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1 A systems engineering approach to medicine

Abstract: Human physiology is a complex system of systems such that it is impossible for clinicians to be able to consider all elements in a diagnosis. Medicine is becoming more quantitative and predictive mathematical models are becoming much more common and are being used to help in diagnosis and treatment. Chemical engineers have much experience of developing and using methodologies to tackle systems analysis for example with chemical manufacturing systems consisting of complex chemistry, fluid flow and collections of connected units. The paper seeks to show parallels with the complex metabolism, blood flow and interconnected systems of organs and how engineering methodologies are needed to make the use of these systems of models to help clinicians make most use of all information available and to manage risks associated with complexity. Examples are drawn from cardiology, cancer and liver disease where some progress has been made.

Keywords: complex systems; systems engineering; quantitative medicine; cardiology; liver disease

1.1 Introduction

We know the causes of a heart attack right? However, it seems that it is not so straightforward - it results from a set of complex interacting physiological and metabolic systems influenced by many factors. The blockage of the coronary artery can be caused by several mechanisms arising from physical, chemical and metabolic changes in the body. Monaco, Mathiur and Martin [1] have discussed the causes of acute coronary syndrome and divided them into those arising from the role of the vessel wall and those from the role of the blood. Both arise from complex physical and chemical changes and can be treated chemically using medicines provided the correct diagnosis leads to the right therapy. However the cause in a specific case is rarely clear because this is a very complex system.

Engineers solve problems of analysis, simulation, optimisation and control of complex systems. These have very close parallels in medicine: analysis seeks to understand in order to make a diagnosis, simulation predicts short or long term behaviour enabling a

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prognosis, optimisation aims to find a set of actions – therapy – which can result in an optimal outcome, and control systems implement a set of real time actions that keep a process stable - healthy or at least clinically stable – through feedback and the addition of agents (medicines) that can bring a system back to its stable state to manage the condition [2].

This paper arose from discussions between a chemical engineer and a clinical cardiologist about the depth of complexity facing medical practitioners. We aim to show how engineering methodologies (with a particular bias towards chemical engineering because of the chemical nature) can help to find solutions to complex medical and physiological problems and that this is a fascinating area where chemical engineers working together with clinical colleagues can contribute much.

Taking the cardiology case further, in a heart attack artherosclerotic lesions in the arteries can restrict the blood flow but this is not usually blood-limiting. It seems the causes arise from the two sources mentioned above: the cell wall and the blood interacting. Those arising from the role of the cell wall can come from plaque rupture, endothelial disfunction (expression of certain molecules causing a loss of anti-coagulant properties), or plaque thrombogenicity where exposed tissue factor initiates a blood coagulation cascade arising from metabolic processes. The blood has several components that can activate clotting: increased platelet (blood clot cells) reactivity and volume, alteration of the physiological balance between coagulation and fibrinolytic (breaking down of clots) cascades resulting from expression of coagulant factors, the well-known effect of cholesterol and other lipo-proteins, and inflammation which can cause changes in lipoprotein balance, susceptibility to infection agents or antigens disturbing the autoimmune process. All of these are the result of changes in physiology and metabolism arising from a host of short and long term effects. Monaco et al. [1] concluded that when intracoronary thrombosis occurs the exact chain of events that might cause the final event is not fully understood. Indeed many diseases (so called) are not diseases but syndromes i.e. a collection of signs and symptoms. The prevention of heart attacks will not be achieved until the specific diseases causing the syndrome are identified as specific cellular of metabolic changes contributing to a system's failure.

The heart is at the centre of the cardiovascular system. But even within this there are systems such as the one that regulates the platelet cells (the megakaryocyte-platelet system [3]). The complexity of medical problems such as heart attack (myocardial infarction) confronting clinicians is huge and increasing as understanding of biology increases. How can clinicians keep on top of all of this information let alone navigate a path to appropriate diagnosis and treatment without decision-support systems? With the advent of molecular biology biological scientists have lost the ability to think in systems.

Physiology and clinical medicine have become splintered into specialists in very specific areas. Knowledge has become much deeper on all physiological processes making it impossible to be able to view the whole body and to understand system level interactions which may be affected by phenomena or defects at genetic, metabolic, vascular or organ level. The knowledge is being codified by researchers through data

models and predictive models which can be brought together to assist in understanding whole body physiology and of the effects of health, diet and disease but there is still much to do to have models of sufficient accuracy and to bring these models together to make systems that might be of use to clinicians.

1.2 Physiological systems and complexity

Physics is inherently simple in so far as its complexity is predictable. Biology is inherently complex; even though it ultimately obeys the rules of physics in its parts, it is not predictable in its totality. This property of biology affects our ability to understand how biology works and how it can malfunction. This is a formidable challenge for the scientist whose job is to unravel the function of biological systems and brings difficulties for the clinician who needs to understand how mammalian biology malfunctions. The problem is amplified by the therapeutic pharmacologist who wants to make molecules that interfere in biological malfunction. In experiments to probe malfunction single molecules are used to observe change in function. The constraint is that the biological system probed by pharmacology is complex even if it is a single cell. Cells make tissues then tissues make organs and then organs make systems within an individual animal. The information gained from such experiments is greater the less complex the system: more information from a cell, less information from an organ. However, often the information gained from a cell is less useful than the information gained from a whole organ. The agents used to probe biological systems may become therapeutic drugs. However the complexity of the systems being probed means that the process of discovering new therapeutics is inherently hit and miss. It is inefficient, costly and time consuming. The pharmaceutical company Pfizer invested $3.5 billion per year for three years into pharmacological discovery and discovered nothing useful. So, the complexity of biological systems is a fundamental problem for the understanding of biology and creating new drugs to change it when it goes wrong.

This is true in many systems, however there are differences. If the endocrine system malfunctions it is relatively easy to intervene therapeutically. For example in hypothyroidism the diagnosis is made by measuring the level of the hormone thyroxine in the blood. If the level is low it needs replacing. This is a replacement therapy which is the simplest form of therapeutics. However in more complex diseases the problem of treating the totality of the disease, as in hypothyroidism, is almost impossible. Cancer and cardiovascular disease are the two most common diseases which cause death in developed society. The former is caused by a change at the level of the cell. The latter is caused by the interaction of changes in many different cells, different tissues and different organs. The development of drugs to change cardiovascular disease has taken place over the last 50 years. However cardiovascular disease still kills more people prematurely in developed society than any other disease. The mismatch between the effort of research and achievement is probably a reflection of the inherent complexity involved. Tools to understand that biological complexity are lacking.

Models and their use in systems analysis could be useful for both clinicians and biological scientists: “A biological scientist … must question whether the various mechanisms form part of a single process … or whether each proposed mechanisms is capable of giving rise to the syndrome by itself. Similarly, a clinical scientist should question whether we should tackle therapeutically all components together … or each component individually.” [1].

Although there is still so much yet to be understood there are some predictive models of physiological systems. As these are put together into computational systems of systems (through project such as the virtual physiological human http://www.vph-institute.org, the Physiome Project http://physiomeproject.org/ and HumMod http://hummod.org/) there is a need for engineering tools to make best use of the systems of connected models.

There is a similar mindset between clinicians and engineers: both are problem solvers. “Engineers make things, they make things work and they make things work better” (http://www.raeng.org.uk/education/what-is-engineering#sthash.q8O7jQXK.dpuf.). Complex physiological systems can be approached in the way that chemical engineers tackle manufacturing problems through analysis, modelling and design of complex “flowsheets”. In the 1930s Kahn presented the idea of “Man as Industrial Palace” with a set of cartoons illustrating five cycles within the human factory: respiration, blood circulation, digestive circuit, control centre (brain), and metabolism (see http://www.industriepalast.com/ for an animation). In the 1950s Guyton [4, 5] pioneered the use of systems analysis in the cardiovascular system integrating many factors affecting peripheral circulation, the heart, the endocrine system, the autonomous nervous system, the kidneys and body fluids. Noble developed the first computational model of the heart including electrical, mechanical and chemical elements which has been used by the Food and Drug Administration for drug testing [6]. Recently Christ et al. [7] demonstrate how computational modelling and systems medicine can be used in surgery of the liver.

When considered in this light we can see that Engineers have a role to play in helping to make the most of the knowledge of physiology that is becoming increasingly quantified, modelled and computational. Engineers have much experience with modelling, optimising and controlling complex systems involving chemical and physical change. Some chemical engineers in particular have been involved in modelling and experimental investigations in medical fields. For example Yin [8] consider challenges in virology and Netti et al. [9] in fluid transport in tumours. Peppas and Langer [10] reviewed the contributions of chemical engineers to biomedical engineering over the years concentrating on biomaterials, drug delivery and tissue engineering. Engineers have been engaged in looking at the systems engineering of medicine (see [11–13] for recent reviews and [14] for an example for inflammation response to infection or trauma). The report Convergence–The Future of Health” [15] sets out the range of challenges for bringing together disciplines, including Chemical Engineering, to solve healthcare problems highlighting imaging, nanotechnology, regenerative engineering and medicine, and big data.

Our aim in this paper is to look in particular at the challenges where modelling and Systems Engineering techniques can explore and manage the complexity to find effective solutions and help manage the risk associated with making decisions about very complex interacting systems.

The paper is presented in four parts: “how complicated can this really be?” exploring in more detail the interconnected complexity, “The power of purpose” which influences the modelling approach, “Do we really understand?” very briefly discusses the state of the art of quantitative modelling, and “What can we do?” looks at how we might be able to deploy our skills and toolboxes. The references in this paper are not meant to be comprehensive and the examples are drawn mostly from the authors’ own experience and discussions with other medical colleagues.

1.3 How complicated can this really be?

The human system functions through the operation of a number of interacting systems [16]: cardiovascular (includes heart, veins, lymphatics and arteries carrying the blood), digestive, endocrine (chemical communications using hormones), integumentary (skin, hair, nails, seat and other glands), lymphatic (immune system), muscular, skeletal, nervous, renal, reproductive, respiratory and sensory systems. These all involve networks of chemical reactions and transport of fluids within and between cells and organs. Primary transport of fluids is via the blood and lymph both of which are chemically very complex, and air in the respiratory system from which oxygen is absorbed into the blood stream. These fluids transport nutrients and waste around the body between organs, or what Engineers call “unit operations” such as reactors or separators in manufacturing operations, including the heart, liver, lungs, pancreas stomach and so on as shown in Figure 1.1.

Standard Chemical Engineering assumptions consider any system as a collection of unit operations connected by fluid transport and by information networks through a control system. In chemical manufacturing processes this is an approximation with operations by no means confined to the units themselves. The flow of information in human physiology is even more complex through the nervous system, genetics, and through a range of complex chemical signalling entities.

Manufacturing control aims to achieve stable operation through fixed “set points” for certain variables to achieve safe and efficient operation and is achieved by valves, controllers and an information system. The objectives for human operation are not simple. The control of the body, homeostasis, requires smooth and steady operation but this does not necessarily mean that key variables need to track a set point such as a fixed temperature. The system needs to keep these variables within bounds. Homeostasis ensures the following entities are “kept, by carefully regulated mechanisms, within the narrow limits compatible with life”: nutrients, O_2, CO_2, waste, pH, water, salts and other electrolytes, blood pressure and volume, and temperature [16]. For example glucose in the bloodstream needs to be kept within bounds to ensure no hyperglycaemic or

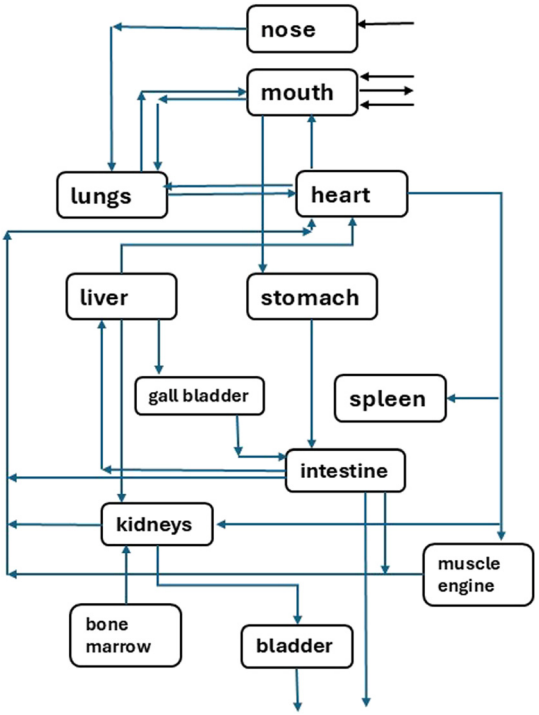

Figure 1.1: An idealised "unit operations" perspective of the human body.

hypoglycaemic attacks. Many controls that are given to the system are periodic and provide a stimulus that keeps the operation within bounds–such as feeding and drug dosages.

The chemistry and biochemistry in these systems is hugely complex. The chemistry of life is a dynamic process governed by very complex reaction networks, is affected by personal genetics, and is spatially distributed by being localised in some parts of organs and of cells. Reactions are of course not confined to the "unit operations". There has been huge progress in unravelling the chemistry of life with vast databases of pathways, genetics, transcription factors and so on which can be exploited in analysis and operation. We would need to be able to quantify fluid and transport properties (through cells, across membrane boundaries, and within fluid streams) where there has been considerable theoretical work but there is considerable need for more modelling across scales and data [17]. This makes the need for a systems approach all the more necessary, not only to help link and solve the complexity but also to identify what really crucial information is missing.

Time varying treatment is common in hospital to keep key functions within safe operating limits. But time varying dosage may be in for more radical reappraisal with the aim of exploiting and regulating changes in the cell cycle. Lee et al. [18] recently demonstrated with very comprehensive experimental and clinical programmes that

using a deferred dosage of a second chemotherapy drug 8 h after the first drug had beneficial effects to cancer patients by exploiting changes in the cell behaviour during its natural cycle. This opens up a new set of opportunities for treatment that will require engineering analysis of dynamic systems once models are available.

This complex system of interacting networks, with chemical and genetic signals, has time and space dependent responses which are mostly not measurable (for now anyway). However it is one where decisions are currently made on very partial information and yet where there is much more relevant information that could influence actions if brought together for the whole system.

1.4 An example: the cardiovascular system

The commonest cause of cardiovascular disease is an occlusion of an artery by a thrombus. This leads to lack of blood flow to the organ supplied by that artery. If the artery supplies the brain then a stroke is caused, if a limb then leg ischaemia is caused, if a coronary artery is involved then myocardial infarction (heart attack) is caused. This latter is an example of the effects of complexity at many levels: chemical signalling, cell-cell interaction, tissue interaction, whole organ interaction and physical forces such as flow.

The final event in the cause of myocardial infarction is a single catastrophic failure. However this event only occurs on a background of pathological change over decades. The single happening has its own complexity which is at a different level from the complexity of the very slow change which precedes it. Autopsies performed on soldiers killed in Vietnam and Korea showed that the start of the slow change, atherosclerosis, probably starts in some people in their late twenties. This change progresses mostly imperceptibly until the final infracting event which occurs at a mean age of around 65.

1.4.1 The arterial wall

In engineering terms the artery is simple: it is a conduit for blood. However the flow of blood has to be regulated through rapid change in diameter along the length of the artery. To achieve this both local and systemic signalling molecules interact with the contractile muscle cells that comprise the bulk of the artery. These signals vary from very low molecular weight molecules like NO to very large proteins like VEGF, many thousand times larger than NO. The lining of the artery, the endothelium, is essential in this signalling process. It also produces agents which act on the blood. Both the smooth muscle and the endothelium is composed of cells which are not all of one type; there are variations in structure and function. The outer layer of the artery, the adventitia has been neglected by researchers. However it has a complex structure. In particular there are small blood vessels within it that penetrate the muscle layer of the artery. These vasa vasorum supply oxygen to the outer layers of the muscular zone. They themselves can undergo the changes that

conduit vessels do. A micro thrombus forming in these vessels can cause change in function of the main artery. Thus the structure and function of the normal artery is complex in itself and in its relationship to signalling systems in the whole body.

Vascular disease is a consequence of malfunction of any component of the vessel wall or its signalling system. A single event, like thrombus formation in the artery, only occurs on a background of years of change in structure and function. The endothelial lining is damaged slowly by high blood pressure, by smoking and by high cholesterol levels in the blood. The latter effect is partly via an effect of the cholesterol on a blood cell, the macrophage, which is stimulated to enter the vessel wall from the blood and cause damage in the wall. Such damage can progress over decades with several blood cells being involved until a plaque of atheroma is formed. Eventually this may become hardened with calcium within it. This process is not simple but involves slow change in components of the wall and blood. Some caused by external influences some by internal ones such as ageing. Most of these changes are, in part, due to a disturbance of a dynamic equilibrium between cells and signalling systems.

1.4.2 The blood

The blood is composed of cells flowing in a medium of soluble elements, mostly proteins. The red cells carry oxygen from lungs to tissues. The white cells have a myriad of types each with a specialised function, mostly being involved in different elements of defence. Platelets are structurally unique as they have no nucleus: an essential element of all other cells. Why this is remains a mystery. Platelets are very small cells with a relatively large surface area. They are essential in stopping bleeding but if they are inappropriately active they can form into a mass which stops the flow of blood in arteries. This function of aggregating into a mass is controlled by more than a dozen signalling systems. Probably the most important being NO and a large prostaglandin called prostacyclin. These two act synergistically to damp down platelet aggregation through modulation of proteins in the platelet which in turn cause changes in the signalling of calcium within the platelet. This small element of the normal function of the artery is itself very complex. It is a system that is held in tension for years then might be activated in a millisecond. The complexity of the platelet system is enhanced as the platelet is produced from a cell which matures in the bone marrow and travels to the lungs where one of these megakaryocytes fragments into 3,000 small functional units, platelets. Every step in this complex process of platelet production can affect the function of the circulating platelet.

1.4.3 The catastrophic event

In an adult human being the gross function of the artery in delivering blood to the heart muscle can remained unchanged for decades while slow deterioration occurs in its

component parts. These slow changes produce no symptoms. However myocardial infarction produces sudden massive pain in the chest. Autopsy studies demonstrate that this pain is caused by the formation of a blood clot in the artery taking blood to the heart. This clot is initiated by platelet aggregation. The source of the agents that cause the aggregation is a sudden rupture of a plaque of atheroma in the arterial wall. This has been likened to the catastrophic breaking of an aircraft wing after years of metal fatigue. The contents of the plaque pore out into the blood delivering a high concentration of agents which stimulate platelets to aggregate. This produces a chain reaction among platelets so they react as though the body was suffering a life-threatening bleed. This causes the production of more procoagulant platelets from the bone marrow. This in turn caused protein ropes to form over the platelet aggregate to stabilize it, making it resistant to forces which can break up clot. A consequence of this catastrophic biological event is sudden death or long-term damage to heart muscle causing chronic heart failure.

1.4.4 Therapeutics

Therapeutic intervention to prevent or treat these pathological processes is based on the study of normal tissues in the laboratory. For example small pieces of rat artery can be suspended on a wire and agents applied to them which cause then to contract or relax. Once such a deterministic system has mapped the normal function of an artery, agents which modify the function can be tested. These tests may be considered as binary, giving rise to one agent which may become a drug which modifies one element in a very complex system. The same applies to platelets which can be suspended in plasma in the laboratory and caused to aggregate in a quantifiable way. Although the experimental output is elegant dynamic dose response curves again the experiments can be considered as binary: the results for one agent produce one blocker of a process which can give rise to one drug. Even though aspirin was developed for the prevention of platelet aggregation and statins were developed to prevent the slow effect of cholesterol over many years on the artery wall, people taking both aspirin and statins still suffer fatal myocardial infarction. The binary study of individual events has not solved the problem of treating or preventing myocardial infarction.

1.4.5 The system

It is understandable that a complex system has been understood only in part through deterministic steps since only deterministic experimental methods were used. However the failure of 50 years of therapeutic science to produce a definitive therapeutic approach to the prevention or treatment of myocardial infarction must question the use of deterministic experimentation as the only approach to therapeutics. The biological system which delivers blood to the heart in a controlled way is the product of 120 million

years of mammalian evolution which has produced a complex system. (The simplicity of physics did not evolve). Both the evolution of the system and the present function of the system need to be examined as a whole. Modern laboratory science has in fact gone in a different direction. Molecular biology has the power to examine the products of thousands of genes in samples taken from cells. This science can in fact be considered a regression from physiology to anatomy: the study of structure; the structure involved in smaller and smaller events. What may be lacking is progress from physiology and pathophysiology to study of the complex system as a whole. In this way patterns of function which are crucial to function might be identified. Further crucial choke points in dynamic systems might be identified as places where effective intervention might produce effective therapeutics. In particular the slow change in the arterial wall leading to atherosclerosis could be modelled and compared to the instantaneous catastrophic change which causes myocardial infarction. The study of dynamic systems has not been undertaken in therapeutics since it requires a different language to be applied. The change from thinking in deterministic quanta to a systems approach requires a cross disciplinary connection which has been lacking.

1.5 The power of purpose

Diagnosis and disease management will need different models and data. Clinicians use their experience for diagnosis requesting specific diagnostics based on their analysis of the symptoms. The choice of measurements depends on experience and they can be vague and conflicting. Systems models could aid this process but as engineers know the requirements of a model depend very much on purpose to which it is being put [19]. Here are a few examples where the purpose dictates model requirements.

Much chemical engineering is based on models which assume homogeneity (“lumped” models) as are some organ models. If we are interested in glucose regulation in the bloodstream for diabetes for example, lumped models of liver and pancreas give good prediction of behaviour and allow discovery of system behaviour characteristics [20]. Metabolic dysfunction-associated steatotic liver disease (MASLD) is a condition of accumulation of lipids and fats in the liver and liver cells (hepatocytes) arising from malfunction in the hepatocyte metabolic processes. Conditions such as MASLD (and also paracetamol poisoning) do affect the liver cells across the liver in a differential way resulting in the need for the “distributed” model [21] shown in Figure 1.2. This figure is explored in more detail in one of the companion articles [22].

Many patients have long standing chronic liver disease resulting in complex management, hospitalisation, and eventually death. Patients’ condition can be stable for extended periods and then experience a sudden degradation in their condition without warning. There are many causes and indicators for this to occur but in this case an early warning system would need many data points where some causative models may be

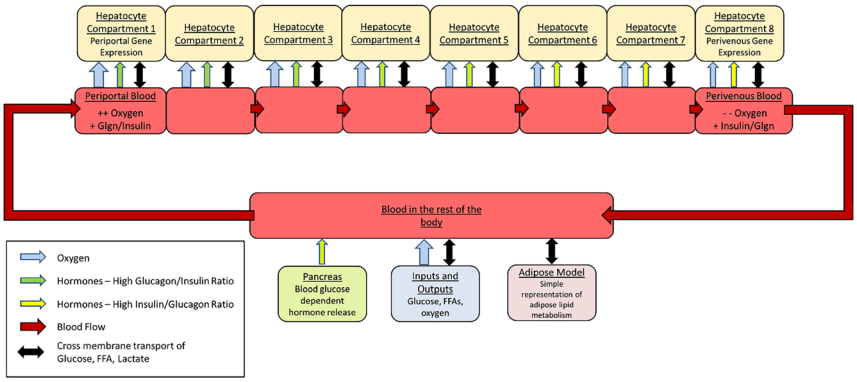

Figure 1.2: An engineering representation of zonated behaviour of hepatocyte cells processing nutrients from the blood across the liver (from [21]).

more useful than detailed predictive models [23]. The architecture of fault detection systems used in manufacturing could be used [24].

To control the production of insulin to manage type 1 diabetes Percival et al. [25] developed and implemented a real time control system using feedback of the glucose signal to adjust insulin flow in real time. Control algorithms require a precise and quantifiable objective to enable calculation of control actions. Their controller is a traditional engineering controller (an Internal Model Control tuned Proportional-Integral action controller) and has been used successfully on patients.

If we are interested in well-being of non-diseased populations or individuals a model could be used to investigate the impact of different foods, as defined by their key chemical ingredients, on metabolism and potential fat accumulation. The model could be used to explore efficient energy utilisation of nutrients for example.

The optimization and control of physiological processes to treat disease are very ambitious goals currently with significant limitations. Their effectiveness will depend on the quality of model predictions. To solve any design or optimisation problem we need to articulate clearly the design objectives and be able to determine the precise quantifiable objective function of the optimisation problem. Modellers need to ensure that the key phenomena related to the required purpose are included. At the moment this is still a matter of judgement.

1.6 Do we really understand?

Modelling of physiological processes is widespread. There is a huge range of models from the very simple to the very complex, from the entirely data driven to the fully deterministic and all points in between (see for example collections of papers in [26, 27]). Many

models have been developed to explore individual phenomena and hypotheses. Fewer look at systems and even fewer attempt to link together systems. The VPH, Physiome and HumMod projects referred to above do this.

The multi-scale links between different networks and effects on health are important and not well integrated yet. Cancer is the result of metabolic defects causing cell proliferation. Causes are varied and unclear but often the result of genetic changes. For example malfunctions in the epidermal growth factor receptor (EGFR) network is a cause of some cancers. It is a well-studied network [28] and yet the behaviour and effects of treatments are not fully understood or predictable because of the huge data requirements for properly characterising its behaviour. The network is very complex and pathway bypasses can give the cell more robustness resulting in greater proliferation. Multiple drug targets are necessary which would need to be identified by network optimisation techniques.

The models to treat MASLD of the liver require both the equations for the metabolism describing the processing of nutrients to fats and lipids together with the ability to predict differentiated amounts across the plate of liver cells. Figure 1.2 shows an engineering representation which uses the approach used for industrial chemical reactors. This requires information on a range of metabolic processes, but particularly accurate information on the insulin sensitivity which causes the disease. This is not directly measurable but can be inferred from experiments allowing the effectiveness of the system to different treatments to be explored [21]. The behaviours are not fully understood but the engineering approaches to modelling help to direct experimental investigations towards key data and information required to predict behaviour.

There is still much that is not well understood about human physiology which limits the contribution modelling can make. But that was also said at the start of the modelling and simulation revolution in the process industries in the 1950s. Progress can be made by developing systems, solving partial problems (but considerably more complete than single individuals can do now), linking these models of systems within systems, and helping to identify important information that is lacking. This sort of systems biology work is going on already (see [29] for a recent review) but mostly to aid understanding. As well as models this requires fitting models together, bringing in data often available in significant amounts but with mixed quality, and then directing further experiments resulting in an iterative process between model and experiment.

1.7 What can we do? An expanded role for engineers

Healthcare is a matter of such concern and interest to society that engineering would like to play a greater role in it. Chemical processes are central to the way our physiology functions. Physiological processes are much more complex than those we are used to tackling in manufacturing but engineers have the skill set to help make progress.

Engineers are adept at using models for solving problems so there is much scope for using the tools of control and optimization with models and interlinked groups of models in medicine. A model can be used to optimise an objective such as minimise energy or minimise a particular metabolic product. Solutions are almost always on constraints which are often poorly characterised. In the first instance solutions would be most useful in indicating actions and highlighting their consequences in the systems involved in the model to highlight physiological effects which might not otherwise be expected because of the complexity of the system. By bringing together patient databases, with a wide range of data on patients' condition, models can become richer and used to understand potential wider effects of treatments. Precision medicine [30] cites the use of large datasets for guiding therapy but it needs a framework of models to help integrate the data and incorporate known predictable quantitative behaviour in an efficient way, particularly for predicting beyond the range of the individual's known data.

Engineering became a very quantitative discipline many years ago by developing predictive models and using them to design, control and troubleshoot complex chemical manufacturing processes. The life and medical sciences is becoming more quantitative. Engineers are adept at using complex models for decision making, sometimes instructing decisions in real time or in an advisory capacity. Working together with medical colleagues engineers are in a position to help deploy these techniques of design, control and optimisation in medicine.

By bringing together all information relevant into a model or system of models engineering methods could help answer questions such as: what is the optimal drug dosage, timings and location for effective treatment? amongst all the competing phenomena what according to the system models what is the most likely cause of a condition? amongst all the information available which affect the outcomes most and need therefore to be most accurate? These are ambitious goals that elude us at the moment but the explosion of data and models and the deployment of engineering problem-solving tools will give sufficient information in the future.

The chapters in this book demonstrate some of the progress that chemical engineers have made in modelling and systems analysis of certain physiological systems.

Engineering methodologies can have a very significant role to play in the future as the world works towards model-based personalised medicine. It needs joint teams of engineers, biologists and clinical scientists working together to tackle complex systems using all information available.

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