UNIT 6 MODELLING IN MEDICINE

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6.1 INTRODUCTION

Over the past few decades there has been a considerable increase in the application of quantitative methods to the study of physiological systems. This is because new techniques for making physiological measurements are being constantly developed and there is more classification of clinical data. Also, there has been a corresponding increase in the mathematical/statistical methods available for the analysis and interpretation of such data.

Mathematical modelling is increasingly being applied to the field of medicine as well, especially i) to interpret and predict the dynamics and control of diseases in order to improve global health and ii) to improve the diagnosis and decide on the dosage of medicines. Specific examples include predicting the impact of vaccination strategies against common infections such as measles and rubella and determining optimal control strategies against HIV and vector-borne diseases. There is tremendous potential for using computer based numerical techniques to study the effects of the drug on the patient by comparing the growth of blood supply to a tumour and its invasion into the normal tissue. A mathematical model could predict what would happen to the tumour, whether it would respond to treatment or not.

All physiological systems are characterized by their complexity. It is important that we should understand this complexity, since a mathematical model that we create will be a simplification, an approximation of that complex reality. By understanding something of this complexity we shall be in a better position to make the simplifying assumptions that correspond to the particular model formulation that we shall adopt. In essence, the model that we develop needs to have taken into account both this inherent complexity that we have simplified and the availability of measurement or clinical data which will be used in estimating the parameters of our model.

In this unit, we have illustrated the application of mathematical modelling in the field of medicine by considering two examples where we have formulated simple models for tumour growth and diabetes. Before formulating these models we have given briefly the complexities associated with the corresponding physiological system for each model. In Sec. 6.2, we have started with describing the process of progression of solid tumours and then discussed models for the growth of solid tumours. Different stages in the growth of a tumour and models for avascular tumours are also discussed here.

In Sec. 6.3, after giving a brief physiological detail of blood glucose metabolism, we have discussed a model for the detection of diabetes mellitus which can be used to diagnose diabetes on the basis of the data obtained by the glucose tolerance test of a patient. As a matter of interest, we have given the complete pathophysiology of diabetes mellitus in an Appendix at the end of the unit.

Objectives

After studying this unit, you should be able to:

- state the essential factors to be considered in the modelling of growth development in solid tumours;
- formulate a model for the growth of solid tumour and use it to find the density of the cancer cells in the tumour's surface area at any point of time;
- describe different stages in the growth of a tumour;
- formulate a model for avascular tumour and estimate the growth of tumour in terms of Malthus/logistic equations;
- describe the blood glucose regulatory system;
- use the model for the detection of diabetes to diagnose mild diabetes on the basis of data obtained from glucose tolerance test of a patient.

6.2 TUMOUR MODELS

Tumour is the unbounded proliferation of cells. Specifically, it is the uncontrolled growth of a host's own "self" cells. Much of the mechanism of tumour development and proliferation is still unknown. But, it is known that abnormal cell growth occurs because of malfunctioning in the mechanisms that control cell growth and differentiation.

Neoplasia literally means "new growth", and the new growth is a "Neoplasm". The term "tumour" was originally applied to the swelling casued by inflammation. Neoplasm also may induce swellings, and the term tumour is now equated with neoplasm. Oncology is the study of tumours of neoplasm. Cancer is the common term for all malignant tumours. Tumour growth modelling has been the subject of much recent literature, but the existing mathematical models appear to neglect the local interaction between cancer and tissue cells. This interaction between cancer and tissue cells affects the cancer cells reproduction rate the way that it becomes dependent on their local concentration. Therefore, tumour growth is mainly determined by the behaviour of cancer cells adjacent to the tumour surface. This process, in its turn, is largely dependent on the tumour's local curvature.

A mathematical model should be viewed as an attempt to understand the growth dynamics of a single vascularized solid tumour growing within the confines of an organ, such as a primary lung or breast. A model can be formulated by stressing the competition within the environment provided by that organ. Therefore, the model may give rise to useful tools that oncologists can use to help decide the proper course of treatment for specific patients.

You may try the following exercise.

E1) What do your mean by malignant tumours? Also, which study deals with tumours?

6.2.1 Growth of Solid Tumour

One can try to investigate the macroscopic effects of tumour growth in a homogeneous tissue. The effects of local interaction can be most simply described in terms of reproduction function. Fig. 1 shows hypothetical non-monotone curves 1-3 describing the reproduction rate of cancer cells i.e., $\dot{c}$ vs local concentration i.e., c.

The curves represent the interaction of carcinogenic factors with the immune system, the availability of nutrients and the local cellular interaction.

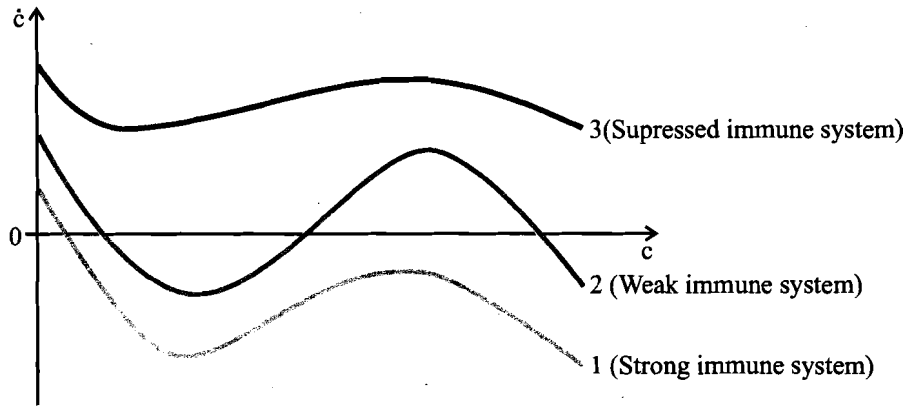

Fig. 1: Reproduction rates of cancer cells as a function of their local concentration c (curves 1-3).

Furthermore, as the concentration of cancer cells increases, the suppression of their reproduction through local interaction between cancer and tissue cells is first slowed, then completely stopped. Finally, it gives way to a reverse process in wich cancer cells stimulate the pathological division of the tissue cells. In Fig. 1, this process corresponds to the interval of increase. A still higher concentration of cancer cells causes a deficit of nutrients which results in the inhibition of cancer cells' reproduction rate and finally to their death. In Fig. 1, this process corresponds to the second interval of decrease. Curve 1 describes the case when tumour onset in the tissue is fully suppressed. Curve 2 represents the case when the immune system cannot provide complete suppression and tumours can spontaneously arise and develop. This case is the subject of our study. Curve 3 images a suppressed immune system when the tumour spreads throughout the organism.

Formulation

For the sake of simplicity, we shall model this problem in two dimensions which corresponds to the behaviour of tumour sections. The difference between the three- and two-dimensional formulations is of minor importance as

we consider the processes only qualitatively. Assume that the reproduction function is given by $\phi(c)$. Let R be the radius of a spherical tumour, and r the radius of cancer and tissue cells. $c = x/(x+y)$, where x and y are the number of cancer and tissue cells, respectively, in the considered tissue area. (For simplicity and without loss of generality, cancer and tissue cells are assumed hereafter to be of the same size). The density c of cancer cells in the vicinity of the surface is defined as $\frac{S_c}{S_c + S_t}$, where $S_c = 4\pi r(R-r)$ is the area of a layer of tumour cells that contact the surface from inside, and $S_t = 4\pi r(R+r)$ is the area of a layer of tissue cells that contact the surface from outside. This implies

$$c = \frac{R-r}{2R} \tag{1}$$

R and $\dot{R}$ are found from Eqn. (1) as

$$R = \frac{r}{1-2c} \tag{2}$$

$$\therefore \dot{R} = \frac{2r\dot{c}}{(1-2c)^2}. \tag{3}$$

Let a tumour occupy the area $A = \pi R^2$. Then,

$$\dot{A} = 2\pi R\dot{R}. \tag{4}$$

On the other hand, $\dot{A}$ is the area of cancer cells produced per unit time in the area $S_c + S_t$. Therefore,

$$\dot{A} = (S_c + S_t)\,\varphi(c) = 8\pi r R\varphi(c) \tag{5}$$

From Eqns. (4) and (5), we obtain

$$\dot{R} = 4r\varphi(c) \tag{6}$$

Substituting Eqn. (6) in Eqn. (3) we obtain the differential equation for the density of cancer cells in the tumour's surface layer:

$$\dot{c} = 2\varphi(c)\,(1-2c)^2 = \psi(c) \tag{7}$$

Fig. 2 shows the plot of $\psi(c)$ (blue curve) compared with the plot of $\varphi(c)$ (red curve).

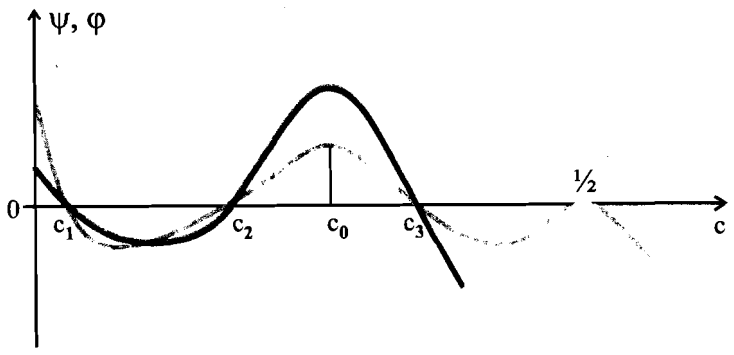

Fig. 2: Derivative of cancer cells density at the tumour surface $\psi(c)$ (blue curve), and initial reproduction function $\varphi(c)$ (red curve).

Example 1: A spherical tumour is occupying the space in an organ with outer and inner radii 0.2×10^{-6} mm and 0.001×10^{-9} mm, respectively, for tumour and cancer cells. Find the density of cancer cells in the vicinity of the surface.

Solution: Let $R = 0.2\times10^{-6}$ mm and $r = 0.001\times10^{-9}$ mm denote these radii. We know that the density c of the cancer cells in the vicinity of the surface is given by $c = \frac{S_c}{S_c + S_t}$, where $S_c = 4\pi r(R-r)$ and

$$S_t = 4\pi r(R+r).$$

Thus, $c = \frac{S_c}{S_c + S_t} = \frac{1.999\times10^{-7}}{10^{-7}\times(2.001+1.999)} = 0.49975\text{mm}.$

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You may now try the following exercises.

E2) Find the reproduction rate of the tumour cells proliferation within the tissue of an animal brain with the density of cancer and local cells 0.3×10^{2} and 3×10^{15} cells respectively.

E3) The reproduction function of the cancer cells within a spherical tumour is given by $\varphi(c) = \frac{3c+1}{(1-2c)^2}; c \neq \frac{1}{2}$ with initial conditions given by $c = c_0$ at $t = 0$. Find the density of the cancer cells in the tumour's surface area at $t = 30$ days.

6.2.2 Avascular Tumour

There are several different stages in the growth of a tumour before it becomes so large that it causes the patient to die or reduces permanently their quality of life. There is a lot of controversy over how exactly cancer is initiated, but it is a generally accepted view that it requires several gene mutations to turn a normal cell into a cancer cell. The factors that trigger these mutations are largely unknown, but are thought to include both environmental and hereditary effects. One of the outcomes of this series of mutations is an increase in the proliferation rate and a decrease in the death rate of the cells, giving rise to a clump of tumour cells growing faster than the host cells. However, even a fast growing clump of tumour cells cannot grow beyond a certain size, since there is a balance between cells inside the clump consuming nutrients and nutrient diffusion into the clump. Therefore, one of the most important steps in malignant tumour growth is angiogenesis, which is the process by which tumours develop their own blood supply. For this reason novel drugs are being developed specifically to target tumour blood vessels. Once the tumours have acquired their own blood supply, the tumour cells can escape the primary tumour via the circulatory system (metastasis) and set up secondary tumours elsewhere in the body. After angiogenesis and metastasis, the patient is left with multiple tumours in different parts of the body that are very difficult to detect and even more difficult to treat. Because there are three distinct stages (avascular, vascular, and metastatic) to cancer development, researchers often concentrate their efforts on answering specific questions on each of these stages. **Avascular tumours are tumours without blood vessels**. This may not be the most important aspect of tumour growth. On the contrary, from a

clinical point of view angiogenesis and vascular tumour growth together with metastasis are what cause the patient to die, and modelling and understanding these is crucial for cancer therapy. Nevertheless, when attempting to model any complex system it is wise to try and understand each of the components as well as possible, before they are all put together in a model. Avascular tumour growth is much simpler to model mathematically, and yet contains many of the phenomena which are needed to address in a general model of vascular tumour growth. Moreover, the ease and reproducibility of experiments with avascular tumours means that the quality and quantity of experimental evidence exceeds that for vascular tumours, for which it is often difficult to isolate individual effects.

You may now try this exercise to test your understanding of whatever we have discussed above.

E4) Write a short note on angiogenesis.

Different regions of both avascular and vascular tumours are shown in Fig. 3. Avascular tumour modelling can be of use when making predictions and designing experiments on vascular and metastatic tumours, which are much more time consuming and difficult.

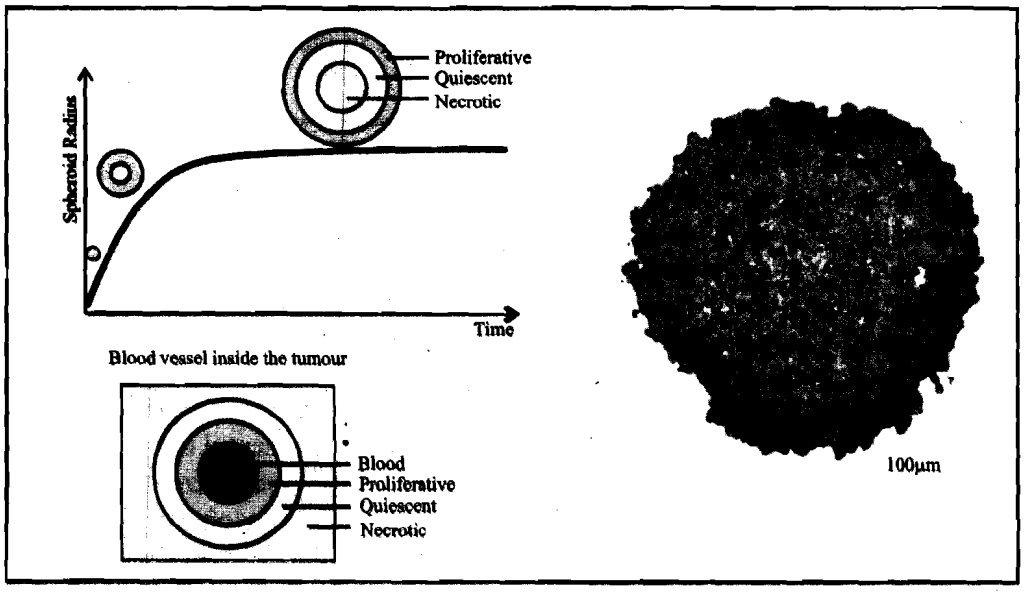

Fig. 3: Schematic illustration showing tumour spheroid growth.

The main finding of in vitro tumour spheroid experiments so far has been that the spheroids grow until they reach a critical size, when growth stops. This critical size is determined by a balance between cell proliferation and cell death inside the spheroid. The main experimental observations have been that when cancer cells are in a high nutrient environment they proliferate, in low nutrient levels the tumour cells trigger cell death (apoptosis), and in intermediate nutrient levels the tumour cells stay quiescent. This translates into the schematic growth curve shown in the above figure. The different nutrient levels inside the tumour spheroid are determined by the movement and consumption of nutrients within the tumour.

The fact that in vitro experiments clearly showed that nutrient (in particular oxygen) diffusion limits tumour spheroid growth paved the way for the angiogenesis hypothesis. This hypothesis is that, in order to grow large, tumours need to obtain their own blood vessels and, therefore, must recruit vessels from the host vasculature through angiogenesis.

Tumour cells consume nutrients. Nutrients diffuse into the tumour tissue from the surrounding tissue. Therefore, if the tumour is very large, the nutrients cannot reach all parts of the tumour tissue. This leads to a decrease in tumour cell proliferation and eventual cell death in regions lacking nutrients. The steady size of the tumour spheroid is reached when the cell proliferation in regions rich in nutrients balances cell death in regions poor in nutrients.

Formulation

The dynamics of solid tumours which are large enough to be directly observable, at least prior to therapeutic or experimental treatment, e.g., are roughly 1 to 3 mm or more in diameter "initially". Modelling such comparatively late stages is important to carcinogenesis models when comparing to observed outcomes. Models of tumour growth and treatment based on a small number of ordinary differential equations have a very long history, dating back to the equation of exponential growth,

$$\frac{dc}{dt} = \lambda c, \quad \lambda = \text{constant}. \tag{8}$$

Here, c(t) is the number of cells in a tumour, regarded as so large that small-number ("demographic") fluctuations are negligible and c can be treated as a continuous, deterministic function of the time t.

Mathematically speaking, models of this kind, using one or several ordinary differential equations, are naive and oversimplified compared to various other kinds of models. Reaction-diffusion partial differential equations are one example among many used in current mathematical and computer biology and medicine. However, a mathematician who looks in the literature for the models used routinely by experimental biologists and clinicians will see that it is the simplest ordinary differential equation models which form the foundation of applied biological modelling in practice. The most important case in point is the equation of exponential growth itself. Discussions of the value of the Malthusian growth parameter λ under various conditions still form a major portion of practical tissue culture and tumour modelling. More generally, it is usually the specification of parameter values for simple ordinary differential equation models that is the crux of the discussion. Such models aim to capture key features using a small number of adjustable parameters and, equally important, aim to neglect peripheral features judiciously.

Often a mathematically quite sophisticated model is basically a marginal elaboration of some simple ordinary differential equation model.

Example 2: Suppose that the tumour cell population is 20,000 cells, growth and decay rate is 300 and 150 cells per day. Then the rate of increase in the tumour growth can be calculated by

$$r = \frac{300-150}{20000} = 0.0075\%$$

where r is called the intrinsic rate of increase.

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You may try these exercises.

E5) In Eqn. (8), if the tumour cells in a particular organ of a human body are 5×10^3, their growth increases up to 7.2×10^5 within five days. Find the value of λ.

E6) Consider the Malthusian model. If the number of tumour cells in a particular organ is 2×10^5 and $\lambda = 6$, what will be the growth of the tumour after fifteen days?

The tumour growth has further been estimated in terms of logistic equations. This model governs the growth of tumour cells in a bounded environment. We have classified the growth of malignant cells into two categories:

Tumour Growth in a Closed Region

We define c(t) the population of tumour cells. Let G(c) and D(c) respectively denote the growth rate and decay rate of parenchyma cells in the tissues.

Then, clearly,

$$\frac{d}{dt}(c(t)) = G(c) - D(c)$$

let $G(c) = \lambda c$ and $D(c) = \mu c^2$ then we can write

$$\frac{d}{dt}(c(t)) = \lambda c - \mu c^2 = c(\lambda - \mu c) \qquad (9)$$

where λ and μ are positive constants representing the growth and decay control of the tumour.

The initial condition associated with Eqn. (9) is

$c = c_0$ at $t = 0$.

Solution

Eqn. (9) can be written in the form

$$\frac{dc}{c(\lambda - \mu c)} = dt.$$

By using partial fraction, we can integrate the equation, and get

$\ln c - \ln(\lambda - \mu c) = \lambda t + \ln a$ where a is integration constant.

or, $$\ln\frac{c}{a(\lambda - \mu c)} = \lambda t$$

or, $$\frac{c}{a(\lambda - \mu c)} = e^{\lambda t}. \qquad (10)$$

Using the given initial condition, we obtain

$$\frac{c_0}{(\lambda - \mu c_0)} = a. \tag{11}$$

Therefore, combining Eqns. (10) and (11), we get

$$c(t) = \frac{\frac{c_0}{(\lambda - \mu c_0)}\lambda e^{\lambda t}}{\frac{c_0}{(\lambda - \mu c_0)}\mu e^{\lambda t} - 1}$$

or, $$c(t) = \frac{\frac{c_0}{(\lambda - \mu c_0)}\lambda}{\frac{c_0}{(\lambda - \mu c_0)}\mu - e^{-\lambda t}} = \frac{c_0 \lambda}{c_0 \mu - (\lambda - \mu c_0)\, e^{-\lambda t}}. \tag{12}$$

From Eqn. (12) it follows that the growth of tumour cells $c(t) \to \frac{\lambda}{\mu}$ as $t \to \infty$.

From Eqn. (12), if $c_0 < \lambda/\mu$, $c(t)$ simply increases monotonically to λ/μ, while if $c_0 > \lambda/\mu$ it decreases monotonically to λ/μ. In former case there is a quantitative difference depending on whether $c_0 > (\lambda/\mu)/2$ or $c_0 < (\lambda/\mu)/2$; with $c_0 < (\lambda/\mu)/2$ the form has a typical sigmoid character, which is commonly observed.

The main point about the model is that it is a particularly convenient form to take when seeking qualitative dynamic behaviour in tumour cell populations in which $c = 0$ is an unstable state and $c(t)$ tends to finite positive stable steady state.

It is instructive to try to understand why this form was accepted since it highlights an important point in modelling in the biomedical sciences. The growth form in Eqn. (12) has three parameters, c_0, λ and μ with which to assign to compare with actual data.

You may try this exercise now.

E7) For $\lambda = 20$, $\mu = 15$ and initial tumour cell concentration is $c_0 = (2 \times 10^{12})$ in the above model, what will be the growth of tumour cells in five days?

Tumour Growth in the Open Region

The equation for this category is defined as

$$\frac{d}{dt}(c(t)) = \lambda c - \mu c \pm \gamma c = c(\lambda - \mu \pm \gamma) \tag{13}$$

where γ is the migration and emigration of cells from the tumour region due to vascularization.

Solution

The solution of the Eqn. (13) is to be obtained under the initial condition given

earlier. Solving Eqn. (13), we obtain

$$\ln c(t) = (\lambda - \mu \pm \gamma)\, t + \ln d \quad \text{where d is integration constant}$$

or, $$\ln\left(\frac{c(t)}{d}\right) = (\lambda - \mu \pm \gamma)\, t$$

or, $$\left(\frac{c(t)}{d}\right) = e^{(\lambda-\mu\pm\gamma)t} \text{ or } c(t) = de^{(\lambda-\mu\pm\gamma)t}$$

using initial conditions $t = 0$, $c = c_0$, we get

$$c(t) = c_0 e^{(\lambda-\mu\pm\gamma)t} \tag{14}$$

Eqn. (14) gives the proliferation of tumour cells in the open region.

Limitations

We may caution that the models presented here were not designed for direct clinical applications. Much more specific information and rigorous comparisons between model results and actual tumours is required before they are applied to treatment decisions in any way.

You may now try this exercise.

E8) The control parameters of growth and decay of a tumour are respectively 1500 and 800 per day. Also, the damaged cells migrate due to vascularization of blood at a rate of 300 cells per day. Use logistic model to find the ratio of the growth of tumour after 20 days with the initial tumour.

We shall now discuss the model for the detection of diabetes.

6.3 A MODEL FOR DETECTING DIABETES

Diabetes mellitus, often referred to as diabetes, is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar/glucose levels. If glucose concentration level in blood is constantly out of the range (70-110 mg/dl) then the person is considered to have blood glucose problem known as **hyperglycemia**. It mainly develops due to insufficient secretion of insulin by the β cells of pancreas. Before formulating a mathematical model for the detection of diabetes, we give you, in brief, the physiological details of blood glucose metabolism.

The blood glucose regulating system is complicated. However, we are giving here only the essential details to understand the rationale behind the model we shall be presenting.

Carbohydrates in our food are absorbed by the digestive system of the body and converted into glucose. This glucose is oxidized and is used as an important source of energy for the functioning of the body. The **liver** helps to regulate the blood glucose concentration. It acts as a major storehouse for glucose. When the blood glucose concentration is high, the excess is stored in the liver as glycogen. When the concentration is low i.e., in between meals or

when we are fasting, the glycogen is split into glucose to maintain the glucose concentration in the bloodstream. A wide variety of hormones like insulin, glucagon, epinephrine, glococorticoids, thyroxin help regulate the blood glucose cycle. The **hormone insulin**, secreted by the β cells of the pancreas, predominates to maintain the blood glucose level in the body. Whenever carbohydrates are eaten, signal is sent by the digestive tract to the pancreas to secrete more insulin. Insulin facilitates the absorption of glucose by the tissues to prdocue energy and it also enhances the storehouse effect of the liver. We can thus say that insulin regulates the blood glucose concentration by

i) increasing the rate of glucose metabolism (glycolysis).

ii) increasing glycogen store in liver and muscle mass.

Fig. 4 shows the glucose-insulin interaction loop.

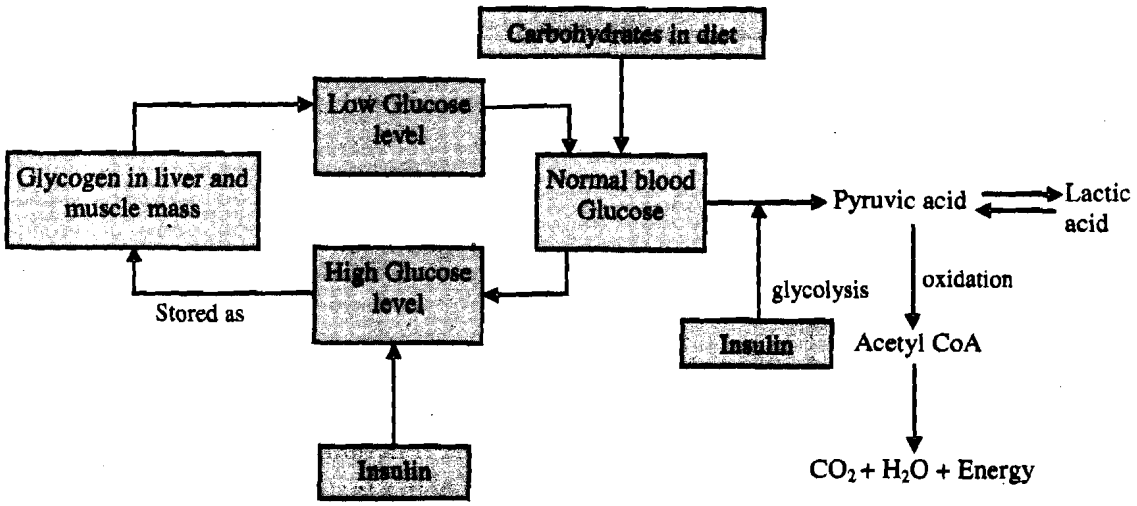

Fig. 4: Glucose-insulin interaction loop.

In diabetes mellitus, due to lack of insulin and excess of blood glucose, glucose starts excreting through urine leading to excessive thirst, hunger and weight loss which are the main symptoms of diabetes. It is, therefore, necessary to maintain the blood glucose concentration within normal range, to remain healthy. If you are interested in knowing the complete pathophysiology of diabetes mellitus then you may refer to **Appendix** at the end of the unit.

Usually, the **glucose tolerance test** (GTT) is used to diagnose diabetes. In this test, the patient who has fasted overnight, is given a large dose of glucose. During the next 2-3 hours, several measurements of the patient's blood glucose concentration are made. These measurements are then used in the diagnosis of diabetes. There is no universally accepted criterion available for interpreting the results of GTT. The criterion which we shall use in our model was given by Dr. Rosevear and Dr. Molnar, of the Mayo Clinic (USA) and Dr. Ackerman and Dr. Gatewood of the University of Minnesota (USA). They developed a simple model to obtain a criteria for distinguishing normal people from prediabetics and mild diabetics from a few blood samples during a GTT. This simplified model centers attention on two concentrations, that of glucose in the blood and net hormonal concentration which represents the cumulative effect of all the pertinent hormones. This model can still provide an accurate description of the blood glucose regulatory system due to two reasons. **Firstly**,

under normal conditions, the interaction of hormone insulin, with blood glucose is so predominant that a simple 'lumped parameter' model is quite adequate. **Secondly**, normoglycemia does not depend, necessarily, on the normalcy of each kinetic mechanism of the blood glucose regulatory system. It depends on the overall performance of the blood glucose regulatory system, and this system is dominated by insulin-glucose interactions.

Lumped parameters are simplification in a mathematical model where variables that are spatially distributed fields are represented as single scalars instead. For example, a temperature field is replaced by average temperatures.

Let us now consider the formulation of this model.

Formulation

Consider the concentration of the following two substances:

G = concentration of blood glucose

H = net hormonal concentration

Those hormones, such as insulin, that decrease the blood glucose concentration are found to increase H while hormones like cortisol which increase the blood glucose concentration decrease H. The basic model is described by the equations

$$\frac{dG}{dt} = F_1(G,H) + I(t) \tag{15}$$

$$\frac{dH}{dt} = F_2(G,H) \tag{16}$$

You may **note** that the changes in G and H are determined by both G and H as specified by the functions F_1 and F_2. The function I(t) represents the rate at which the blood glucose concentration is being increased externally. We assume that G and H have assumed their steady-state values G_0 and H_0 by the time the fasting patient reaches the hospital. This means that

$$F_1(G_0, H_0) = 0 = F_2(G_0, H_0). \tag{17}$$

Thus, Eqns. (15) and (16) give the formulated model. Let us now obtain the solution of this model.

Solution

We are interested here in considering only the small deviations of G and H from their steady-state values because the model is constructed to detect prediabetics and mild diabetics. Thus, we make the substitution

$$g = G - G_0, \quad h = H - H_0 \tag{18}$$

Rewriting Eqns. (15) and (16) in terms of these deviations, we get

$$\frac{dg}{dt} = F_1(G_0 + g, H_0 + h) + I(t) \tag{19}$$

$$\frac{dh}{dt} = F_2(G_0 + g, H_0 + h) \tag{20}$$

Expanding F_1 and F_2 in Eqns. (19) and (20) using Taylor series expansion and neglecting the second and higher order terms in the expansion, we can rewrite Eqns. (5) and (6) in the form

$$\frac{dg}{dt} = g\frac{\partial F_1}{\partial G}\bigg|_{(G_0, H_0)} + h\frac{\partial F_1}{\partial H}\bigg|_{(G_0, H_0)} + I(t) \tag{21}$$

$$\frac{dh}{dt} = g\frac{\partial F_2}{\partial G}\bigg|_{(G_0H_0)} + h\frac{\partial F_2}{\partial H}\bigg|_{(G_0H_0)} \tag{22}$$

There is no way of determining theoretically the partial derivatives appearing in Eqns. (21) and (22) since the functions F_1 and F_2 are unknown. However, using the properties of the blood glucose regulatory system, we can determine their signs.

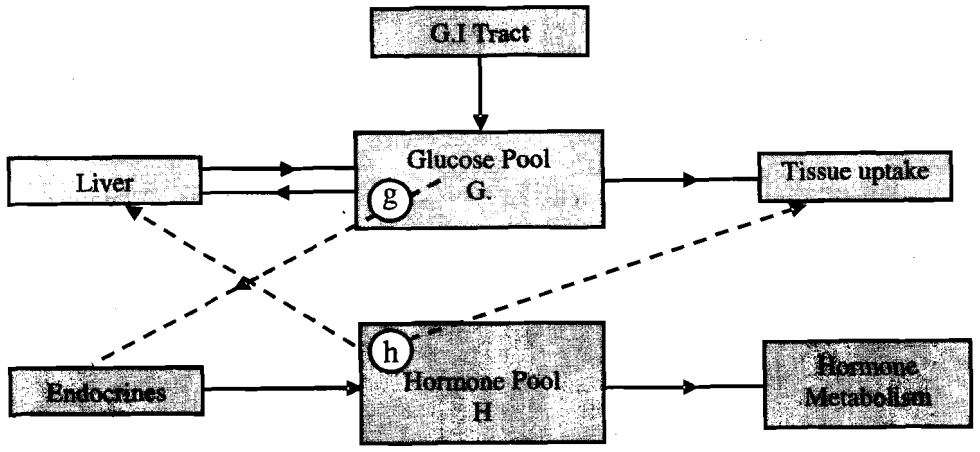

Fig. 5: Blood glucose regulatory system.

Referring to Fig. 5, we see that if $g > 0$ and $h = 0$ then the blood glucose concentration will decrease due to tissue uptake of glucose and storage of excess glucose by the liver as glycogen. Hence $\frac{dg}{dt} < 0$. Consequently, from Eqn. (21) we conclude that $\frac{\partial F_1}{\partial G}\Big|_{(G_0, H_0)}$ must be negative. Similarly, $\frac{\partial F_1}{\partial H}\Big|_{(G_0, H_0)}$ is negative, since a positive value of h tends to decrease the blood glucose concentration by facilitating tissue uptake of glucose and also increasing the conversion rate of glucose into glycogen. Further, a positive value of g causes the endocrine glands to secrete those hormones which tend to increase H and so $\frac{dh}{dt} > 0$ implying that $\frac{\partial F_2}{\partial G}\Big|_{(G_0, H_0)} > 0$. Finally, $\frac{\partial F_2}{\partial H}\Big|_{(G_0, H_0)} < 0$, since the concentration of hormones in the blood decrease through hormone metabolism. Thus, Eqns. (21) and (22) can be written in the form

$$\frac{dg}{dt} = -ag - bh + I(t) \tag{23}$$

$$\frac{dh}{dt} = -ch + dg \tag{24}$$

where a, b, c and d are positive constants. Since we only measure the concentration of glucose in the blood, we will eliminate the variable h from Eqns. (23) and (24). Differentiating Eqn. (23) with respect to t and substituting

for $\frac{dh}{dt}$ from Eqn. (24), we get

$$\frac{d^2g}{dt^2} = -a\frac{dg}{dt} + bch - bdg + \frac{dI}{dt} \tag{25}$$

Substituting $bh = -\frac{dg}{dt} - ag + I(t)$ as obtained from Eqn. (23) into Eqn. (25), we obtain

$$\frac{d^2g}{dt^2} + 2A\frac{dg}{dt} + B^2g = E(t) \tag{26}$$

where $A = \frac{a+c}{2}, B^2 = ac + bd$ and $E(t) = cI + \frac{dI}{dt}$.

You may **note** that $E(t)$ is identically zero except for short interval of time when the glucose is being ingested. Let $t = 0$ be the time when the glucose load is completely ingested. Then $E(t) = 0$ for $t \geq 0$ and Eqn. (26) reduces to

$$\frac{d^2g}{dt^2} + 2A\frac{dg}{dt} + B^2g = 0 \tag{27}$$

Eqn. (27) is a second order ordinary differential equation with constant (positive) coefficients. You must have studied such equations in your differential equations course at the undergraduate level. You know that the solutions of this equation are of three different types, depending upon whether $A^2 - B^2$ is positive, negative or zero. These three types correspond to the overdamped, underdamped and critically damped cases, respectively. We shall discuss here the case $A^2 - B^2 < 0$ (the other cases you may deal in a similar manner). The characteristic equation corresponding to this case has complex roots and solution of the form

$$g(t) = C_1 e^{-At}\cos(B_1 t - \theta) \tag{28}$$

where $B_1^2 = B^2 - A^2$. Hence, the complete solution is

$$G(t) = G_0 + C_1 e^{-At}\cos(B_1 t - \theta) \tag{29}$$

Eqn. (29) has five unknown constants G_0, A, B_1, C_1, θ. One way of finding them is as follows.

The patient's blood glucose concentration before the glucose load is ingested is G_0. Hence, we can determine G_0 by measuring the patient's blood glucose level immediately upon his arrival at the hospital. Next, we measure the patient's blood glucose concentrations G_1, G_2, G_3 and G_4 at times t_1, t_2, t_3 and t_4 respectively. These concentrations satisfy the equations

$$G_j = G_0 + C_1 e^{-At_j}\cos(B_1 t_j - \theta) \qquad (j = 1,2,3,4)$$

The constants A, C_1, B_1, θ can be determined by solving these equations and then $B = (B_1^2 + A^2)^{1/2}$

A second way of determining the five constants is by using least squares. The patient's blood glucose concentrations $G_1, G_2, \cdots, G_n$ are measured at times $t_1, t_2, \ldots, t_n$ respectively. The optimal values of G, A, C_1, B_1 and θ are found by minimizing

$$M = \sum_{j=1}^{n} [G_j - G_0 - C_1 e^{-At_j} \cos(B_1 t_j - \theta)]^2 .$$

This method is preferable to the first method, since Eqn. (29) is only an approximation to G(t). It is possible to find the values of the five constants satisfying Eqn. (29) exactly at time t_1, t_2, t_3 and t_4 but gives a poor fit to the data at other times. The method of least squares gives a better fit to the data on the entire time interval, since more measurements are involved. Observations have shown that the parameter B could be used as the basic discriminator in the GTT, since the value of the parameter B was relatively insensitive to experimental errors in G. The results obtained on the basis of data from many sources indicate that if the period $T_0 = \frac{2\pi}{B}$ is less than 4 hrs, the patient is normal, while the value of T_0 more than 4 hrs indicates mild diabetes.

Limitations of the Model

This model can only be used to diagnose mild diabetes or prediabetes and it sometimes yields a poor fit to the data 2-3 hours after the ingestion of the glucose load. The first difficulty is due to the fact that the deviation of G from G_0 must be small. The second difficulty arises during the recovery phase of the GTT response, when the glucose levels may be lowered below the fasting level. The model is a lumped-parameter model where we have not considered the effect of other hormones like epinephrine and glucose separately but lumped them together with insulin. This model also ignores the effects of diet and exercise.

You may now try the following exercises.

E9) Derive Eqn. (28)

E10) A patient arrives at the hospital after an overnight fast with a blood glucose concentration of 70 mg/100 ml blood. His blood glucose concentrations 1 hour, 2 hours and 3 hours after fully absorbing a large amount of glucose are 95, 65 and 75 mg glucose/100 ml blood, respectively. Show that the patient is of normal health.

We now end this unit by giving a summary of what we have covered in it.

6.4 SUMMARY

In this unit, we have covered the following:

1. Description of the tumour and different stages in its growth.

2. Mathematical study of the tumour growth inside the organ of any animal body.
3. Study of avascular tumors and their description in terms of mathematical formulation.
4. Tumour development within closed and open regions.
5. Physiological details of the blood glucose metabolism.
6. Mathematical model for the detection of diabetes mellitus to diagnose mild diabetes in a patient.

6.5 SOLUTIONS/ANSWERS

E1) A malignant tumour is a growth of tissue that forms an abnormal mass. Malignant tumors generally provide no useful function and grow at the expense of healthy tissues.

In general, a *malignant tumour* is caused by abnormal regulation of cell division. Typically, the division of cells in the body is strictly controlled. New cells are created to replace older ones or to perform new functions. Cells which are damaged or no longer needed die to make room for healthy replacements.

If the balance of cell division and death is disturbed, a malignant tumour may form. Malignant tumours are classified as either benign (slow-growing and often harmless depending on the location) or malignant (faster-growing and likely to spread to other parts of the body and cause problems). Malignant tumours are what we call cancer.

Abnormalities of the immune system, which usually detects and blocks aberrant growth, can lead to malignant tumours. Other causes include radiation, genetic abnormalities, certain viruses, sunlight, tobacco, benzene, certain poisonous mushrooms, and aflatoxins (a poison produced by an organism which sometimes grows on peanut plants). Tobacco causes more deaths from cancer than any other environmental agent.

A malignant tumour may be more common in one sex than the other, some are more common among children or the elderly, and some vary with diet, environment, and genetic risk factors. Oncology is the study of cancerous tumours.

E2) The density of cancer cells is $0.3\times10^{2} = 30 = x$, say.

Also, the density of healthy local cells is $3\times10^{15} = y$, say

The reproduction rate of tumour cell proliferation is given by the ratio

$$c = \frac{x}{x+y} = \frac{30}{(30+3\times10^{15})} = \frac{1}{10^{14}+1}$$

Thus, c is the required reproduction of the tumour cell proliferation.

E3) Given, $\varphi(c) = \frac{3c+1}{(1-2c)^2}$; $c \neq \frac{1}{2}$ and $c = c_0$ at $t = 0$

Therefore, from Eqn. (7) it follows that

$$\psi(c) = \dot{c} = 2\left(\frac{3c+1}{(1-2c)^2}\right)(1-2c)^2$$

or, $\dfrac{dc(t)}{(3c+1)} = 2dt$

Integrating the above equation, we get

$$\frac{1}{3}\ln(3c+1) = 2t + \frac{1}{3}\ln a$$

$$\Rightarrow \quad \frac{1}{3}\ln\frac{(3c+1)}{a} = 2t \text{ or } \frac{3c+1}{a} = e^{6t}.$$

Using the initial conditions, we get $a = 3c_0 + 1$.

Therefore, $c(t) = \dfrac{(3c_0+1)e^{6t} - 1}{3}$.

The value of $c(t)$ at $t = 30$, is given by

$$c(30) = \frac{(3c_0+1)e^{180} - 1}{3}.$$

E4) One of the most important steps in malignant tumour growth is angiogenesis, which is the process by which tumours develop their own blood supply. For this reason, novel drugs are being developed specifically to target tumour blood vessels. Once the tumours have acquired their own blood supply, the tumour cells can escape the primary tumour via the circulatory system (metastasis) and set up secondary tumours elsewhere in the body. After angiogenesis and metastasis, the patient is left with multiple tumours in different parts of the body that are very difficult to detect and even more difficult to treat.

E5) The initial growth of the tumor is 5×10^3, and the size after five days is 7.2×10^5. From Eqn. (8), we get

$$c = c_0 e^{\lambda t}$$

Therefore, $7.2\times10^5 = (5\times10^3)e^{5\lambda}$

or, $\quad e^{5\lambda} = \dfrac{7.2\times10^5}{5\times10^3} = 144$

or, $\quad \lambda = \dfrac{1}{5}\ln(144) = 0.994$.

E6) Given the initial population of tumor cells $c_0 = 2\times10^5$.

Then $c = c_0 e^{\lambda t} = (2\times10^5)\, e^{6t}$

Therefore, $c = (2\times10^5)\, e^{90} = 2.4408$

is the required growth of tumor cells in fifteen days.

E7) Using Eqn. (12) the growth of tumour cell is given by

$$c(t) = \frac{c_0\lambda}{c_0\mu - (\lambda - \mu c_0)e^{-\lambda t}}$$

Given the initial size $c_0 = 2\times10^{12}$, $\lambda = 20$, and $\mu = 15$, we have,

$$c(t) = \frac{(2\times10^{12})\times 20}{(2\times10^{12})\times 15 - (20-[30\times10^{12}])e^{-20t}} \approx \frac{1.34e^{20t}}{e^{20t}-1}.$$

E8) Given $\lambda = 1500, \mu = 800$ and $\gamma = 300$.
From Eqn. (14), the net growth of the tumour in 20 days is

$$c(t) = c_0 e^{(1500-800+300)20} = c_0 e^{20000}$$

Thus, the ratio of the growth of tumour after 20 days with initial tumour is given by

$$\frac{c(t)}{c_0} = e^{20000}.$$

E9) Given equation is $\frac{d^2g}{dt^2} + 2A\frac{dg}{dt} + B^2 g = 0$
The roots of the corresponding auxiliary equation are

$$r_1, r_2 = -A \pm \sqrt{A^2 - B^2}$$

When $A^2 - B^2 < 0$ then solution of given equation can be written as

$$g(t) = e^{-At}[C_2 \cos\sqrt{B^2 - A^2}\, t + C_3 \sin\sqrt{B^2 - A^2}\, t]$$

or, $g(t) = e^{-At}[C_2 \cos B_1 t + C_3 \sin B_1 t]$
where C_1, C_2 are constants and $B_1^2 = B^2 - A^2$.
Further $g(t)$ can be written as

$$g(t) = C_1 e^{-At}\cos(B_1 t - \theta)$$

where $C_1 = \sqrt{C_2^2 + C_3^2}$ and $\tan\theta = \frac{C_2}{C_3}$.

E10) The concentration of glucose satisfy the equations

$$G_j = G_0 + C_1 e^{-At_j}\cos(B_1 t_j - \theta) \qquad (j = 1, 2, 3)$$

For $j = 1, 2, 3$, we get

$$25 = C_1 e^{-A}\cos(B_1 - \theta)$$
$$-5 = C_1 e^{-2A}\cos(2B_1 - \theta)$$
$$-5 = C_1 e^{-3A}\cos(3B_1 - \theta)$$

Solve these equations and obtain C_1, A, B, and θ and hence get the value of $T = \frac{2\pi}{B}$ where $B = (B_1^2 + A^2)^{1/2}$.

—x—

APPENDIX

The complete pathophysiology of diabetes mellitus is depicted in Fig. 1 below.

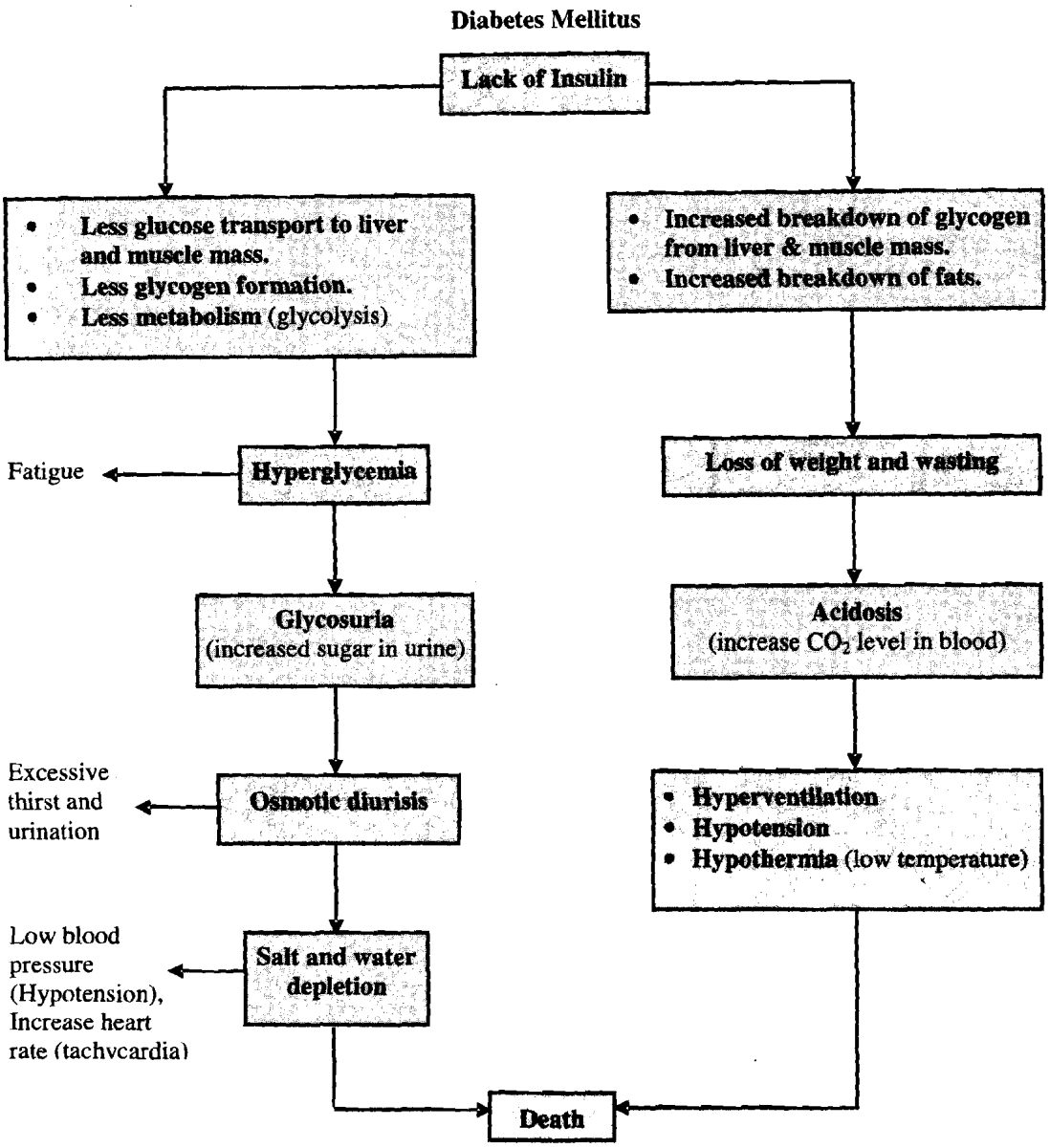

Fig. 1: Pathophysiology of diabetes mellitus.