

# Mathematical Biology

January 27, 2018

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## 0 Miscellaneous

Course notes online: Julia Gog([www.damtp.cam.ac.uk/research/dd/teaching](http://www.damtp.cam.ac.uk/research/dd/teaching), 2013-2017), Peter Haynes([www.damtp.cam.ac.uk/user/phh/mathbio.html](http://www.damtp.cam.ac.uk/user/phh/mathbio.html))

Moodle page: Handwritten notes by lecture; Matlab/Python programming examples; solved exercises.

This course involves 3 models: Deterministic temporal models (11 lectures), Stochastic temporal models (5 lectures), Deterministic spatio-temporal models (8 lectures).

The focus of this course is biochemical reactions and population processes.

(some introductory speech)

**Example.** (1, Transient population) If we use  $n(t)$  to denote the size of a population, we may want to model  $\frac{dn}{dt} = f(n)$  by an ODE, or maybe if we have several components  $\mathbf{n}(t)$  then we may want to model  $\frac{d\mathbf{n}}{dt} = \mathbf{f}(\mathbf{n})$  which is a system of ODEs.

Note that although  $n$  should be an integer (discrete), when  $n \gg 1$  we may model it with continuous equations.

**Example.** (2)  $n \rightarrow \partial_t P(n, t) = W \cdot P(n, t)$ , Markov processes. Here  $P(n, t)$  is a probability(?),  $n$  being a state, and  $W$  being the transition matrix.

**Example.** (3)

If we include spatial aspect, we may have  $n(t)$  becoming  $n(x, t)$ . Now there might be 'diffusion':  $\partial_t n(x, t) = f(n(x, t)) + D \nabla^2 n(x, t)$  where  $\nabla^2 = \frac{\partial^2}{\partial x^2}$ ; this is the reaction-diffusion equation.

## 1 Birth-death models

The general idea is that we have a population of size  $n(t)$ ; per capita per unit time, we have births of rate  $b$  and deaths of rate  $d$ . Then we can write

$$n(t + \Delta t) = n(t) + bn\Delta t - dn\Delta t$$

So we have an ODE

$$\frac{dn}{dt} = (b - d)n = rn$$

where  $r = b - d$ . This has an easy solution  $n(t) = n_0 e^{rt}$ , assuming  $r$  is a constant. We see that if  $r$  is positive then the population grows exponentially, and if  $r$  is negative then the population decreases to 0 asymptotically.

Now probably  $b$  and  $d$  are related to  $n$  by  $b(n) = bn$  and  $d(n) = dn^2$  due to competition. Then we have

$$\frac{dn}{dt} = bn - dn^2$$

which we can definitely rewrite as

$$\frac{dn}{dt} = \alpha n(1 - n)$$

by some change of variable on  $n$ . Now

$$\begin{aligned} \frac{dn}{n(1-n)} &= \alpha dt \\ \implies \frac{dn}{n} + \frac{dn}{1-n} &= \alpha dt \\ \implies \ln n - \ln(1-n) &= \alpha t + c \\ \implies n &= \frac{n_0 e^{\alpha t}}{(1-n_0) + n_0 e^{\alpha t}} \end{aligned}$$

where we are given that  $t = 0$ ,  $n = n_0$ . If  $t \gg \frac{1}{\alpha}$ , when  $t \rightarrow \infty$  we have  $n(t) \rightarrow 1$ . Now we can investigate if the population size is stable, and if it has any fixed points.

Let's now define  $\mathbf{n} = (n_1, \dots, n_p)$ , i.e.  $p$  populations, and  $\frac{d\mathbf{n}}{dt} = \mathbf{f}(\mathbf{n})$ . If  $\mathbf{n} = \mathbf{n}^*$  is a fixed point, then  $\frac{d\mathbf{n}}{dt} = 0$ , i.e.  $\mathbf{f}(\mathbf{n}) = 0$ . Now if we apply a small perturbation  $\mathbf{n} = \delta\mathbf{n}^* + \delta\mathbf{n}$ , i.e.

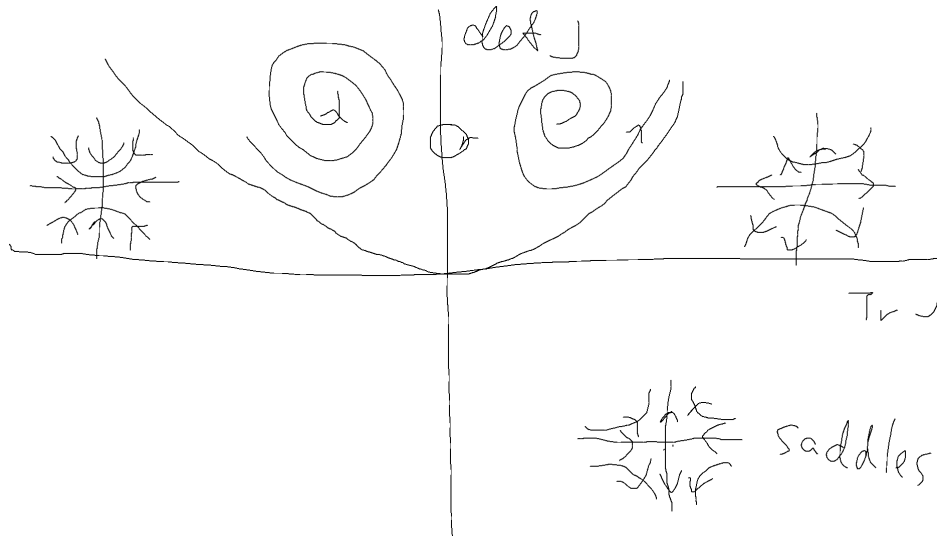
$$\begin{aligned} \frac{d}{dt}\delta\mathbf{n} &= \mathbf{f}(\mathbf{n}^* + \delta\mathbf{n}) \\ a &= \mathbf{f}(\mathbf{n}^*) + \frac{\partial f_i}{\partial n_j} \delta n_j + \frac{1}{2} \frac{\partial^2 f_i}{\partial n_j \partial n_k} \delta n_j \delta n_k \end{aligned}$$

So  $\frac{d}{dt}\delta\mathbf{n} = J \cdot \delta\mathbf{n}$ , so  $\delta\mathbf{n}(t) = e^{Jt} \cdot \delta\mathbf{n}(0)$ . If  $\lambda_i$ 's are the eigenvalues of  $J$ , we consider the real part of  $\lambda_i$ : if  $\text{Re}(\lambda_i) < 0$ , then if  $p \geq 5$  we only have numerical solutions, if  $3 \leq p \leq 5$  we have analytic solutions, and  $p = 2$  is an easy case (recall  $p$  is the number of populations):

- If  $p = 2$ ,  $\mathbf{n} = (n_1, n_2)$ , then

$$\frac{d}{dt} \begin{pmatrix} \delta_{n_1} \\ \delta_{n_2} \end{pmatrix} = \begin{pmatrix} \frac{\partial f_1}{\partial n_1} & \frac{\partial f_1}{\partial n_2} \\ \frac{\partial f_2}{\partial n_1} & \frac{\partial f_2}{\partial n_2} \end{pmatrix} \cdot \begin{pmatrix} \delta_{n_1} \\ \delta_{n_2} \end{pmatrix}$$

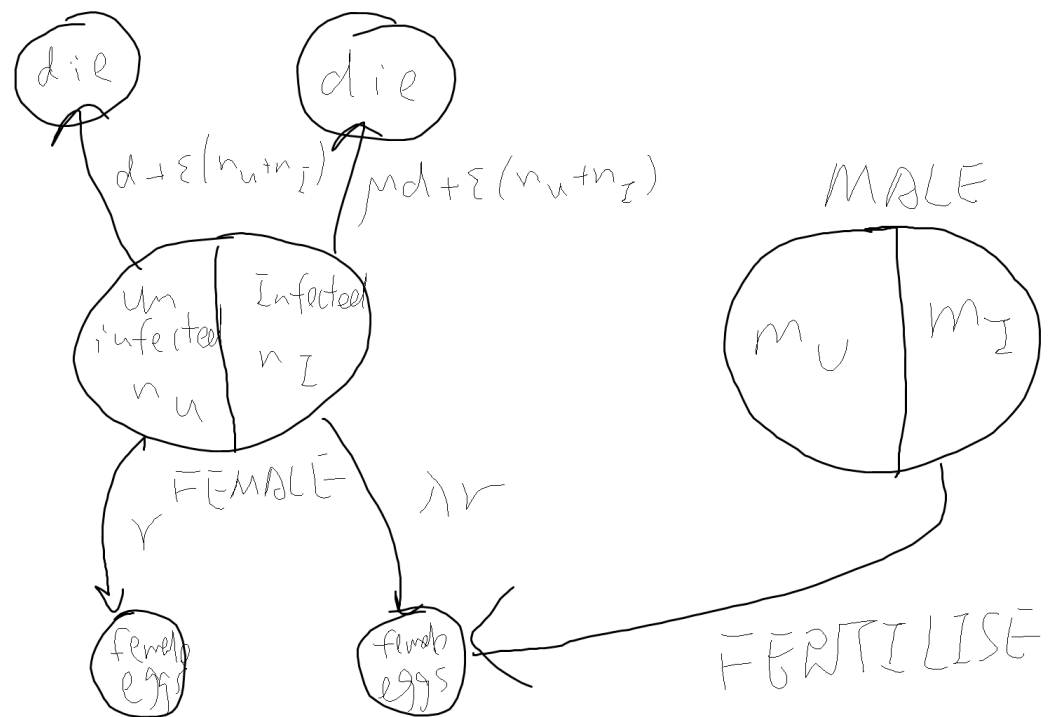
Where the matrix is  $J$ . Now we have  $\lambda_1 \lambda_2 = \det J$  and  $\lambda_1 + \lambda_2 = \text{tr } J$ . Determined by the signs of those two, we have different possible behaviours:



Now let's consider the spread of Dengue. There are several processes going on at the same time:

- (1) Mosquitos carry dengue;
- (2) Wolbachia infect mosquitos;
- (3) Infected mosquitos do not transmit dengue;
- (4) Wolbachia transmission only across generations.

Question: will an intially infected population of mosquitos eventually spread over the entire population as  $t \rightarrow \infty$ ?



F	M	frequency	rate	outcome	
U	U	$n_u \cdot m_u$	$r$	U	$m_u =$
U	I	$n_u \cdot m_i$		X	$\frac{n_u}{n_u + n_i}$
I	U	$n_i \cdot m_u$	$\lambda_U$	I	$m_i =$
I	I	$n_i \cdot m_i$	$\lambda_I$	I	$\frac{n_i}{n_u + n_i}$

We always assume that there are enough males to fertilise the female eggs.

Now consider  $\frac{d}{dt}$  of  $n_U$  and  $n_I$  (uninfected and infected females). From the above tables we should be able to get (hopefully)

$$\begin{aligned}\frac{d}{dt}n_U &= rn_U \frac{n_U}{n_U + n_I} - dn_U - \varepsilon(n_U + n_I)n_U \\ \frac{d}{dt}n_I &= \lambda rn_I \frac{n_U}{n_U + n_I} + \lambda rn_I \frac{n_I}{n_U + n_I} - \mu dn_I - \varepsilon(n_U + n_I)n_I \quad (*)\end{aligned}$$

This is our model when  $p = 2$ . The term with  $\varepsilon$  is the death rate associated with competition.

We'll try to simplify these equations. By rescaling the time as  $t \rightarrow rt$ , and rescaling the population as  $n \rightarrow \frac{\varepsilon}{r}n$ , we get (?)

$$\begin{aligned}\frac{d}{dt}n_U &= n_U \frac{n_U}{n_U + n_I} - \frac{d}{r}n_U - (n_U + n_I)n_U \\ &= n_U \left[ \frac{n_U}{n_U + n_I} - \frac{d}{r} - (n_U + n_I) \right] \quad (1)\end{aligned}$$

and the second equation becomes (???)

$$\frac{d}{dt}n_I = n_I \left[ \lambda - \mu \frac{d}{r} - (n_U + n_I) \right] \quad (2)$$

We'd like to see that the model has at least the fixed points  $\mathbf{n}^* = (n_U^*, 0)$  and  $(0, n_I^*)$ . The lecture then somehow defines

$$\begin{aligned}n_I^* &= \lambda - \mu \frac{d}{r} \\ n_U^* &= 1 - \frac{d}{r}\end{aligned}$$

so that our differential equations become

$$\begin{aligned}\frac{d}{dt}n_U &= n_U \left[ n_U^* - \frac{n_I}{n_U + n_I} - (n_U + n_I) \right] \\ \frac{d}{dt}n_I &= n_I [n_-^* (n_U + n_I)]\end{aligned}$$

which has fixed points  $(0, 0)$ ,  $(n_U^*, 0)$ ,  $(0, n_I^*)$ ,  $(n_I^*(1 - n_I^* - n_U^*), n_I^*(n_U^* - n_I^*))$ . The first is unstable, the second two are stable and the last fixed point is a saddle. This is disappointing because we want a small infection to be spread out to the whole population, but in that case the second fixed point needs to be unstable.

Global analysis:

We can plot the flow of the ode system

$$\frac{d}{dt} \begin{pmatrix} n_U \\ n_I \end{pmatrix} = \begin{pmatrix} f_U(n_U, n_I) \\ f_I(n_U, n_I) \end{pmatrix}$$

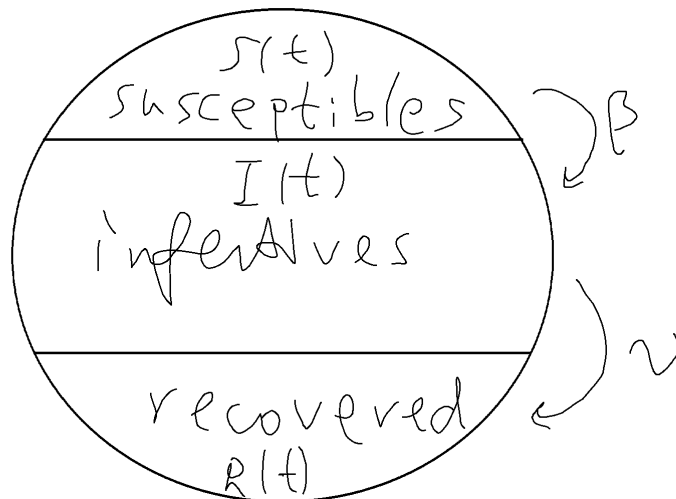
This is usually done by programming. We'll try to sketch the flow of this model:



Qualitative behaviour: we need a finite (large)  $n_I(0)$  (in order to converge to  $(n_I^*, 0)$ ).

For quantitative part we can only do numerical integrations.

Now we consider an epidemic model, where each individual may pass through three phases: susceptibles, infectives, recovered (compartment models – same individual for different phases). We use  $S(t), I(t), R(t)$  to denote the population of each of them.



Now we want to know what is the rate of their change. We use biological datum, from which we know there is a per capita infection rate  $\beta$ , a recovery rate  $\nu$ , so



in conclusion we have

$$\begin{aligned}\frac{d}{dt}S &= -\beta SI \\ \frac{d}{dt}I &= \beta SI - \nu I \\ \frac{d}{dt}R &= \nu\end{aligned}$$

Also we expect the population to be closed, i.e. the total population should not change over time (unlike the previous model), so

$$\frac{d}{dt}(S + I + R) = 0$$

Which is true. So it's sufficient to look at just two equations,

$$\begin{aligned}\frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \nu I\end{aligned}$$

What are the questions we want to ask? We may want to know:

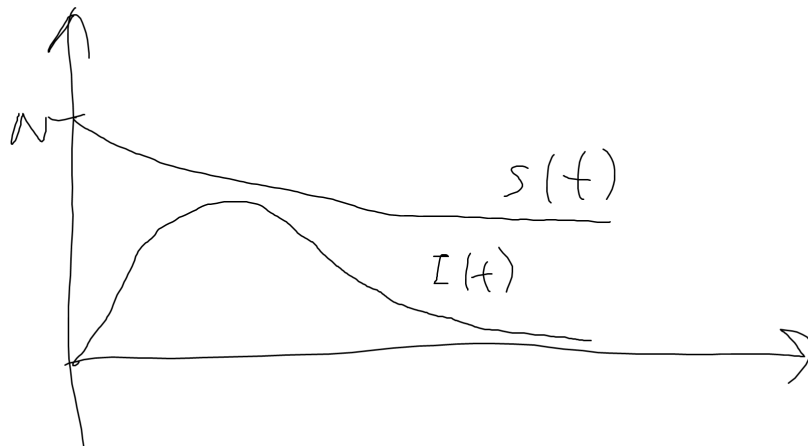
- When can you have an *outbreak*, i.e.  $\frac{dI}{dt} > 0$ ;
- What is the final size of the outbreak?
- What vaccination strategy would work best?
- Endemic  $\implies I^* > 0$ , finite number of  $I$  in steady state.

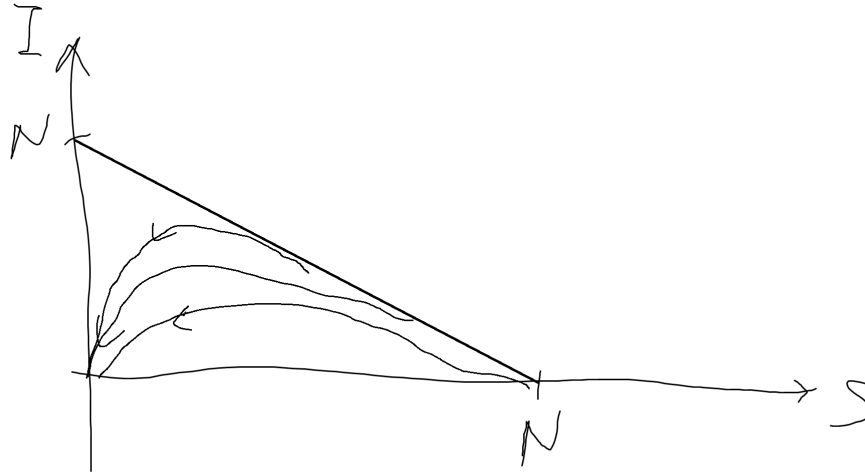
For obvious reason we call this the "SIR model".

(Q1)

at  $t = 0$ ,  $\frac{d}{dt}I = [\beta S(0) - \nu] \cdot I(0)$ , so  $\frac{\beta}{\nu}S(0) > 1 \implies \frac{\beta N}{\nu} > 1 = \mathcal{R}_0$ , the reproduction ratio, or the mean number of susceptibles infected per infective.

(Q2)





We had  $dS = -\beta SI dt$ ,  $dI = (\beta SI - \nu I) dt$ , so

$$\begin{aligned}\frac{dI}{dS} &= \frac{(\beta SI - \nu I)}{-\beta SI} = -1 + \frac{\nu}{\beta} \cdot \frac{1}{S} \\ &= \frac{N}{\mathcal{R}_0} \cdot \frac{1}{S} - 1\end{aligned}$$

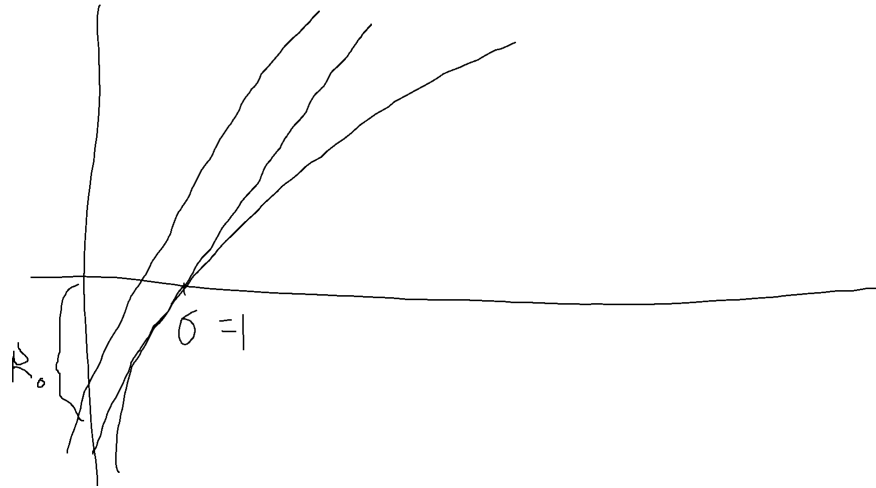
So

$$I = \frac{N}{\mathcal{R}_0} \ln S - S + \text{const}$$

Now  $I(t) - I(0) = \frac{N}{\mathcal{R}_0} \ln \frac{S(t)}{S(0)} - (S(t) - S(0))$ . As  $t \rightarrow \infty$ ,  $S(t) = \sigma N$  ( $\sigma < 1$ ),  $I(t) \rightarrow 0$ . So

$$\begin{aligned}0 &= \frac{N}{\mathcal{R}_0} \ln \sigma - (\sigma N - N) \\ \sigma - \frac{1}{\mathcal{R}_0} \ln \sigma &= 1\end{aligned}$$

We can rewrite the second equation as  $\mathcal{R}_0(\sigma - 1) = \ln \sigma$ . Clear  $\sigma = 1$  is a solution, but we are not interested in that. For  $\mathcal{R}_0 \gg 1$ ,  $\sigma \approx e^{-\mathcal{R}_0}$ . (by sketching curves be-



low and analyze intersections?)

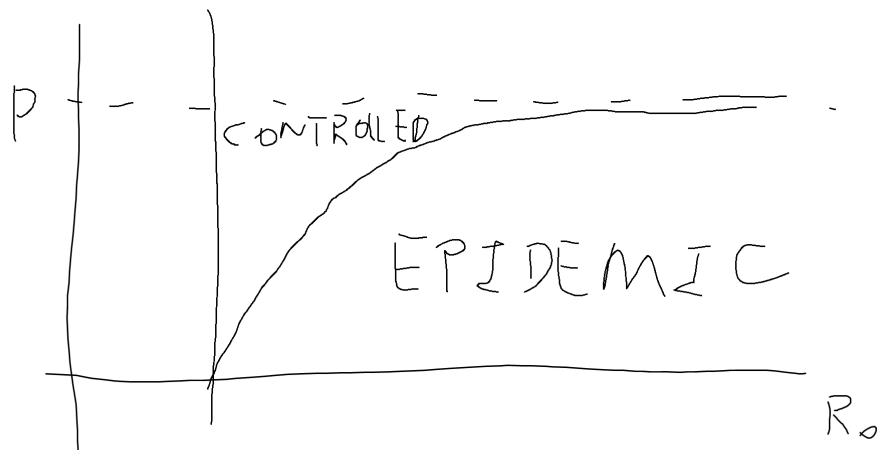
Insight: in any epidemic, only a fraction of the population is infected. Size of the epidemic  $= (1 - \sigma)N$ .

(Q3)

Vaccination? We can use pre-vaccination, i.e. vaccinate in anticipation of an outbreak. Let  $p$  be the fraction of the population being vaccinated. At  $t = 0$  we have

$$S(0) \approx (1 - p)N$$

$$\frac{\beta}{\nu} S(0) > 1 \implies \frac{\beta}{\nu} (1 - p)N = (1 - p)\mathcal{R}_0 > 1$$



so  $p > 1 - \frac{1}{\mathcal{R}_0}$ .

(Q4)

Endemic:  $I(t) \rightarrow I^* > 0$  as  $t \rightarrow \infty$ .

Biological datum: suppose we have a finite rate of birth of  $S$ , and of death of

$S, I, R$ . Now

$$\frac{d}{dt}S = -\beta SI - \mu S + \mu N$$

$$\frac{d}{dt}I = \beta SI - \nu I - \mu I$$

$$\frac{d}{dt}R = \nu I - \mu R$$

at  $t = 0$ ,  $\mathcal{R} = \frac{\beta}{\nu + \mu}N(??)$ . So

$$S^* = \frac{\mu + \nu}{\beta} = \frac{N}{\mathcal{R}_0}$$

$$I^* = \frac{\mu(N - S^*)}{\beta S^*} = \frac{\mu}{\beta}(\mathcal{R}_0 - 1)$$

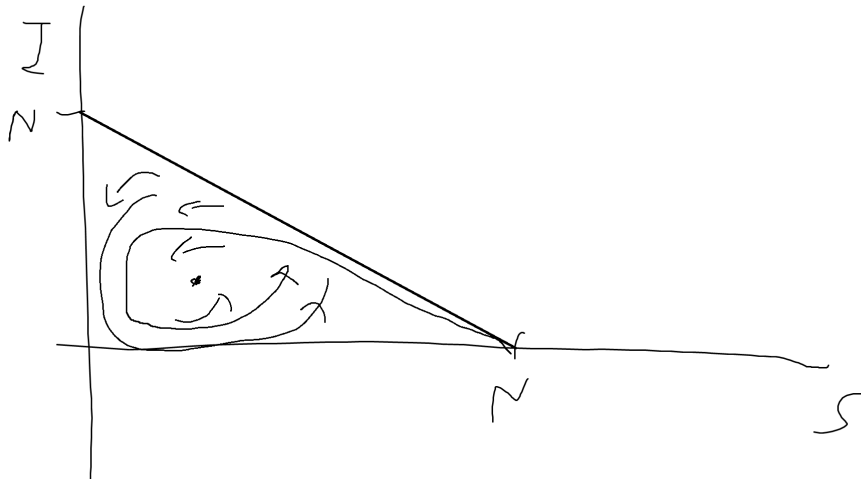
We had a Jacobian (?)

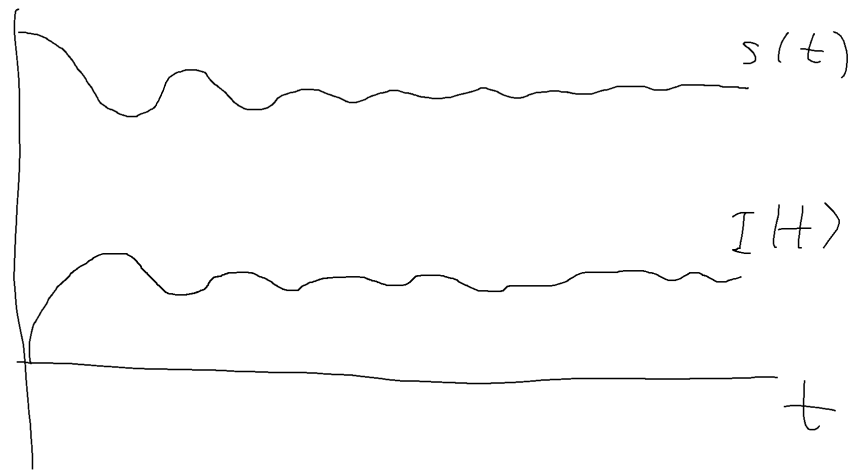
$$J = \begin{pmatrix} -\beta I - \mu & -\beta S \\ \beta I & \beta S - \nu - \mu \end{pmatrix}$$

so

$$J^* = \begin{pmatrix} -\mu \mathcal{R}_0 & -(\mu + \nu) \\ \beta(\mathcal{R}_0 - 1) & 0 \end{pmatrix}$$

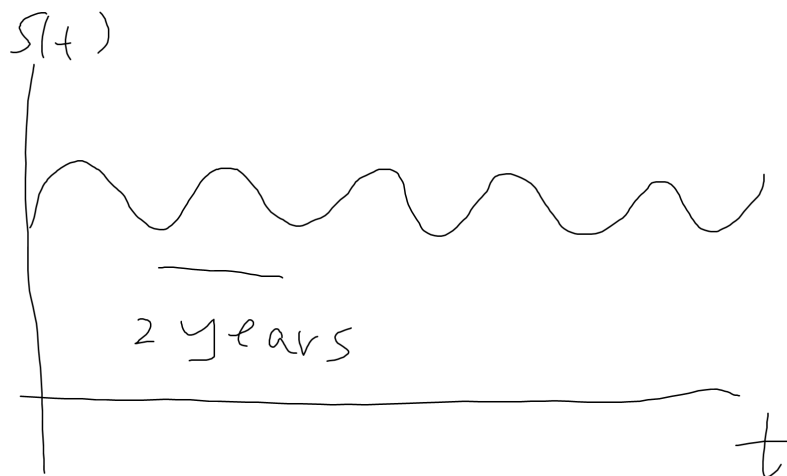
$\lambda = -\frac{1}{2}\mu \mathcal{R}_0 \pm i\sqrt{\mu\nu(\mathcal{R}_0 - 1)}$  (?). If we assume  $\nu \gg \mu$ , then rate of recovery  $\gg$  rate of death, so we get a short lived disease.





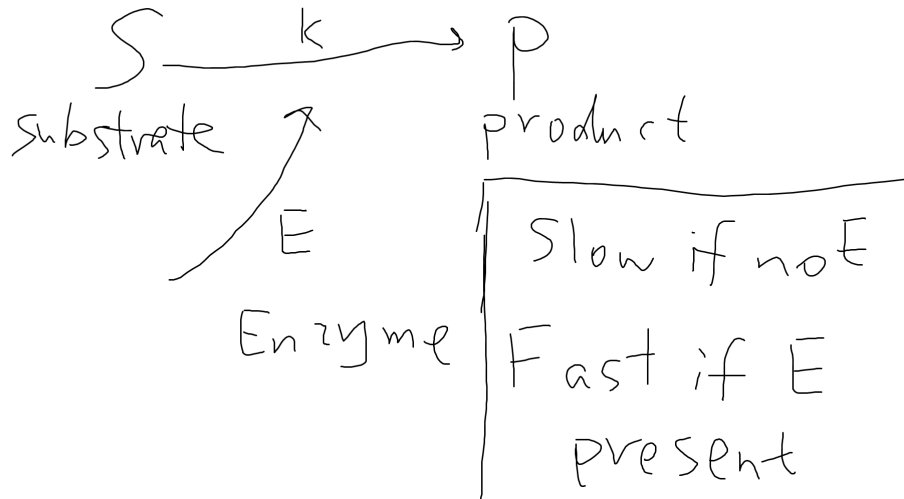
Time period is  $T = \frac{2\pi}{\omega} = \frac{2\pi}{\sqrt{\mu\nu(R_0-1)}}$

If  $\mu \gg \nu$ , for example, for Measles we have  $\mu \sim \frac{1}{70}$  years,  $\nu \sim \frac{1}{10}$  days,  $R_0 \sim 20$ , so the period of oscillation  $T \approx 2.18$  years. Then we have the following pattern.



## 2 Enzyme Kinetics

Enzyme is biological catalyst, which speeds up the process of reaction (substrate turning to product) without being consumed in the process.



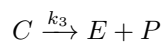
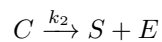
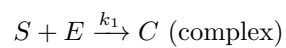
Suppose we have the model

$$\frac{dS}{dt} = -\bar{k}S \text{ no enzyme}$$

$$\frac{dS}{dt} = -kS \text{ enzyme present}$$

where  $k \gg \bar{k}$ .

Hypothesis: (Michaelis-Menten, ~1915)



Under this model, we have

$$\frac{d}{dt}S = -k_1ES + k_2C$$

$$\frac{d}{dt}E = -k_1ES + k_2C + k_3C$$

$$\frac{d}{dt}C = k_1ES - k_2C - k_3C$$

$$\frac{d}{dt}P = k_3C$$

We see that  $\frac{d}{dt}(E + C) = 0$ , and  $\frac{d}{dt}(S + C + P) = 0$ . Therefore,  $E + C = e_0$  is constant and  $S + C + P = s_0$  is constant. There are 4 equations and 2 constraints,

so we can reduce the dimension of the equation. We will choose

$$\begin{aligned}\frac{d}{dt}S &= -k_1(e_0 - C)S + k_2C = -k_1e_0S + (k_1S + k_2)C \\ \frac{d}{dt}C &= k_1(e_0 - C)S - k_2C - k_3C = k_1e_0S - (k_1S + k_2 + k_3)C\end{aligned}$$

We use our old trick (?) of rescaling variables by  $n_S = \frac{S}{s_0}$ ,  $n_C = \frac{C}{e_0}$ , then  $n_S = 1$  and  $n_C = 0$  at  $t = 0$ . The equations become

$$\begin{aligned}\frac{d}{dt}n_S &= -n_S + (n_S + \mu - \lambda)n_C \\ \varepsilon \frac{d}{dt}n_C &= n_S - (n_S + \mu)n_C\end{aligned}$$

where  $\mu = \frac{k_3}{k_1s_0}$ ,  $\lambda = \frac{k_2+k_3}{k_1s_0}$ ,  $\varepsilon = \frac{e_0}{s_0} \ll 1$ .

Steady state value of  $n_C$  assuming  $n_S$  is fixed:

$n_C = \frac{n_S}{n_S + \mu}$  as  $t \rightarrow \infty$ . Plug them back into  $n_S$  equation, get

$$\begin{aligned}\frac{d}{dt}n_S &= -n_S + (n_S + \mu - \lambda)\frac{n_S}{n_S + \mu} \\ \frac{d}{dt}n_S &= -\frac{\lambda n_S}{n_S + \mu} \quad (*)\end{aligned}$$

This is called the Michaelis-Menten equation.

### 3 Prey-predator system

Suppose we have rabbits with number  $n_R$ , and foxes with number  $n_F$ . Our biological datum is that if there is no predation then rabbits grow unboundedly, and foxes die (as they have nothing to eat). With predation, rabbits die at a rate  $b$  per capita, and foxes reproduce at a rate  $c$  per capita. We have

$$\begin{aligned}\frac{d}{dt}n_R &= a \cdot n_R - bn_Rn_F \\ \frac{d}{dt}n_F &= cn_Rn_F - dn_F\end{aligned}$$

we write as

$$\begin{aligned}\frac{d}{dt}n_R &= n_R(1 - n_F) \\ \frac{d}{dt}n_F &= -\alpha n_F(1 - n_R)\end{aligned}$$

This has fixed points  $(0, 0)$  and  $(1, 1)$ , and has Jacobian

$$\begin{pmatrix} 1 - n_F & -n_R \\ \alpha n_F & -\alpha(1 - n_R) \end{pmatrix}$$

evaluate at the two fixed points, we see that  $(0, 0)$  is unstable (actually a saddle), and the  $(1, 1)$  fixed point has eigenvalue (of Jacobian)  $\pm i\sqrt{\alpha}$ . Since the real

part is 0 we don't know (yet) whether it is stable or not. We have to solve the equations of motion:

$$\begin{aligned}dn_R &= n_R(1 - n_F)dt \\ dn_F &= -\alpha n_F(1 - n_R)dt\end{aligned}$$

so  $\frac{dn_R}{dn_F} = \frac{n_R(1-n_F)}{-\alpha n_F(1-n_R)}$ , i.e.  $\alpha \frac{1-n_R}{n_R} dn_R = -\frac{1-n_F}{n_F} dn_F$  so  $\alpha(\log n_R - n_R) = -(\log n_F - n_F) + c$ . We get  $H(n_R, n_F) = \alpha(n_R - n_R) + \log n_F - n_F = \text{constant}$ , where  $H(n_R, n_F)$  is the integral of motion. So we should observe the number  $n_R$  and  $n_F$  show a pattern of oscillation with some period  $T$  which we wish to find.

