Memorial University of Newfoundland

A Periodic Disease Transmission Model with Asymptomatic Carriage and Latency Periods

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Outlines

- Introduction
- Model Derivation
- Basic Reproduction Ratio
- Threshold Dynamics
- Uniqueness of Epidemic State with Constant Coefficients
- Numerical Computation and Simulations

1 Introduction

- Asymptomatic carriers: For certain infectious diseases, there are individuals who have been infected and are able to transmit their illness but do not display any symptoms.

- They are potential sources for transmission of some diseases:
  - Typhoid Fever
  - HIV
  - Epstein-Barr Virus (EBV)
  - Chlamydia
  - ⋮

Typhoid Mary in a 1909 newspaper illustration (Wikipedia)

Mary Mallon is the first person in the United States identified as an asymptomatic carrier of typhoid fever.

- Asymptomatic carriers are common and invisible, can have serious long term health consequences.

The hidden epidemic

Chlamydia is the most common treatable STD; Three-quarters of all women and half of all men with chlamydia have no STD symptoms

Meningococcal disease

According to WHO report, up to $5 - 10\%$ of population may be asymptomatic carriers in Meningococcal disease, which is spread by person-to-person contact through respiratory droplets of infected people.

- Carriers have been incorporated in a variety of epidemic models:
  - Hepatitis B virus with carriers
    - G. F. Medley, N. A. Lindop, W. J. Edmunds and D. J. Nokes, Hepatitis-B virus endemicity: Heterogeneity, catastrophic dynamics and control, Nature Medicine, 7(5) (2001), 619-624.
    - S. Zhao, Z. Xu and Y. Lu, A mathematical model of hepatitis B virus transmission and its application for vaccination strategy in China, Int. J. Epidemiol., 29(4) (2000), 744-752.
  - Meningococcal meningitis
    - T.J. Irving, K.B. Blyuss, C. Colijn and C.L. Trotter, Modelling meningococcal meningitis in the African meningitis belt, Epidemiol. Infect., 140(5) (2012), 897-905.
    - C. L. Trotter, N. J. Gay and W. J. Edmunds, Dynamic models of meningococcal carriage, disease, and the impact of serogroup C conjugate vaccination, American J. Epidemiology, 162(1) (2005), 89-100.

- General mathematical models that incorporates disease carriers

  - M. Ghosh, P. Chandra, P. Sinha and J. B. Shukla, Modelling the spread of carrier-dependent infectious diseases with environmental effect, Appl. Math. Comput., 152(2) (2004), 385-402.
  - D. Kalajdzievska and M. Y. Li, Modeling the effects of carriers on transmission dynamics of infectious disease, Math. Bio. & Eng., 8(3) (2011), 711-722.
  - J. T. Kemper, The effects of asymptotic attacks on the spread of infectious disease: A deterministic model, Bull. Math. Biology, 40(6) (1978), 707-718.
  - R. Naresh, S. Pandey and A. K. Misra, Analysis of a vaccination model for carrier dependent infectious diseases with environmental effects, Nonlinear Analysis: Modelling and Control, 13(3) (2008), 331-350.

Why periodic coefficients?

- In the real world, periodicity and other oscillatory behaviors have been observed in the incidence of many infectious diseases, including measles, influenza and chickenpox, etc.

- The appearance of such oscillatory behaviors is mostly due to seasonally variations in environmental factors such as temperature and humidity.

- Works on seasonal fluctuations in epidemic models:

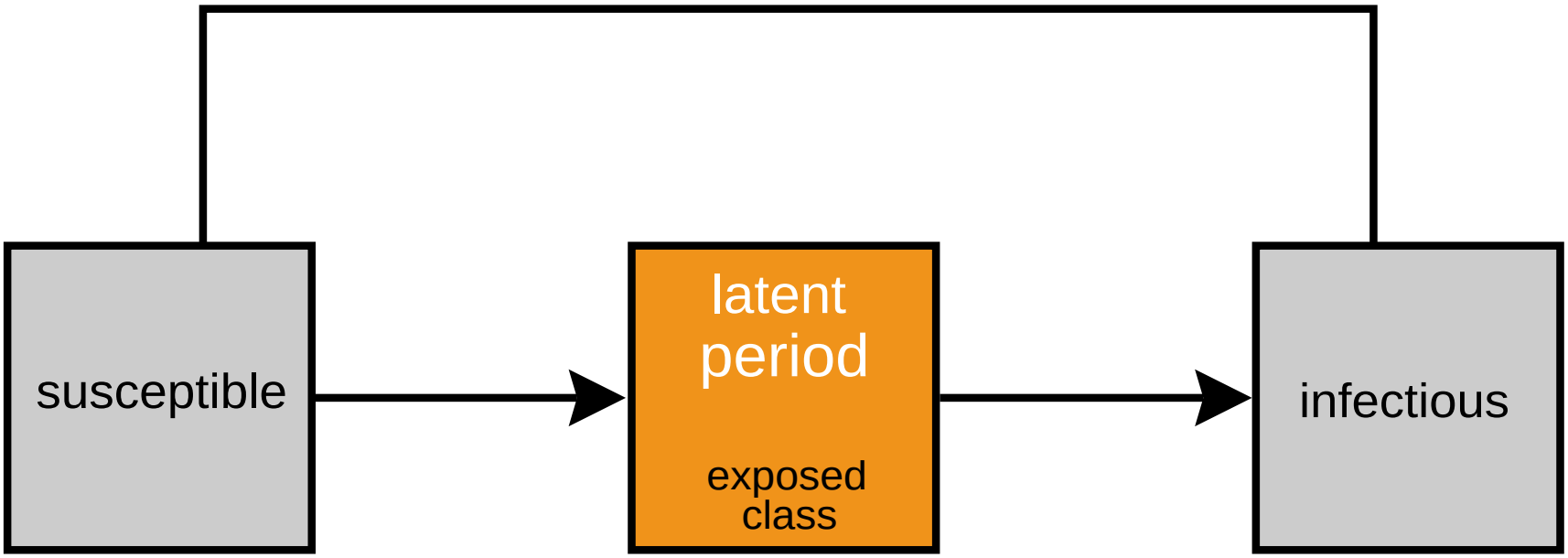
  - X. Liu and X.-Q. Zhao, A Periodic Epidemic Model with Age Structure in a Patchy Environment, SIAM J. Appl. Math., 71(6) (2011), 1896-1917.

  - Y. Lou and X.-Q. Zhao, A climate-based malaria transmission model with structured vector population, SIAM J. Appl. Math., 70(6) (2010), 2023-2044.

  - T. Zhang and Z. Teng, On a nonautonomous SEIRS model in epidemiology, Bull. Math. Biology, 69(8) (2007), 2537-2559.

Why latent periods?

- In the real world, when adequate contact with an infectious happen, a susceptible individual becomes infected but is not yet infectious.



- Time delays have been included in a variety of epidemic models:

  - Y. Yuan and J. Belair, Threshold dynamics in an SEIRS model with latency and temporary immunity, J. Math. Biol., 69 (2014), 875-904.

  - K. Cooke and P. van den Driessche, Analysis of an SEIRS epidemic model with two delays, J. Math. Bioscience, 35 (1996), 240-260.

  - Y. Lou and X.-Q. Zhao, Threshold dynamics in a time-delayed periodic SIS epidemic model, Discrete and Continuous Dynamical Systems-B, 12(1) (2009), 169-186.

  - S. Ruan, D. Xiao and J. C. Beier, On the delayed RossMacdonald model for malaria transmission, Bull. Math. Biology, 70(4) (2008), 1098-1114.

- The latent period has a profound effect on the generation time, epidemic growth/transmission.

- We introduce a time delay to represent the time-lag that asymptomatic carriers take to develop the disease symptoms (the asymptomatic carriage letency period).

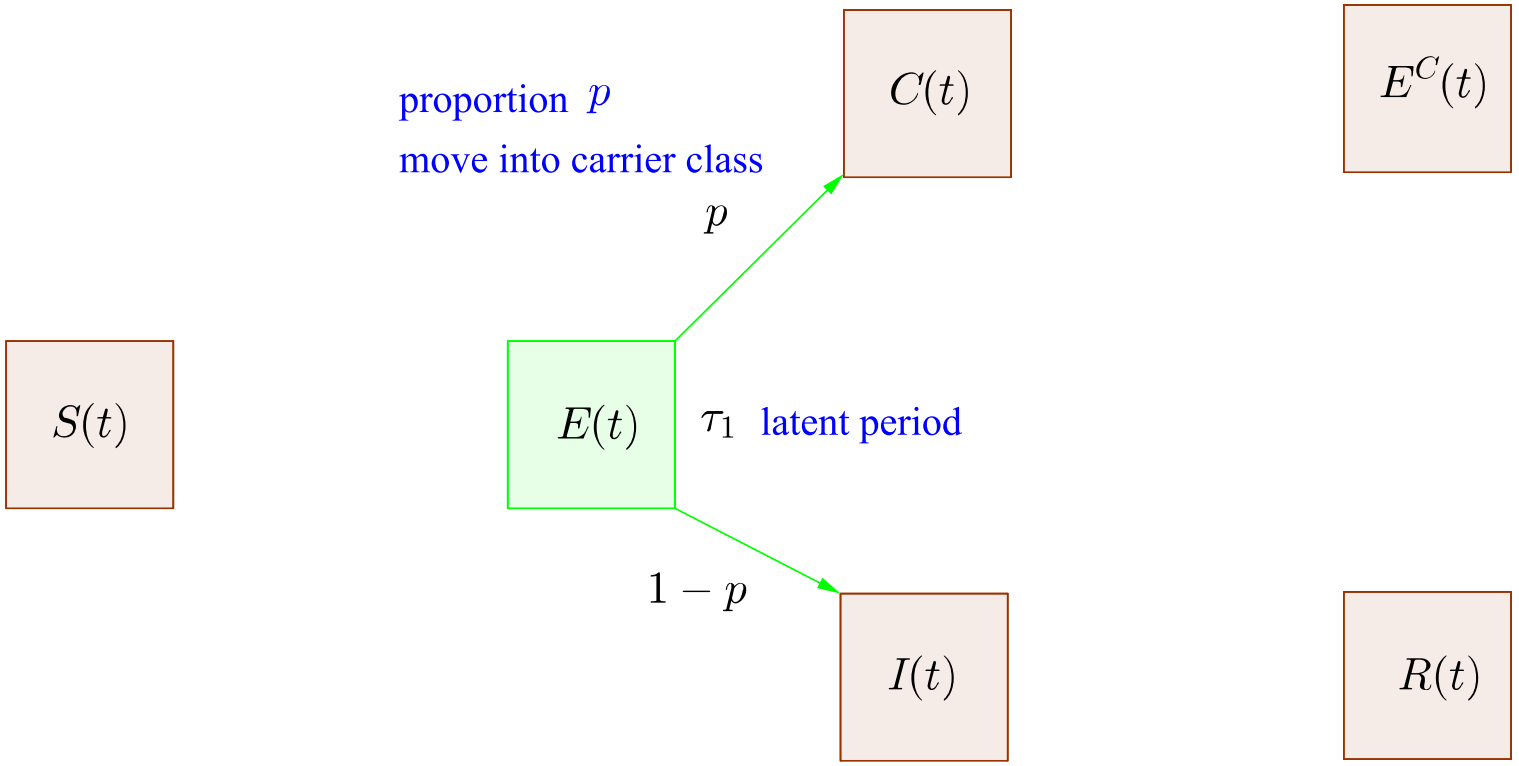
2 Model Derivation

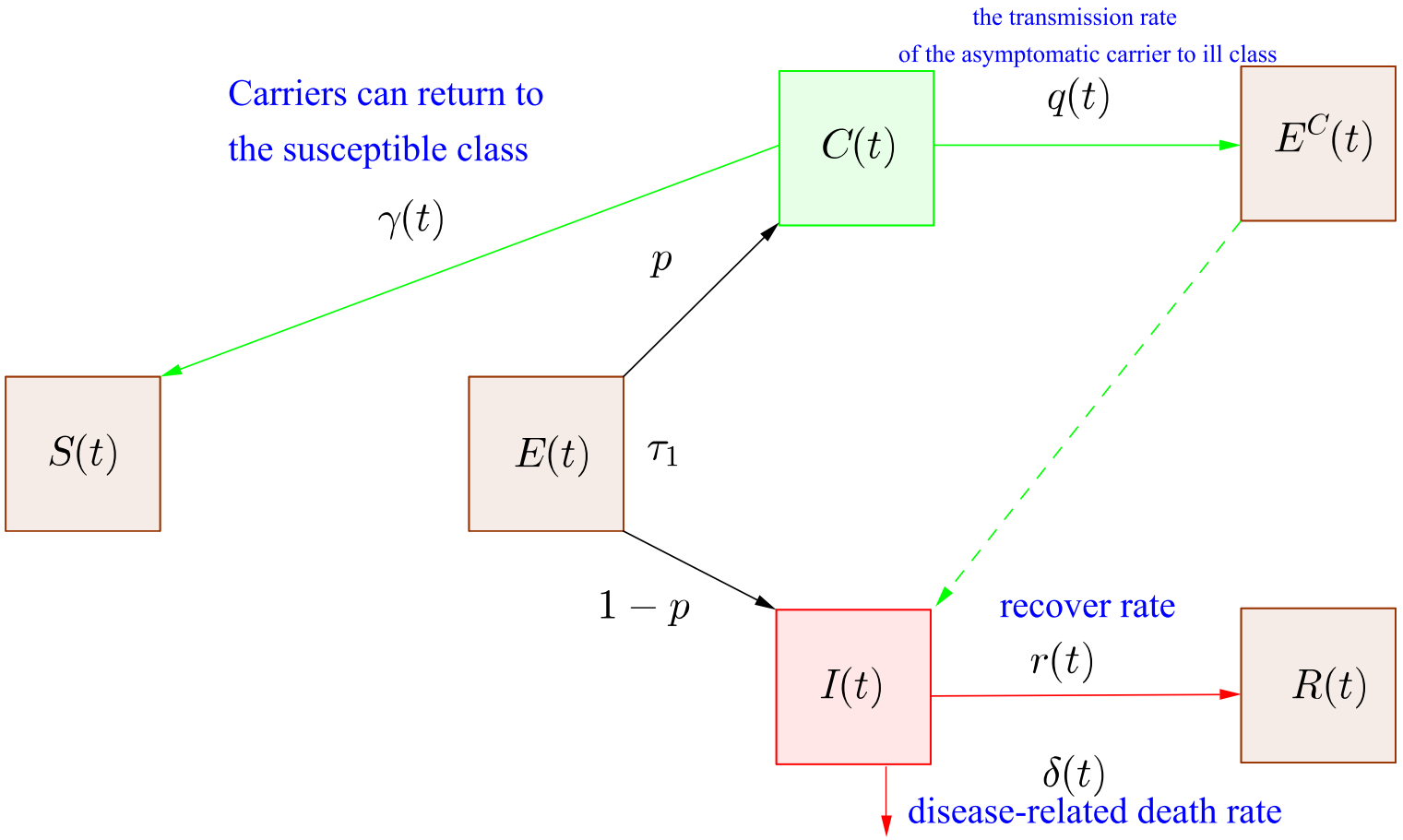
- Total population $N(t)$ is divided into six categories:

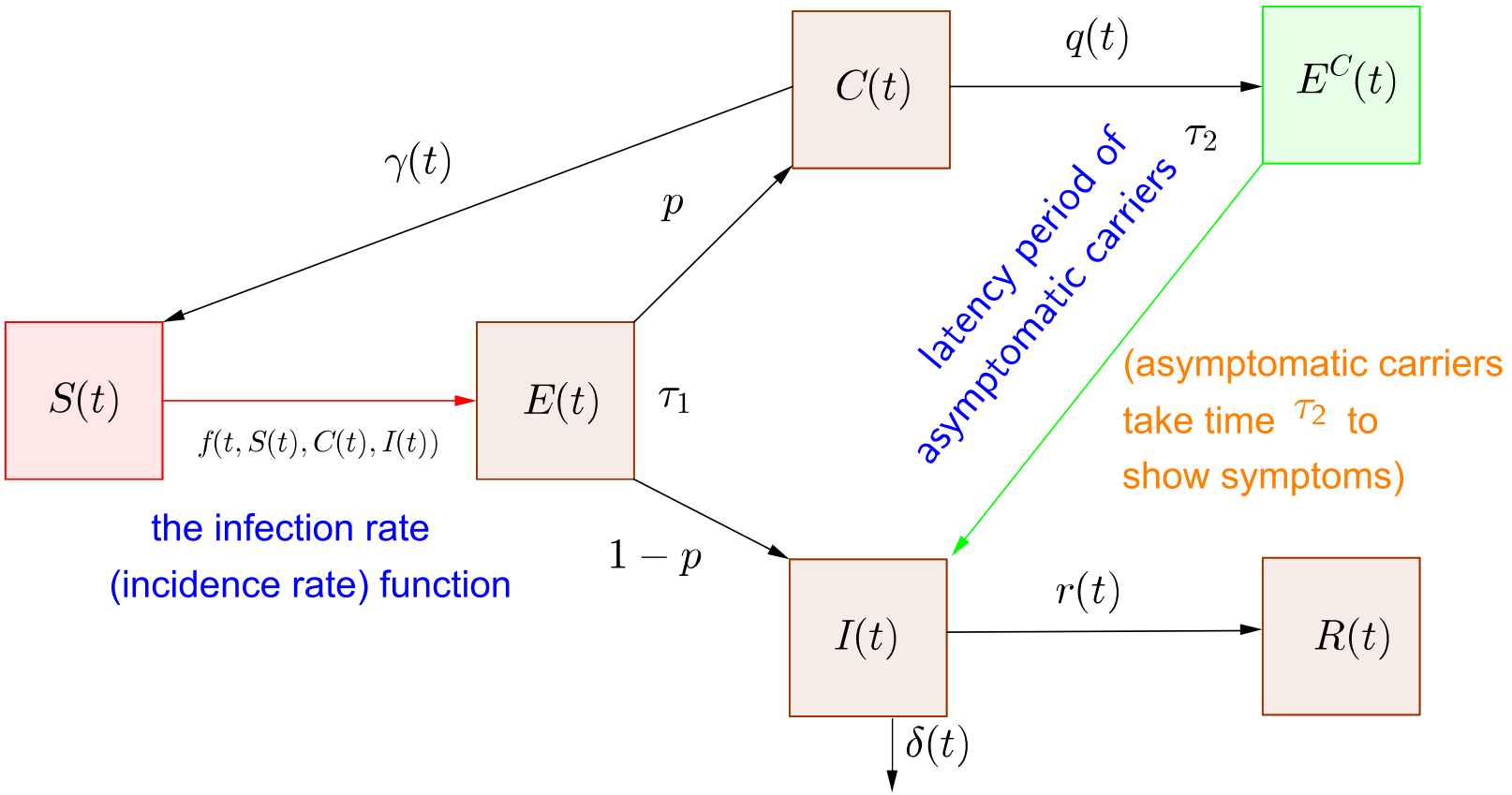
  (i) Two disease-free classes: susceptible ($S(t)$) and recovered ($R(t)$);

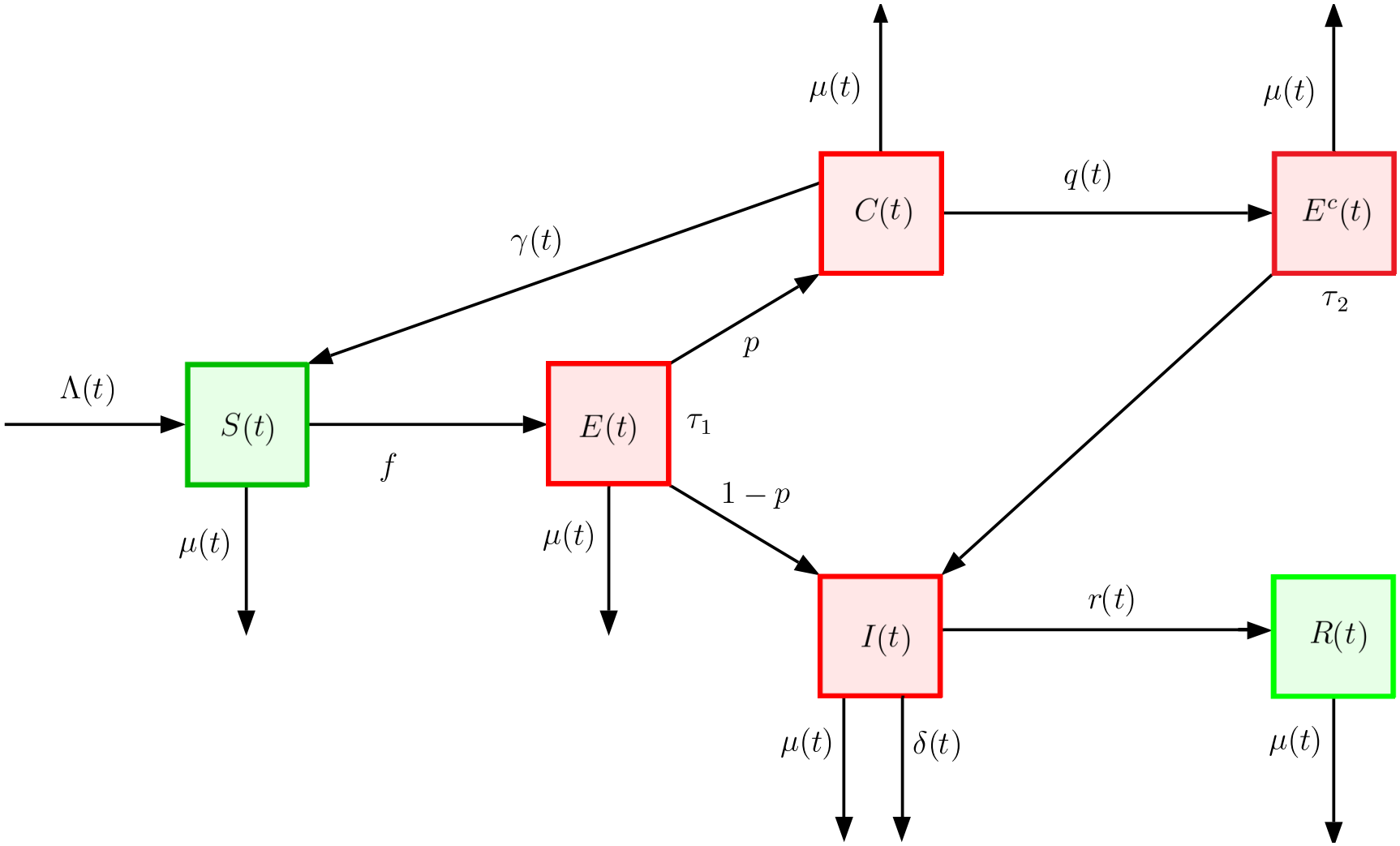
  (ii) Four disease-related classes:

  - Exposed class ($E(t)$): individuals are infected but not yet infectious.
  - Asymptomatic carrier class ($C(t)$): individuals are infectious but not showing any disease symptoms.
  - Carrier-latent class ($E^c(t)$): individuals are developing the disease symptoms.
  - Ill class ($I(t)$): individuals are infectious and showing disease signs and symptoms.


proportion p
move into carrier class
p
$C(t)$
$E^C(t)$
$S(t)$
$E(t)$
τ_1 latent period
$1-p$
$I(t)$
$R(t)$


the transmission rate
of the asymptomatic carrier to ill class
Carriers can return to
the susceptible class
$\gamma(t)$
$C(t)$
$q(t)$
$E^C(t)$
p
$S(t)$
$E(t)$
τ_1
$1-p$
recover rate
$r(t)$
$I(t)$
$R(t)$
$\delta(t)$
disease-related death rate


$C(t)$
$q(t)$
$E^C(t)$
$\gamma(t)$
p
τ_2
latency period of asymptomatic carriers
$S(t)$
$E(t)$
τ_1
(asymptomatic carriers take time τ_2 to show symptoms)
$f(t, S(t), C(t), I(t))$
the infection rate (incidence rate) function
$1-p$
$I(t)$
$r(t)$
$R(t)$
$\delta(t)$


$\mu(t)$
$\mu(t)$
$C(t)$
$q(t)$
$E^c(t)$
$\gamma(t)$
τ_2
p
$\Lambda(t)$
$S(t)$
$E(t)$
τ_1
f
$1-p$
$\mu(t)$
$\mu(t)$
$r(t)$
$I(t)$
$R(t)$
$\mu(t)$
$\delta(t)$
$\mu(t)$

- Let $e(t,a)$ be the density of individuals in the exposed class, at time t with infection age a, then $E(t) = \int_0^{\tau_1} e(t,a)da$

- To address the variation w.r.t. $E(t)$,

$$\frac{\partial e(t,a)}{\partial t} + \frac{\partial e(t,a)}{\partial a} = -\mu(t)e(t,a),$$

- $e(t,0) = f(t, S(t), C(t), I(t))$. $\Longrightarrow$

$$\frac{dE(t)}{dt} = -\mu(t)E(t) - e(t,\tau_1) + e(t,0) = f(t,S(t),C(t),I(t)) - \mu(t)E(t) - e(t,\tau_1).$$

- $$e(t, \tau_1) = f(t - \tau_1, S(t - \tau_1), C(t - \tau_1), I(t - \tau_1))e^{-\int_{t-\tau_1}^{t} \mu(\eta)d\eta}.$$

- Consequently,

$$\frac{dE(t)}{dt} = f(t, S(t), C(t), I(t)) - f(S(t - \tau_1), C(t - \tau_1), I(t - \tau_1))e^{-\int_{t-\tau_1}^{t} \mu(\eta)d\eta} - \mu(t)E(t).$$

- $\Longrightarrow$

$$E(t) = \int_{t-\tau_1}^{t} f\left(s, S(s), C(s), I(s)\right) e^{-\int_{s}^{t} \mu(\eta)d\eta} ds.$$

- Similarly denote $\hat{e}(t,a)$ as the density of individuals in the asymptomatic carrier class $\Longrightarrow$

$$\frac{\partial \hat{e}(t,a)}{\partial t} + \frac{\partial \hat{e}(t,a)}{\partial a} = -(\mu(t)+\gamma(t))\hat{e}(t,a),$$

- $C(t) = \int_{\tau_1}^{\hat{a}} \hat{e}(t,a)da. \Longrightarrow$

- $$\frac{dC(t)}{dt} = -(\mu(t)+\gamma(t))C(t) - \hat{e}(t,\hat{a}) + \hat{e}(t,\tau_1)$$

- $\hat{e}(t,\tau_1) = pe(t,\tau_1)$ and $\hat{e}(t,\hat{a}) = q(t)C(t)$.

- $$\begin{aligned}\frac{dC(t)}{dt} &= pf(t-\tau_1, S(t-\tau_1), C(t-\tau_1), I(t-\tau_1))e^{-\int_{t-\tau_1}^{t}\mu(\eta)d\eta} \\ &\quad -(\mu(t)+q(t)+\gamma(t))C(t).\end{aligned}$$

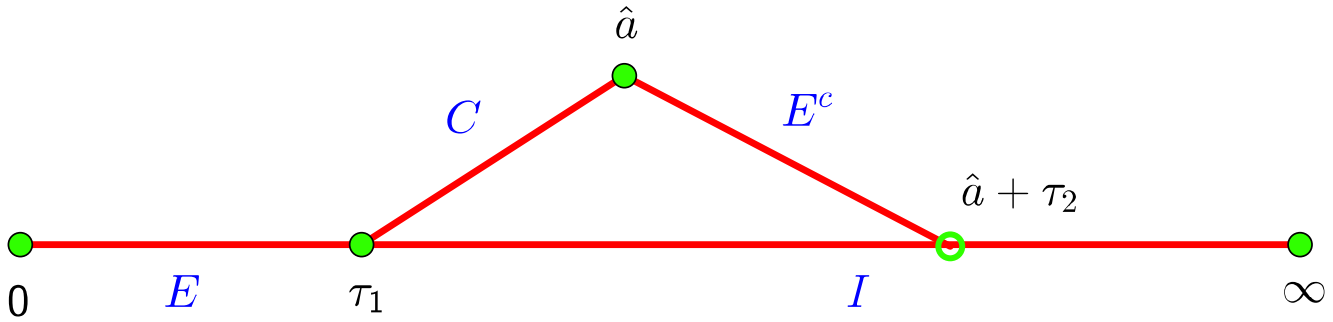
- Parallelly, $E^c(t) = \int_{\hat{a}}^{\hat{a}+\tau_2} e^c(t,a)da$. Thus,

$$\frac{dE^c(t)}{dt} = q(t)C(t) - q(t-\tau_2)C(t-\tau_2)e^{-\int_{t-\tau_2}^{t}\mu(\eta)d\eta} - \mu(t)E^c(t).$$

- $\Longrightarrow$

$$E^c(t) = \int_{t-\tau_2}^{t} q(s)C(s)e^{-\int_s^t \mu(\eta)d\eta}ds.$$

- Disease-related classes with their infection age



- Let $\tilde{e}(t,a)$ be the density of individuals in the ill class. Then

$$I(t) = \int_{\tau_1}^{\infty} \tilde{e}(t,a)da.$$

- $$\frac{\partial \tilde{e}(t,a)}{\partial t} + \frac{\partial \tilde{e}(t,a)}{\partial a} = -(\mu(t) + r(t) + \delta(t))\tilde{e}(t,a).$$

- $$\tilde{e}(t,a) = \begin{cases} (1-p)e(t,a) & \tau_1 < a \leq \hat{a} + \tau_2 \\ (1-p)e(t,a) + e^c(t,a) & \hat{a} + \tau_2 < a. \end{cases}$$

- $$\begin{aligned} \frac{dI}{dt} &= (1-p)f(t-\tau_1, S(t-\tau_1), C(t-\tau_1), I(t-\tau_1))e^{-\int_{t-\tau_1}^{t}\mu(\eta)d\eta} \\ &\quad +q(t-\tau_2)C(t-\tau_2)e^{-\int_{t-\tau_2}^{t}\mu(\eta)d\eta} - (\mu(t) + r(t) + \delta(t))\, I(t). \end{aligned}$$

$$
\begin{aligned}
\frac{dS(t)}{dt} =& \Lambda(t) - \mu(t)S(t) - f(t, S(t), C(t), I(t)) + \gamma(t)C(t), \\
\frac{dE(t)}{dt} =& f(t, S(t), C(t), I(t)) - f(t-\tau_1, S(t-\tau_1), C(t-\tau_1), I(t-\tau_1))e^{-\int_{t-\tau_1}^{t} \mu(\eta)d\eta} - \mu(t)E(t), \\
\frac{dC(t)}{dt} =& pf(t-\tau_1, S(t-\tau_1), C(t-\tau_1), I(t-\tau_1))e^{-\int_{t-\tau_1}^{t} \mu(\eta)d\eta} - (\mu(t) + q(t) + \gamma(t))C(t), \\
\frac{dE^c(t)}{dt} =& q(t)C(t) - q(t-\tau_2)C(t-\tau_2)e^{-\int_{t-\tau_2}^{t} \mu(\eta)d\eta} - \mu(t)E^c(t), \\
\frac{dI(t)}{dt} =& (1-p)f(t-\tau_1, S(t-\tau_1), C(t-\tau_1), I(t-\tau_1))e^{-\int_{t-\tau_1}^{t} \mu(\eta)d\eta} \\
& + q(t-\tau_2)C(t-\tau_2)e^{-\int_{t-\tau_2}^{t} \mu(\eta)d\eta} - (\mu(t) + r(t) + \delta(t))I(t), \\
\frac{dR(t)}{dt} =& r(t)I(t) - \mu(t)R(t).
\end{aligned}
$$

- (H_1) $\Lambda(t)$, $\mu(t)$, $\delta(t)$, $r(t)$, $q(t)$ and $\gamma(t)$ are all continuous periodic and positive functions with period T.

and

- (H_2) $f(t, S, C, I)$ is a nonnegative C^1-function with the following properties:
  - (i) $f(t, 0, C, I) = 0$ and $f(t, S, 0, 0) = 0$ for all $t \in \mathbb{R}$, $S > 0, C > 0$ and $I > 0$;
  - (ii) $\frac{\partial f(t,S,C,I)}{\partial S} > 0$, $\frac{\partial f(t,S,C,I)}{\partial C} > 0$, $\frac{\partial f(t,S,C,I)}{\partial I} > 0$ for all $(t, S, C, I) \in \mathbb{R} \times \mathbb{R}^3_+$.

- Let $\tau = \max\{\tau_1, \tau_2\} = \tau_2$, $X := C([-\tau, 0], \mathbb{R}^6)$ and $X^+ = C([-\tau, 0], \mathbb{R}^6_+)$. For $\phi = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5, \phi_6) \in X$, denote $\|\phi\| = \sum_{i=1}^{6} \|\phi_i\|_\infty$ with $\|\phi_i\|_\infty = \max_{-\tau \le \theta \le 0} |\phi_i(\theta)|$. Then, (X, X^+) is an ordered Banach space and X^+ is a normal cone of X with nonempty interior in X. For any given continuous function $u : [-\tau, \sigma_\phi) \to \mathbb{R}^6$ with $\sigma_\phi > 0$, we define $u_t \in X$ for $t \ge 0$ by $u_t(\theta) = u(t + \theta)$ for all $\theta \in [-\tau, 0]$.

- We choose the initial data in the following set:

$$D_X = \left\{ \phi \in X^+ : \phi_2(0) = \int_{-\tau_1}^{0} f(\vartheta, \phi_1(\vartheta), \phi_3(\vartheta), \phi_4(\vartheta)) e^{-\int_\vartheta^0 \mu(\eta) d\eta} d\vartheta,\ \phi_4(0) = \int_{-\tau_2}^{0} q(\vartheta)\phi_3(\vartheta) e^{-\int_\vartheta^0 \mu(\eta) d\eta} d\vartheta \right\}.$$

Well-posedness Property

Theorem 2.1. *For any $\phi \in D_X$, under the hypotheses (H_1) and (H_2), the system has a unique nonnegative solution $u(t, \phi)$ with the initial condition $u_0 = \phi$, and all solutions are ultimately bounded and uniformly bounded. In addition, the solution semiflow $\Phi(t) = u_t(\cdot) : D_X \to \mathbb{R}^6$ has a compact global attractor and*

$$\Gamma = \left\{ (S, E, C, E^c, I, R) \in \mathbb{R}^6_+ : 0 \leq S + E + C + E^c + I + R \leq \frac{\Lambda^u}{\mu^l} \right\}$$

is positively invariant.

3 Basic Reproduction Ratio

- To find the disease-free state, letting $E = I = C = E^c = 0$, then $R = 0$ and

$$\frac{dS(t)}{dt} = \Lambda(t) - \mu(t)S(t).$$

Hence, there is only one disease-free $T-$ periodic state $E_1(t) = (S^*(t), 0, 0, 0, 0, 0)$ where

$$S^*(t) = e^{-\int_0^t \mu(\eta)d\eta} \left(S(0) + \int_0^t e^{\int_0^s \mu(\eta)d\eta} \Lambda(s)ds \right)$$

with

$$S(0) = \frac{e^{-\int_0^T \mu(\eta)d\eta}}{1 - e^{-\int_0^T \mu(\eta)d\eta}} \int_0^T e^{\int_0^s \mu(\eta)d\eta} \Lambda(s)ds.$$

- In the linearized system at $E_1(t)$, the following disease-related subsystem is decoupled from others:

$$\frac{dC(t)}{dt} = pa_1(t)C(t-\tau_1) + pa_2(t)I(t-\tau_1) - b_1(t)C(t)$$
$$\frac{dI(t)}{dt} = (1-p)a_1(t)C(t-\tau_1) + (1-p)a_2(t)I(t-\tau_1) + a_3(t)C(t-\tau_2) - b_2(t)I(t)$$

where

$$a_1(t) = h(t,\tau_1)\frac{\partial f(t-\tau_1, S^*(t-\tau_1), 0, 0)}{\partial C},$$
$$a_2(t) = h(t,\tau_1)\frac{\partial f(t-\tau_1, S^*(t-\tau_1), 0, 0)}{\partial I},$$
$$a_3(t) = h(t,\tau_2)q(t-\tau_2),$$
$$b_1(t) = \mu(t) + q(t) + \gamma(t)$$
$$b_2(t) = \mu(t) + r(t) + \delta(t).$$

Here $h(t,\tau) := e^{-\int_{t-\tau}^{t}\mu(\eta)d\eta}$.

- We use the theory developed in [Zhao[1]] to introduce the basic reproduction ratio.
- Let

$$\mathcal{F}_1(t) = \begin{bmatrix} pa_1(t) & pa_2(t) \\ (1-p)a_1(t) & (1-p)a_2(t) \end{bmatrix}, \mathcal{F}_2(t) = \begin{bmatrix} 0 & 0 \\ a_3(t) & 0 \end{bmatrix}, \mathcal{V}(t) = \begin{bmatrix} b_1(t) & 0 \\ 0 & b_2(t) \end{bmatrix}.$$

Rewrite the linearized and decoupled model as

$$\frac{du(t)}{dt} = \mathcal{F}_1(t)u(t-\tau_1) + \mathcal{F}_2(t)u(t-\tau_2) - \mathcal{V}(t)u(t),$$

where $u(t) = (C(t), I(t))^T$.

- $-\mathcal{V}$ is cooperative;

[1] X.-Q. Zhao, Basic reproduction ratios for periodic compartmental models with time delay, J. Dynam. Differential Equations (2017), 29: 67-82

- Define $\mathcal{F}(t) : X_2 = C([-\tau, 0], \mathbb{R}^2) \to \mathbb{R}^2$ by

$$\mathcal{F}(t) \begin{pmatrix} \tilde{\phi}_1 \\ \tilde{\phi}_2 \end{pmatrix} = \begin{pmatrix} p\ a_1(t)\tilde{\phi}_1(-\tau_1) + p\ a_2(t)\tilde{\phi}_2(-\tau_1) \\ (1-p)\ a_1(t)\tilde{\phi}_1(-\tau_1) + (1-p)\ a_2(t)\tilde{\phi}_2(-\tau_1) + a_3(t)\tilde{\phi}_1(-\tau_2) \end{pmatrix}.$$

- From the hypotheses (H_1)-(H_2) $\Longrightarrow$

  $\mathcal{F}(t)$ is positive in the sense that $\mathcal{F}(t)X_2^+ \subseteq \mathbb{R}^2_+$ where $X_2^+ = C([-\tau, 0], \mathbb{R}^2_+)$.

- Let C_T be the ordered Banach space of all $T-$periodic functions from $\mathbb{R}$ to $\mathbb{R}^2$, which is equipped with the maximum norm and the positive cone $C_T^+ = \{v \in C_T : v(t) \geq 0, \forall t \in \mathbb{R}\}$. Then we can define a linear operator on C_T by

$$[Lv](t) = \int_0^\infty Z(t, t-s)\mathcal{F}(t-s)v(t-s+\cdot)ds,\ \ v \in C_T.$$

where $Z(t,s) = e^{-\int_s^t \mathcal{V}(\eta)d\eta}$ is the evolution operator.

- Basic reproduction ratio $\mathcal{R}_0 = \rho(L)$, the spectral radius of L.

In periodic environments, the definition of $\mathcal{R}_0$ can be biologically interpreted as the asymptotic per generation growth rate [N. Bacaër and E. Dads[a]]

[a] N. Bacaër and E. H. A. Dads, On the biological interpretation of a definition for the parameter R 0 in periodic population models, J. Math. Biology, 65(4) (2012), 601-621.

- We cannot find the explicit form of $\mathcal{R}_0 = \rho(L)$ in general, we can provide a numerical algorithm to obtain an approximation value of $\mathcal{R}_0$

4 Threshold Dynamics

- Since the S, C and I equations are decoupled in the model, it suffices to study the following $T-$periodic system:

$$\begin{aligned}
\frac{dS(t)}{dt} =& \Lambda(t) - \mu(t)S(t) - f(t, S(t), C(t), I(t)) + \gamma(t)C(t),\\
\frac{dC(t)}{dt} =& pf(t-\tau_1, S(t-\tau_1), C(t-\tau_1), I(t-\tau_1))e^{-\int_{t-\tau_1}^{t}\mu(\eta)d\eta} - (\mu(t)+q(t)+\gamma(t))C(t),\\
\frac{dI(t)}{dt} =& (1-p)f(t-\tau_1, S(t-\tau_1), C(t-\tau_1), I(t-\tau_1))e^{-\int_{t-\tau_1}^{t}\mu(\eta)d\eta} + q(t-\tau_2)C(t-\tau_2)e^{-\int_{t-\tau_2}^{t}\mu(\eta)d\eta}\\
& - (\mu(t)+r(t)+\delta(t))I(t).
\end{aligned}$$

- Additional assumption:

$$(H_3)\quad \frac{\partial^2 f(t,S,C,I)}{\partial C^2} \le 0,\ \frac{\partial^2 f(t,S,C,I)}{\partial C \partial I} \le 0,\ \frac{\partial^2 f(t,S,C,I)}{\partial I^2} \le 0,\ \forall t \in \mathbb{R},\ S>0,\ C>0\ ,\ I>0,$$

Disease Persistence

Theorem 4.1. *When $\mathcal{R}_0 > 1$ and $(H_1) - (H_3)$ hold, then the sub-system admits at least one positive periodic solution $E_2(t) = (S^*(t), C^*(t), I^*(t))$, and there exists a positive constant $\eta_1 > 0$ such that any solution $(S(t,\psi), C(t,\psi), I(t,\psi))$ satisfies*

$$\lim_{t\longrightarrow\infty} \inf(C(t,\psi), I(t,\psi)) \geq (\eta_1, \eta_1)$$

Global Attractivity of the Disease-free State

Theorem 4.2. *When $\mathcal{R}_0 < 1$ and $(H_1) - (H_3)$ hold, $(S^*(t), 0, 0)$ is globally attractive.*

- Ideas in the proof:
  - Monotonicity
  - The comparison theorem [H. Smith][2])
  - Results in [X.-Q. Zhao][3], and [P. Magal & X.-Q. Zhao][4]
  - Limiting system
  - The theory of internally chain transitive sets

[2]H. Smith, Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems, American Mathematical Society, 1995.

[3]X.-Q. Zhao, Dynamical Systems in Population Biology, Springer-Verlag, New York, 2017.

[4]P. Magal and X.-Q. Zhao, Global attractors and steady states for uniformly persistent dynamical systems, SIAM J. Math. Analysis, 37 (2005), 251-275.

For Original Model

Theorem 4.3. *Assume* $(H_1) - (H_3)$ *hold*

(i) when $\mathcal{R}_0 < 1$, *then*

$$\lim_{t\to\infty} [(S(t), E(t), C(t), E^c(t), I(t), R(t)) - (S^*(t), 0, 0, 0, 0, 0)] = 0$$

in D_Y;

(ii) when $\mathcal{R}_0 > 1$, *then model admits at least one positive periodic solution*

$$(S^*(t), E^*(t), C^*(t), E^{c^*}(t), I^*(t), R^*(t))$$

and there exists a positive constant $\eta_2 > 0$ *such that any solution* $(S(t,\hat{\psi}),\ E(t,\hat{\psi}),\ C(t,\hat{\psi}),\ E^c(t,\hat{\psi}),\ I(t,\hat{\psi}),\ R(t,\hat{\psi}))$ *satisfies*

$$\lim_{t\longrightarrow\infty} \inf(C(t,\hat{\psi}), I(t,\hat{\psi})) \geq (\eta_2, \eta_2)$$

where

$$E^*(t) = \int_0^{\tau_1} f(t-s, S^*(t-s), C^*(t-s), I^*(t-s)) e^{-\int_{t-s}^{s} \mu(\eta) d\eta} ds > 0,$$

$$E^{c*}(t) = \int_0^{\tau_2} q(t-s) C^*(t-s) e^{-\int_{t-s}^{s} \mu(\eta) d\eta} ds > 0,$$

$$R^*(t) = R(0) e^{\int_0^t \mu(s) ds} + \int_0^t e^{\int_t^s \mu(\eta) d\eta} \left(r(s) + \delta(s)\right) I^*(s) ds > 0.$$

5 Uniqueness of the Epidemic State with Constants Coefficients

- With constant coefficients, the basic reproduction ratio $\mathcal{R}_0$ becomes explicit

$$[\mathcal{R}_0] = \rho((F_1 + F_2)V^{-1}) = \frac{T + \sqrt{T^2 + 4D}}{2}$$

with

$$T = \frac{pe^{-\mu\tau_1}\frac{\partial f}{\partial C}(\frac{\Lambda}{\mu}, 0, 0)}{q + \gamma + \mu} + \frac{(1-p)e^{-\mu\tau_1}\frac{\partial f}{\partial I}(\frac{\Lambda}{\mu}, 0, 0)}{r + \delta + \mu} > 0, \; D = \frac{pq\frac{\partial f}{\partial I}(\frac{\Lambda}{\mu}, 0, 0)e^{-\mu(\tau_1+\tau_2)}}{(q + \gamma + \mu)(r + \delta + \mu)} > 0$$

where $\frac{\Lambda}{\mu}$ is the global asymptotic stable equilibrium of $\frac{dN(t)}{dt} = \Lambda - \mu N(t)$.

- To examine the existence of the positive equilibrium point $E_2 = (S^*, C^*, I^*)$, we have to solve

$$\begin{aligned} f(S, C, I) &= \Lambda - \mu S + \gamma C, \\ pe^{-\mu\tau_1} f(S, C, I) &= qC + (\gamma + \mu)C, \\ (1-p)e^{-\mu\tau_1} f(S, C, I) &= (r + \delta + \mu)I - qe^{-\mu\tau_2}C. \end{aligned}$$

Proposition 5.1. *Under the hypothesis* $(H_2) - (H_3)$*, if the endemic equilibrium point* E_2 *exists, we have*

$$\frac{\partial f(S^*, C^*, I^*)}{\partial C} + \frac{A_1 + A_2}{A_3} \frac{\partial f(S^*, C^*, I^*)}{\partial I} \leq A_1,$$

where the strict equality holds only if

$$\frac{\partial^2 f(S, \frac{A_1+A_2}{A_3}C, C)}{\partial C^2} = \frac{\partial^2 f(S, \frac{A_1+A_2}{A_3}C, C)}{\partial C \partial I} = \frac{\partial^2 f(S, \frac{A_1+A_2}{A_3}C, C)}{\partial I^2} = 0$$

for all $S > 0$, $C > 0$ *with*

$$A_1 = \frac{q + \gamma + \mu}{p e^{-\mu\tau_1}}, \; A_2 = \frac{q e^{-\mu\tau_2}}{(1-p) e^{-\mu\tau_1}}, \; A_3 = \frac{r + \delta + \mu}{(1-p) e^{-\mu\tau_1}}.$$

Existences and Uniqueness of Endemic Equilibrium

Theorem 5.1. *Given the assumptions* $(H_2) - (H_3)$. *If* $[\mathcal{R}_0] > 1$, *then the positive equilibrium point* $E_2 = (S^*, C^*, I^*)$ *exists in the sub-system and is uniquely determined. Consequently, a unique endemic equilibrium point* $(S^*, E^*, C^*, E^{c*}, I^*, R^*)$ *exists in the model with* $E^* = \frac{1}{\mu}(1 - e^{-\mu\tau_1})f(S^*, C^*, I^*)$, $E^{c*} = \frac{q}{\mu}(1 - e^{-\mu\tau_2})C^*$ *and* $R^* = \frac{r+\delta}{\mu}I^*$.

6 Numerical Computation and Simulation

A: Calculation of $\mathcal{R}_0$.

- The infection linear operator

$$[Lv](t) = \int_0^\infty \mathcal{K}(t,s)v(t-s)ds = \sum_{m=0}^{\infty}\int_0^T \mathcal{K}(t,s+mT)v(t-s)ds = \int_0^T G_{\mathcal{K}}(t,s)v(t-s)ds$$

$$G_{\mathcal{K}}(t,s) = \sum_{m=0}^{\infty}\mathcal{K}(t,s+mT), \qquad \mathcal{K}(t,s) = \begin{pmatrix} K_{11}(t,s) & K_{12}(t,s) \\ K_{21}(t,s) & K_{22}(t,s) \end{pmatrix}.$$

for $s \geq \tau_1$,

$$K_{11}(t,s) = pa_1(t-s+\tau_1)e^{-\int_{t-s+\tau_1}^{t} b_1(\eta)d\eta},$$

$$K_{12}(t,s) = pa_2(t-s+\tau_1)e^{-\int_{t-s+\tau_1}^{t} b_1(\eta)d\eta},$$

$$K_{21}(t,s) = \begin{cases} (1-p)\,a_1(t-s+\tau_1)e^{-\int_{t-s+\tau_1}^{t} b_2(\eta)d\eta} + a_3(t-s+\tau_2)e^{-\int_{t-s+\tau_2}^{t} b_2(\eta)d\eta} & \text{if} \quad s \geq \tau_2, \\ (1-p)\,a_1(t-s+\tau_1)e^{-\int_{t-s+\tau_1}^{t} b_2(\eta)d\eta} & \text{if} \quad \tau_1 \leq s < \tau_2, \end{cases}$$

$$K_{22}(t,s) = (1-p)\,a_2(t-s+\tau_1)e^{-\int_{t-s+\tau_1}^{t} b_2(\eta)d\eta},$$

for $s < \tau_1$, $K_{ij}(t,s) = 0$ $i,j \in \{1,2\}$.

- When $(H_1) - (H_2)$ hold, $\Longrightarrow$ approximate $G_{\mathcal{K}}$ by a finite sum $G_{\mathcal{K}}(s,t) \approx \sum_{m=0}^{M_{\mathcal{K}}} \mathcal{K}(t, s+mT)$ [Posny & Wang[5]]

- Partition the interval $[0,T]$ uniformly into n subintervals $[t_i, t_{i+1}]$ with $t_i = \frac{i\,T}{n}$ for $i = 0, \ldots, n-1$

- Then $\mathcal{R}_0 \approx \frac{T}{n}\rho(\mathcal{A})$ where $\mathcal{A}$ is $2n \times 2n$ matrix

$$\mathcal{A} = \begin{bmatrix} \tilde{G}_{\mathcal{K}}(t_0,t_0) & G_{\mathcal{K}}(t_0,t_{n-1}) & \cdots & \cdots & \cdots & G_{\mathcal{K}}(t_0,t_2) & G_{\mathcal{K}}(t_0,t_1) \\ G_{\mathcal{K}}(t_1,t_1) & \tilde{G}_{\mathcal{K}}(t_1,t_0) & \cdots & \cdots & \cdots & G_{\mathcal{K}}(t_1,t_3) & G_{\mathcal{K}}(t_1,t_2) \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ G_{\mathcal{K}}(t_j,t_j) & G_{\mathcal{K}}(t_j,t_{j-1}) & \cdots & \tilde{G}_{\mathcal{K}}(t_j,t_0) & \cdots & G_{\mathcal{K}}(t_j,t_{j+2}) & G_{\mathcal{K}}(t_j,t_{j+1}) \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ G_{\mathcal{K}}(t_{n-2},t_{n-2}) & G_{\mathcal{K}}(t_{n-2},t_{n-3}) & \cdots & \cdots & \cdots & \tilde{G}_{\mathcal{K}}(t_{n-2},t_0) & G_{\mathcal{K}}(t_{n-2},t_{n-1}) \\ G_{\mathcal{K}}(t_{n-1},t_{n-1}) & G_{\mathcal{K}}(t_{n-2},t_{n-2}) & \cdots & \cdots & \cdots & \tilde{G}_{\mathcal{K}}(t_{n-1},t_1) & \tilde{G}_{\mathcal{K}}(t_{n-1},t_0) \end{bmatrix}$$

with $\tilde{G}_{\mathcal{K}}(t_j,t_0) = \frac{1}{2}(G_{\mathcal{K}}(t_j,t_0) + G_{\mathcal{K}}(t_j,t_n))$ and $j = 0, \ldots, n-1$.

[5] D. Posny and J. Wang, Computing the basic reproductive numbers for epidemiological models in nonhomogeneous environments, Appl. Math. Comput., 242 (2014), 473-490.

B: Case study.

● We study the transmission of meningococcal meningitis disease in Dori, Burkina Faso.

*Image credit: www.africaguide.com & wikimedia.org.

- Meningococcal meningitis disease is a major public health problem in a large area of sub-Saharan Africa, known as the meningitis belt.

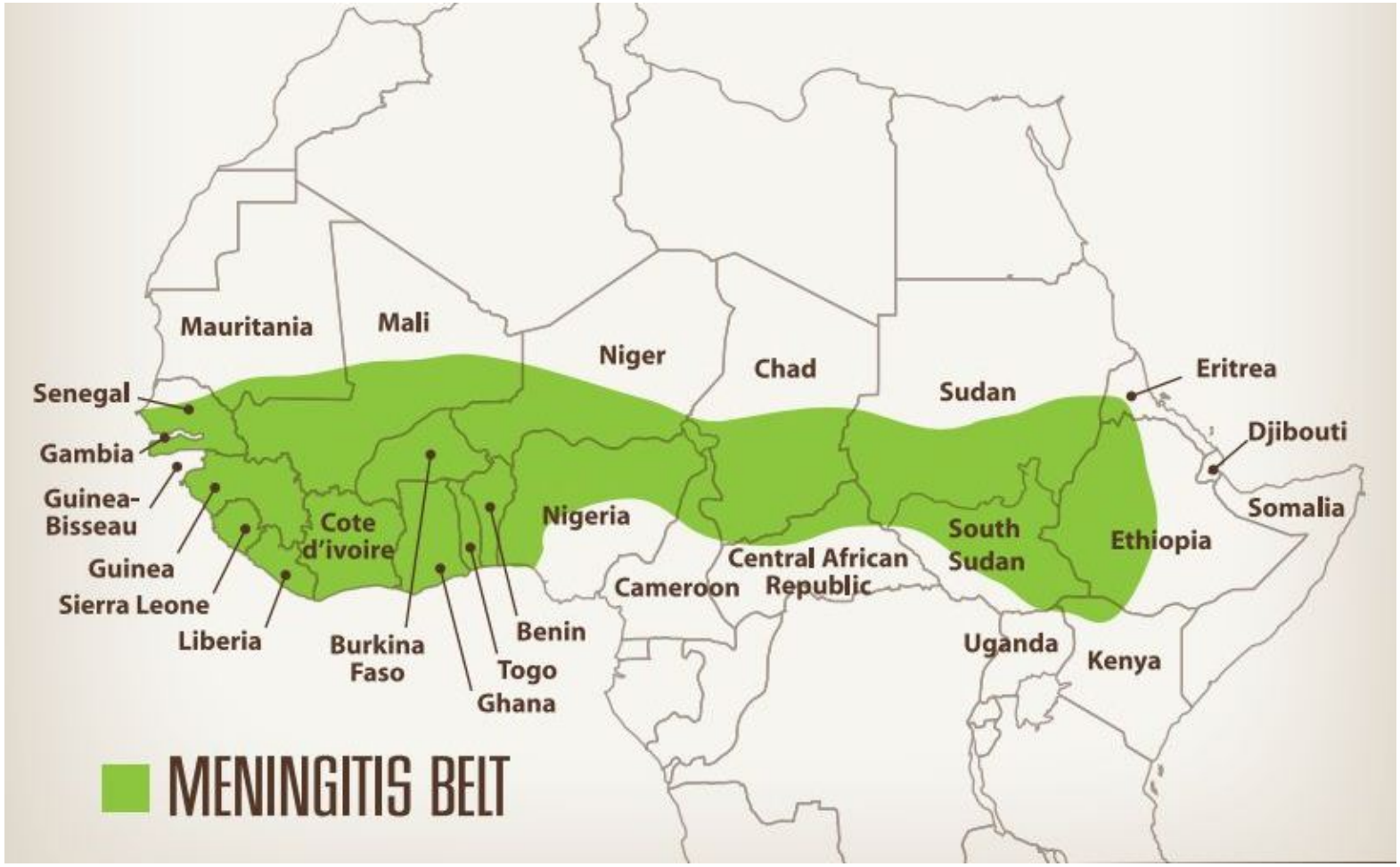
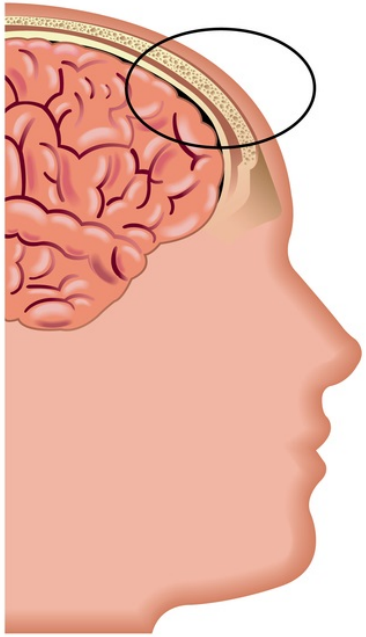
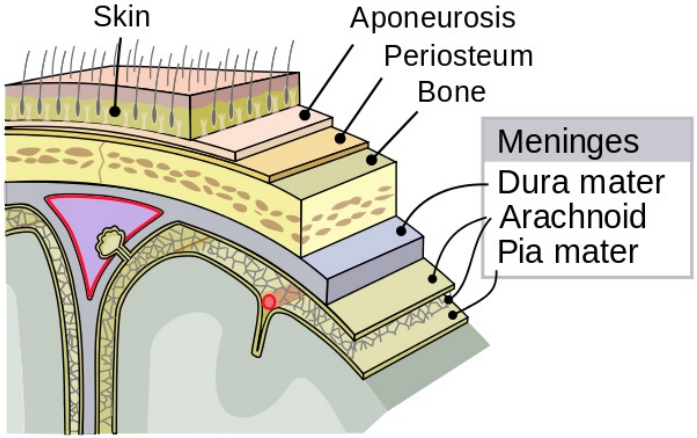


*Image credit: www.humanosphere.org.

- According to WHO, meningococcal meningitis is a bacterial form of meningitis caused by the bacterium Neisseria meningitidis.
- It is a serious infection of the thin lining that surrounds the brain and spinal cord.





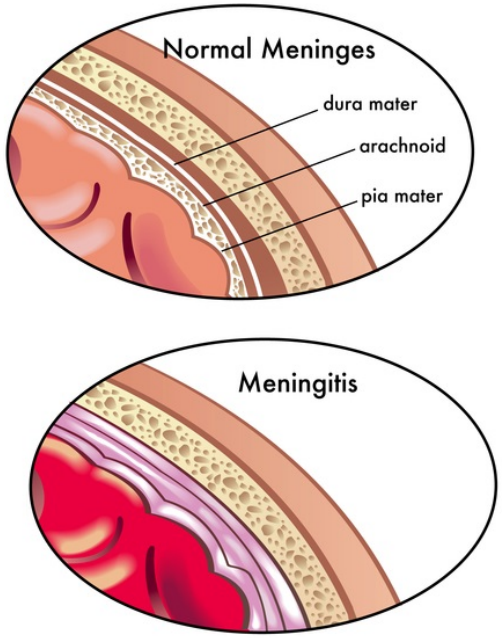


*Image credit:wikipedia & spinalmeningitis.org.

- The bacteria are transmitted from person-to-person through droplets of respiratory or throat secretions from carriers such as sneezing or coughing on someone.

● In Burkina Faso, the annual number of meningitis cases exhibits an oscillatory behavior, although with irregular patterns of epidemics varying in size and duration.

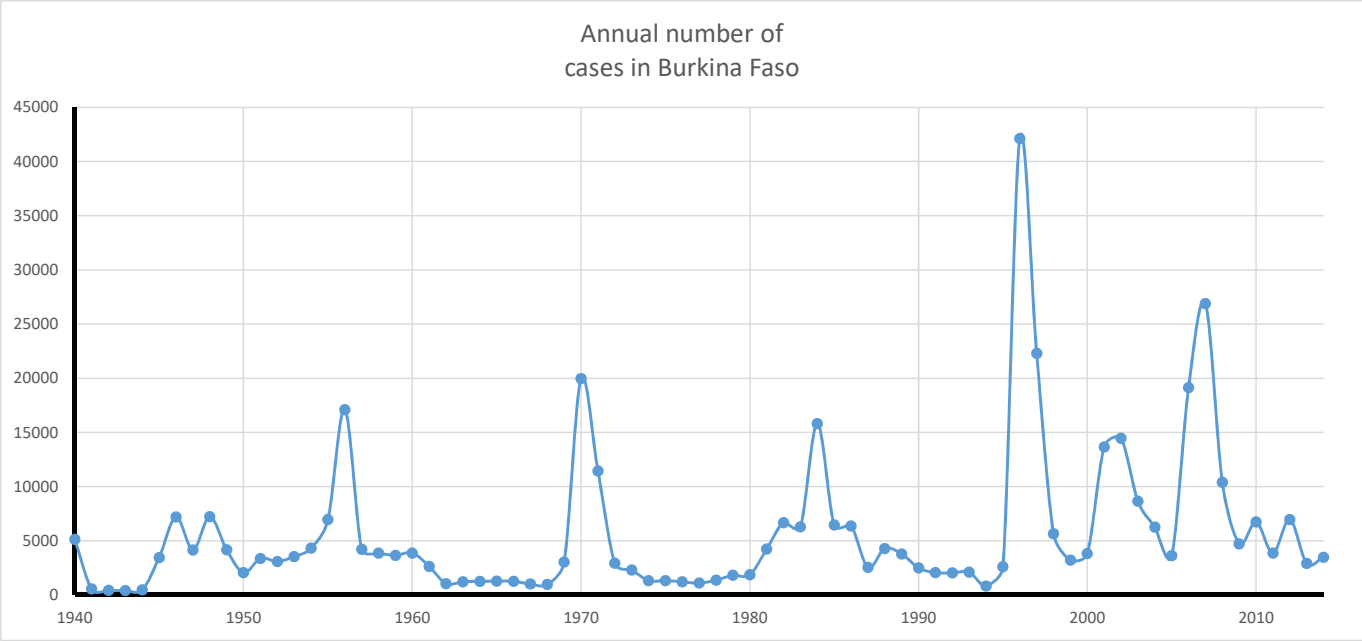
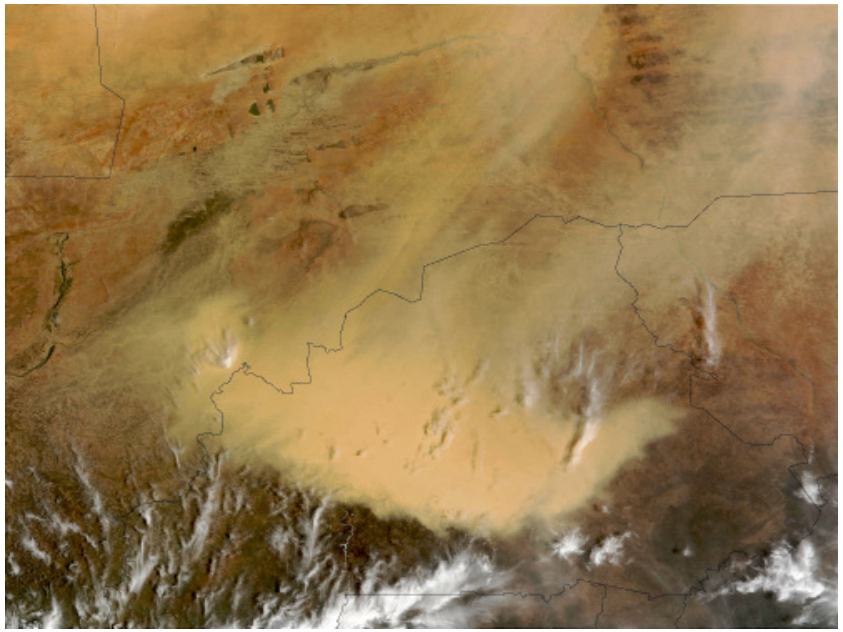


Figure 1: Annual number of reported suspected meningitis cases in Burkina Faso, 1940-2014.

- This can be related to environmental factors, particularly the Harmattan (a dry and dusty trade wind that blows across the region during the dry season).

The Harmattan in Burkina's capital of Ouagadougou



Satellite image of the Harmattan's dust covering Burkina

*Image credit:Life in Burkina Faso, https://polifaso.wordpress.com.

- According to the 2012 World Bank report, the life expectancy in Burkina Faso is 55.86 year. So we choose the natural death rate $\mu(t) \equiv \mu = 1/55.86 = 0.018$ year^{-1}.

- The total population in Dori is 21078 (2006), that is, the recruitment rate $\Lambda(t) \equiv \Lambda = 21078 \times \mu \approx 379$ people per year.

- We take the incidence rate function form as $f(t, S, C, I) = f_1(t, S, C, I) + f_2(t, S, C, I)$, where

$$f_1(t, S, C) = \frac{l\beta(t)S(t)C(t)}{1 + \alpha_1 C(t)} \qquad \text{and} \qquad f_2(t, S, I) = \frac{\beta(t)S(t)I(t)}{1 + \alpha_2 I(t)}$$

with $l = 0.8$, $\alpha_1 = 0.07$ and $\alpha_2 = 0.05$

Estimation of a periodic $\beta(t)$

- The disease transmission rate ($\beta(t)$) is between $50 - 200$ year^{-1}.
- The meningitis incidence is the lowest during rainfall season and it increases to reach the highest during the dry season in most districts of the meningitis belt.
- We assume that there is a higher transmission rate in the most dry period and it decreases as the average precipitation increases.

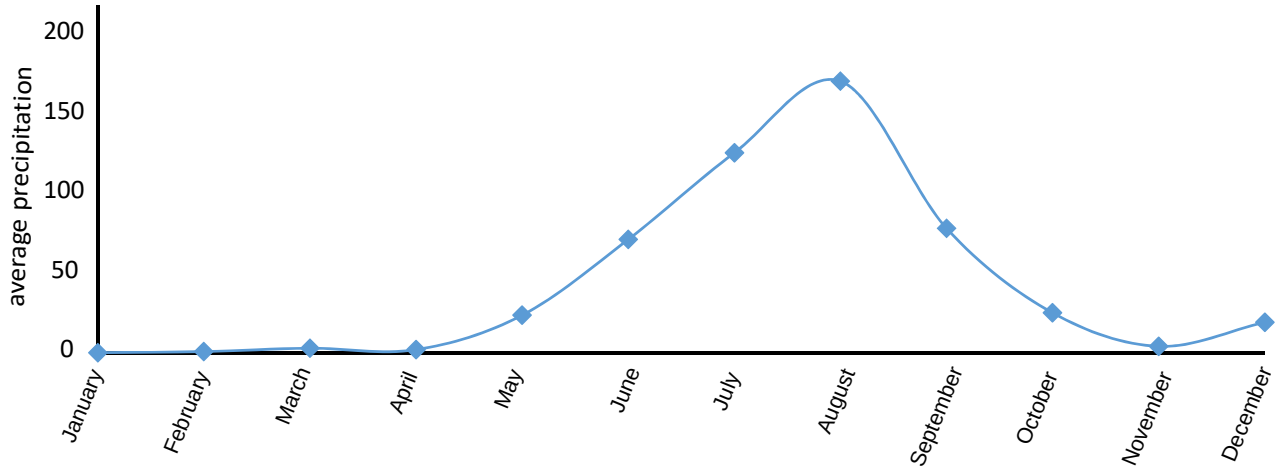


Figure 2: Average precipitation per month in Dori from 2000 to 2012.

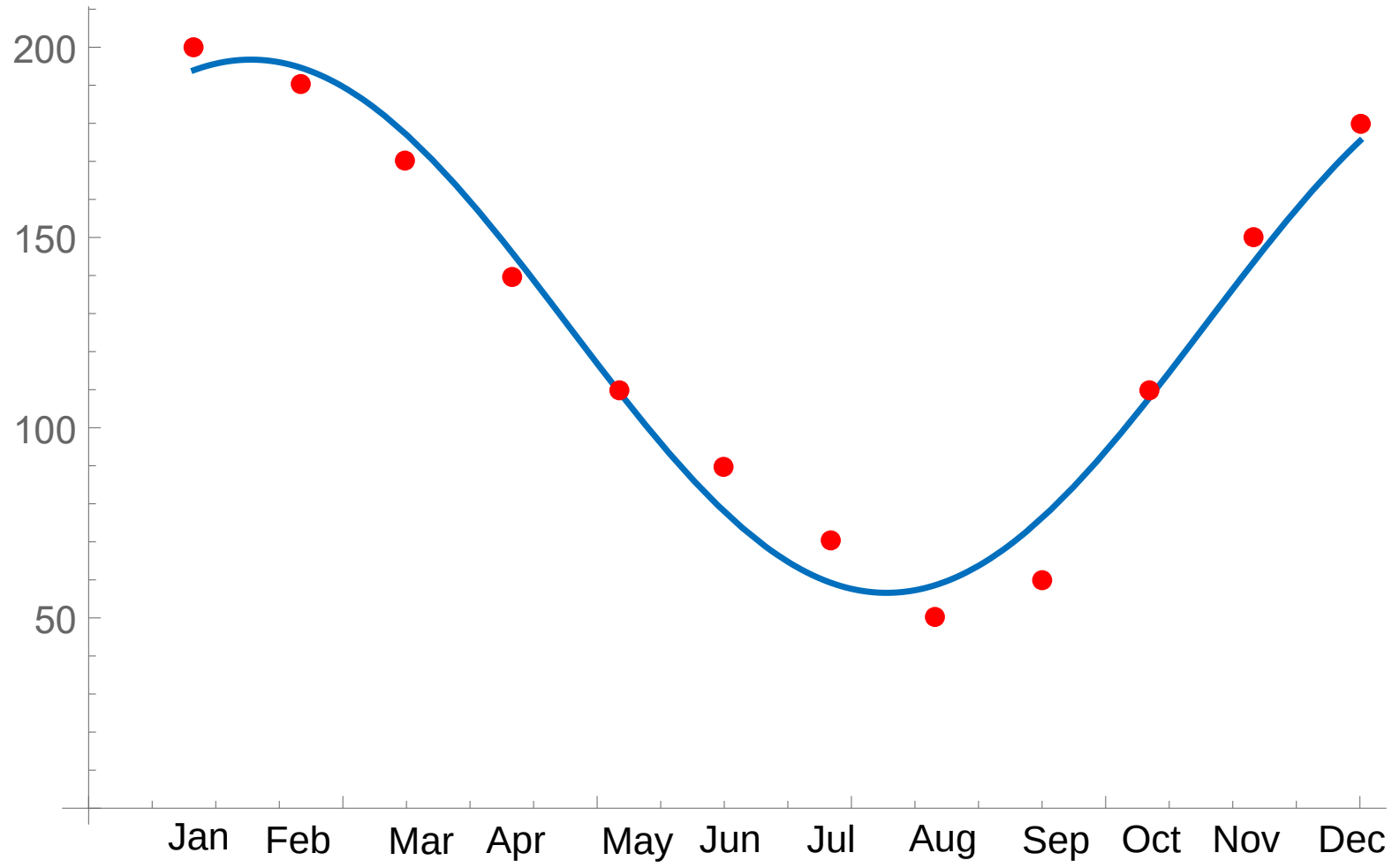
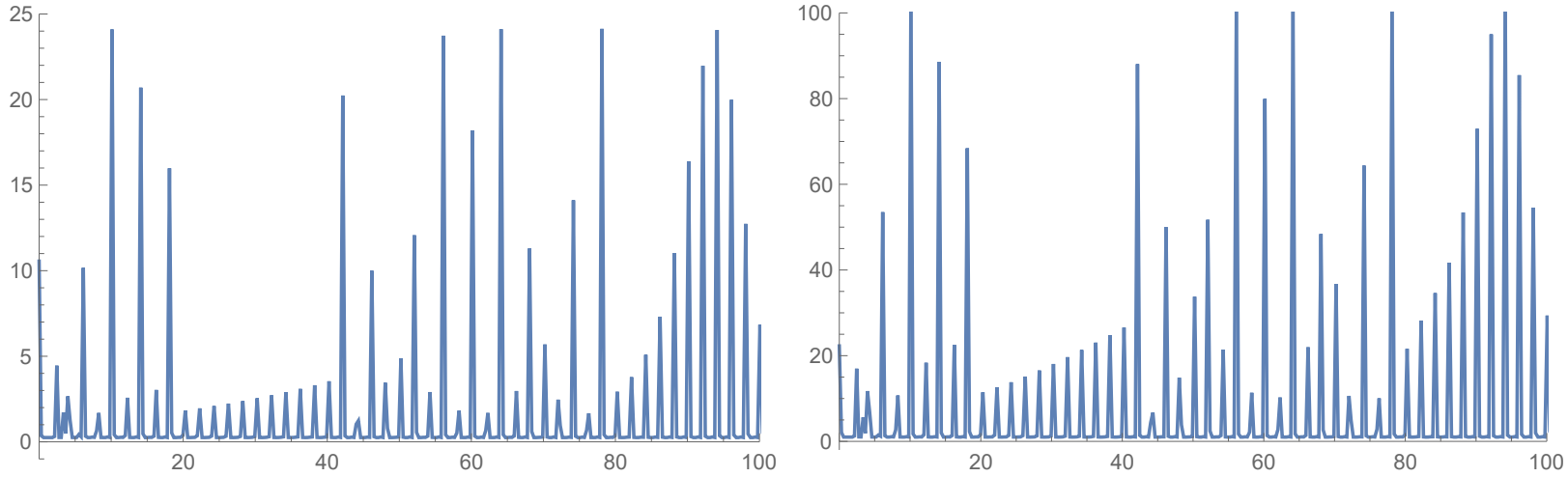


Figure 3: $\beta_1(t) = 128.333 + 52.0374\cos(2\pi t) + 50.3707\sin(2\pi t)$



(a) $C(t)$ (b) $I(t)$

Figure 4: Time series $C(t)$ and $I(t)$. $S(0) = 15000$, $E(0) = 30$, $C(0) = 20$, $E^C(0) = 5$, $I(0) = 20$ and $R(0) = 5$.

Parameters: We choose $\tau_1 = 0.008$ year, $\tau_2 = 0.083$ year, $q(t) = 30(1 + 0.5\cos(2\pi t))$, $r(t) \equiv r = 52$ year^{-1}, $\delta(t) \equiv \delta = 5.2$ year^{-1}, and $\gamma(t) \equiv \gamma = 20$ year^{-1}; and assume that 20% of infected susceptible individuals become carriers (i.e. $p = 0.2$).

$$\mathcal{R}_0 \approx 2.6601$$

C: Sensitivity of $\mathcal{R}_0$ and $[\mathcal{R}_0]$.

- With constant coefficients,

$$\begin{aligned}
\frac{\partial[\mathcal{R}_0]}{\partial\tau_1} &= -\frac{\mu}{2}\left(T+\frac{T^2+2D}{\sqrt{T^2+4D}}\right)<0, \qquad \frac{\partial[\mathcal{R}_0]}{\partial\tau_2} = -\frac{-\mu D}{\sqrt{T^2+4D}}<0,\\
\frac{\partial[\mathcal{R}_0]}{\partial f_C} &= \frac{1}{2}\left(1+\frac{T}{\sqrt{T^2+4D}}\right)\frac{pe^{-\mu\tau_1}}{q+\gamma+\mu} = \frac{[\mathcal{R}_0]}{\sqrt{T^2+4D}}\frac{pe^{-\mu\tau_1}}{q+\gamma+\mu}>0,
\end{aligned}$$

and for $s\in\{\gamma,p,q\}$,

$$\frac{\partial[\mathcal{R}_0]}{\partial s} = \frac{1}{\sqrt{T^2+4D}}\left([\mathcal{R}_0]\frac{\partial T}{\partial s}+\frac{\partial D}{\partial s}\right)$$

with

$$\begin{aligned}
\frac{\partial T}{\partial\gamma} &= \frac{-pe^{-\mu\tau_1}f_C}{(q+\gamma+\mu)^2}<0, \qquad \frac{\partial D}{\partial\gamma} = \frac{-pqe^{-\mu(\tau_1+\tau_2)}f_I}{(r+\delta+\mu)(q+\gamma+\mu)^2}<0\\
\frac{\partial T}{\partial p} &= e^{-\mu\tau_1}\left(\frac{f_C}{q+\gamma+\mu}-\frac{f_I}{r+\delta+\mu}\right), \qquad \frac{\partial D}{\partial p} = \frac{qf_Ie^{-\mu(\tau_1+\tau_2)}}{(q+\gamma+\mu)(r+\delta+\mu)}>0,\\
\frac{\partial T}{\partial q} &= -\frac{pf_Ce^{-\mu\tau_1}}{(q+\gamma+\mu)^2}<0, \qquad \frac{\partial D}{\partial q} = \frac{pf_Ie^{-\mu(\tau_1+\tau_2)}}{r+\delta+\mu}\frac{\gamma+\mu}{(q+\gamma+\mu)^2}>0.
\end{aligned}$$

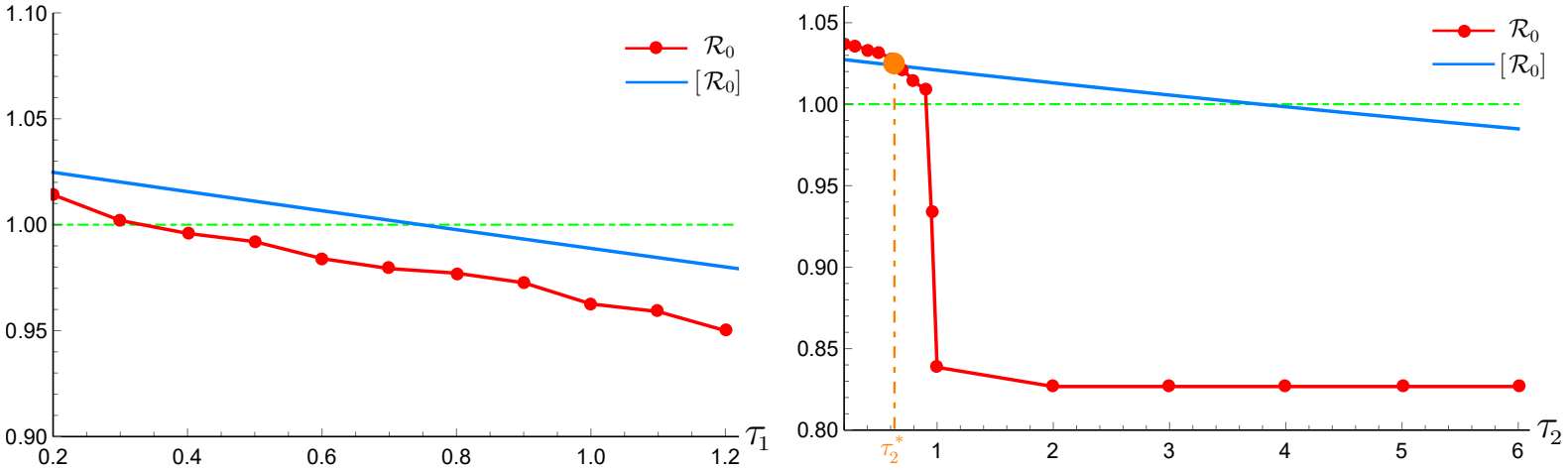
where $\frac{\partial f}{\partial C}\left(\frac{\Lambda}{\mu},0,0\right)=f_C$ and $\frac{\partial f}{\partial I}\left(\frac{\Lambda}{\mu},0,0\right)=f_I$.

Parameter	Condition
τ_1, τ_2	Reduce τ_1 or τ_2
f_C	Increase f_C
γ	Reduce γ
p	Increase p and one of the following conditions holds (i) $\frac{f_C}{q+\gamma+\mu} > \frac{f_I}{r+\delta+\mu}$ or (ii) $[\mathcal{R}_0] < \frac{q f_I e^{-\mu\tau 2}}{f_I(q+\gamma+\mu) - f_C(r+\delta+\mu)}$
q	Increase q and the condition (iii) $[\mathcal{R}_0] < e^{-\mu\tau_2}\frac{f_I}{f_C}\frac{\gamma+\mu}{r+\delta+\mu}$ holds

Table 1: Conditions for increasing $[\mathcal{R}_0]$.

- Comparison between $[\mathcal{R}_0]$ in the autonomous system and $\mathcal{R}_0$ in the periodic system.

- We take the average value of $[\beta_1] = \frac{1}{T}\int_0^T \beta_1(t)dt = 128.333$ and $[q] = 30$ in Figure 4 over the interval $[0, T]$.



(a) Fixed $\tau_2 = 0.8$ and τ_1 varies.

(b) Fixed $\tau_1 = 0.2$ and τ_2 varies.

Figure 5: The graph of $\mathcal{R}_0$ and $[\mathcal{R}_0]$ when τ_1, τ_2 varies. $\mu = 0.0525$, $p = 0.4$ and the other parameters as in Figure 4.

The time-average basic reproduction number $[\mathcal{R}_0]$

- Underestimates the disease transmission risk when the asymptomatic carriage period is short;
- Overestimates it when asymptomatic carriage duration is long enough.
- While $[\mathcal{R}_0]$ overestimates $\mathcal{R}_0$ when τ_1 varies

In general, $[\mathcal{R}_0]$ may coincide with the basic reproduction ratio $\mathcal{R}_0$ or underestimate/overestimate infection risks

Thank You