pattern of bile in the cystic duct. Bile rheology is non-Newtonian and is presented as Casson fluid model. The mathematical analysis is done for model of bile flow in a uniform, cylindrical and rigid cystic duct. The rigid duct is having axially symmetry stones and the role of valves of heister in the cystic duct is assumed to be negligible. Further in this chapter, the effect of the plug core radius on the resistance to flow and the wall shear stress or shear stress (skin friction) is graphically analyzed.

Chapter 6 entitled ‘A theoretical analysis of the effect of the non-Newtonian bile flow on the flow characteristics in the diseased cystic duct’ discusses the effect on the flow characteristics of the bile through the constricted cystic duct. The bile rheology is assumed to be non-Newtonian. Herschel-Bulkley model has been taken to represent the non-Newtonian character of bile in the cystic duct. The flowing bile is assumed to be steady, laminar and incompressible in a cylindrical cystic duct. Assuming the geometry of cystic duct to be cosine shaped, the duct to be rigid and the stone present in the cystic duct is axially symmetric. The roles of valves of heister in the cystic duct are assumed to be negligible. The cosine shaped geometry of the cystic duct presents a complicated non-
Newtonian behavior under different pathological conditions. Here, the flow of bile through the cystic duct due to the squeezing of the gallbladder is investigated.

Chapter 7 entitled ‘Analysis of flux flow in the elastic cystic duct with variation in Transmural Pressure: Non-Newtonian Fluid flow’ discusses the flux flow in elastic cystic duct. The present chapter deals with the flow of a non-Newtonian fluid with zero yield stress, namely, power law fluid, to study the changes in the bile flow pattern into an elastic cystic duct. The theoretical investigation of the flow of incompressible fluid bile in the elastic cystic duct with variation in pressure difference is investigated. The steady, laminar and incompressible power law fluid in an elastic cystic duct is considered. It is assumed that the bile enters the inlet pressure and leaves it with lower pressure, while pressure outside the tube is $p_0$. As the consequence of the pressure difference $p(z) - p_0$, known as transmural pressure, between the inside and outside of the duct, the duct may expand or contract, and hence the shape of its cross-section may deform due to the elastic property of the wall. Therefore, the conductivity of the duct at a location will depend on the pressure difference. The role of valves of heister is assumed to be negligible in the cystic duct.

Chapter 8 entitled ‘Effect on the flow of bile due to radially varying viscosity in the cystic duct’ is presented. In this chapter, the flow of bile in the elastic cystic duct during the emptying phase is studied. The bile behaves as a non-Newtonian fluid and power law fluid model is taken in account to study the flow of bile in the duct. It is assumed that the viscosity of bile is varying radially. A thorough investigation has been done to investigate the impact of various parameters on the flow pattern of bile. As the gallbladder bile is layered so there is a change in viscosity along the radius. It was found that the bile in the gallbladder is in the form of layers. Using this fact we are trying to establish relationship between flow and radially changing viscosity. The effect of flow index parameter, viscosity and other parameters on flow pattern of bile in the duct is studied.

Chapter 9 entitled ‘An analysis of the effect of the peripheral viscosity on the bile flow characteristics through cystic duct with stone: Study of two layer model with squeezing’ is presented. In this chapter, the effect of an overlapping stone in the cystic duct on the flow characteristics of bile is observed. The mathematical model considers a two-fluid
model of bile, consisting of a core region of suspension of bile salts, cholesterol and bilirubin and peripheral layer of mucosa. The theoretical model used enables one to observe the simultaneous effect of bile suspension in the core region and of the peripheral layer, on the flow characteristics of bile due to the presence of an overlapping constriction in the cystic duct. Cholecystokinin (CCK) stimulation not only causes the gallbladder to contract, but also allows the cystic and common bile ducts to contract. The squeezing of the gallbladder causes bile to flow from gallbladder to the cystic duct and finally into the common bile duct. Here, the effect of peripheral layer viscosity on the flow characteristics of bile in the presence of overlapping stone in the cystic duct has been studied.

Finally the bibliography is given at the end of the thesis comprising mainly the works cited in the text and notes, covers relevant books and significant papers on the study of bile flow problems in the human biliary system.