INTERNATIONAL ATOMIC ENERGY AGENCY
UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION

INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS
34100 TRIESTE (ITALY) - P.O.B. 586 - MIRAMARE - STRADA COSTIERA 11 - TELEPHONES: 224281/2/3/4/5 6
CABLE: CENTRATOM - TELEX 460392-1

SMR/99-24

AUTUMN COURSE ON MATHEMATICAL ECOLOGY

(16 November - 10 December 1982)

POPULATION BIOLOGY OF INFECTIOUS DISEASES
LECTURES II AND III

R.M. MAY

Department of Biology
Princeton University
Princeton, NJ 08544
U.S.A.

R. M. May : Lecture 2

Dynamical Aspects of Microparasitic Infections (in constant total host populations)

In this lecture, I consider first a very simple, but illuminating, model; then various extensions and refinements of this model are noted (briefly). Last, I indicate how these ideas can apply to the short-term dynamics of a vaccination programme.

* * * * * * * *

1 A SIMPLE, DYNAMIC MODEL

$X_t \equiv$ total number of susceptibles, at time t

$Y_t \equiv$ " " " infectious individuals, " " t

$N \equiv$ total population ($N = X_t + Y_t + Z_t$), assumed constant

Let everything change in discrete time steps, of duration τ : τ is the (average) interval between an individual acquiring infection and passing it on to the next infectee. For measles, rubella, etc., $\tau \simeq 10$–20 days (latent + infectious periods); for some arthropod-borne viruses (e.g., yellow fever), τ can be longer.

We now want equations linking X_t, Y_t at time t with the corresponding

quantities, $X_{t+\tau}$ and $Y_{t+\tau}$, one time step later. Assuming homogeneous mixing, as discussed in Lecture 1, we get

$$Y_{t+\tau} = (R_0 X_t / N) Y_t \; ; \qquad (1)$$

each case (Y_t) would give R_0 if all were susceptible, and gives $R_0 \times (X_t/N)$ if a fraction X_t/N are susceptible. Susceptibles are lost by infection (eqn (1)), and gained by new births:

$$X_{t+\tau} = X_t - Y_{t+\tau} + B . \qquad (2)$$

Here B represents net births in the interval τ: if the per capita annual birth rate is a, then

$$B = a \tau N . \qquad (3)$$

EQUILIBRIUM in this simple model is found by putting $X_{t+\tau} = X_t = X^*$ and $Y_{t+\tau} = Y_t = Y^*$:

$$\left.\begin{aligned} Y^* &= B = a\tau N \\ X^* &= N/R_0 \quad \text{(as in Lecture 1)} \end{aligned}\right\} (4)$$

LOCAL STABILITY follows by the usual techniques. Put $X_t = X^* + x_t$, $Y_t = Y^* + y_t$, and expand in Taylor series, ignoring terms of order x^2, y^2, xy, etc :

$$\left.\begin{aligned} y_{t+\tau} &= y_t + (R_0 B/N) x_t \; , \\ x_{t+\tau} &= x_t - y_{t+\tau} \; . \end{aligned}\right\} (5)$$

In these equations — now linearized — we factor out the time dependence, via the eigenvalues Λ, defined as

$$x_t \sim x_0 \Lambda^n \quad , \quad y_t \sim y_0 \Lambda^n \quad ,$$

where $n = t/\tau$ is the number of time steps from 0 to t. Thence eqn (5) becomes (putting $B = \alpha z N$)

$$\left.\begin{aligned} \Lambda y &= y + \varepsilon x \\ \Lambda x &= x - \Lambda y \end{aligned}\right\} \quad (6)$$

where ε is defined as

$$\varepsilon \equiv R_0 B/N = (R_0 a)\tau$$

Or, recalling from lecture 1 that $R_0 \simeq L/A$, where (i) if the population is in balance, life expectancy $L = 1/a$ (reciprocal of birth rate), and (ii) A is average age at infection:

$$\underline{\varepsilon \simeq \tau/A} \quad (7)$$

Since $\tau \sim$ 10-20 days (or at most a month or so), while $A \sim 2 - 10$ years, $\varepsilon \ll 1$.

!! Back to eqn(6): we have a quadratic for the eigenvalue Λ,

$$\Lambda^2 - (2-\varepsilon)\Lambda + 1 = 0$$

$$\Lambda = \left(1 - \tfrac{\varepsilon}{2}\right) \pm i\left[1 - \left(1 - \tfrac{\varepsilon}{2}\right)^2\right]^{\frac{1}{2}} \quad (8)$$

Λ is a complex number, with modulus unity: write

$$\Lambda = e^{i\theta\tau} \quad , \quad (9)$$

with the definition

$$\theta = \frac{\tan^{-1}\left\{\left[1-(1-\frac{\varepsilon}{2})^2\right]^{\frac{1}{2}} / (1-\frac{\varepsilon}{2})\right\}}{\tau} = \frac{\cos^{-1}(1-\frac{\varepsilon}{2})}{\tau} \quad . \quad (10)$$

That is to say, the time dependence of the perturbations x_t and y_t are characterized by the behaviour of the function $\Lambda^{t/\tau}$,

$$x_t, y_t \sim e^{i\theta t} \quad . \quad (11)$$

Since the magnitude of the eigenvalue is unity, a small disturbance to the equilibrium state of eqns ( ) + ( ) simply oscillates indefinitely, exhibiting the neutral stability of the frictionless pendulum (like the Lotka–Volterra prey–predator model). The period, T, of these continuing oscillations is given from eqn (11):

$$T = 2\pi/\theta$$

And for $\varepsilon \ll 1$ (see page 3), $\cos^{-1}(1-\frac{\varepsilon}{2}) \simeq \sqrt{\varepsilon}$, so

$$\underline{\underline{T \simeq \frac{2\pi\tau}{\sqrt{\varepsilon}} \simeq 2\pi\sqrt{A\tau}}} \quad (12)$$

measles: $\tau \sim \frac{1}{25}$ yr, $A \sim 4$-5 yr : $T \sim 2$-3 yrs

rubella: $\tau \sim \frac{1}{17}$ yr, $A \sim 9$-10 yr : $T \sim 5$ yrs

[Digression on stability properties of difference equations — stable points, cycles, chaos — NOT in notes: see NATURE, 261, 459 (1976)]

2 Realistic Complications

Most changes to the above model will tip it off the razor's edge of neutral stability, either to damped oscillations, or to stable limit cycles — in either case, the basic period is still given by the above: $T \sim 2\pi\sqrt{AZ}$.

Examples

(i) Continuous version of above (Soper, 1929)

X = total susceptibles
Y = " infected
Z = " immune

constant death rate, μ
birth rate = death rate

$\lambda = \beta Y$

$$\frac{dX}{dt} = \mu N - (\lambda+\mu)X$$
$$\frac{dY}{dt} = \lambda X - (\nu+\mu)Y$$
$$\frac{dZ}{dt} = \nu Y - \mu Z$$
$$\frac{dN}{dt} = 0 \; ; \quad N = \text{constant}$$

EQUILIBRIUM

$$X^* = \frac{\nu+\mu}{\beta}$$
$$Y^* = \left(\frac{\mu}{\nu+\mu}\right)(N - X^*)$$
$$Z^* = \left(\frac{\nu}{\nu+\mu}\right)(N - X^*)$$

STABILITY

$$X(t) = X^* + x$$
$$Y(t) = Y^* + y \qquad x+y+z = 0$$
$$Z(t) = Z^* + z$$

Taylor expansion:

$$\frac{dx}{dt} = -(\mu+\beta Y^*)x - \beta X^* y$$
$$\frac{dy}{dt} = \beta Y^* x + (0)y$$

Again, factor out time dependence — only now for continuous (not discrete) time:

$$x(t), y(t) \sim e^{\Lambda t}$$

and the eigenvalues follow from the matrix equation

$$\det \begin{vmatrix} -(\mu+\beta Y^*) - \Lambda & -\beta X^* \\ \beta Y^* & -\Lambda \end{vmatrix} = 0$$

$$\Lambda^2 + A\Lambda + B = 0$$

where A and B defined as:

$$A = \mu + \beta Y^* = \mu(N/X^*) = \mu R_0$$
$$B = (\beta Y^*)(\beta X^*) = (\nu+\mu)\mu\left(\frac{N}{X^*} - 1\right) = (\nu+\mu)\mu(R_0 - 1)$$

$$\Lambda = -\frac{A}{2} \pm \left(\left(\frac{A}{2}\right)^2 - B\right)^{\frac{1}{2}}$$

Notice that ν (recovery rate) $\sim \frac{1}{\text{days}}$ and
μ (death rate) $\sim \frac{1}{\text{decades}}$

so $\nu \gg \mu$ and $B > A^2$: hence

$$\Lambda \simeq -\frac{A}{2} \pm i\sqrt{\nu\mu(R_0-1)}$$

Complex ... weak damping ... time $\sim \frac{1}{A} \sim \frac{1}{\mu R_0}$

with oscillations ... $T \sim \frac{2\pi}{\sqrt{\nu\mu(R_0-1)}}$

But $\nu \sim \frac{1}{\tau}$
$\mu(R_0-1) \sim \frac{1}{A}$

} So period of weakly damped oscillations is $T \sim 2\pi\sqrt{A\tau}$

(ii) Stochastic fluctuations (Bartlett).

If the basic difference model (or a slightly more stable version) is modified to include <u>fluctuations</u> in births, the neutral stability is tipped to cycles at period T [unless population is too small -- "fade out" occurs — or ~~huge (billions)~~].

(iii) Time lags, or defined intervals in latent and infectious classes (replacing decay rates), can "pump" the propensity to oscillate at period T.

(iv) Seasonality ---- with one year period -- can also "pump" the system and give longer-term cycles with period an <u>integer</u> number of years, <u>near T</u> (this can get very complicated: Yorke et al and later workers).

---

3 Application to Vaccination dynamics

"Realistic" ... use partial differential equations, discussed in <u>Lecture 1</u>, with initial [$t=0$] age profile as for <u>before vaccination</u>, and then introduce specified vaccination schedule for $t>0$; SOLVE NUMERICALLY !!

Some rough insights ... use (continuous) model for <u>total</u> susceptibles, etc, as above. Initial values of $X(t=0)$, $Y(t=0)$, $Z(t=0)$ as on page 5 (before vaccination).

After policy starts, assume a proportion <u>p</u> of each cohort vaccinated at birth:

$$\frac{dX}{dt} = \mu(1-p)N - (\beta Y + \mu)X \qquad (13)$$

$$\frac{dY}{dt} = Y\left(\beta X - [\nu + \mu]\right) \qquad (14)$$

$$N = X + Y + Z = \text{constant}$$

These eqns (13) and (14) can be rewritten as equations for λ $(=\beta Y)$ and x $(=X/N)$, using $R_0 = N/X^* = \beta N/(\nu+\mu)$!

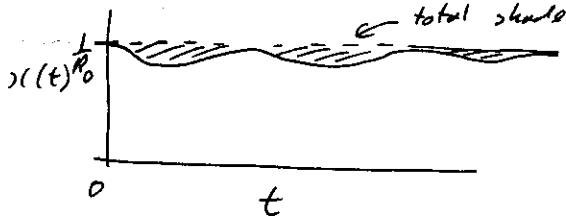
$$\frac{dx}{dt} = \mu[1-p] - (\lambda+\mu)x \qquad (15)$$

$$\frac{d\lambda}{dt} = (\nu+\mu)\lambda\left[R_0 x - 1\right] \qquad (16)$$

$$\log\frac{\lambda(t)}{\lambda(0)} = (\nu+\mu)\int_0^t \left[R_0 x(t') - 1\right]dt'$$

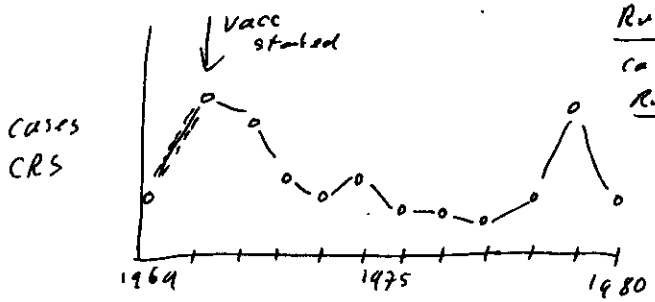
We can see that the force of infection, λ, begins as $\lambda(0) = \mu(R_0 - 1)$ and ends as $\lambda(\infty) = \mu\left[R_0(1-p) - 1\right]$. The fraction susceptible, $x(t)$, starts at the pre-vaccination equilibrium value, $x(0) = 1/R_0$,

dips below this, oscillates, and finally settles back to $x(\infty) \to 1/R_0$



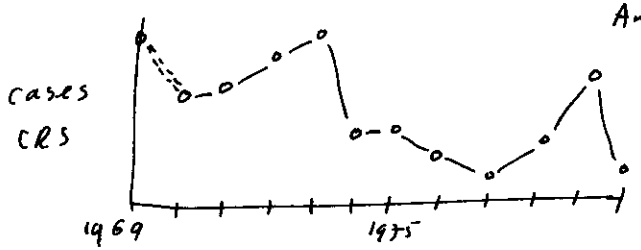
Period can be shown to start as $T \sim 2\pi\sqrt{Az}$, (with $A = \frac{1}{\lambda} = \frac{1}{\mu(R_0-1)}$ and $z \sim \frac{1}{\nu}$), and lengthen toward $T \sim \frac{2\pi\sqrt{Az}}{\sqrt{1-\rho}}$ as $t \to \infty$

These trends seem to show up in real vaccination programmes:



Rubella in UK: cases of Congenital Rubella Syndrom

And in USA

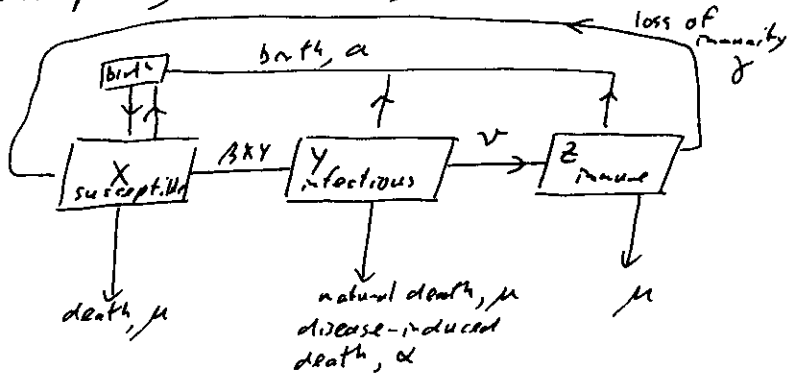


LECTURE 3

Populations regulated by infectious diseases

[See Nature review by Anderson and May]

Work with total population of susceptible, infectious, immune



$$\frac{dX}{dt} = \underbrace{\alpha N}_{\text{births}} - \underbrace{\mu X}_{\text{deaths}} - \underbrace{\beta XY}_{\text{loss to infected class}} + \underbrace{\gamma Z}_{\text{loss of immunity}}$$

$$\frac{dY}{dt} = \beta XY - (\nu + \underbrace{\alpha + \mu}_{\text{deaths}}) Y$$
ν: recovery

$$\frac{dZ}{dt} = \nu Y - (\gamma + \mu) Z$$

Total population is now also a variable: $N = X + Y + Z$

$$\frac{dN}{dt} = (\alpha - \mu) N - \alpha Y$$

EQUILIBRIUM

"threshold" host density

$$X^* = N_T \equiv \frac{\nu+\alpha+\mu}{\beta}$$

$Y^* = \frac{\nu}{\alpha} N^*$ ... $\nu \equiv a-\mu$ = per capita population growth rate with no infection

i.e. fraction infected $= \frac{\nu}{\alpha}$

Also $Z^* = \frac{\nu}{\gamma+\mu} Y^*$, so $Z^* + Y^* = \left(1+\frac{\nu}{\gamma+\mu}\right)\frac{\nu}{\alpha} N^*$

and $X^* = N_T$

$$\therefore \left(1+\frac{\nu}{\gamma+\mu}\right)\frac{\nu}{\alpha} N^* + N_T = N^*$$

$$\boxed{N^* = \frac{N_T}{1 - \frac{\nu}{\alpha}\left(1+\frac{\nu}{\gamma+\mu}\right)}}$$

This is the equilibrium value of the host population *if* it is regulated by the disease; regulation is possible if

$$\alpha > \nu\left[1+\frac{\nu}{\gamma+\mu}\right]$$

For invertebrates, where no immunity exists ($\gamma \to \infty$), this regulatory condition is simply

$$\alpha > \nu$$

If α is not large enough to regulate the population, then it continues to grow, at an exponential rate (but is less than ν): calculation of diminished rate is EXERCISE!

If $\alpha > \nu\left(1+\frac{\nu}{\gamma+\mu}\right)$, the equilibrium can be shown to be stable: EXERCISE: use standard linear analysis for eigenvalues λ; three differential equations $\Rightarrow$ cubic for λ, and all eigenvalues have negative real parts iff [for λ from $\lambda^3 + a\lambda^2 + b\lambda + c = 0$] $a>0$, $b>0$, $c>0$ and $ab>c$. This is true for the above system.

If a population *is* regulated by such a disease ... what fraction of deaths must be due to disease?

Answer:

$$\frac{\text{deaths from disease}}{\text{total deaths}} = \frac{a-\mu}{a}$$

Proof:

ratio $= \frac{\alpha Y}{\mu N + \alpha Y}$. But $\alpha Y = (a-\mu)N$. So

$$\text{ratio} = \frac{(a-\mu)N}{\mu N + (a-\mu)N} = \frac{a-\mu}{a}$$

(*) If $a \simeq \mu$ (births roughly equal to deaths), the population can have a disease as

its essential regulatory mechanism, even though few observed deaths are due to the disease. Conversely, for invertebrates and other populations where usually $a \gg \mu$, essentially all deaths must be from the disease if it is indeed regulating.

For discussion of biological facts, see Nature review (distributed with notes) or recent discussion in Population Biology of Infectious Diseases (eds: R. M. Anderson and R. M. May), Springer Verlag, Berlin / New York, 1982

Applications to actual populations

[1] laboratory mice infected with Pasteurella muris and with ectromelia: see Nature review for details of mathematics and biology

[2] Invertebrates in general, and forest insects infected with viruses or protozoans: see Anderson and May, Science, 210, 655 (1980) or — for a more detailed treatment — Philosophical Transactions of The Royal Society, B291, 452–524 (1981)

[3] Rabies and its effect on fox populations in Europe: Anderson et al., Nature, 289, 765 (1981)

[4] General speculations about role in human history -- see Nature review

[5] Specific calculation for transmission, maintenance, and control of microparasites (smallpox, measles, etc) in human populations which are growing (birth rate > death rate), and where $\alpha \neq 0$ (deaths from disease are significant). This is a subject of current research by Anderson & myself, and others

---