Optimal Vaccination Strategies in Periodic Settings

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Introduction:

Vaccination is key in controlling Childhood diseases.

But what **vaccination strategies are optimal** given constraint on resources.

Pulse vaccination (Agur(1993), …) better results than **Homogeneous Constant vaccination.**

Success cases of PVS.(D'Onofrio,2002):
-Central and South America-Polio, Measles
-U.K, measles-1994.

Justification of PVS

- Reimmunization
- Periodic resonance between contact and vaccination rates leading to disease eradication
- Better use of vaccination doses
- Campaings preceeding vaccination day.

The Model

$$\frac{dS}{dt} = b - \mu S - \psi(t)S - \beta(t)SI, \qquad S(t_0) = S_0 > 0$$

$$\frac{dI}{dt} = -\mu I + \beta(t)SI - \alpha I, \qquad I(t_0) = I_0 > 0$$

$$\frac{dR}{dt} = -\mu R + \psi(t)S + \alpha I, \qquad R(t_0) = R_0 > 0$$

An SIR Model with:

- Population Dynamics
- Periodic contact rate
- Periodic vaccination rate.

$$Contact\ \ rate: \quad \beta(t) \in L_+^{\infty}(0,T)$$

$$Vaccination\ \ rate: \quad \psi(t) \in L_+^{\infty}(0,T)$$

Proposition 1. Existence of Disease Free Stable State (DFPO).

Given $\psi(t) \in L_{+}^{\infty}(0,T), \quad I(t) \equiv 0,$

There exists a unique periodic solution and all solutions with initial condition I(t)=0, tend to this periodic solution.

Proof:

- I(0)=0, I(t)=0 at all times.
- The remaining linear equation is not dependent on R(t) and has solution,

$$s[\psi](t) = s(0)e^{-\int_0^t \mu+\psi(\tau)d\tau} + b\int_0^t e^{-\int_\sigma^t \mu+\psi(\tau)d\tau} d\sigma$$

- Periodic Solution: Periodic vaccination (and contact) rates,
- This is a unique solution:

Stability Analysis

Floquet Theory

- Standard—Periodically driven systems.
- Systems with similar Time scales

Singular Pertubation Theory

- Systems with different time scales
- Fast , slow systems analysed seperately and then jointly.

Floquet Theory

- **linearize the system about a solution.**

$$\left(S[\psi](t), \quad 0, \quad \frac{b}{\mu} - S[\psi](t) \right)^T$$

- **Obtain independent solutions of the linearized system,**

✓ **initial conditions (1,0,0), (0,1,0), (0,0,1).**

✓ **the solution vectors form columns of the Monodromy matrix.**

FLOQUET THEORY

- **The Monodromy matrix reads**

$$\begin{pmatrix} \exp\left(-\int_0^T \mu+\psi(t)dt\right) & * & 0 \\ 0 & \exp\left(-\int_0^T \mu+\alpha dt+\int_0^T \beta(t)S[\psi](t)dt\right) & 0 \\ * & * & \exp\left(-\int_0^T \mu dt\right) \end{pmatrix}$$

- The main diagonal defines the **spectrum of the matrix.**
- disease free periodic orbit (DFPO) is orbitally stable if

$$\widetilde{F} = \int_0^T \beta(t)S[\psi](t)dt < T(\mu+\alpha)$$

Proposition 2:

If the Uninfected periodic orbit is orbitally stable, it attracts all solutions with non-negative initial conditions.

- Proposition 2.1: the solution is unique

$$\hat{S}(t) \xrightarrow[\infty]{t} S[\psi](t)$$

- Proof:

$$\frac{d(\hat{S}(t)-S[\psi](t))}{dt} = -(\mu+\psi(t))(\hat{S}(t)-S[\psi](t));$$

$$\hat{S}(0)-S[\psi](0)=\tilde{S},$$

$$\hat{S}(t)-S[\psi](t)=\tilde{S}e^{-\int_{\sigma}^{t}\mu+\psi(\tau)d\tau}=0; \quad t\to\infty.$$

Infective solution tends to zero

- Proposition 2.3:

$$I(t) \xrightarrow[\infty]{t} 0$$

- Proof:

$$\frac{dI(t)}{dt} = -(\mu + \alpha - \beta(t)S(t))I(t); \qquad I(t) \geq 0$$

$$I(t) = I(0)\exp\left\{-\int_0^t (\mu+\alpha) - \beta(\tau)S(\tau)d\tau\right\}$$

$$= I(0)\exp\left\{-\int_0^t (\mu+\alpha) - \beta(\tau)S[\psi](\tau)d\tau\right\}\exp\left\{-\int_0^t \beta(\tau)\left[S[\psi](\tau) - S(\tau)\right]d\tau\right\}$$

$$= I(0)\exp\left\{-\int_0^t (\mu+\alpha) - \beta(\tau)S[\psi](\tau)d\tau\right\}\exp\left\{-\int_0^t \beta(\tau)\tilde{S}e^{-\int_\sigma^t \mu+\psi(\tau)d\tau} d\tau\right\} = I(0)p_0 p_1$$

$$t \to \infty, \quad \psi(\tau) \to \infty \qquad \Rightarrow p_1 = 1.$$

Due to Periodicity, $p_0(nT) = (p_0 T)^n$

$$p_0(nT) = \exp\left\{-n\int_0^T \mu + \alpha - \beta(\tau)S[\psi](\tau)d\tau\right\} \to 0; \quad n \to \infty$$

Singular Perturbation Theory

- Slow timescales (population dynamics) and fast time scales (epidemics).
- time scales for epidemics: fast contact and recovery rates.
- autonomous system aids in the Geometric Interpretation.

$$
\begin{aligned}
\frac{dS}{dt} &= b - \mu S - \psi(q)S - \frac{1}{\varepsilon}\beta(q)SI, && S(t_0) = S[\psi](t_0),\ 0 < \varepsilon << 1 \\
\frac{dI}{dt} &= -\mu I + \frac{1}{\varepsilon}\beta(q)SI - \frac{1}{\varepsilon}\alpha I, && I(t_0) = I_0 \\
\frac{dR}{dt} &= -\mu R + \psi(q)S + \frac{1}{\varepsilon}\alpha I, && R(t_0) = \frac{b}{\mu} - S[\psi](t_0) \\
\frac{dq}{dt} &= 1, && q(t_0) = t_0
\end{aligned}
$$

- Separate time scales

- Introducing an invariant functional X,

$$X : \mathbb{R}^2 \to \mathbb{R}$$

$$X = -S + \frac{\alpha}{\beta(q)} \ln S - I;$$

Why X?

- Lets change to the fast time scale of epidemics and
- Set epsilon to zero to get limiting fast system.
- The result is the SIR model without Pop. Dyn.
- X is constant on the fast time scale, so X can represent the slow variable.

$$X = -S + \frac{\alpha}{\beta(q)} \ln S - I;$$

$$t = \varepsilon\tau \quad (\tau \quad faster)$$

$$\frac{dS}{d\tau} = \varepsilon\{b - \mu S - \psi(q)S\} - \beta(q)SI,$$

$$\frac{dI}{d\tau} = -\varepsilon\mu I + \beta(q)SI - \alpha I,$$

$$\frac{dq}{d\tau} = \varepsilon,$$

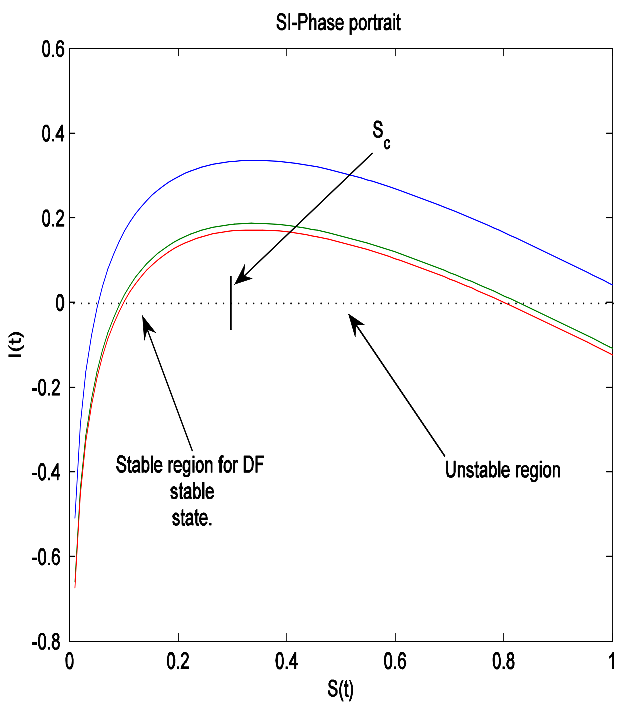
$$\varepsilon \to 0, \quad \frac{dS}{d\tau} = -\beta(q)SI,$$

$$\frac{dI}{d\tau} = \beta(q)SI - \alpha I,$$

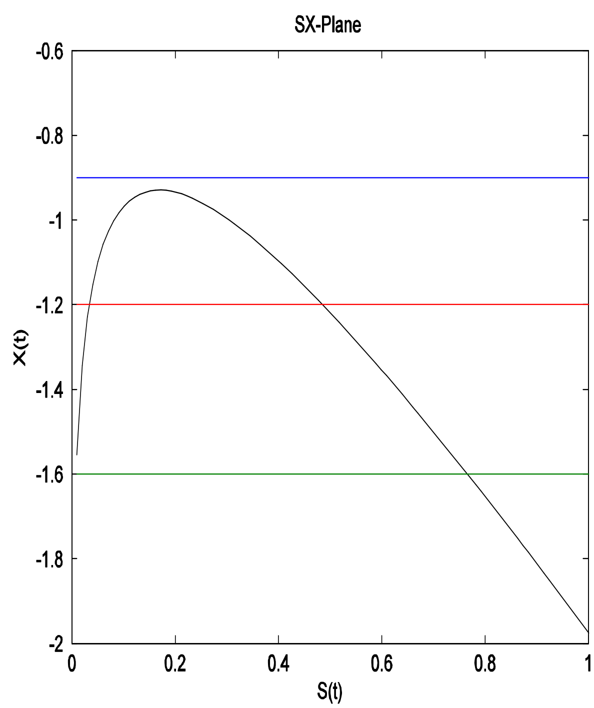
$$\frac{dq}{d\tau} = 0,$$

Transformation from (S,I) to (S,X)

SI-Plane



SX-Plane



Fast-Slow Systems

- **direct computation on X leads to the slow system**

$$\frac{dX}{dt} = -b - \mu X - g(S,q) - \frac{\alpha\beta'(q)q'\ln S}{[\beta(q)]^2}$$

$$\varepsilon\frac{dS}{dt} = \varepsilon\left\{b - \mu S - \psi(q)S\right\} - \beta(q)S\left\{-S + \frac{\alpha}{\beta(q)}\ln S - X\right\}$$

$$\frac{dq}{dt} = 1,$$

- **And the fast system**

$$\frac{dX}{d\tau} = \varepsilon\left\{-b - \mu X + g(S,q) - \frac{\alpha\beta'(q)q'\ln S}{[\beta(q)]^2}\right\}$$

$$\frac{dS}{d\tau} = -\beta(q)S[-S + \frac{\alpha}{\beta(q)}\ln S - X] + \varepsilon[b - \mu S - \psi(q)S]$$

$$\frac{dq}{d\tau} = \varepsilon, \qquad t = \varepsilon\tau.$$

Limiting fast and slow systems

$\varepsilon \to 0$

Limiting fast

$$\frac{dX}{d\tau} = 0$$

$$\frac{dS}{d\tau} = -\beta(q)S[-S + \frac{\alpha}{\beta(q)}\ln S - X]$$

$$\frac{dq}{d\tau} = 0,$$

Limiting slow

$$\frac{dX}{dt} = -b - \mu X - g(S,q) - \frac{\alpha\beta'(q)q'\ln S}{[\beta(q)]^2}$$

$$0 = -\beta(q)S[-S + \frac{\alpha}{\beta(q)}\ln S - X]$$

$$\frac{dq}{dt} = 1,$$

Slow Manifold:

$$0 = -\beta(q)S[-S + \frac{\alpha}{\beta(q)}\ln S - X]$$

Stability along the slow manifold.

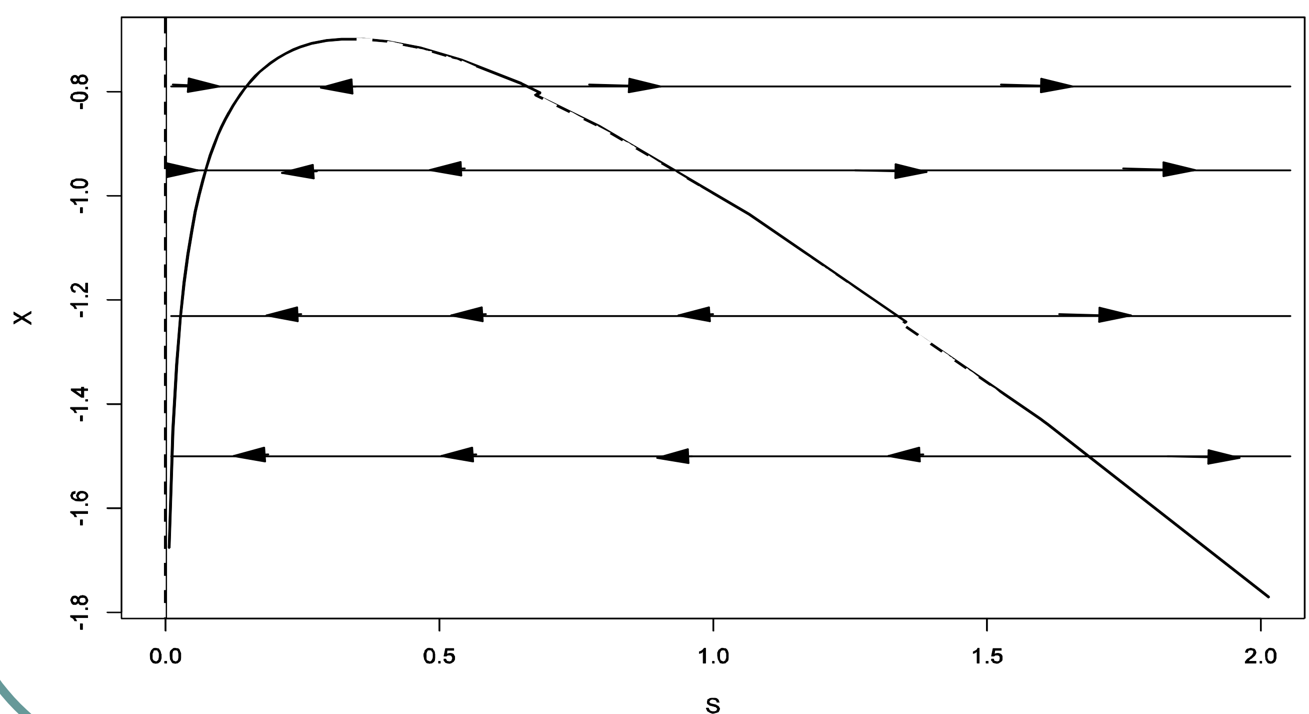
$$h(S) = -\beta(q)S[-S + \frac{\alpha}{\beta(q)}\ln S - X]$$

$$\frac{dh(S)}{dS} = -\beta(q)[-S + \frac{\alpha}{\beta(q)}\ln S - X] - \beta(q)S[-1 + \frac{\alpha}{\beta(q)S}]$$

$$\frac{dh(S)}{dS} < 0 \quad \Rightarrow \text{Stability}$$

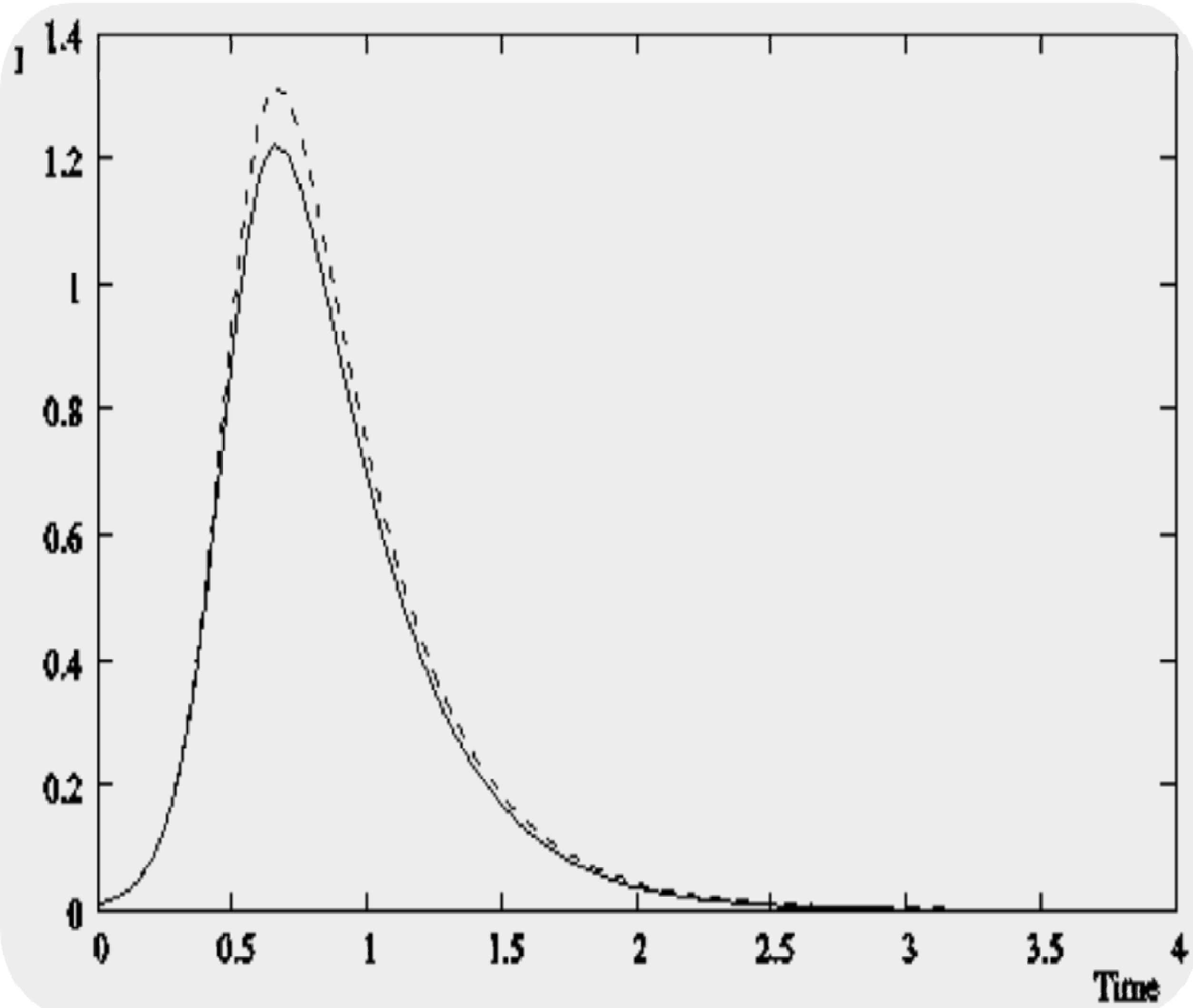
- **the uninfected periodic orbit is instantaneously stable if**

$$\|R_v[\psi]\|_{L^\infty} < 1, \quad where\, R_v[\psi] = \frac{\beta(t)S[\psi](t)}{\alpha}$$



A simulation of the epidemic.

time independent contact rate (dashed curve), varying periodic contact rate (solid curve), constant case, β=1.4 , varying case, β=0.9+cos(t)0.5.



Remarks.

- Orbital stability may not necessarily imply instantaneous stability
- If we start close to DFPO, we eventually converge back to it, though an outbreak is possible.
- One has a choice to use any approach, bearing in mind the possible limitations.

Optimization Problems and Existence of Solutions

Measuring Efficiency of vaccination efforts:

- Orbital Stability
- Instatenious Stability of DFPO.

- **Problem 1:**

$$\min \tilde{F}[\psi] = \int_0^T \beta(t) S[\psi](\tau) d\tau,$$

$$\text{given \# vacc. doses } \tilde{C}[\psi] = C_0$$

where

$$\tilde{C}[\psi] := \int_0^T \psi(\tau) S[\psi](\tau) d\tau,$$

- **Problem 2:**

$$\text{minimize } ||R_v[\psi]||_\infty$$

$$\text{where, } R[\psi](t) = \frac{\beta(t) S[\psi](t)}{\alpha},$$

$$\text{given } \tilde{C}[\psi] = C_0$$

$$\tilde{C}[\psi] := \int_0^T \psi(\tau) S[\psi](\tau) d\tau,$$

Existence of Solutions in the set of vaccination strategies.

- Define the set of vaccination strategies by

$$\Omega_d = Cl\{\tilde{\Omega} = S[\psi](t) \mid \psi \in L_+^\infty\},$$

$$d(\psi_1, \psi_2) = \| S[\psi_1] - S[\psi_2] \|_{L^1} .$$

- Compact in L1 for existence of solutions(Müller, 1998).

$$\Omega_d \text{ is compact in } L^1$$

- The objective function and cost functional (the conditions of optimizations) have continuous extensions in the set.

$$\tilde{F}[\psi] = \int_0^t \beta(t) S[\psi](t)\,dt$$

$$\tilde{C}[\psi] = \int_0^t \psi(t) S[\psi](t)\,dt$$

- Solutions exist for Problem 1 in this set.

Convexity.

Proposition 6.

The set of vaccination strategies is compact and convex and therefore is fully characterised by ist extremal points. (Krein-Milman Theorm)

Proof

$$S_\tau(t) = \tau S_1(t) + (1-\tau)S_2(t)$$

Differentiating the expression w.r.t.t

$$\frac{dS_\tau(t)}{dt} = b - \mu S_\tau(t) + \psi_\tau S_\tau(t);$$

where,

$$\psi_\tau(t) = \frac{\tau\psi_1(t)S_1(t) + (1-\tau)\psi_2(t)S_2(t)}{S_\tau(t)},$$

$$Is \quad \psi_\tau(t) \in L^\infty \ ?$$

$$\begin{aligned}
\|\psi_\tau(t)\|_\infty &= \left\| \frac{\tau\psi_1(t)S_1(t)}{S_\tau(t)} + \frac{(1-\tau)\psi_2(t)S_2(t)}{S_\tau(t)} \right\|_\infty \\
&\le \left\| \psi_1(t)\frac{\tau S_1(t)}{S_\tau(t)} \right\|_\infty + \left\| \psi_2(t)\frac{(1-\tau)S_2(t)}{S_\tau(t)} \right\|_\infty \\
&\le \left\| \psi_1(t) \right\|_\infty + \left\| \psi_2(t) \right\|_\infty < \infty
\end{aligned}$$

Concluding Remarks.

- We have some guarantee that the set of population profiles contains at least a solution.
- The solutions (optimal solutions) need to be defined.
- That is on-going.

END