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:**

\[
\frac{dp(t)}{dt} = rp(t), \quad t \geq 0
\]

\[
p(0) = p_0
\]
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\[ \lim_{t \to \infty} p(t) = \infty \text{ whenever } r > 0 \text{ ("Unlimited growth")} \]
2. Limited population growth (Logistic equation)

- In 1838, the Belgian mathematician Pierre Verhulst introduced a model where the population has some self-limitation.

\[ \frac{dp}{dt} = r \left(1 - \frac{p}{K}\right)p = R(p), \quad p(0) = p_0, \quad (1) \]

where \( r > 0 \) is the intrinsic growth rate; and \( K > 0 \) is the carrying capacity; \( R(p) = r \left(1 - \frac{p}{K}\right) \).
2. **Limited population growth (Logistic equation)**

- 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

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

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

- The Logistic equation (1) assumes that population density negatively affects the per capita growth rate according to

\[
\frac{1}{p} \frac{dp}{dt} = r \left( 1 - \frac{p}{K} \right) \text{ due to environmental degradation.}
\]
The solution is \[ p(t) = \frac{p_0 K}{p_0 - (p_0 - K)e^{-rt}}, \]
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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 $R(p(t - \tau))$:

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

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

Figure: Transmission Cycle of the Zika virus
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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 $\tau$, and $a > 0$

Figure: $y' = -ay(t - \tau)$ with larger $\tau$, and $a > 0$
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- The only equilibrium solution is $u^*(t) = 0$ for all $t$.
- We look for solutions of the form: $u(t) = ce^{\lambda t}$, where $c$ is a constant and the eigenvalues $\lambda$ are solutions of the transcendental equation:

$$\lambda + \beta e^{-\lambda t} = 0 \quad \Leftrightarrow \quad \lambda = -\beta e^{\lambda t}$$

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

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

(a) If $\beta < 0$

\[
\frac{d}{dt}u(t) = \lambda u(t) - \beta u(t-\tau)
\]

As $t \to \infty$, $u(t) \to 0$, and $u^* = 0$ is unstable.

(b) If $0 < \beta < e^{-1}$

Then it has exactly two negative real roots where $\lambda_1 < -1$ and $-1 < \lambda_2 < 0$.

As $t \to \infty$, $u(t) \to 0$, and $u^* = 0$ is asymptotically stable.
**Stability of the Zero Equilibrium**

- **Proposition:** Suppose that $\lambda \in \mathbb{R}$.
  
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Then it has exactly two negative real roots where $\lambda_1 < -1$ and $-1 < \lambda_2 < 0 \Rightarrow u(t) \rightarrow 0$ as $t \rightarrow \infty$, and $u^* = 0$ is asymptotically stable.
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then there are no real roots.
Suppose that $\lambda \in \mathbb{C}$. Set $\lambda = x + iy$. Separating the real part and imaginary parts of the characteristic equation $\lambda + \beta e^{-\lambda} = 0$, we obtain:

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

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

We get the parametric equations:

\[
\begin{align*}
    x &= -y \cot(y) \\
    \beta &= \frac{y}{e^y \cot(y) \sin y}
\end{align*}
\]
Definition:
The leading roots \( \{ \lambda_L \} = \{ x_L + iy_L \} \) of an equation are those that are such that
\[ x_L > x = \text{Re}(\lambda) \] 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 \( \pm \frac{\pi}{2}i \). 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 $\beta$ small positive then the solution decays exponentially towards the zero equilibrium without any oscillatory behavior.

2. When $\beta$ hits a value round $0.37 \approx e^{-1}$, the solution becomes oscillatory but it would still decay to the zero equilibrium.

3. When $\beta$ 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 progresses.

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

Vector Borne Diseases Model

Numerical Observations

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

$\phi(t) = -e^t$

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

(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).
\[ S = \text{Number of Susceptible Individuals} \]
\[ z = \text{Number of Infected Mosquitoes} \]
\[ E = \text{Number of Exposed Individuals} \]
\[ I = \text{Number of Infected Individuals} \]
\[ \beta = \text{Biting Rate} \]
\[ c = \text{Disease Recovery Rate} \]

*We are interested in the dynamics of infected humans.*
Assumptions

1. Upon biting an infectious human $I$, with a biting rate $\beta$, 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 $\tau_h$ in humans, that is a delay between an individual receiving infection and becoming fully infected.
4. There is an incubation period \( \tau_v \) 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 \( E(t) = qI(t) \).
4. There is an incubation period $\tau_v$ in vectors, that is a delay between the vector receiving infection and becoming fully infected.

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6. The exposed human population (population developing the disease) is proportional to the infected human population, that is $E(t) = qI(t)$.

**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)
- \( I^* = \frac{1}{e} \left( 1 - \frac{c}{b} \right) \) (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:

\[ \lambda = be^{(-\tau_v - \tau_h)\lambda} - c \]  \hspace{1cm} (9)

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

\[ z + a_1 + a_2e^{-z} = 0, \]  \hspace{1cm} (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:

\[ \lambda + c = ce^{(-\tau_h - \tau_v)\lambda} + (c - b)e^{-\tau_h\lambda} \]  \hspace{1cm} (11)

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

\[ z + a_1 + a_2e^{-z} = 0, \]  \hspace{1cm} (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 \( \lambda \).
Stability Analysis: Results

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

Moreover, if $\tau_v = 0$ and $R_0 > 1$, then there exists a specific $b_0$ such that $3c < b_0 < \tau_h \left[ \left( \pi^2 + \tau^2 h^2 c^2 \right) \right]^{1/2} + 2\tau h c]$ and a change in stability occurs when $R_0 = \frac{b}{c}$. 
**Stability Analysis: Results**

- 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 $b$
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Thank you!