Mathematical Biology

January 27, 2018

Contents

0 Miscellaneous

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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 $n >> 1$ we may model it with continuous equations.

Example. (2) $n \to \partial_t P(n,t) = W \cdot P(n,t)$, Markov processes. Here $P(n,t)$ is a probablity(?), 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': $\partial_t n(x,t) = f(n(x,t)) + D\nabla^2(x,t)$ 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 $t \to \infty$ we have $n(t) \to 1$. Now we can investigate if the population size is stable, and if it has any fixed points.

Let's now define $\mathbf{n} = (n_1, ..., n_p)$, 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.

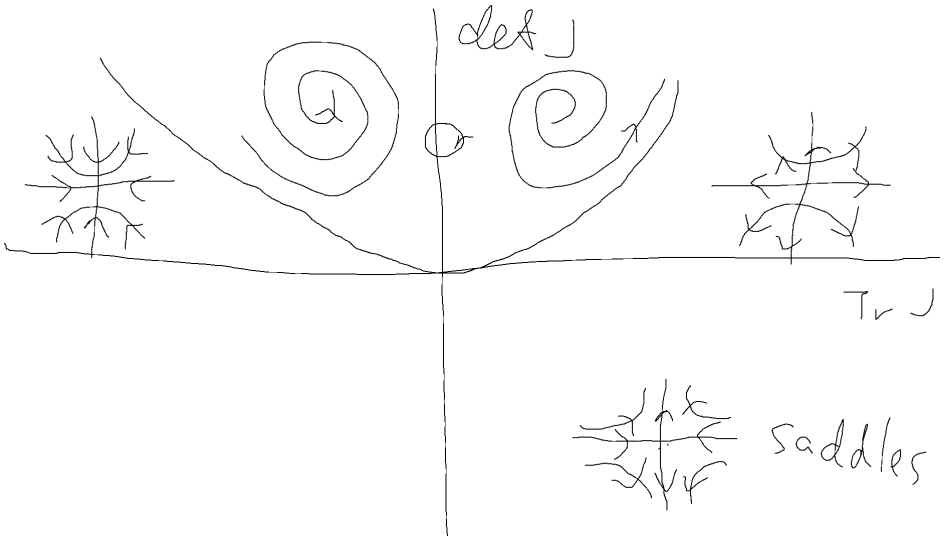
$$\begin{aligned} \frac{d}{dt}\delta\mathbf{n} &= \mathbf{f}(\mathbf{n}^* + \delta\mathbf{n}) \\ a &= \mathbf{f}(\mathbf{n}^*) + \frac{\partial f_i}{\partial n_j}\delta_{nj} + \frac{1}{2}\frac{\partial^2 f_i}{\partial n_j \partial n_k}\delta_{n_j}\delta_{n_k} \end{aligned}$$

So $\frac{d}{dt}\delta\mathbf{n} = J \cdot \partial\mathbf{n}$, so $\delta n(t) = e^{Jt} \cdot \delta n(0)$. If λ_i's are the eigenvalues of J, we consider the real part of λ_i: if $Re(\lambda_i) < 0$, 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

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

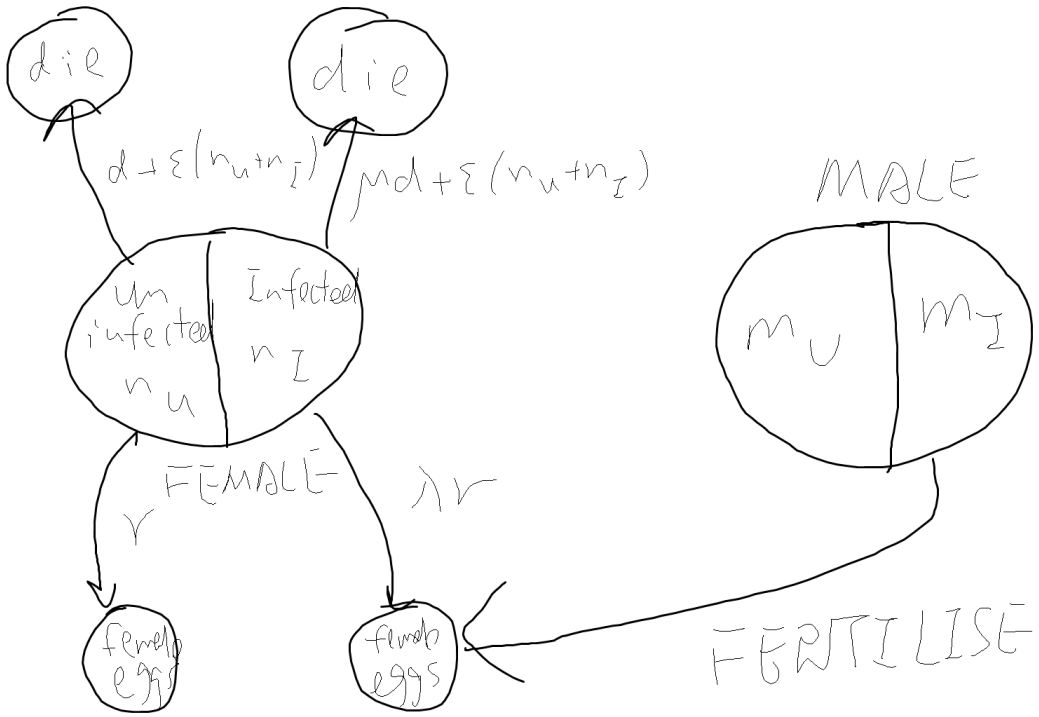
Where the matrix is J. Now we have $\lambda_1\lambda_2 = \det J$ and $\lambda_1 + \lambda_2 = \operatorname{tr} J$. Determined by the signs of those two, we have different possible behaviours:



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 $t \to \infty$?



F	M	frequency	rate	Outcome
U	U	$n_U \cdot m_U$	r	U
U	I	$n_U \cdot m_I$		X
I	U	$n_I \cdot m_U$	λr	I
I	I	$n_I \cdot m_I$	λr	I

$$m_U = \frac{n_U}{n_U + n_I}$$

$$m_I = \frac{n_I}{n_U + n_I}$$

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)

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

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

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

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

and the second equation becomes (???)

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

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

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

so that our differential equations become

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

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

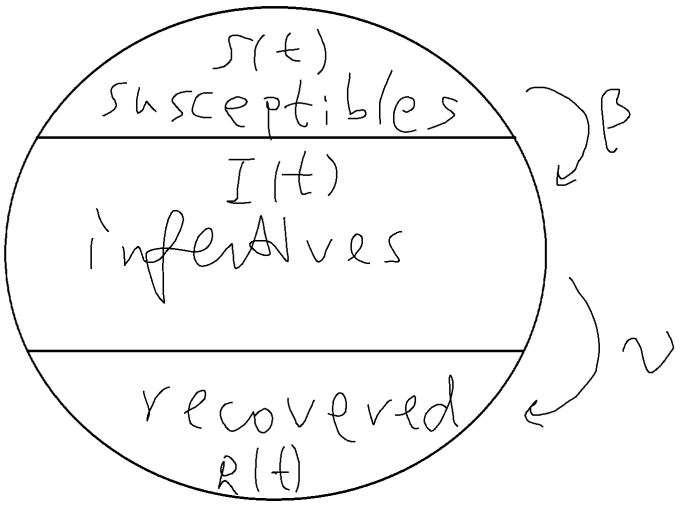
$$\frac{d}{dt}\begin{pmatrix}n_U\\n_I\end{pmatrix} = \begin{pmatrix}f_U(n_U,n_I)\\f_I(n_U,n_I)\end{pmatrix}$$

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 β, a recovery rate ν, so

in conclusion we have

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

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,

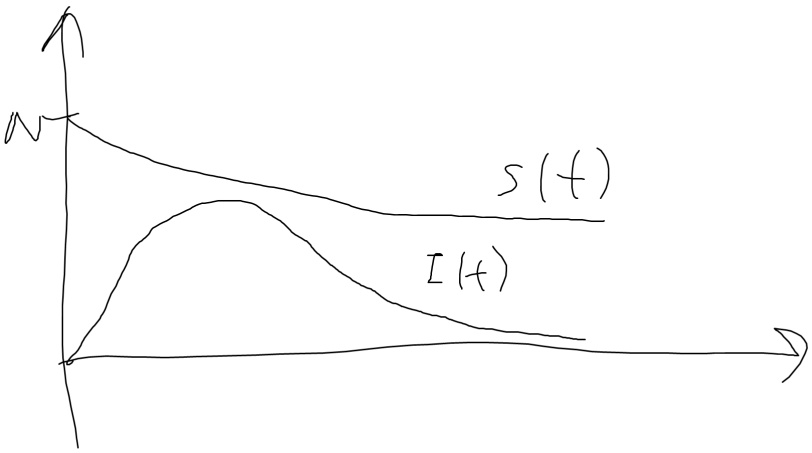
$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \nu I$$

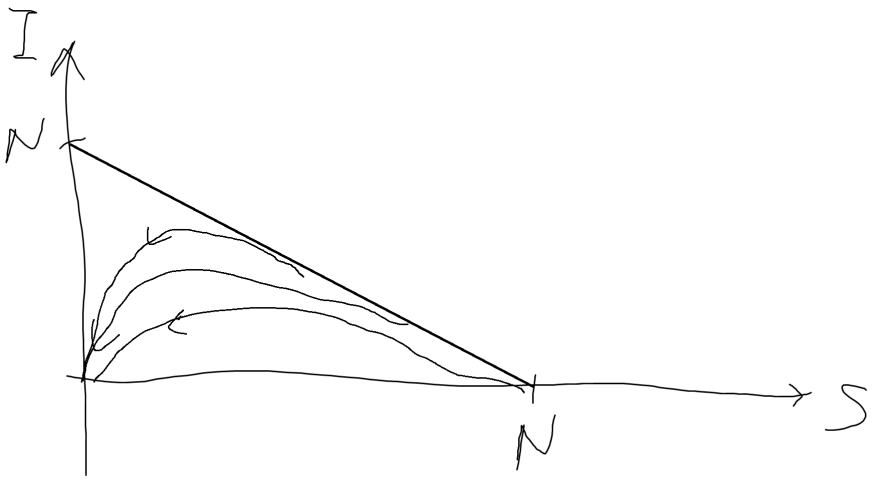
What are the questions we want to ask? We may want to know:
• When can you have an *outbreak*, i.e. $\frac{dI}{dt} > 0$;
• What is the final size of the outbreak?
• What vaccination strategy would work best?
• Endemic $\implies I^* > 0$, finite number of I in steady state.

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 $\frac{\beta}{\mu}S(0) > 1 \implies \frac{\beta N}{\nu} > 1 = \mathcal{R}_0$, the reproduction ratio, or the mean number of susceptibles infected per infective.

(Q2)





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

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

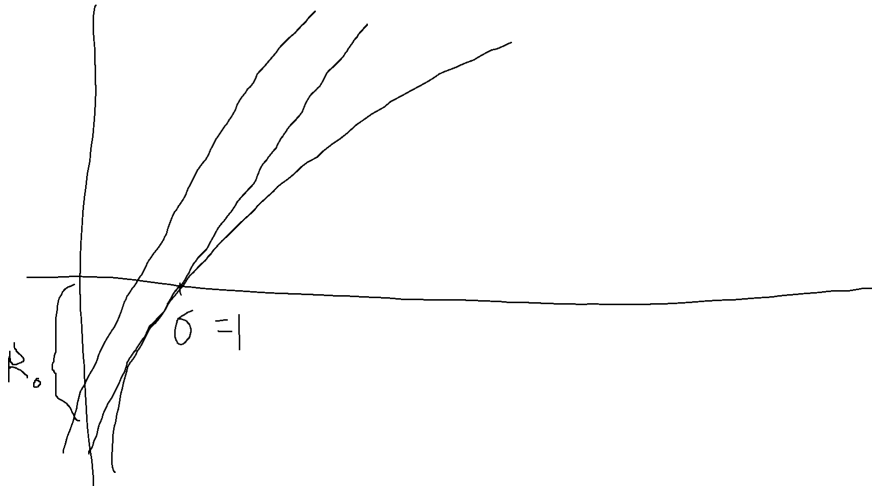
So

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

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

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

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-



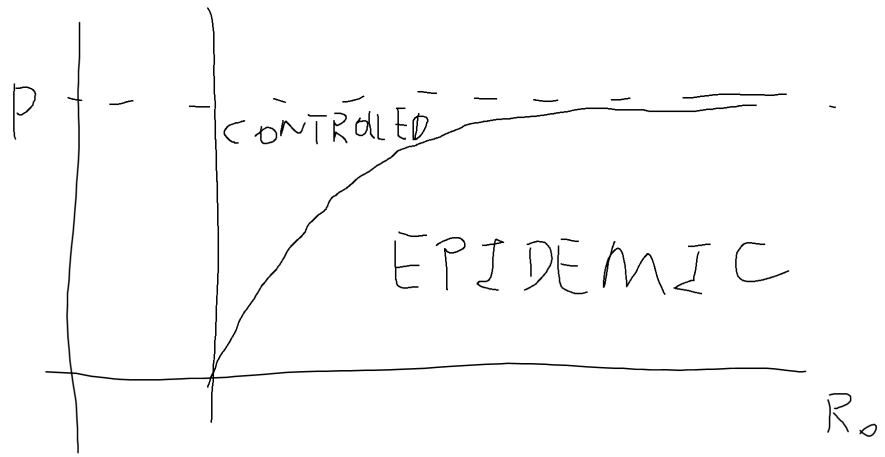
low and analyze intersections?)

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

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

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



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

(Q4)
Endemic: $I(t) \to I^* > 0$ as $t \to \infty$.
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

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

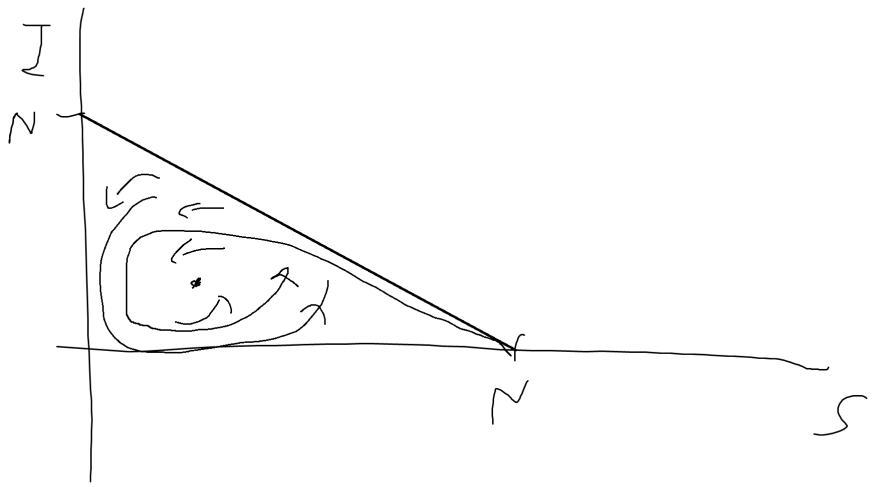
We had a Jacobian (?)

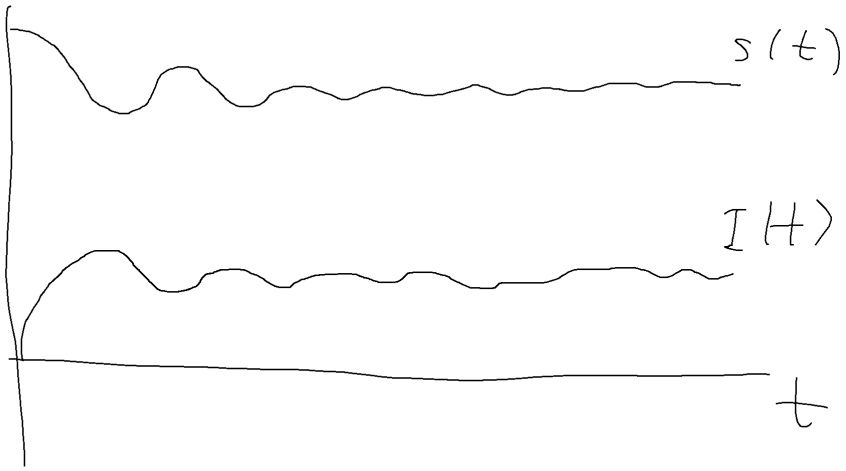
$$J = \begin{pmatrix} -\beta I - \mu & -\beta S \\ \beta I & \beta S - \nu - \mu \end{pmatrix}$$

so

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

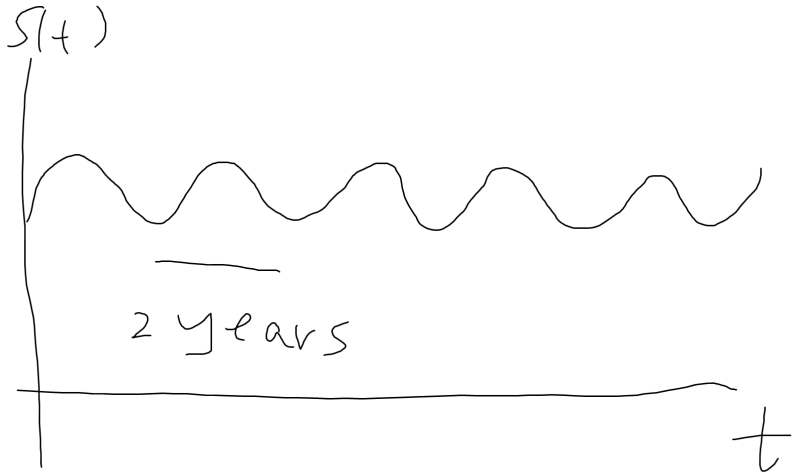
$\lambda = -\frac{1}{2}\mu\mathcal{R}_0 \pm i\sqrt{\mu\nu(\mathcal{R}_0 - 1}$ (?). If we assume $\nu \gg \mu$, then rate of recovery $\gg$ rate of death, so we get a short lived disease.





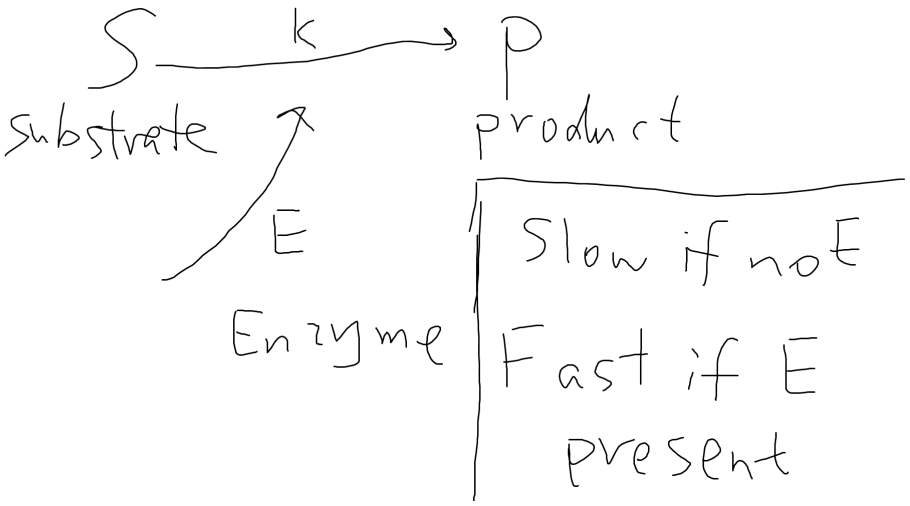
Time period is $T = \frac{2\pi}{\omega} = \frac{2\pi}{\sqrt{\mu\nu(R_0-1)}}$

If $\mu \gg \nu$, for example, for Measles we have $\mu \sim \frac{1}{70}$ years, $\nu \sim \frac{1}{10}$ days, $\mathcal{R}_0 \sim 20$, 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)

$$S + E \xrightarrow{k_1} C \text{ (complex)}$$
$$C \xrightarrow{k_2} S + E$$
$$C \xrightarrow{k_3} E + P$$

Under this model, we have

$$\frac{d}{dt}S = -k_1 ES + k_2 C$$
$$\frac{d}{dt}E = -k_1 ES + k_2 C + k_3 C$$
$$\frac{d}{dt}C = k_1 ES - k_2 C - k_3 C$$
$$\frac{d}{dt}P = k_3 C$$

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

$$\frac{d}{dt}S = -k_1(e_0 - C)S + k_2 C = -k_1 e_0 S + (k_1 S + k_2)C$$
$$\frac{d}{dt}C = k_1(e_0 - C)S - k_@ C - k_3 C = k_1 e_0 S - (k_1 S + k_2 + k_3)C$$

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

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

where $\mu = \frac{k_3}{k_1 s_0}, \lambda = \frac{k_2+k_3}{k_1 s_0}, \varepsilon = \frac{e_0}{s_0} \ll 1$.

Steady state value of n_C assuming n_S is fixed:
$n_C = \frac{n_S}{j_S+\mu}$ as $t \to \infty$. Plug them back into n_S equation, get

$$\frac{d}{dt}n_S = -n_S + (n_S + \mu - \lambda)\frac{n_S}{n_S + \mu}$$
$$\frac{d}{dt}n_S = -\frac{\lambda n_S}{n_S + \mu} \ (*)$$

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

$$\frac{d}{dt}n_R = a \cdot n_R - b n_R n_F$$
$$\frac{d}{dt}n_F = c n_R n_F - d n_F$$

we write as

$$\frac{d}{dt}n_R = n_R(1 - n_F)$$
$$\frac{d}{dt}n_F = -\alpha n_F(1 - n_R)$$

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:

$$dn_R = n_R(1 - n_F)dt$$
$$dn_F = -\alpha n_F(1 - n_R)dt$$

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 $H(n_R, n_F) = \alpha(n_R - n_R) + \log n_F - n_F$ =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.