Re-examining Incidence Rates in Models of Infectious Disease and Substance Use Disorder

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DEPARTMENT OF MATHEMATICS

Outline

1) How do non-person-to-person infections affect infectious disease model dynamics?

2) Analysis approaches, optimal control

3) Delayed information effects on infectivity rates, consequences for model dynamics.

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Mathematical epidemiology of substance use disorders

Infectious disease epidemiology and social contagion theory have cast a long shadow over efforts to model **substance use disorder**.

The result is that models have focused almost exclusively on scenarios where disease is acquired solely by person-to-person "infection", known as *social contagion*.

Examples include:

- Alcohol (especially on college campuses)
- Cocaine
- Heroin
- Ecstasy
- Obesity
- Violence
- Fanaticism

Example: Sánchez *et al.*, 2007

Population model for problem drinkers (D) within a "specified drinking environment."

$$\frac{dS}{dt} = \mu - \beta SD - \mu S$$
$$\frac{dD}{dt} = \beta SD + \rho RD - (\mu + \phi)D$$
$$\frac{dR}{dt} = \phi D - \rho RD - \mu R$$
$$1 = S + D + R$$

This models problem drinking "**as the result of contacts of 'at-risk' individuals with individuals in distinct drinking states**."

Analysis is based on existence of a drinking-free equilibrium and stability results, including a *basic reproductive number*, R_0.

Example: White and Comiskey, 2007

Population model for **heroin use** (before heroin was involved in the prescription opioid epidemic, c. 2010):

$$\frac{dS}{dt} = \mu + \delta_1 D + \delta_2 R - \beta SD - \mu S$$
$$\frac{dD}{dt} = \beta SD + \beta_3 RD - (\mu + \delta_1 + p)D$$
$$\frac{dR}{dt} = pD - \beta_3 RD - (\mu + \delta_2)R$$
$$1 = S + D + R$$

Blue rates describe person-to-person infectivity.

Includes equilibrium analysis, results about existence of backward bifurcation, and *basic reproduction number analysis* (next generation matrix method).

However: infectious disease does not always occur *solely* via person-to person transmission

Examples:

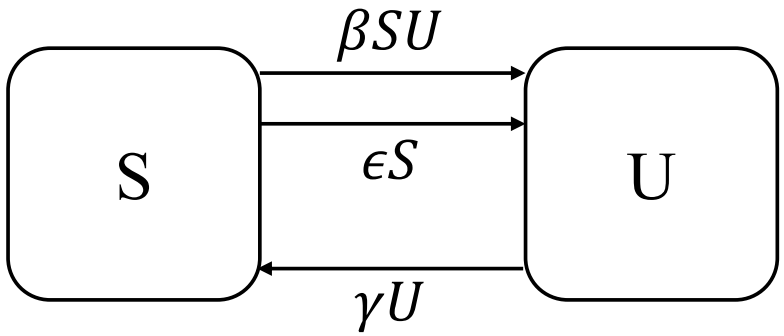
- Substance use disorder (SUD) is associated with
  - Depression
  - PTSD
  - Prescription opioids
  - Self-medicating behaviors

- Mental health can be impacted by events, physiological conditions, or other experiences which may or may not involve others with mental health concerns.

- Infectious, pathogenic disease may come from an environmental reservoir that is not human in origin, and potentially not well described by a single additional species.

When can we neglect non-person-to-person disease sources?

Consider an SIS model with linear perturbation, e.g. for a substance use disorder.



$$\frac{dS}{dt} = -\beta SU - \epsilon S + \gamma U,$$
$$\frac{dU}{dt} = \beta SU + \epsilon S - \gamma U,$$
$$S + U = 1.$$

If $\epsilon = 0$:

$$U^e_{0,1} = \frac{\beta - \gamma \pm \sqrt{(\beta-\gamma)^2}}{2\beta} = \begin{cases} 0 & \text{if } \beta \le \gamma \\ 1 - \frac{\gamma}{\beta} & \text{if } \beta > \gamma \end{cases}$$

$$S^e_{0,1} = 1 - U^e_{0,1}.$$

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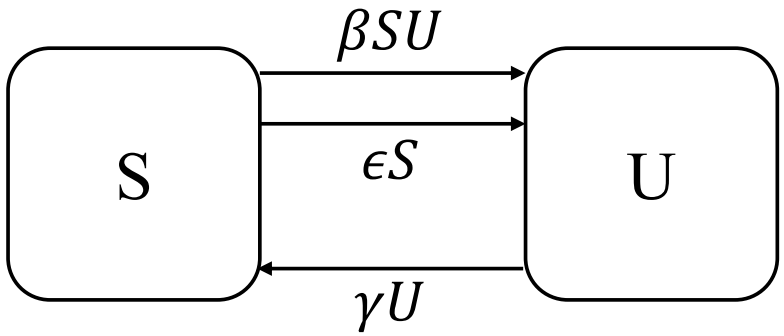

$$\frac{dS}{dt} = -\beta SU - \epsilon S + \gamma U,$$
$$\frac{dU}{dt} = \beta SU + \epsilon S - \gamma U,$$
$$S + U = 1.$$

But, when $\epsilon > 0$: Only one feasible equilibrium exists!

$$U^e = \frac{\beta - (\gamma + \epsilon) + \sqrt{(\beta - (\gamma + \epsilon))^2 + 4\beta\epsilon}}{2\beta}$$
$$S^e = 1 - U^e.$$

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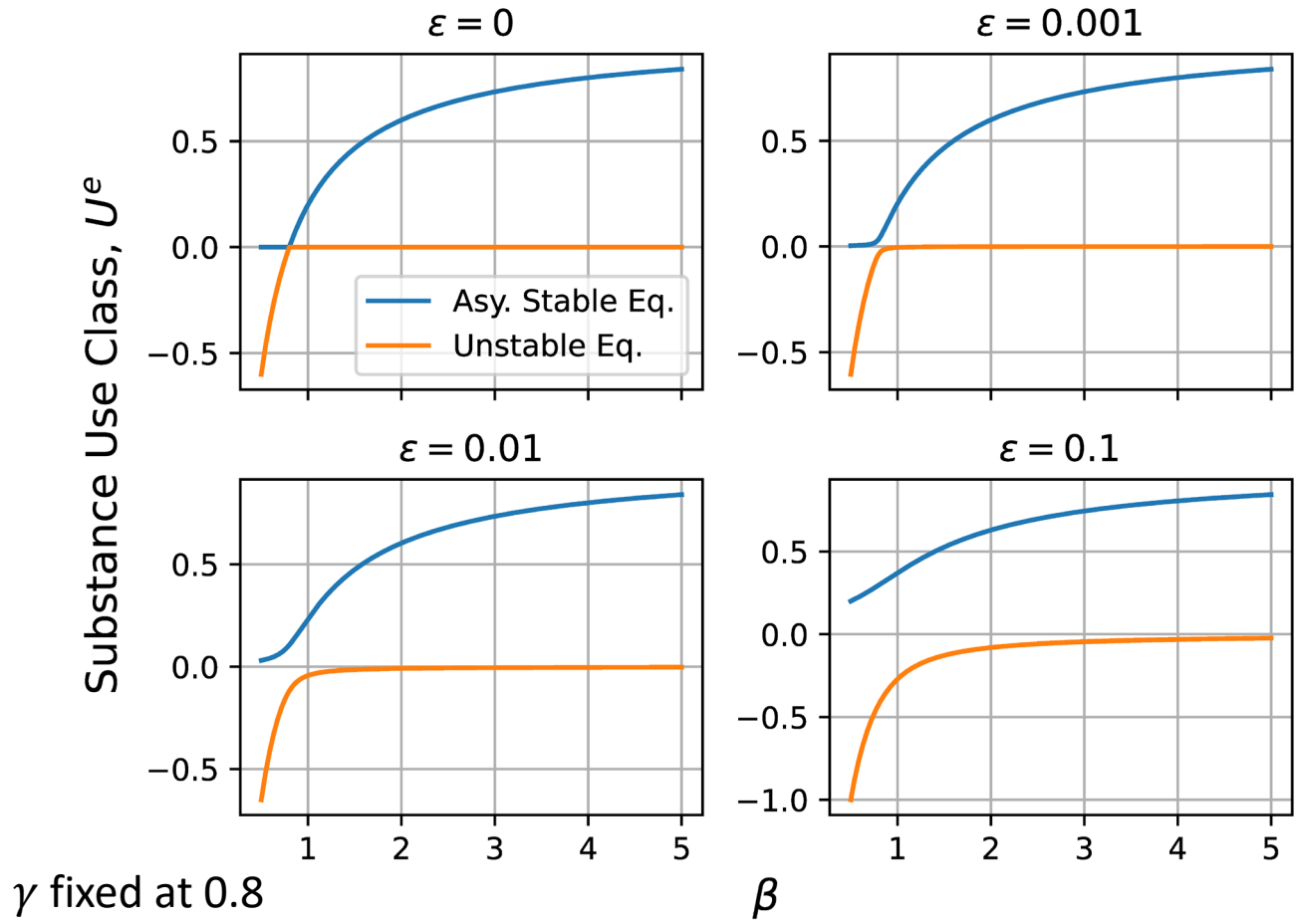
When can we neglect non-person-to-person disease sources? *Generally, we can't.*

Even a simple SIS model is *structurally unstable* with respect to a "spontaneous" infectivity rate, ε!



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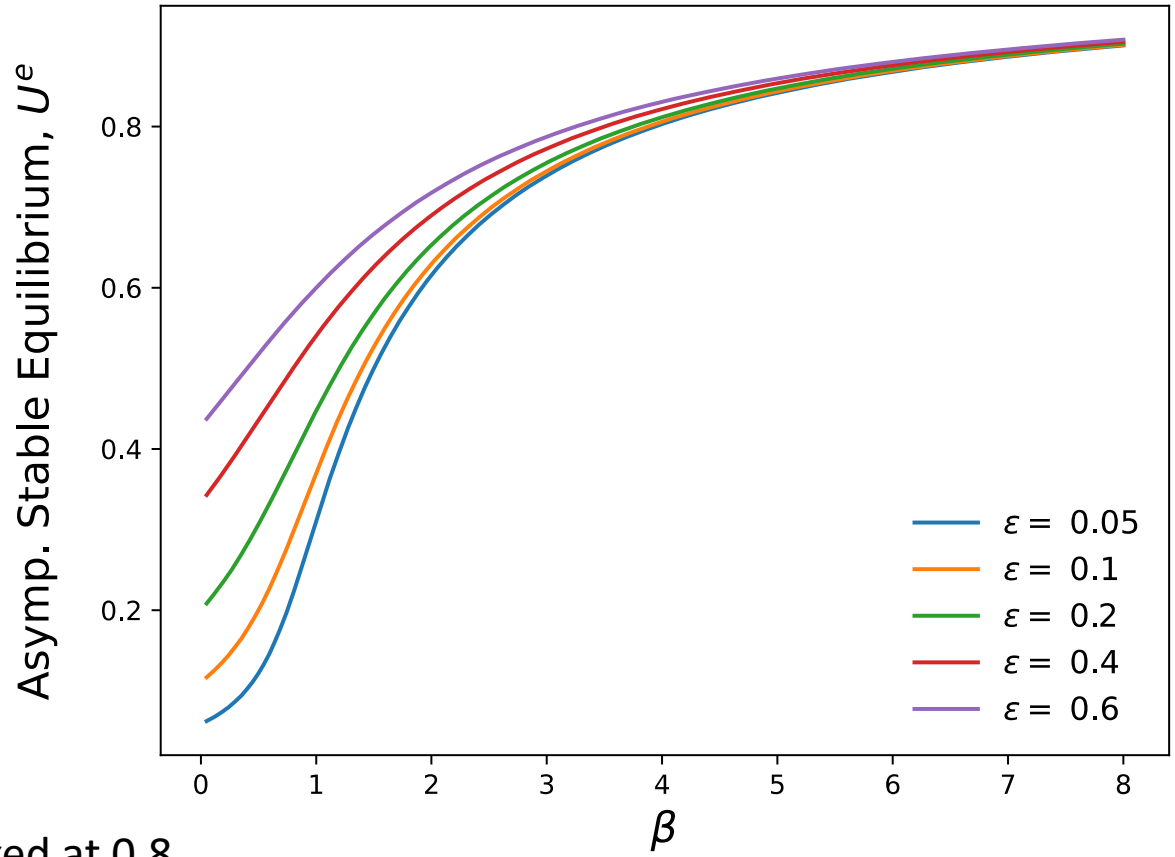
When can we neglect non-person-to-person disease sources? *Generally, we can't.*

This departure is most pronounced for **low values** of person-to-person infectivity, β; e.g., where R_0 is close to or below 1.



γ fixed at 0.8

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This has important consequences for model analysis

- NO disease-free equilibrium exists, so…
- R_0 is completely *undefined* (relies on perturbation analysis nearby disease-free equilibrium)
- Dynamics are typically of a single, asymptotically stable equilibrium.
- But that equilibrium is hard to analytically specify! It requires solving a non-linear system of algebraic equations that does not reduce.

Battista, Pearcy, WCS (2019) *Bull. Math. Bio.* 81(7)
Phillips, Lenhart, WCS (2021) *Bull. Math. Bio.* 83(97)
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So: what approaches can we take?

One first step:

Calculate R_0 for the submodel *without* the linear incidence rate.

This **does not** tell you about disease trajectories. But it establishes *the necessity of the linear incidence rate for endemic disease.*

E.g.,

- If $R_0 > 1$, linear incidence is *sufficient, but not necessary* for endemic disease.
- If $R_0 < 1$, linear incidence is *necessary* for endemic disease.

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So: what approaches can we take?

A second suggestion:

Formulate an optimal control problem aimed at reducing both types of infectivity. Example:

$$\min_{u,v \in V} \left[\int_0^T (U + b_1 u + b_2 v + d_1 u^2 + d_2 v^2)\, dt \right]$$

$$\begin{aligned}
\text{subject to} \quad & \frac{dU}{dt} = (1 - c_1 u)\beta(1 - U)U + (1 - c_2 v)\epsilon(1 - U) - \gamma U, \\
& U(0) = U_0, \ 0 \le U_0 \le 1, \\
\text{where} \quad & V = \{v : [0, T] \to [0, \rho] \mid v \text{ is Lebesgue measurable.}\} \\
& \rho < 1 \text{ constant}, \ 0 < c_1, c_2 \le 1 \text{ constant.}
\end{aligned}$$

ρ represents the maximum feasible reduction on both infectivity rates
$c_1 c_2$ are scaling factors allowing for proportional responses from β and ε

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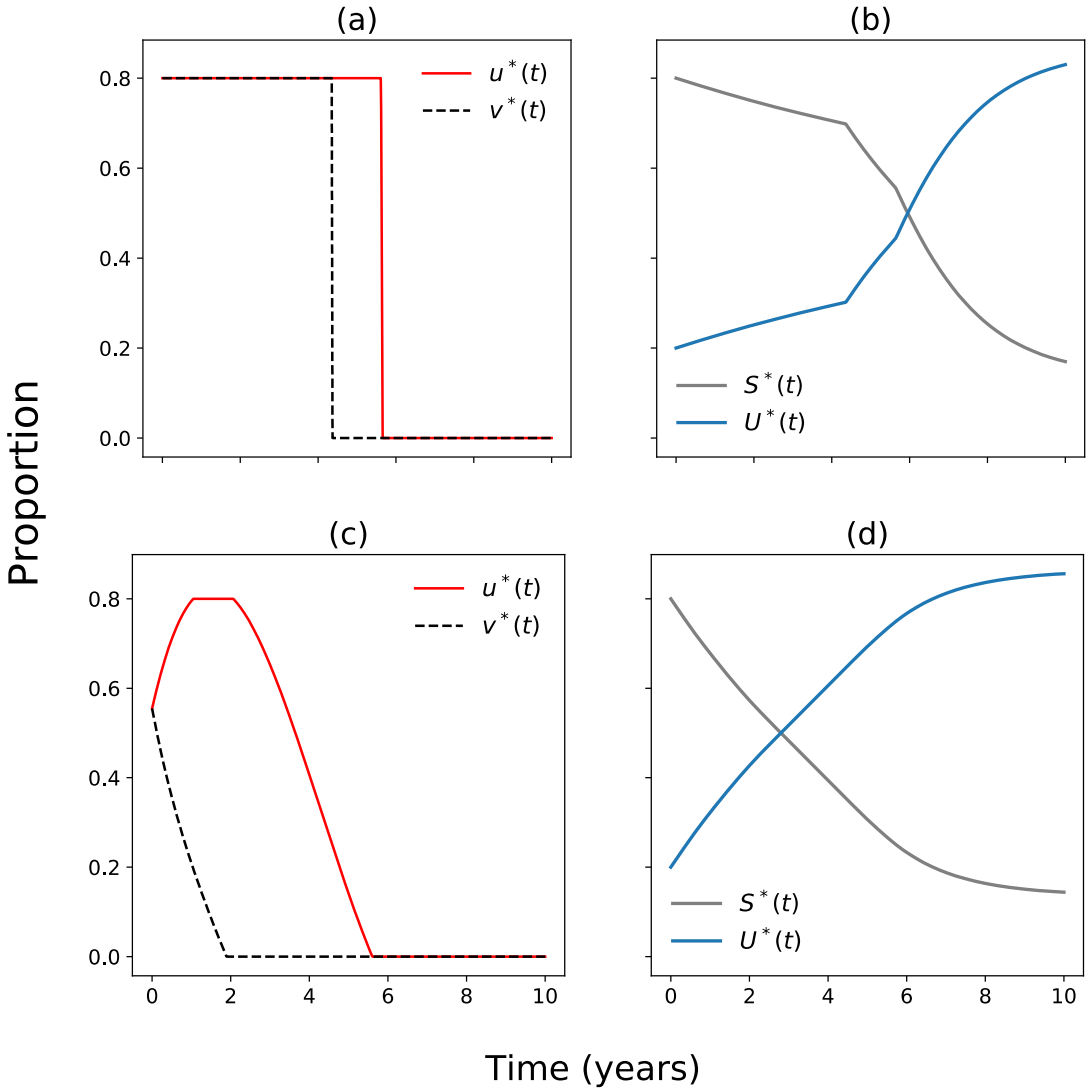
Optimal Control



$$\begin{cases} u^*(t) = 0 & \text{if } \frac{\partial H}{\partial u} > 0 \\ 0 \le u^*(t) \le \rho & \text{if } \frac{\partial H}{\partial u} = 0 \\ u^*(t) = \rho & \text{if } \frac{\partial H}{\partial u} < 0 \end{cases},$$

$$\begin{cases} v^*(t) = 0 & \text{if } \frac{\partial H}{\partial v} > 0 \\ 0 \le v^*(t) \le \rho & \text{if } \frac{\partial H}{\partial v} = 0 \\ v^*(t) = \rho & \text{if } \frac{\partial H}{\partial v} < 0 \end{cases}.$$

Plots (a), (b): The linear cost terms affect the time at which the strategy switches for u^* and v^*.

Plots (c), (d): When the quadratic costs are large, the controls decrease to zero more quickly.

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Human behavioral response influences infectivity

Another **key component** to infectivity is the human behavioral response to disease prevalence, especially in cases where mortality rates are high.

This is often neglected in compartmental model approaches, but avoidance behaviors can be seen in contexts as varied as drug epidemics and widespread pandemics (e.g. COVID-19).

Behavioral response is based on **delayed** information & reaction.

- Symptoms may take days to escalate, even while a person is infectious, and any mortality will be delayed further still.
- Data compiling and reporting introduces further information lags.
- News reports can lag behind current drug trends.
- Data assimilation and decision-making on the part of individual viewers introduces more delay.

Human behavioral response influences infectivity

A foundational model for this can be found in d'Onofrio and Manfredi (2009) *Journal of Theoretical Biology.*

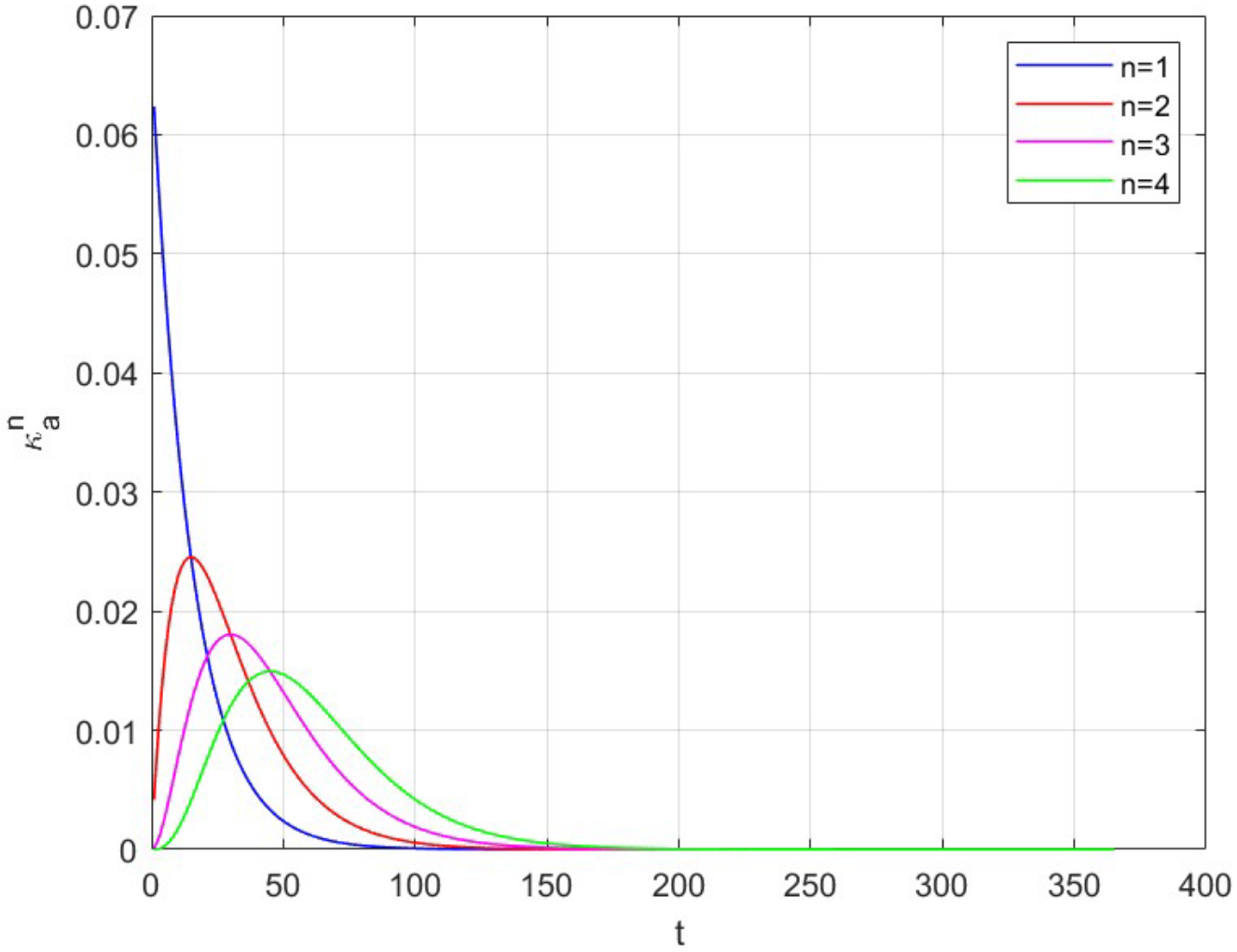
$$\frac{dS}{dt} = \mu(I+R) - \beta(M)IS$$
$$\frac{dI}{dt} = \beta(M)IS - (\mu+\nu)I$$
$$\frac{dR}{dt} = \nu I - \mu R$$
$$M(t) = \int_0^\infty g(I(t-\tau))\sigma(\tau)d\tau$$

$g(I)$ relates disease prevalence to information and $\sigma(t)$ is a delay kernel describing how the past is weighed.

$g(I)$ is generally chosen to be $g(I) = kI.$

$\sigma(t)$ is often taken to be an Erlang distribution (special case of Gamma)

Example Erlang kernels for delay distribution



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If $\sigma(t)$ is an Erlang distribution, the linear chain trick converts the integral into a system of differential equations, resulting in a finite spectrum for local asymptotic analysis.

- Erlang-1 delays (exponential) typically lead to globally asymptotically stable endemic equilibria.
- This remains true across many model structures.

e.g. Buonomo, d'Onofrio, Lacitignola (2012), Vargas-de-León, d'Onofrio (2017), López-Cruz (2022)

Human behavioral response influences infectivity

$$\frac{dS}{dt} = \mu(I+R) - \beta(M)IS$$
$$\frac{dI}{dt} = \beta(M)IS - (\mu+\nu)I$$
$$\frac{dR}{dt} = \nu I - \mu R$$
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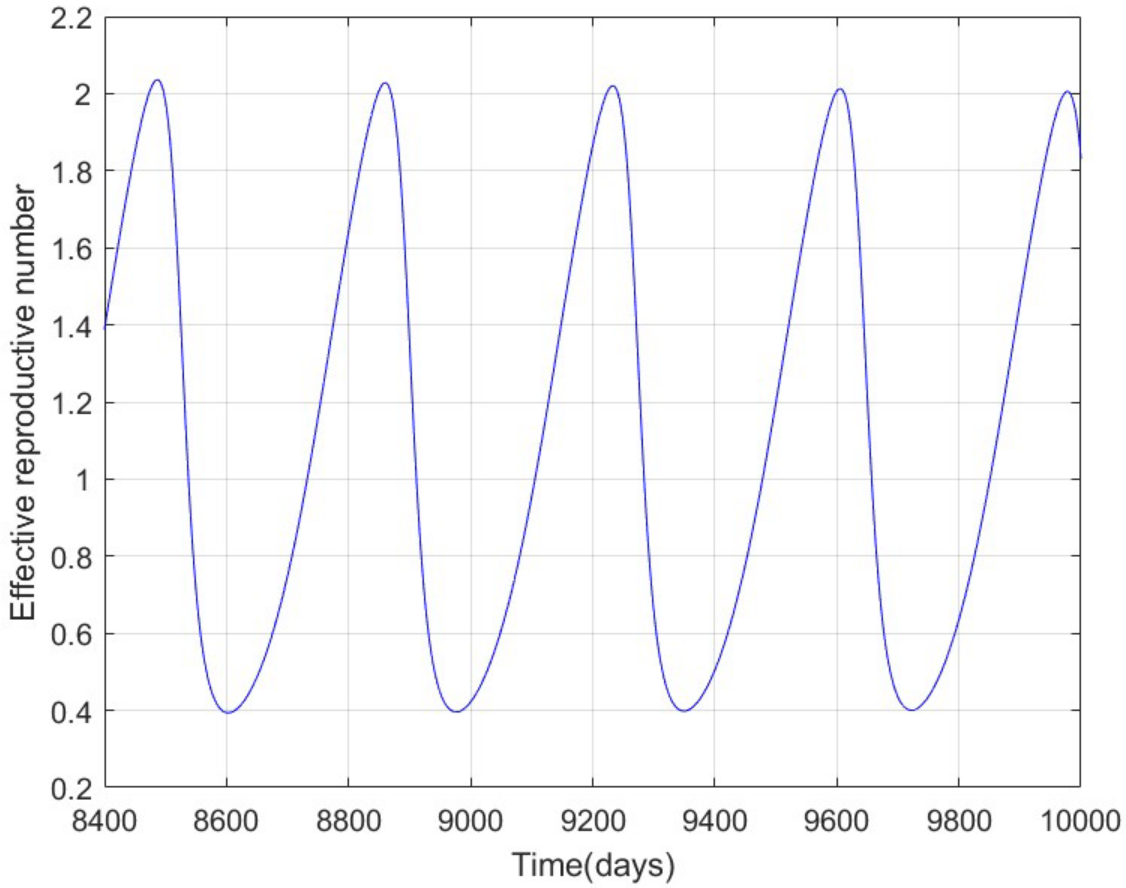
If $\sigma(t)$ is an Erlang distribution, the linear chain trick converts the integral into a system of differential equations, resulting in a finite spectrum for local asymptotic analysis.

- Erlang-2 can yield limit cycles in certain parameter regimes if a fractional, saturation form of $\beta(M)$ is used!
- Our recent work shows these limit cycles disappear for linear $\beta(M)$, including in SEIR models. So, the functional form of $\beta(M)$ is important.

Bouka, WCS (2024) *In prep.*

Oscillations in R_{eff}

When they occur, we show that Erlang-2 oscillations can be understood by fluctuations in the effective reproductive number due to a combination of susceptible numbers and changing $\beta(M)$.

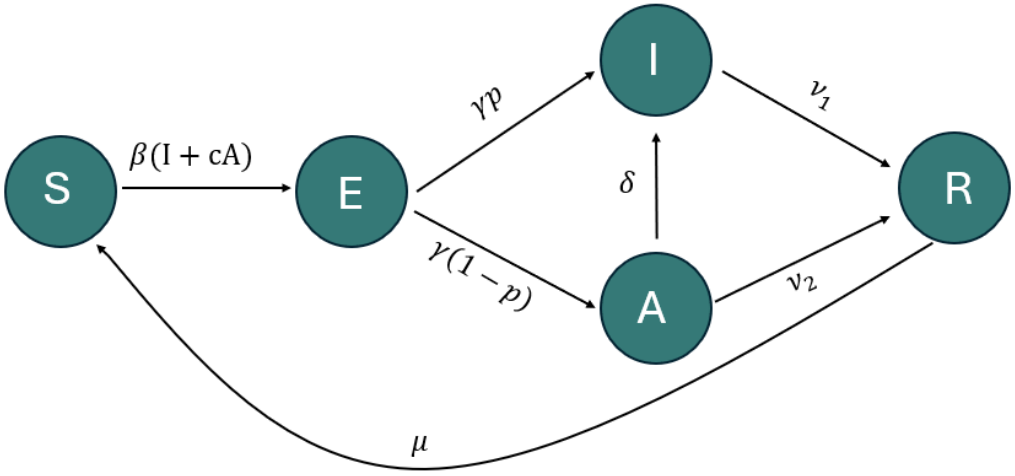


Bouka, WCS (2024) *In prep.*

Another result: significant SEIAR oscillations!

Consider the following model that includes an asymptomatic infectious class and limited exposure immunity that can lead to reinfection.

$$\frac{dS}{dt} = -\beta(I + cA)S + \mu R$$
$$\frac{dE}{dt} = \beta(I + cA)S - \gamma E$$
$$\frac{dI}{dt} = \gamma pE + \delta A - \nu_1 I$$
$$\frac{dA}{dt} = \gamma(1-p)E - (\delta + \nu_2)A$$
$$\frac{dR}{dt} = \nu_1 I + \nu_2 A - \mu R$$



$$M(t) = \int_{-\infty}^{t} kI(\tau)\kappa_a^2(t-\tau)d\tau$$

Convert $\beta \rightarrow \beta(M)$ where M is Erlang-2 delayed information based on kI. The following form of β is used:

$$\beta(M) = \frac{\beta_0}{1 + \alpha(M/I^*)}$$

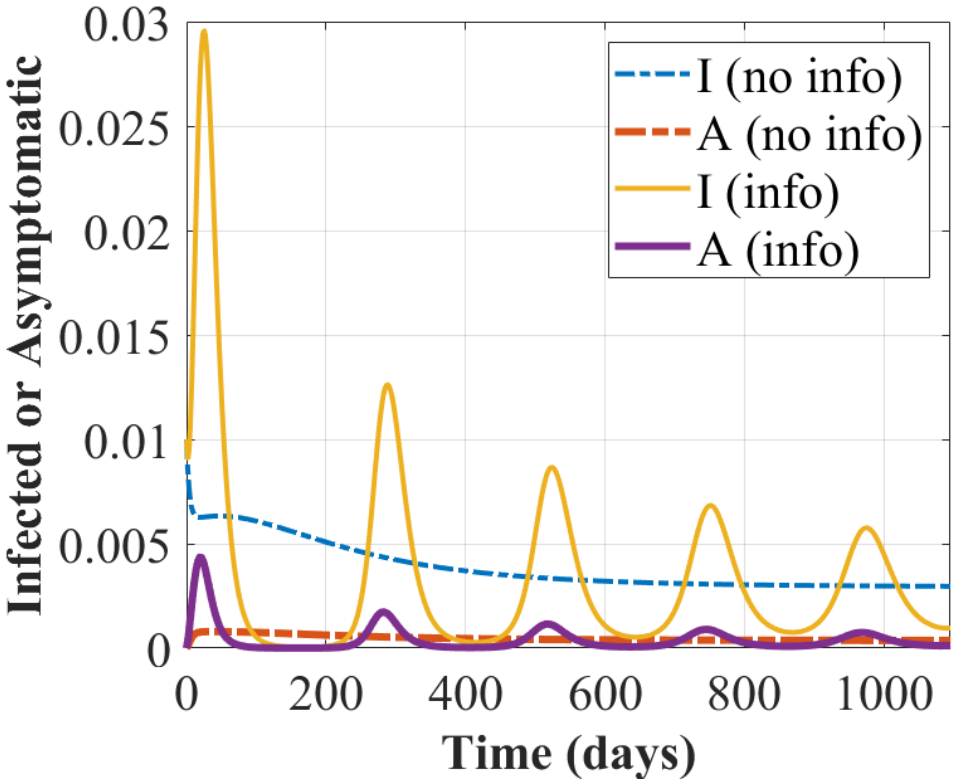
Bouka, WCS (2024) *In prep.*

Information delay can contribute to infection waves

We compare the results where:

1. Infectivity is informed by delayed information.
2. Infectivity rate is held constant at the average of case (1).

- *Substantial* oscillations occur in case (1). The peaks have the potential to overwhelm health services.
- The period can be less than a year (compare with COVID-19 waves).
- Strong evidence of limit cycle.



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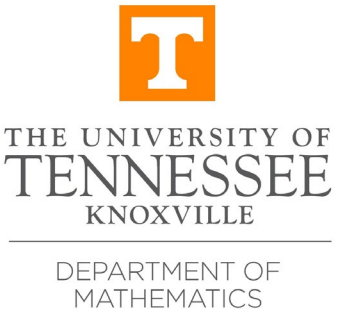
Conclusions

- Infectious disease models are structurally unstable with respect to a linear perturbation in infectivity.
- Non-transmission sources of infection cannot be neglected when they are present.
- Analysis is more difficult in these cases; model structure analysis and optimal control approaches provide some paths forward.
- Human response is also a key component to infectivity.
- Information-delay is intrinsic to most response mechanisms and can be significant to the overall dynamics.
- These feedback-effects are mathematically tractable and can be considered as oscillations in R_{eff}.

Thank you for your attention!



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