Delay Differential Equations in Epidemiology

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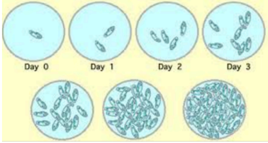
"Qu' est-ce que le passé, sinon du présent qui est en retard?"

(What is the past, if not the present, which is late?)
(Pierre Dac, a French humorist (1893-1975))

Motivation

1. A scientist studying the growth of a population, $p(t)$, may make a very simple assumption that a population grows at a rate directly proportional to its size.



- **Malthus model:**

$$\frac{dp(t)}{dt} = r\,p(t), \qquad t \geq 0$$

$$p(0) = p_0$$

- The solution of the DE is

$$p(t) = p_0 e^{rt}$$

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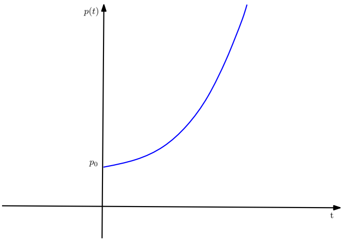

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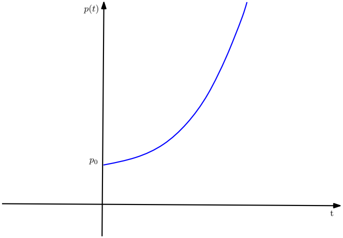

- $\lim_{t\to\infty} p(t) = \infty$ whenever $r > 0$ ("Unlimited growth")

2. **Limited population growth (Logistic equation)**

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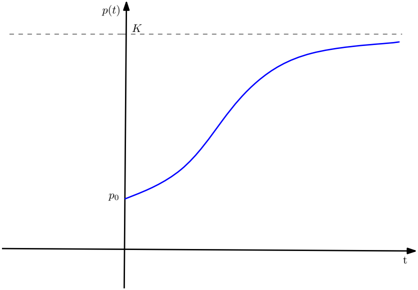
- In 1838, the Belgian mathematician Pierre Verhulst introduced a model where the population has some self-limitation.
- Assume that the per capita growth rate decreases linearly as a function of population.
- The growth equation is given by

$$\frac{dp}{dt} = r\left(1 - \frac{p}{K}\right)p = R(p)p; \qquad p(0) = p_0, \tag{1}$$

where $r(> 0)$ is the intrinsic growth rate; and $K(> 0)$ is the carrying capacity; $R(p) = r(1 - \frac{p}{K})$.

- The Logistic equation (1) assumes that population density negatively affects the per capita growth rate according to $\frac{1}{p}\frac{dp}{dt} = r\left(1 - \frac{p}{K}\right)$ due to environmental degradation.

The solution is $p(t) = \frac{p_0 K}{p_0 - (p_0 - K)e^{-rt}}$, The solution is $p(t) = \frac{p_0 K}{p_0 - (p_0 - K)e^{-rt}}$,



3. In 1948, G. E. Hutchinson pointed out that negative effects that high population densities have on the environment influence birth rates at later times due to developmental and maturation delays.

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- Hutchinson modified the logistic equation to incorporate a delay into the growth rate, so $R(p)$ becomes $R(p(t-\tau))$:

$$\frac{dp}{dt} = r\left(1 - \frac{p(t-\tau)}{K}\right)p(t) \quad \text{(Hutchinson's eq or logistic DDE)}, \tag{2}$$

where the constant $\tau > 0$ is the time delay.

Example

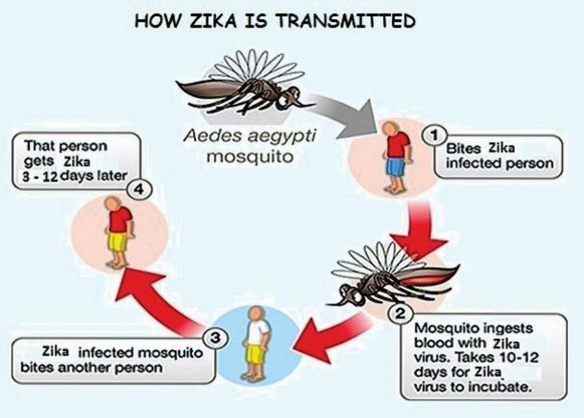

Figure: Transmission Cycle of the Zika virus
http://health.gov.bz/www/images/stories/zika

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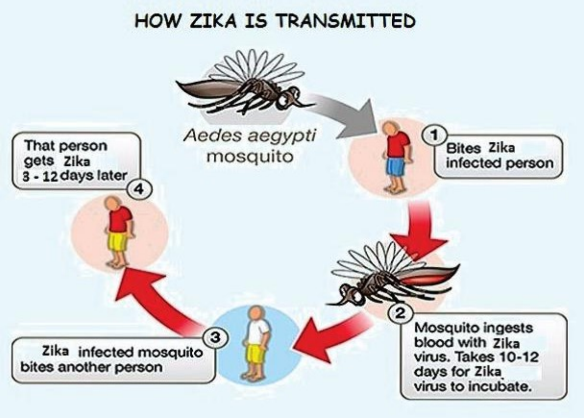

Figure: Transmission Cycle of the Zika virus
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Incubation period is the time it takes for the disease to develop inside of a newly infected being (this is the delay time).

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$$y'(t) = -ay(t-\tau), \qquad t > 0, \tag{3}$$

where $a \in \mathbb{R}$, and $\tau > 0$ is the delay or time lag.

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- A single DDE is capable of producing oscillatory motion, in contrast to a first-order ODE.

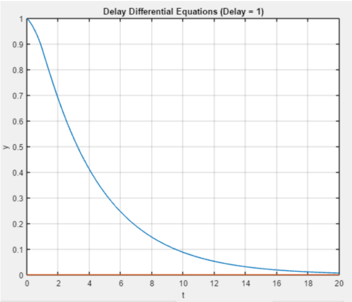

Figure: $y' = -ay(t-\tau)$ with small τ, and $a > 0$

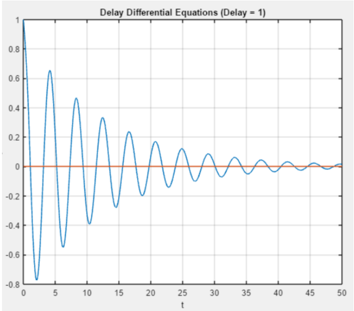

Figure: $y' = -ay(t-\tau)$ with larger τ, and $a > 0$

Setting $y(\tau t) = u(t)$, we get

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$$\lambda + \beta e^{-\lambda} = 0 \quad \text{(Characteristics equation)} \tag{5}$$

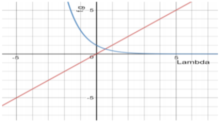
$\iff \lambda = -\beta e^{-\lambda}$

- Solving and understanding the roots of (5) would be helpful in studying the stability of the equilibrium and the oscillatory behavior of the solution.

Stability of the zero equilibruium

- **Proposition:** Suppose that $\lambda \in \mathbb{R}$.

(a) If $\beta < 0$



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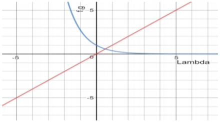

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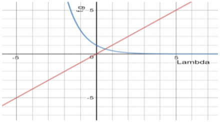

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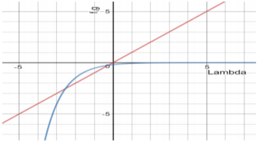

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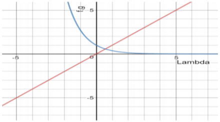

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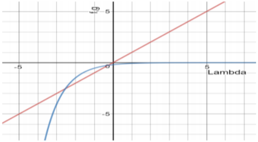
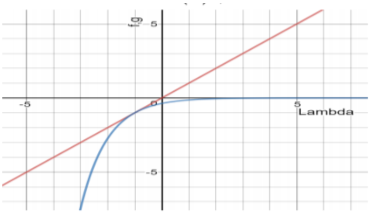


Then it has exactly two negative real roots where $\lambda_1 < -1$ and $-1 < \lambda_2 < 0 \Rightarrow u(t) \to 0$ as $t \to \infty$, and $u^* = 0$ is asymptotically stable.

(c) If $\beta = e^{-1}$



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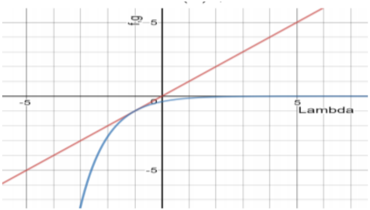

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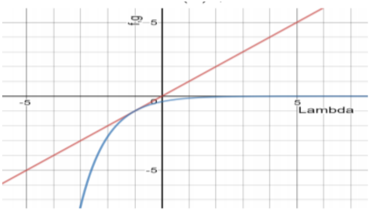

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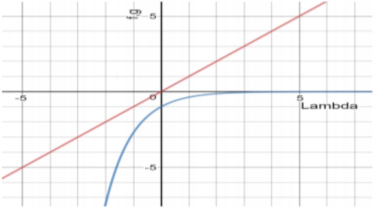

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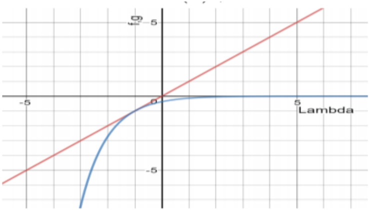

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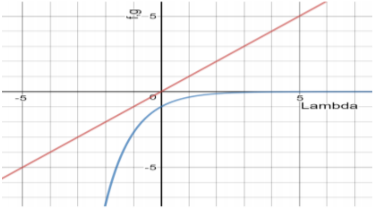

then there are no real roots.

• Suppose that $\lambda \in \mathbb{C}$. Set $\lambda = x + i\,y$.
Separating the real part and imaginary parts of the characteristic equation $\lambda + \beta e^{-\lambda} = 0$, we obtain:

$$\begin{cases} x = -\beta e^{-x} \cos y \\ y = \beta e^{-x} \sin y \end{cases} \tag{6}$$

$$\Rightarrow \frac{x}{y} = -\cot(y) \Longrightarrow x = -y\cot(y)$$

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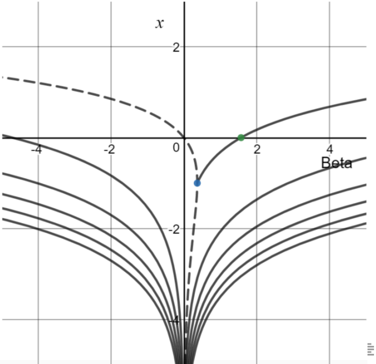
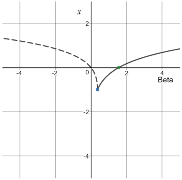
We get the parametric equations:

$$\begin{cases} x = -y\cot(y) \\ \beta = \dfrac{y}{e^{y\cot(y)} \sin y} \end{cases} \tag{7}$$



Definition:
The leading roots $\{\lambda_L\} = \{x_L + iy_L\}$ of an equation are those that are such that $x_L > x = Re(\lambda)$ for all $\lambda = x + iy$.



Proposition:

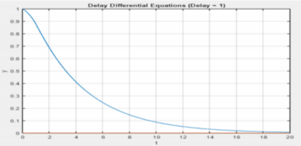
1. If $\beta < 0$ then there is only one leading real root that is positive. Therefore, $u^* = 0$ is unstable.
2. If $0 < \beta < e^{-1}$ then there is only one leading real root and it is negative. Therefore, $u^* = 0$ is asymptotically stable.
3. If $e^{-1} < \beta < \pi/2$ then there is only one pair of complex conjugate leading roots with negative real part. Therefore, $u^* = 0$ is asymptotically stable.
4. If $\beta = \pi/2$ then there is only one pair of complex conjugate leading roots $\pm\dfrac{\pi}{2}i$. Therefore, $u^* = 0$ is unstable.
5. If $\beta > \pi/2$ then there is only one pair of complex conjugate leading roots with positive real parts. $\Rightarrow u^* = 0$ is unstable.

So, $u^* = 0$ **is asymptotically stable for** $\beta \in (0, \pi/2)$.

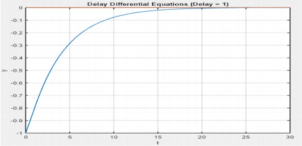
Oscillatory behavior: We observe that

1. For β small positive then the solution decays exponentially towards the zero equilibrium without any oscillatory behavior.
2. When β hits a value round 0.37 ($\approx e^{-1}$), the solution becomes oscillatory but it would still decay to the zero equilibrium.
3. When β hits a value around 1.5 ($\approx \pi/2$), oscillations would still take place but the zero equilibrium would no more be stable; the amplitude of the oscillations grows indefinitely as time progress

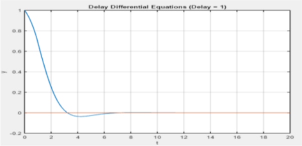
Theorem: Every Solution of the DDE (4) is oscillatory if and only if $\beta > e^{-1}$.



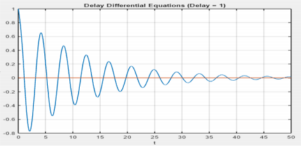
(a) Small Rate: $\beta = 0.2$



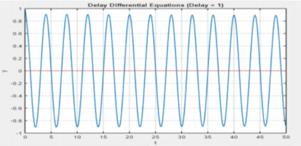
(b) Small Rate: $\beta = 0.2$
$\phi(t) = -e^t$



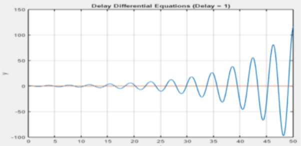
(c) Oscillations Observed: $\beta = 0.5$



(d) Decaying Oscillations: $\beta = 1.4$



(e) Stable Oscillation: $\beta = 1.57$

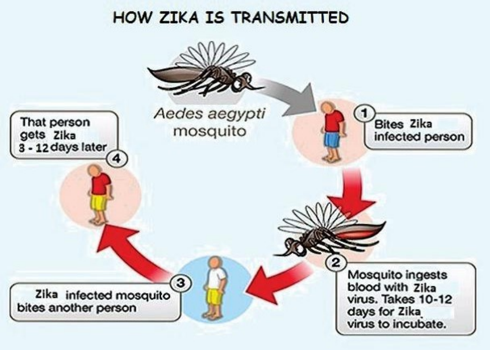


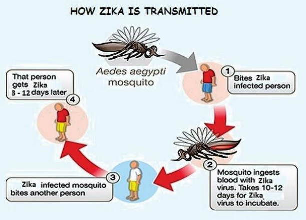
(f) Unstable Oscillation: $\beta = 1.8$
Different Vertical Scaling

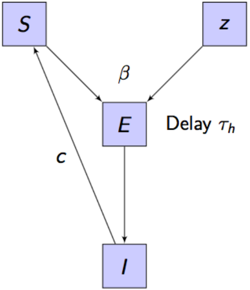
Vector Borne Diseases

- **Definition:** A vector borne disease is a disease transmitted to humans through the bites of an infected arthropod vector (e.g. mosquitoes).
- Malaria and the Zika virus are two well-known examples.
- Understanding the spread of such diseases is vital to their eventual containment and eradication.

Definition:
Incubation period is the time it takes for the disease to develop inside of a newly infected being (this is the delay time).







S = Number of Susceptible Individuals
z = Number of Infected Mosquitoes
E = Number of Exposed Individuals
I = Number of Infected Individuals
β = Biting Rate
c = Disease Recovery Rate

We are interested in the dynamics of infected humans.

Assumptions

1. Upon biting an infectious human I, with a biting rate β, a susceptible vector becomes infected. And upon biting a susceptible human S, an infectious vector z infects the bitten human. Infected humans recover from the disease at a rate c and they confer no immunity after recovery.
2. The size of the human population N is fixed and each human can either be susceptible, exposed, or infected (i.e. $S + I + E = N$).
3. There is an incubation period τ_h in humans, that is a delay between an individual receiving infection and becoming fully infected.

4. There is an incubation period τ_v in vectors, that is a delay between the vector receiving infection and becoming fully infected.
5. The infected vector population is proportional to the infected human population, that is $z(t) = pI(t - \tau_v)$.
6. The exposed human population (population developing the disease) is proportional to the infected human population, that is $E(t) = qI(t)$.

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• The Model

From the assumptions, we have the equation:

$$I'(t) = \beta \frac{S(t - \tau_h)}{N} z(t - \tau_h) - cI(t)$$

Using assumptions 1, 4, and 5 and normalizing, we get a two-lag DDE:

$$I'(t) = [b(1 - eI(t - \tau_h))I(t - \tau_h - \tau_v)] - cI(t), \tag{8}$$

where $b = \beta p$, $e = q + 1$, and I is the proportion of infected individuals in the population.

When setting $\tau_h = 0$, $q = 0$, and $\tau_v \neq 0$, we get a previously studied model by Kenneth Cooke (1979):
$I'(t) = b[(1 - I(t))I(t - \tau_v)] - cI(t)$.

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The equilibria of the model:

- $I^* = 0$ (the disease-free equilibrium)
- $I^* = \dfrac{1}{e}\left(1 - \dfrac{c}{b}\right)$ (the endemic equilibrium which exists when $R_0 = \frac{b}{c} \geq 1$)

Stability Analysis: Approach

- Linearizing around the disease-free zero equilibrium, we derive the following transcendental characteristic equation:

$$\lambda = be^{(-\tau_v - \tau_h)\lambda} - c \tag{9}$$

Setting $z = (\tau_v + \tau_h)\lambda$, then Eq. (9) becomes:

$$z + a_1 + a_2 e^{-z} = 0, \tag{10}$$

where $a_1 = (\tau_v + \tau_h)c$ and $a_2 = -b(\tau_v + \tau_h)$.

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• Linearizing around the endemic equilibrium, we derive the equation:

$$\lambda + c = ce^{(-\tau_h - \tau_v)\lambda} + (c - b)e^{-\tau_h \lambda} \tag{11}$$

Assuming $\tau_v = 0$ and setting $z = \tau_h \lambda$, then Eq. (11) becomes:

$$z + a_1 + a_2 e^{-z} = 0, \tag{12}$$

where $a_1 = \tau_h c$ and $a_2 = -(2c - b)\tau_h$

The stability results follow from the study of the real parts of the roots λ.

Stability Analysis: Results

- The disease-free equilibrium is stable if $R_0 = \frac{b}{c} \leq 1$ and unstable if $R_0 > 1$.

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- The disease-free equilibrium is stable if $R_0 = \frac{b}{c} \leq 1$ and unstable if $R_0 > 1$.

- The endemic equilibrium is unstable if $0 \leq R_0 < 1$. Moreover, if $\tau_v = 0$ and $R_0 > 1$, then there exists a specific b_0 such that $3c < b_0 < \frac{1}{\tau_h}\left[(\pi^2 + \tau_h^2 c^2)^{\frac{1}{2}} + 2\tau_h c\right]$ and a change in stability occurs when $R_0 = \frac{b_0}{c}$.

Numerical Observations

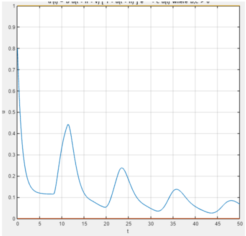

Figure: Stable disease free equilibrium for small values of, transmission rate, b

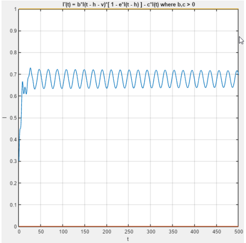

Figure: Stable endemic equilibrium for realistic parameters. (From Zika paper by Agusto et al.)

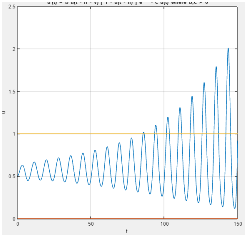

Figure: Unstable Equilibria and Unbounded Solution for even larger values of b

References

Kenneth L. Cooke (1979)
Stability Analysis for a Vector Disease Model.
Rocky Mountain Journal of Mathematics, Vol 9, Number 1, Pages 31-42.

T. Erneux (2009)
Applied Delay Differential Equations, Vol 3.
Springer Science & Business Media.

N. Mavinga and Y. Qaddura (2018)
Analysis of Vector-Borne Diseases Model with a Two-lag Differential Equation.
North Carolina Journal of Math and Stat, Vol 4, Pages 12-28.

Hal Smith (2010)
An Introduction to Delay Differential Equations With Applications to The Life Sciences, Vol 57.
Springer Science & Business Media.

F.B. Agusto, S. Bewick, & W.F. Fagan.
Mathematical model of Zika virus with vertical transmission
Infectious Disease Modelling, Vol 2, Issue 2, Pages 244 - 267.

Thank you!