Q1. What is the Problem?

- The transmission rate is an unobserved process in the modelling of infectious diseases.
- Being able to quickly and easily estimate the transmission rate at each observation is crucial for infectious disease modelers. Why?
- Would like to be able to estimate it by fitting a system of ordinary differential equation or difference equations to data.
  - **Q1a: Why fit to data instead of using a fully mechanistc model?**
    * answer here
- The transmission rate is integral to calculating other epidemiological quantities, such as the effective reproduction number (Rt), and provides the basis for many downstream applications, including evaluating intervention strategies, forecasting disease dynamics, identifying high-risk periods and populations, validating models, understanding transmission dynamics, assessing the impact of variants, and developing and testing hypotheses about factors influencing disease spread.

Q2: What is the general class of models?

- Ecological dynamic models describe how ecological processes drive populations to change over time.
- In this case we are interested in the process of disease transmission, specifically in the rate of transmission.

Q3: What is the model?

- SIR model which can be thought of as a compartmental model, where individuals in the population belong to a single compartment at any point in time. There flow equations determine the movement of individuals from one compartment to another. *

- Mathematically, in the SIR model, the differential equations are given by:

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

where:

- $\frac{dS}{dt}$ is the rate of change of the susceptible population.
- $\frac{dI}{dt}$ is the rate of change of the infectious population.
- $\frac{dR}{dt}$ is the rate of change of the recovered population.
- γ is the recovery rate.

Q4: What role does β play in the flow equation? I.e, how do i understand βSI?

- **Role of β:**
  - β is the transmission rate, which determines the probability of disease transmission per contact between a susceptible and an infectious individual.
  - It encapsulates the rate at which an infectious individual can spread the disease to susceptible individuals.
- **Understanding βSI:**
  - βSI is the term in the SIR model that quantifies the rate of new infections over time.
  - S represents the number of susceptible individuals in the population.
  - I represents the number of infectious individuals.
  - The product SI indicates the number of contacts between susceptible and infectious individuals.
  - Multiplying SI by β gives the number of new infections per unit time, as it scales the contact rate by the probability of transmission.

The term βSI in these equations indicates how the susceptible population decreases and the infectious population increases due to new infections.

Q5: How is the parameter β used in other modelling ?

- A fixed value is the simplest way. here *beta* is constant across all time. This is too simplmplistic.
- Assuming a fixed value for the transmission rate at every time step is often inaccurate because many diseases have dynamic transmission rates influenced by factors such as seasonality or non-pharmaceutical interventions (e.g., social distancing, masking, and changes in mobility patterns). Therefore, it is reasonable to assume that the transmission rate is a time-varying parameter, computed at each observed data point.
- We could assume a parametric functional form. I.e choose a fixed functional form that may or may not have adjustable parameters. These parameters may or may not be estimated. If they are it is often through some MLE. An example could be sinusoidal function. This allows the transmission rate to vary over time. However this is entirely mechanistc as we have prescribed the functional form ahead of time. This may be entirely appropriate if the science supports that qualitative behavior that the functional form prescribes.
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Q6: How can we implement a time varying transmission rate process that is more flexible way?

- This is where non-parametric statistic comes into the picture. When we do not know the correct parametric model for a component of the data. This avoids the model mi specification problem that follows.
- Rather than specifying the functional form of the unknown function a priori, we can adopt a more flexible function estimation method that minimizes incidental assumptions and model misspecification.

Q7: How do we incorporate a non parametric solution with a mechanstic model?

- In an ideal situation we would write down models that contain what is only known about the workings of a biological system.
- A semi_mechanistic model defines the functional forms of the components of the model that relate model variables using a combination of parametric and non parametric methods. So in theory what we know about the biological system has a parametric form and what is unkown or uncertain is defined in flexible way using unknown functions.

Q8: How do we represent these unknown function?

- one approach is to employ a linear transformation of $\mathbf{X}$. This leads to:

$$f(x) = \sum_{m=1}^{M} \beta_m h_m(x),$$

which is a linear basis expansion of x, where $h_m(x) : \mathbb{R}^p \to \mathbb{R}$ represents the m-th transformation of $\mathbf{X}$.

- A notable class of these transformations is restriction methods, where the class of functions that $f(x)$ can assume is limited.
- A common example within this class is *splines*, which define m basis functions $\beta_m h_m(\mathbf{X})$ as local polynomial representations.
  - The domain is divided into contiguous intervals, each represented by a separate polynomial function. The boundaries of these intervals are known as *knots*.
- When the location, derivative order, and number of knots are predetermined, the technique is referred to as regression splines. Natural cubic splines are a specific type where the spline function is composed of cubic polynomial segments.Then it is linear beyond the outermost knots. This spline is represented by K basis functions $\beta_m h_m(\mathbf{X})$, one for each specified knot.

Q9: How does fitting a spline work?

- The complexity of the fit can be adjusted by incorporating regularization to manage the trade-off between data fidelity and smoothness of the curve fit. This is achieved by minimizing a residual sum of squares with an additional penalty term. The penalty term includes a parameter that controls this trade-off, allowing the fit to range between the extremes of pure interpolation and a linear least squares fit. Splines used in this context are known as smoothing splines.

Q10: How does penalization work?

- Smoothing is achieved by minimizing the following objective function:

$$J_2(f) = \sum_{i=1}^{n}(y_i - g(x_i))^2 + \lambda \int g''(x)^2 \, dx, \tag{1}$$

Here, λ serves as a tuning parameter that balances the fidelity to the data with the smoothness of the function g. A higher λ value places greater emphasis on minimizing the integral of the squared second derivative, which encourages a smoother curve for g. Conversely, a lower λ value focuses on closely matching the actual data points, minimizing the sum of squared differences $\sum_{i=1}^{n}(y_i - g(x_i))^2$.

- Furthermore, a computationally efficient form of Equation **??** in terms of these basis functions and matrix elements is:

$$\int_{x_1}^{x_k} f''(x)^2 \, dx = \beta^T \mathbf{D}^T \mathbf{B}^{-1} \mathbf{D} \beta = \beta^T \mathbf{S} \beta,$$

where $\mathbf{S} \equiv \mathbf{D}^T \mathbf{B}^{-1} \mathbf{D}$ is the called the *penalty matrix* for this basis.

Q11: What are some types of splines?

- Cubic Regression Splines
- B-splines
- TPRS

Q12: What is a Guassian Process and how does it fit into the semi-mechanistic modelling framework?

- An order-M spline with knots ξ_j, $j = 1, \ldots, K$, is a piecewise-polynomial of order M and has continuous derivatives up to order $M - 2$.