The Chemostat: Stability at Steady States

- So, in dimensional form, $\alpha_1 > 1$ corresponds to $\frac{1}{K_{max}} < \frac{V}{F}$.
  - As K_{max} is max bacterial repro rate with *unlimited* nutrients $dN/dt = K_{max}N$, $\frac{\ln 2}{K_{max}}$ gives doubling time τ_2 of bacterial pop'n.
  - $V/F =$ time to refill whole growth chamber volume with fresh nutrient.
  - So if emptying time (given by $V/F) \times \ln 2$ is greater than the doubling time ($\tau_2 = \frac{\ln 2}{K_{max}}$), bacteria are washed out quicker than they can reproduce.
- $\alpha_2 > 1/(\alpha_1 - 1)$ corresponds to $C_0/K_n > \bar{c}$ so max (non-dimensional) conc'n $\bar{c}$ will never be more than (non-dimensional) conc'n in stock solution.

Notes

Notes

Chapter 5:

Linear & Non-Linear Interaction Models

Introduction

- Chapter develops models to examine models with interacting species or quantities.
- These lead to simultaneous DEs for coupled quantities due to interaction.
- Firstly, look at *Linear* models, differing from the chemostat in that they can be uncoupled
- Reduces the pair of first order O.D.E.s to a single second order with exact solution.
- As in previous chapter discuss steady states for this with example of Diabetes Detection.
- Move on to more realistic non-linear interaction models.
- No exact solution here & demonstrate how stability concepts may be used with *Phase-Plane models* to show model behaviour.

Notes

Linear Models

- Models of the form:

$$\begin{aligned} \frac{dx}{dt} &= Ax + By + P \\ \frac{dy}{dt} &= Cx + Dy + Q \end{aligned} \tag{5.1}$$

  for constant A, B, C, D are said to be *linear* (i.e. no product terms in x, y), *first order*, & if $P, Q = 0$, *homogeneous*.
- Such models are *compartmental models* as quantities can be compartmentalised.

Notes

Linear Models: Diabetes Detection

Example: Diabetes Detection

- *Glucose*, an end product of carbohydrate digestion, is converted into energy in the body's cells.
- *Insulin*, from pancreas, helps glucose absorption by cells other than those in brain & nervous system.
- A delicate balance is kept between glucose (G) & insulin (H) in the bloodstream:
  - if H is too low, too little glucose is absorbed (& is excreted);
  - if H is too high too much glucose is absorbed by organs other than the brain.

  end result in either case can be coma & even death.
- Diabetes patients need regular injections of insulin to compensate for lack of pancreatic insulin.

Notes

Linear Models: Diabetes Detection cont'd

- Present a simple model for G/ H interaction
- Use this to discuss a clinical test for detection of mild forms of diabetes.
- Model must account for 4 features in glucose-insulin regulation:
  1. $G \uparrow \Rightarrow$ liver absorbs more glucose, converts it & storing it as glycogen. $G \downarrow$ reverses this process,
  2. $H \uparrow \Rightarrow$ more glucose absorbed from bloodstream through cell membranes.
  3. $G \uparrow \Rightarrow$ causes pancreas to produce insulin faster; $G \downarrow$ lowers insulin production rate.
  4. Insulin is constantly being produced by the pancreas & degraded by the liver.

Notes

Linear Models: Diabetes Detection cont'd

- Model treats whole process as a compartmental one:
- Bloodstream is a 'box' where G & H are instantaneously uniform.
- With no recent digestion, glucose & insulin concentrations are in equilibrium,
- Interested in how system responds to change in equilibrium.
- Let $G(t)$ & $H(t)$ be *excess* glucose, insulin concs at time t.
- $\Rightarrow G = H = 0$ at equilibrium & +ive & -ive values refer to deviations from equilibrium.
- If either G, H are given a non-zero value, body will try to restore the equilibrium.

Notes

Linear Models: Diabetes Detection cont'd

- Assuming rates of change of G, H depend only on values G, H, may write:

$$\begin{aligned} \frac{dG}{dt} &= -\alpha G - \beta H \\ \frac{dH}{dt} &= \gamma G - \delta H \end{aligned} \qquad (5.2)$$

  for some constants $\alpha, \beta, \gamma, \delta$.
- To see why these constants must be all +ive, examine second eqn in Eqn.(5.2) & condition 4 above.
- If, at $t = 0$, $G = 0$ & $H > 0$, $\Rightarrow dH/dt < 0$; this is the liver in action as per condition 4.
- Similar reasoning may be applied for other constants.

Notes

Linear Models: Diabetes Detection cont'd

- Eqn.s(5.2) can be reorganised by putting everything in terms of a single variable:

$$\ddot{G} + (\alpha + \delta)\,\dot{G} + (\alpha\delta + \beta\gamma)\,G \;=\; 0 \qquad (5.3)$$

  which has an exact solution of form
- Can find eigenvalues λ_1, λ_2 by putting this into Eqn.(5.3) to get:

$$\lambda^2 + (\alpha + \delta)\,\lambda + (\alpha\delta + \beta\gamma) \;=\; 0 \qquad (5.4)$$

- Insulin concentration H may be got from:

$$H \;=\; -\frac{1}{\beta}\left(\dot{G} + \alpha G\right) \qquad (5.5)$$

Notes

Linear Models: Diabetes Detection cont'd

- To test for diabetes, a *glucose tolerance test* is administered.
- In this, after fasting, an injection of glucose is given.
- Blood samples are then taken after & G is taken to test the glucose-insulin regulatory system.
- G returns to equilibrium faster for healthy patients than diabetic ones.
- Mathematically, test $\equiv G = g_0$ & $H = 0$ at $t = 0$, assuming that G spikes while the H is instantaneously zero.

Notes

Linear Models: Diabetes Detection cont'd

- Can find initial conditions for Eqn.(5.3) by putting these into Eqn.(5.5):

$$G = g_0 \text{ and } \dot{G} = -\alpha g_0 \text{ at } t = 0 \qquad (5.6)$$

  Depending on the constants $\alpha, \beta, \gamma, \delta$ (discussed below) find a number of solution types for Eqn.(5.3) shown in Table 5.1.
- Note: as all $\alpha, \beta, \gamma, \delta$ are +ive, all exponentials in solutions to Eqn.(5.3) decay to zero
- i.e. all are either negative or have negative real part.

Notes

Linear Models: Diabetes Detection cont'd

Solns of Eqn.(5.4)	Solns of Eqn.(5.3)
λ_1, λ_2 real	$G = g_0 \frac{(a+\lambda_2)e^{\lambda_1 t} - (a+\lambda_1)e^{\lambda_2 t}}{\lambda_2 - \lambda_1}$
one real, λ	$G = g_0 \left(1 - (\alpha + \lambda)\right) e^{\lambda t}$
$\lambda = -\upsilon \pm i\omega$	$G = g_0 \left(\cos \omega t - \frac{\alpha}{\omega} \sin \omega t\right) e^{-\upsilon t}$

TABLE 5.1 : Diabetes Model Solutions

Notes

Linear Models: Diabetes Detection cont'd

- Results are backed up by experiment; Bolie found that $\lambda_1 = -1.36$ & $\lambda_2 = -2.34$
- Thus the following equations hold:

$$\begin{aligned} \frac{dG}{dt} &= -2.92G - 4.34H \\ \frac{dH}{dt} &= 0.208G - 0.78H \end{aligned} \tag{5.7}$$

with the solutions

$$\begin{aligned} G(t) &= g_0\left(-0.56e^{\lambda_1 t} + 1.56e^{\lambda_2 t}\right) \\ H(t) &= 0.202g_0\left(-0.56e^{\lambda_1 t} - e^{\lambda_2 t}\right) \end{aligned} \tag{5.8}$$

Notes

Linear Models: Diabetes Detection cont'd

- Putting $G = 0$, see that G goes to zero in about 1 hour for a normal individual.
- So, by measuring G, can see whether curve & time to return to normality mirror these results.
- Results for an initial Glucose concentration $g_0 = 1$[mol][litre]$^{-1}$ are shown in Fig.5.1

Notes

Linear Models: Diabetes Detection cont'd

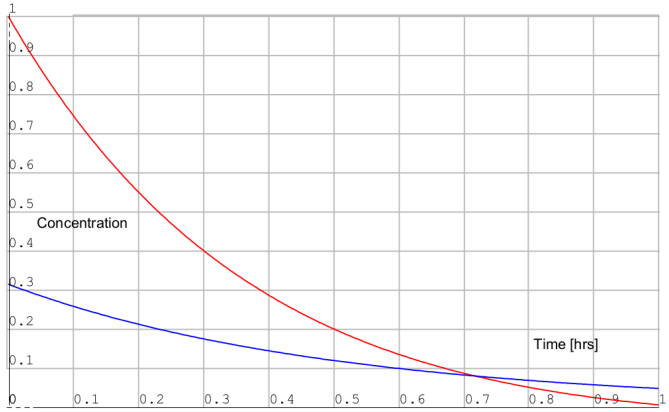

FIGURE 5.1 : Insulin & Glucose Concentrations for $g_0 = 1$ in Diabetes

Notes

Linear Models: Antibiotic Pharmacokinetics

- *Pharmacokinetics* is Kinetics of drug absorption, distribution, & elimination.
- Need to know pharmacokinetics to administer drugs optimally.
- Dose should be less than lethal & greater than the effective dose.
- This range is known as the Drug's *therapeutic range* & may (e.g. chemotherapy) be quite narrow.
- Hence knowing pharmacokinetics of some (especially novel) drugs is critical.
- For this pharmacokinetic modelling use differential equations.

Notes

Linear Models: Antibiotic Pharmacokinetics cont'd

- *Tetracyclines* form quite an old & generally well-tolerated group of antibiotics.
- Tetracyclines such as *doxycycline* used for prophylaxis against anthrax & plague.
- Also widely used for malaria treatment & prophylaxis,
- Can be taken for long time periods without the risk of many side-effects.

Notes

Linear Models: Antibiotic Pharmacokinetics cont'd

- For Tetracycline taken orally, amounts of tetracycline in G.I. tract & plasma at time t are $x_1(t)$ and $x_2(t)$.
- Equations associated with this are:

$$\begin{aligned} \frac{dx_1}{dt} &= -Ax_1 \\ \frac{dx_2}{dt} &= +Ax_1 - Bx_2 \end{aligned} \tag{5.9}$$

i.e. amount of antibiotic in G.I. tract $\downarrow$ at rate defined by A & amount in plasma being excreted at rate defined by B.

Notes

Linear Models: Antibiotic Pharmacokinetics cont'd

- Representing eqn.(5.9) as a matrix and:

$$\mathbf{K}(A,B) = \begin{pmatrix} -A & 0 \\ A & B \end{pmatrix}$$

$$\mathbf{x} = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

- matrix representation of the tetracycline equations is:

$$\dot{\mathbf{x}} = \mathbf{K}\mathbf{x} \qquad (5.10)$$

- Assuming that $A \neq B$, $x_1(0) = D$, & $x_2(0) = 0$, can show:

$$\begin{aligned} \frac{dx_1}{dt} &= De^{-At} \\ \frac{dx_2}{dt} &= D\frac{A}{B-A}\left[e^{-At} - e^{-Bt}\right] \end{aligned} \qquad (5.11)$$

Notes

Linear Models: Antibiotic Pharmacokinetics cont'd

- Plasma conc'n ($x_2(t)$) can be fitted as:

$$x_2(t) = 2.65\left[e^{-0.15(t-0.41)} - e^{-0.715(t-0.41)}\right] \qquad (5.12)$$

- Plasma concentration can be seen in Fig 5.2.

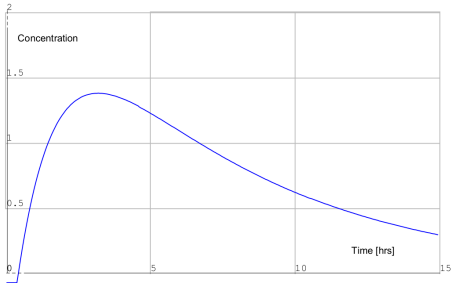

FIGURE 5.2 : Plasma Concentrations for Antibiotic

Notes