Case Studies in Mathematical Modelling

Lennon Ó Náraigh [1]

[1] School of Mathematics and Statistics, University College Dublin, Belfield, Dublin 4, Ireland

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Aim of Talk

In this talk, we will go through two case studies in Mathematical Modelling:

- **Part 1:** Mathematical Modelling of outbreaks of infectious disease;
- **Part 2:** Mathematical Modelling of Pharmacokinetics (PK).

Part 1: Outbreaks of infectious disease

A brief overview of mathematical modelling of outbreaks of infectious disease using **compartmental modelling**.

- Population divided into compartments;
- Individuals move from one compartment to another at a set rate.
- Able to predict e.g. the number of infectious individuals at a given time.

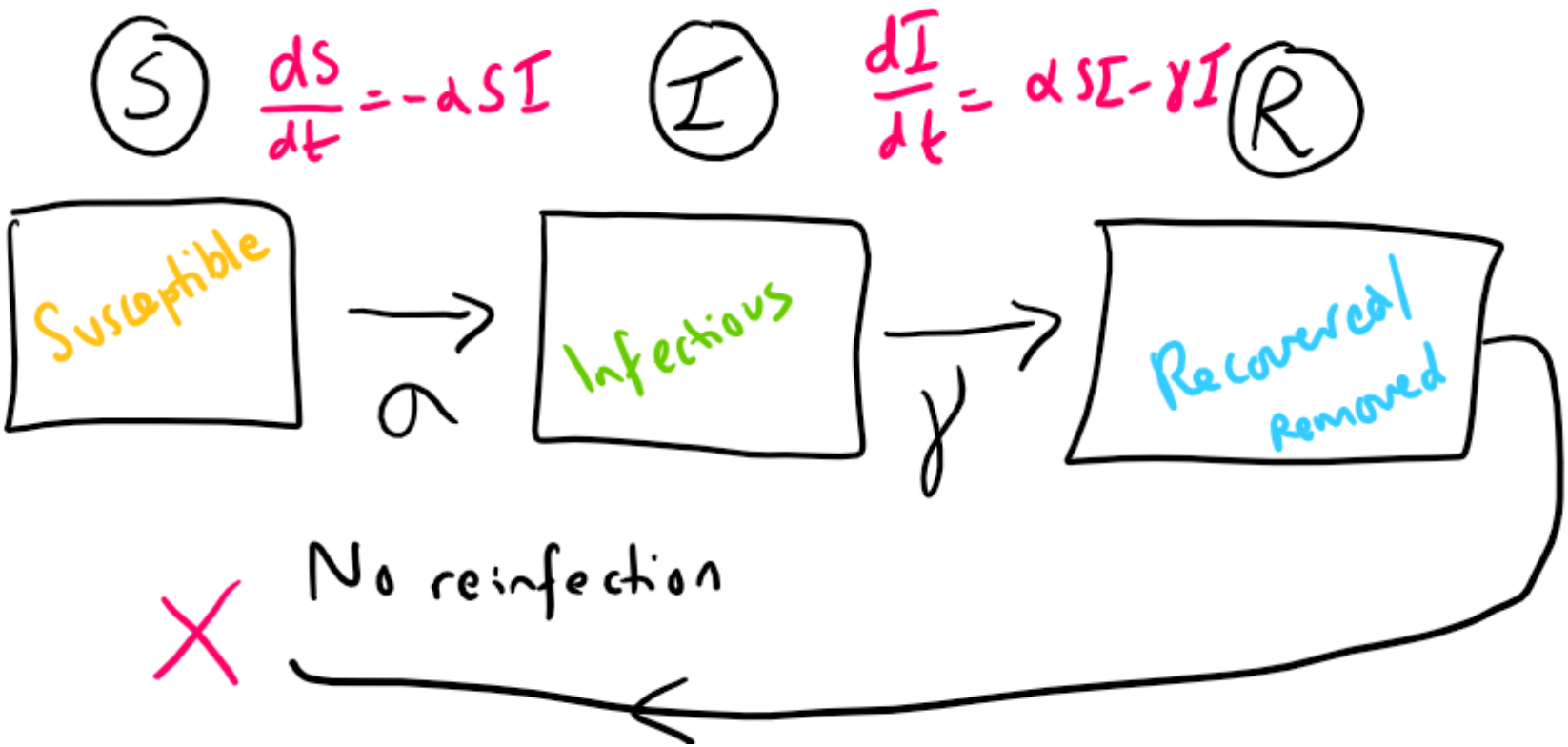
The format of Part 1 is twofold:

- Overview of the famous SIR model;
- Application to outbreak of Covid-19 in Ireland (First Wave).

SIR Model

Key assumption: homogeneous population.

Other assumptions: no natural births/deaths on the timescale of the epidemic.
The model is then just 'conservation of people':



SIR – Equations

With these assumptions, the model equations read:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= -\alpha SI, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \alpha SI - \gamma I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I. \end{aligned}$$

The equations conserve the total number of people, $S + I + R = N = \mathrm{Const.}$.
The initial condition for an outbreak is:

$$S(0) = S_0, \qquad I(0) = N - S_0, \qquad R(0) = 0.$$

With $S_0 = N - 1$ and $I(0) = 1$ we have the idea of 'patient zero'.

SIR – Equations

The constant γ is a rate (1/time). We write $\alpha = \beta/N$ so that β is also a genuine rate:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= -\frac{\beta}{N} SI, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{\beta}{N} SI - \gamma I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I. \end{aligned}$$

These equations can be reduced down to a single ODE:

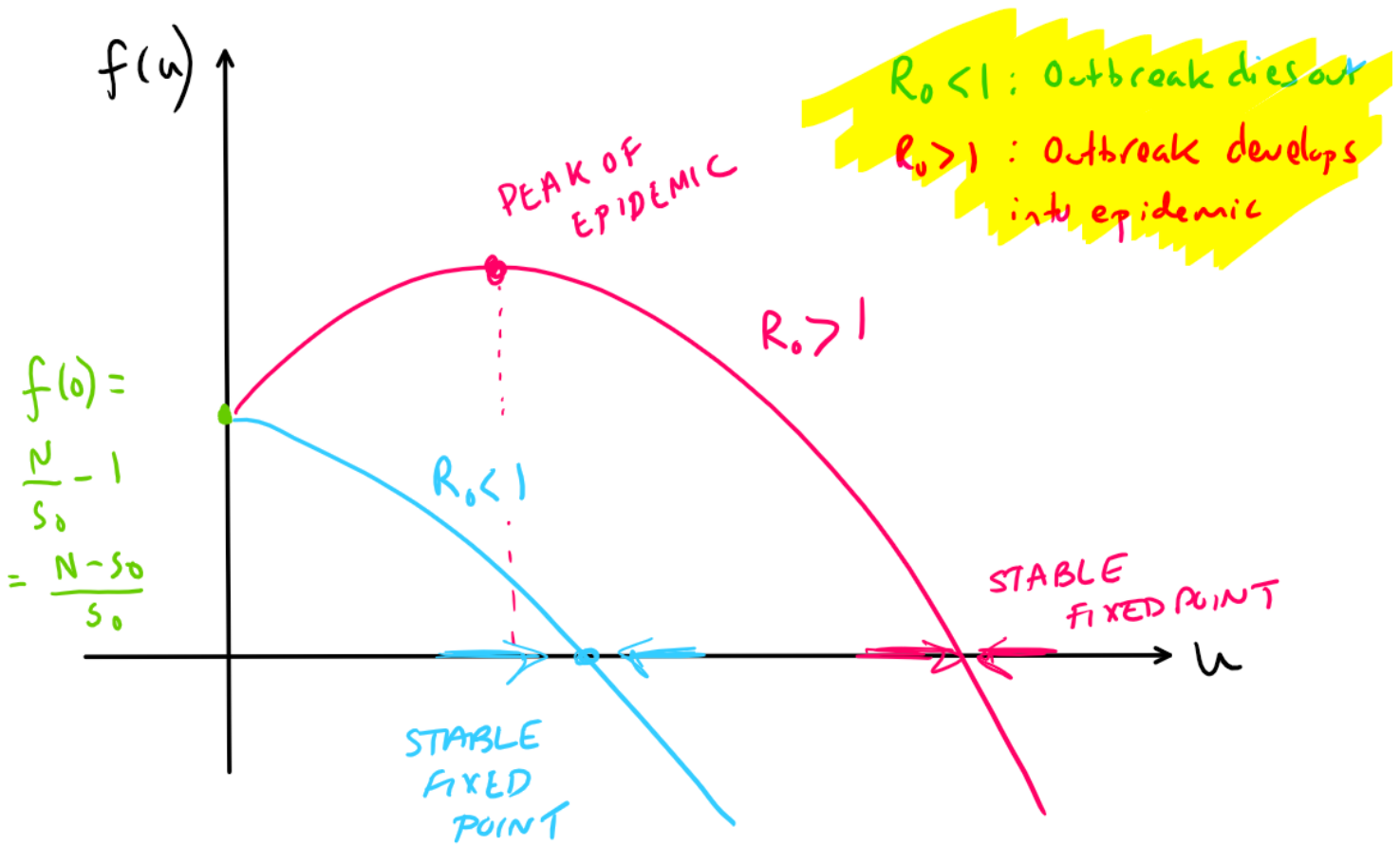
$$\frac{1}{\gamma}\frac{\mathrm{d}u}{\mathrm{d}t} = \frac{\beta}{\gamma} - \frac{\beta}{\gamma}\frac{N}{S_0}\mathrm{e}^{-u} - u, \qquad u = \frac{\beta}{\gamma}\frac{R}{N}.$$

SIR – Equations

The model ODE can again be rescaled to give:

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = \frac{N}{S_0} - \frac{1}{R_0}u - \mathrm{e}^{-u}, \qquad \tau = \beta S_0 t/N.$$

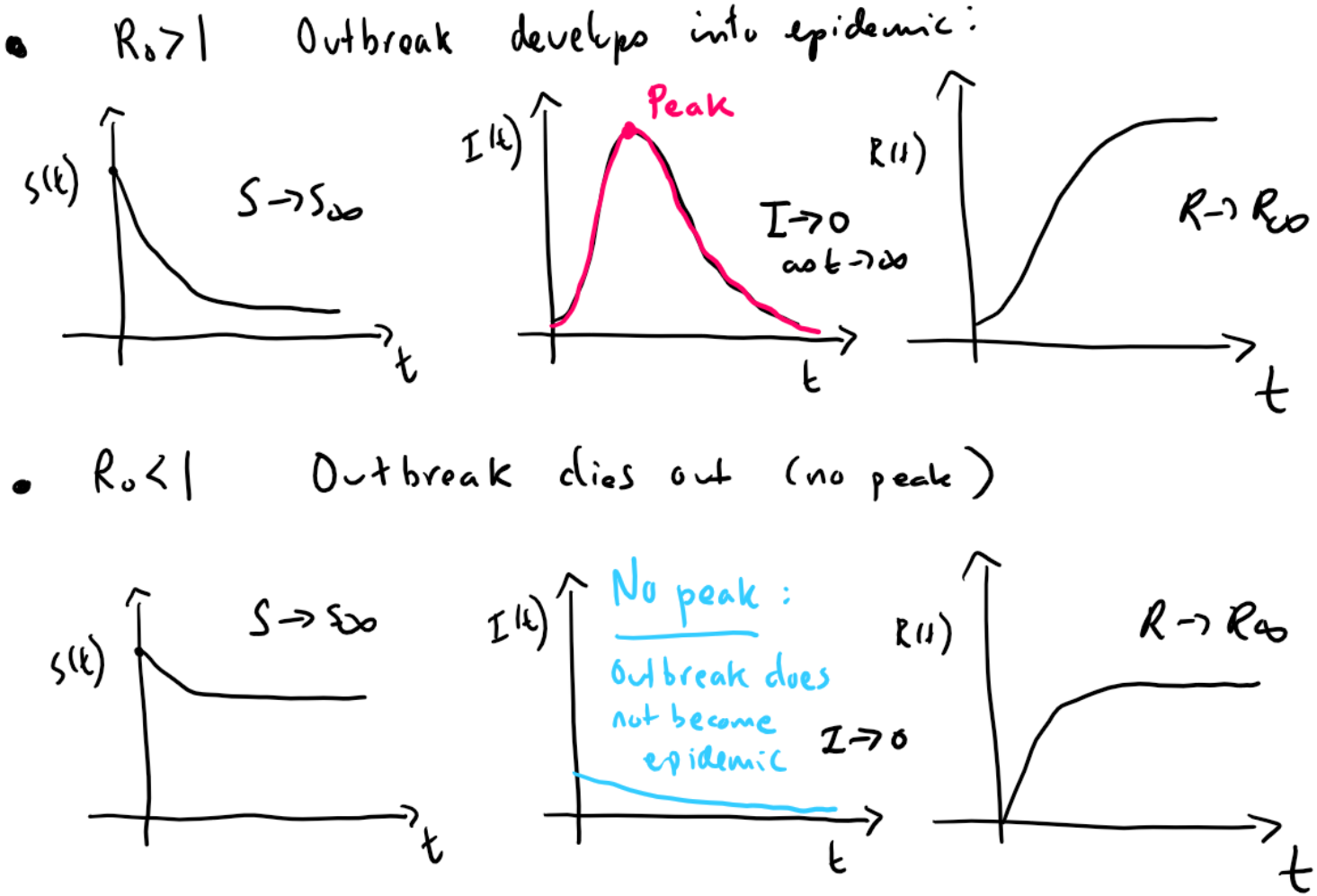
This is an autonomous ODE, $\mathrm{d}u/\mathrm{d}\tau = f(u; S_0/N, R_0)$. Notice, $S_0/N < 1$. A fixed-point analysis yields two scenarios:



Basic Reproductive Number – Formula

The parameter R_0 is the dreaded **basic reproduction number:**

$$R_0 = \frac{\beta S_0}{\gamma N}.$$



Basic Reproductive Number – Intuitive understanding

The familiar meaning of R_0 as '**the number of individuals that an infected person will go on to infect subsequently**' can by obtained integrating the I-compartment across a time interval Δt:

$$I(t+\Delta t) - I(t) = \gamma \Delta t \left[\frac{\beta}{\gamma} \frac{S(t)}{N} - 1 \right] I(t).$$

In the early stages of the outbreak, when the susceptible population is not depleted, $S(t) \approx S_0$, hence

$$I(t+\Delta t) - I(t) = \gamma \Delta t \left[\frac{\beta}{\gamma} \frac{S_0}{N} - 1 \right] I(t).$$

An infections person remains infectious for time γ^{-1}. Hence, take $\gamma \Delta t = 1$ to get

$$I(t+\Delta t) - I(t) \approx \left[\frac{\beta}{\gamma} \frac{S_0}{N} - 1 \right] I(t) = (R_0 - 1) I(t),$$

hence $I(t+\Delta t) = R_0 I(t)$. This gives the required interpretation of R_0: $I(t)$ individuals infect $R_0 I(t)$ further individuals.

Early-stage Exponential Growth, Late-stage burn-out

From the previous slide, in the early stage of the outbreak when $S(t) \approx S_0$, we have

$$I(t_n) = R_0^n I(0), \qquad t_n = n\Delta t.$$

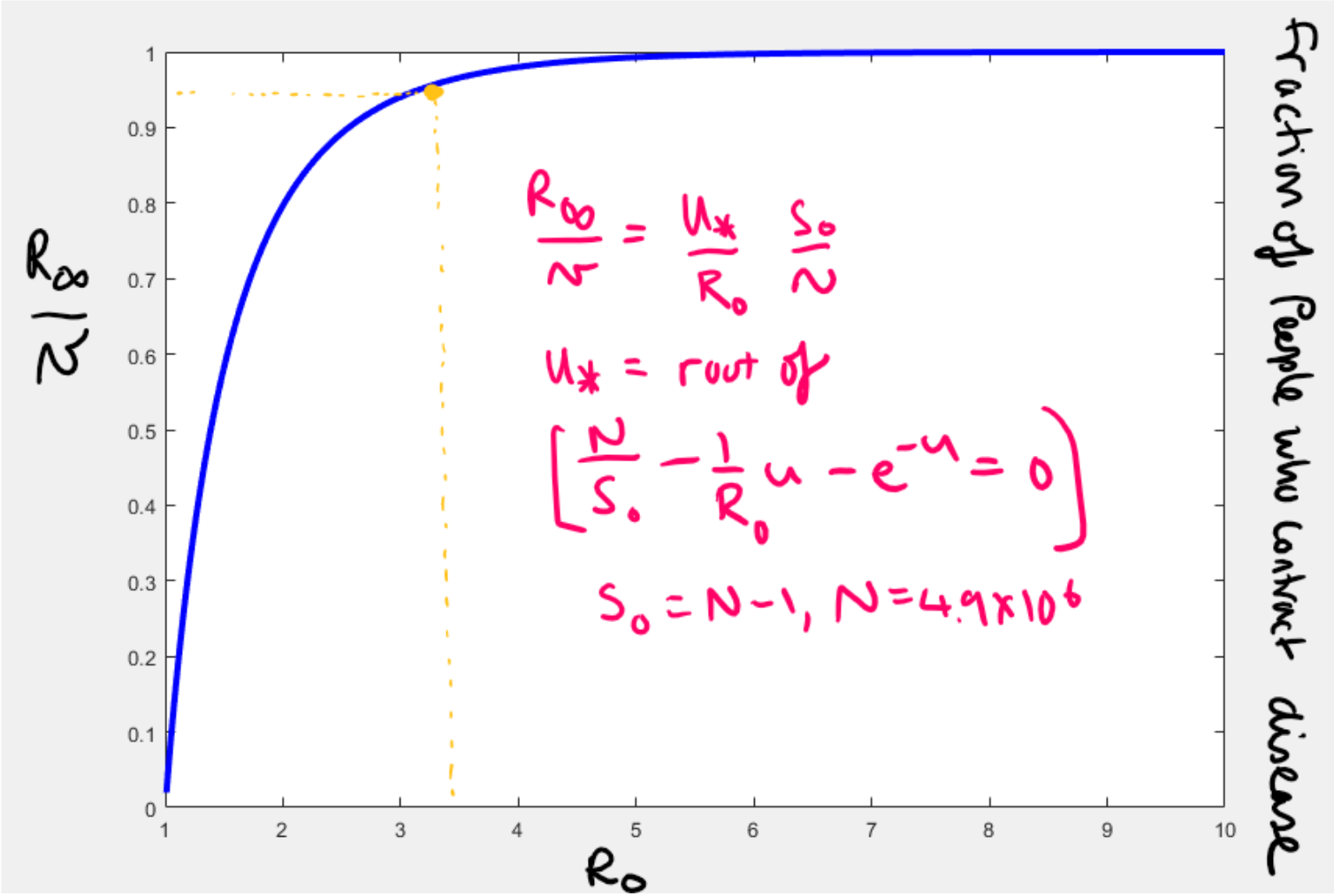
In the late stages of the outbreak, there are not very many people left to infect, and the epidemic burns out. **Not everybody catches the disease:** $S_\infty/N = 1 - (R_\infty/N)$, where

$$\frac{R_\infty}{N} = \frac{u_*}{R_0}\frac{S_0}{N},$$

and where u_* is the fixed point of $\mathrm{d}u/\mathrm{d}\tau = f(u; S_0/N, R_0)$.

The fact that not everybody catches the disease can be thought of as 'burn-out'.

Late-stage burn-out, continued



Vaccination Strategy

Suppose a vaccine for the disease exists. To control a future outbreak, we reduce the number of susceptible individuals from $S_0 = N - 1$ to

$$S_0 = N - \underbrace{1}_{\text{Patient Zero}} - \underbrace{fN}_{\text{Fraction of population vaccinated}}$$

Here, $0 < f < 1$. Starting-value for R_0 is:

$$R_0 = \frac{\beta}{\gamma}\frac{S_0}{N} = \frac{\beta}{\gamma}\frac{N-1}{N} \approx \beta/\gamma.$$

After mass vaccination, the new value is:

$$R_{eff} = \frac{\beta}{\gamma}(1-f).$$

To control the disease, we require a threshold value $R_{eff} = 1$ (ideally $R_{eff} < 1$). Therefore, the fraction of the population that needs to be vaccinated is $f = 1 - (1/R_0)$. When this number of people has been vaccinated we say **herd immunity** has been reached.

No Vaccine

In the absence of a vaccine, and with $S_0 = N - 1$, the way to control the spread of the epdiemic is to reduce $R_0 \approx \beta/\gamma$.

The parameter γ is fixed by biology, so we can only hope to control β.

Recall, $\mathrm{d}S/\mathrm{d}t = -(\beta/N)SI$. Hence, for a contagious disease β can be decomposed as

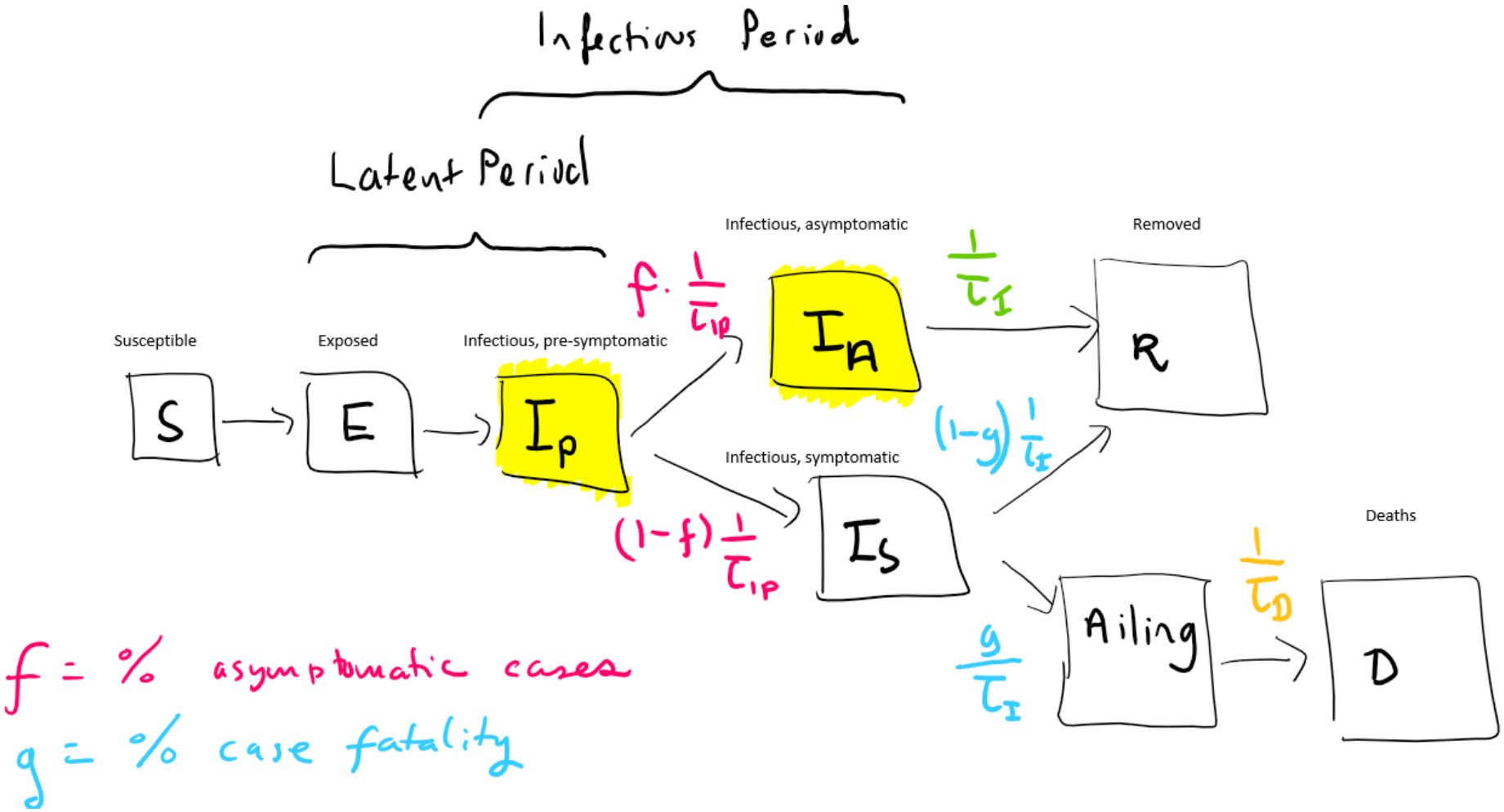
$$\beta = c \times p = (\text{Number of contacts of an individual per unit time}) \times (\text{Probability that a contact leads to infection})$$

Thus, the epidemic can be controlled by:

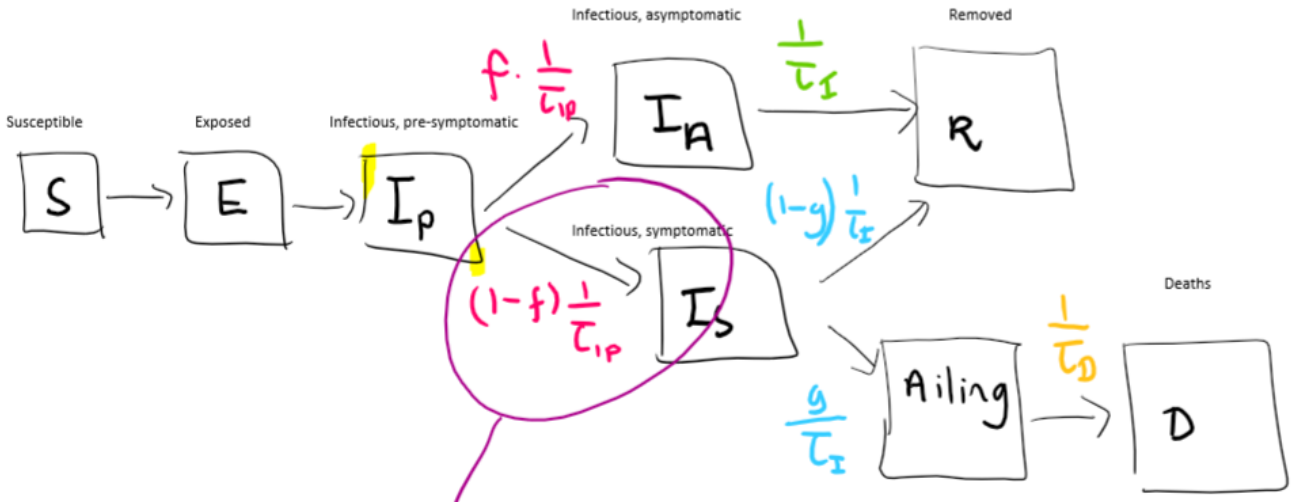
- Reducing contacts ($c \searrow$),
- Making contacts safer ($p \searrow$)

Extended Model for COVID-19

We introduce an extended compartmental model for SARS-CoV-2 (virus) / COVID-19 (disease). The virus has multiple timescales, which means the basic SIR model needs more compartments:



Diagnostic Compartments



$$\frac{d}{dt}(\#\text{ Waiting For Test}) = \left(\begin{array}{l}\text{Rate at which people}\\ \text{go into the } I_S\\ \text{compartment}\end{array}\right) - \left(\#\text{ Waiting for Test}\right) / \text{Waiting Time}$$

$$\frac{d}{dt}\left(\#\text{Confirmed}\right) = \frac{1}{\text{Waiting Time}}\left(\#\text{ Waiting for test}\right)$$

Equations

$$F = \frac{c\left(q_P I_P + q_A I_A + q_S I_S\right)}{N} = \text{force of infection}$$

$$\begin{aligned}
\frac{dS}{dt} &= -\frac{cS\left(q_P I_P + q_A I_A + q_S I_S\right)}{N}, \\
\frac{dE}{dt} &= \frac{cS\left(q_P I_P + q_A I_A + q_S I_S\right)}{N} - \frac{1}{\tau_E} E, \\
\frac{dI_P}{dt} &= \frac{1}{\tau_E} E - \frac{1}{\tau_{IP}} I_P, \\
\frac{dI_A}{dt} &= \frac{f}{\tau_{IP}} I_P - \frac{1}{\tau_I} I_A, \\
\frac{dI_S}{dt} &= \frac{1-f}{\tau_{IP}} I_P - \frac{1}{\tau_I} I_S, \\
\frac{dR}{dt} &= \frac{1}{\tau_I} I_A + \frac{1-g}{\tau_I} I_S.
\end{aligned}$$

Dynamic Model
6 eqns

$$\begin{aligned}
\frac{d}{dt}(\text{Ailing}) &= \frac{g}{\tau_I} I_S - \frac{1}{\tau_D}(\text{Ailing}), \\
\frac{dD}{dt} &= \frac{1}{\tau_D}(\text{Ailing}), \\
\frac{d}{dt}(\text{Awaiting Test}) &= \frac{1-f}{\tau_{IP}} I_P - \frac{1}{\tau_T}(\text{Awaiting Test}), \\
\frac{dC}{dt} &= \frac{1}{\tau_T}(\text{Awaiting Test}).
\end{aligned}$$

Diagnostic Compartments

Set-up

'Patient zero' introduced at $t = -t_{offset}$:

$$S(t = -t_{offset}) = N - 1 = (4.9 \times 10^6 - 1) - 1, \qquad I_P(t = -t_{offset}) = 1.$$

Then, $t = 0$ is the day of the first recorded case of COVID-19 in Ireland (Feb 29th).

- Model fitted to the 'first wave': from February 29th 2020 ($t_j = 0$) and ending on May 17th 2020 ($t_j = 76$)
- Transmission probabilities re-scaled: $\beta_0 = cq_p$, $i_A = q_A/q_P$, $i_S = q_S/q_P$.
- Effective value of β ($=\beta_j$) introduced to take account of public health-interventions:

$$\beta_j = \begin{cases} \beta_0, & j < 13 \\ \beta_1, & 13 \leq j < 28, \\ \beta_2, & j \geq 28. \end{cases}$$

Optimization

Penalty function:

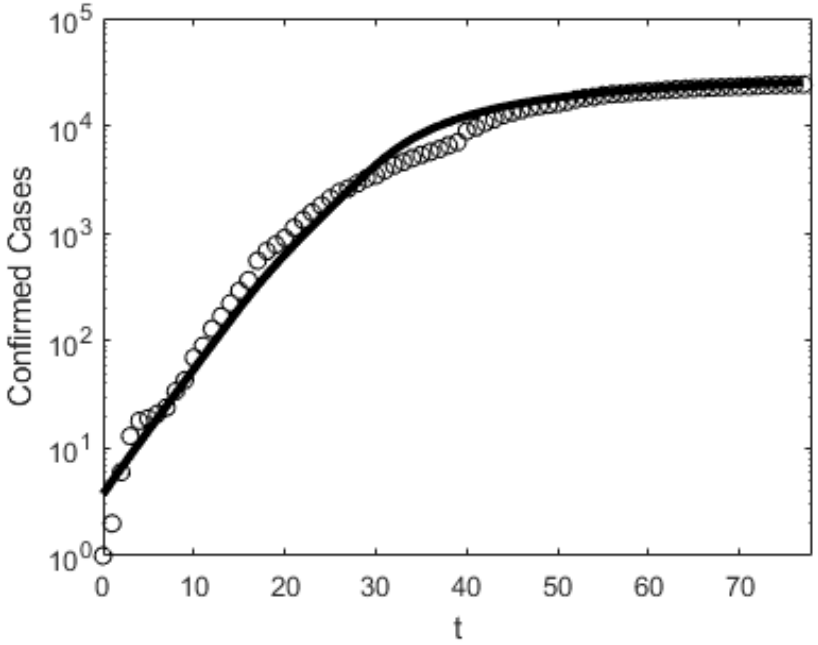
$$\Delta = \sum_{j=0}^{n} \left\{ \ln\left[C_{model}(t_j)\right] - \ln\left[C_{data}(t_j)\right] \right\}^2 + \sum_{j=0}^{n} \left\{ \ln\left(\frac{dC_{model}}{dt}\right)_{t_j} - \ln\left(\frac{dC_{data}}{dt}\right)_{t_j} \right\}^2$$
$$+ \sum_{j=j_{D1}}^{n} \left\{ \ln\left[D_{model}(t_j)\right] - \ln\left[D_{data}(t_j)\right] \right\}^2 + \sum_{j=j_{D2}}^{n} \left\{ \ln\left(\frac{dD_{model}}{dt}\right)_{t_j} - \ln\left(\frac{dD_{data}}{dt}\right)_{t_j} \right\}^2.$$

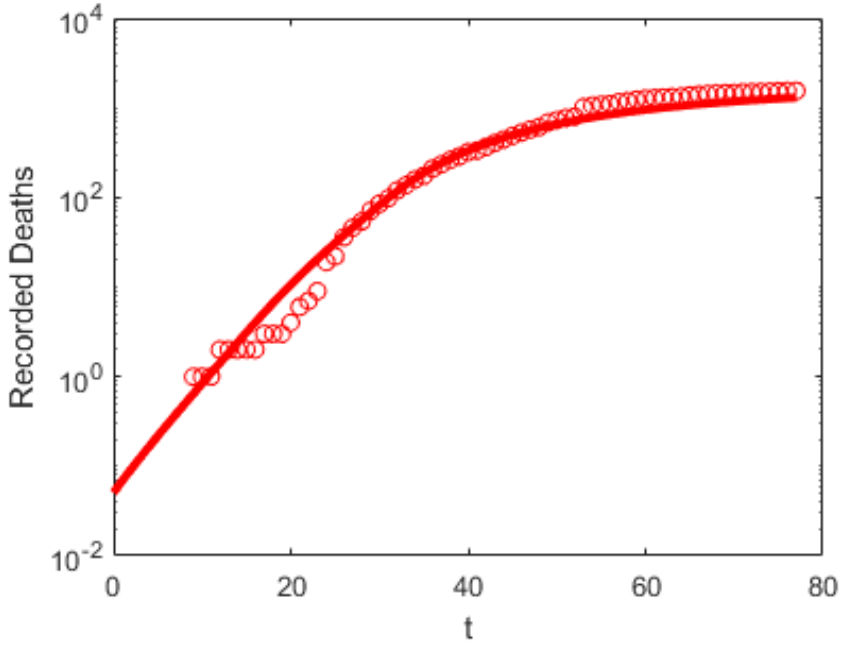
Optimization over parameters:

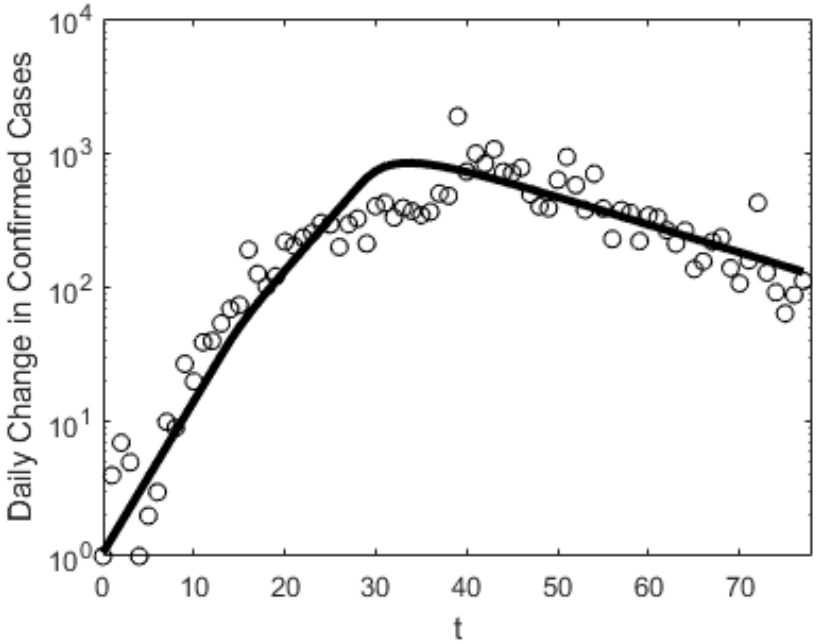
$$\Delta_0 = \min\left[\Delta\left(t_{offset}, \beta_0, \beta_1, \beta_2, f, g, \tau_E, \tau_{IP}, \tau_I, \tau_D, i_A, i_S\right)\right]$$

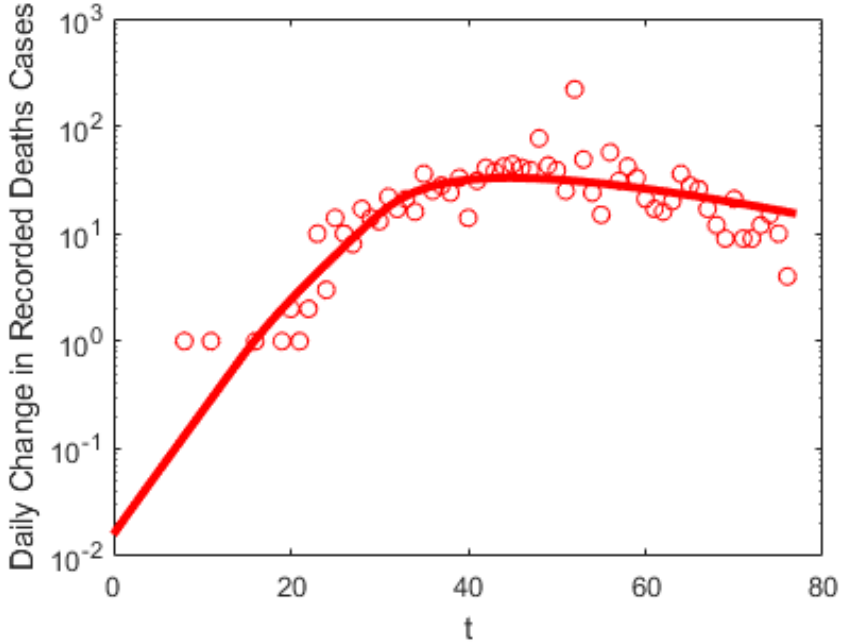
- Bounds on the search space are obtained from medical literature on COVID-19
- Optimization performed using MATLAB's simulated annealing method:
  - Initial guess
  - New draws; each draw involves solving the ODE system for selected parameters
  - A new draw is accepted if it lowers Delta,
  - A new draw is accepted with a certain probability if it increases Delta, this is to stop the algorithm getting stuck in local minima
  - Standard convergence criteria, these are checked for robustness

Results


Confirmed Cases
t


Recorded Deaths
t


Daily Change in Confirmed Cases
t


Daily Change in Recorded Deaths Cases
t

Confidence Intervals

Confidence intervals on the results are generated by bootstrapping. Significant spread in values, especially for fraction asymptomatic.

Table A.3: Optimal parameter values corresponding to the optimization problem (6). The reported confidence intervals use $n_{bootstrap} = 1000$.

	t_{offset} (days)	β_0 $(\text{days})^{-1}$	β_1 $(\text{days})^{-1}$	β_2 $(\text{days})^{-1}$	f	g	τ_E (days)
Lower Bound	7.9057	1.4679	0.9524	0.3205	0.2245	0.0500	3.6257
Best Estimate	9.9831	1.4695	1.1009	0.3576	0.3084	0.0599	3.7486
Upper Bound	9.9936	1.6961	1.2201	0.3908	0.4445	0.0614	3.7976

	τ_{IP}	τ_I	τ_D	τ_T	i_A	i_S
Lower Bound	1.1394	1.9160	14.9812	3.3146	0.3303	0.2741
Best Estimate	1.2938	2.1738	15.2210	3.8911	0.4096	0.3405
Upper Bound	1.3841	2.4337	16.5007	5.2055	0.4758	0.4367

R_0 for a multi-compartment model

R_0 can be computed for a multi-compartment model, in analogy with a simple SIR model. But now it is more difficult:

$$\frac{d}{dt}\delta\underline{x} = J\,\delta\underline{x}$$

around $\underline{x}_0 = (N, 0, 0, \dots)$

$$\frac{d}{dt}\begin{pmatrix}\delta E\\ \delta I_1\\ \vdots\\ \delta I_n\end{pmatrix} = \begin{pmatrix} & & \\ & & \\ & & \end{pmatrix}\begin{pmatrix}\delta E\\ \delta I_1\\ \vdots\\ \delta I_n\end{pmatrix} = (F - V)\begin{pmatrix}\delta E\\ \delta I_1\\ \vdots\\ \delta I_n\end{pmatrix}$$

Notice

$R_0 \propto \beta_0$ .. $\frac{dS}{dt} = -\beta_0 \frac{S}{N} \sum_j I_j$.

$R_0 = \max \text{spec}\,(FV^{-1})$

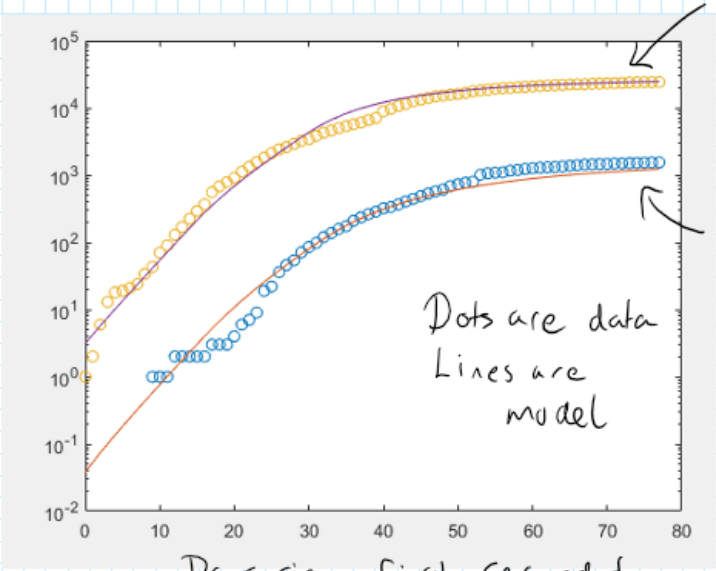
For the model, the matrices F and V are given by:

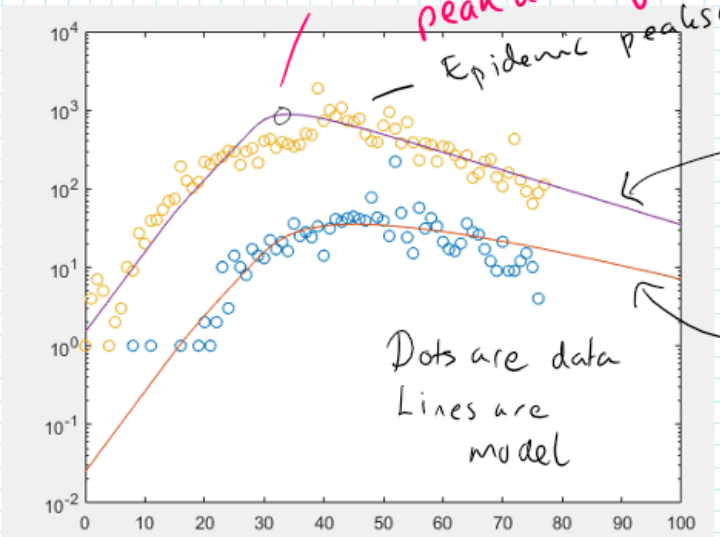
$$F = \begin{pmatrix} 0 & \beta_0 & \beta_0 i_A & \beta_0 i_S \\ 0 & & 0 & 0 \\ 0 & & 0 & 0 \\ 0 & & 0 & 0 \end{pmatrix} \qquad V = \begin{pmatrix} \tau_E^{-1} & 0 & 0 & \\ -\tau_L^{-1} & \tau_{IP}^{-1} & 0 & 0 \\ 0 & -f\tau_{IP}^{-1} & \tau_I^{-1} & 0 \\ 0 & 0 & -(1-f)\tau_{IP}^{-1} & \tau_I^{-1} \end{pmatrix},$$

hence

$$R_0(\beta_0, i_S) = \beta_0 \left(\tau_{IP} + i_A f \tau_I + f(1-f) i_S \frac{\tau_I^2}{\tau_{IP}} \right).$$

R_0 for a multi-compartment model – Results





Parameters of epidemic

$R_0 = 3.6$ ... without case isolation

$R_0 = 2.6$ ... with case isolation

$R_0 = 1.8$ ... with case isolation + schools closed

$R_0 = 0.67$ .. with case isolation + lockdown

f

Fraction asymptomatic: 0.2

(prior assumption is $0.1 < f < 0.5$)

Confidence Intervals

Table A.4: Estimates of the basic reproduction number and the effective reproduction number under various NPIs, with lower and upper bounds generated from the confidence intervals in Table A.3.

Intervention	β (Best Fit)	i_S (Best Fit)	$R_0(\beta, i_S)$ (Lower Bound)	$R_0(\beta, i_S)$ (Best Fit)	$R_0(\beta, i_S)$ (Upper Bound)
No interventions, basic reproduction number	1.4695	1	2.7664	3.4495	4.9079
Case isolation, no other interventions	1.4695	0.3405	2.0798	2.6945	3.7549
Case isolation, schools and universities are closed, mass gatherings are banned	1.1009	0.3405	1.2880	2.0187	2.7204
Case isolation, all non-essential services and industries closed, travel restrictions	0.3576	0.3405	0.4847	0.6557	0.8324

Extremes

Vaccination strategy: $f = 1 - \frac{1}{R_0} \simeq 71\%$

Acknowledgment

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Original Research Article

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Part 2: Pharmacokinetics

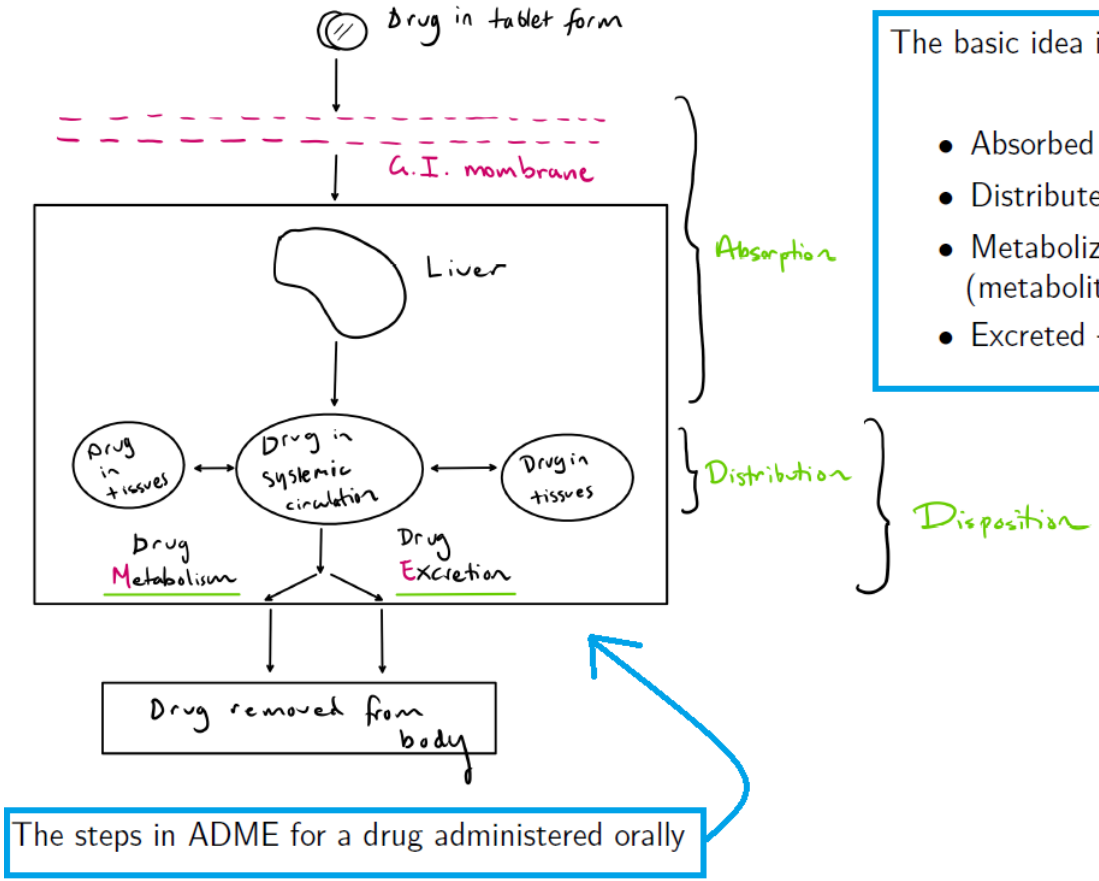
Overview:

- Pharmacokinetics (PK) is the study of what the body does to a drug.
- Pharmacodynamics (PD) is the study of what the drug does to a body.
- PK answers questions such as – what drug dose should be given to a patient, and at what interval?
- Uses Ordinary Differential Equations to describe how the drug concentration in the plasma decreases over time.
- The four processes that need to be accounted for are: ADME.

The plan of **Part 2** is to give an overview of this modelling approach.

ADME

The process of ADME is shown schematically in the figure in the case of **oral administration**.



The basic idea in PK is ADME: a drug administered to the body is:

- Absorbed – the drug is absorbed into the bloodstream;
- Distributed – distribution to the various tissues in the body;
- Metabolized – the breakdown of a drug into other compounds (metabolites) in the liver;
- Excreted – elimination through the liver and/or kidneys.

The amount of the drug in the systemic circulation is of key interest, this is what is modelled in Part 2.

Plasma Concentration

The total amount of drug in the body (A_B) is what is modelled. But it can't be measured directly. Instead, what is measured is the volume of drug in the plasma (a measure of the volume of the drug in the systemic circulation).

$$Cp(t) = \frac{A_B}{V_{eff}}$$

Here, V_{eff} is an 'effective volume' called the 'volume of distribution', more commonly denoted by V_d.

'One-Compartment Model' – Oral Administration

In oral administration, the drug has to pass through the gastro-intestinal (GI) tract before making it to the circulation. The drug concentration in the GI tract is governed by first-order kinetics:

$$\frac{\mathrm{d}A_{GI}}{\mathrm{d}t} = -k_a A_{GI},$$

where $A_{GI}(t=0) = S \cdot F \cdot D$, where:

- S is the salt factor;
- F is the bioavailability – not all of the drug that passes the GI membrane
- D is the dose.

Thus,

$$A_{GI}(t) = (S \cdot F \cdot D)\mathrm{e}^{-k_a t}.$$

A_{GI} gets fed into the systemic circulation

The amount A_{GI} gets passed into the body – assuming a one-compartment model for the systemic circulation, the amount of drug in the body at time t now satisfies:

$$\frac{\mathrm{d}A_B}{\mathrm{d}t} = \underbrace{k_a A_{GI}}_{\text{Source Term}} - kA_B, \tag{1}$$

where the source term represents the rate at which the drug passes from the GI tract into the body (plasma).

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$$A_B(0) = 0.$$

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Solution (ODE):

$$A_B(t) = \frac{k_a}{k_a - k}\left(S \cdot F \cdot D\right)\left(\mathrm{e}^{-kt} - \mathrm{e}^{-k_a t}\right).$$

The model is used on patient data

Time (h)	Cp (mg/L)
0	0
0.6	2.74
0.8	3.13
1	3.37
1.4	3.55
1.8	3.5
2	3.43
2.6	3.12
3	2.89
4	2.33
7	1.17
12	0.37

Plasma concentration of a drug at various times after the adminstration of a 100-mg oral dose

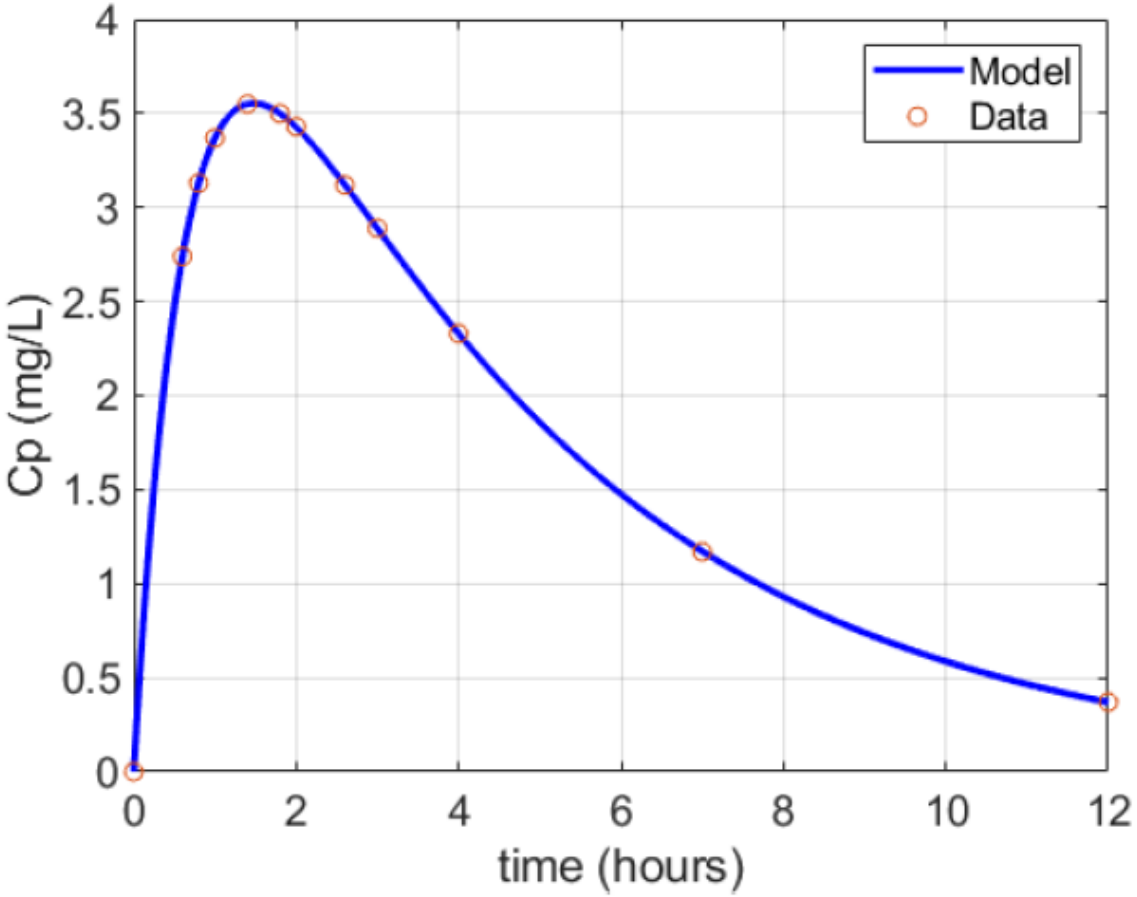
Using nonlinear-least squares, we introduce a penatly function as in Chapter 4 (we use $\phi = V_d/F$

$$J(k_a, k, \phi) = \sum_{i=0} \left[\log(Cp_{model}(t_i) + \epsilon) - \log(Cp_{data}(t_i) + \epsilon)\right]^2,$$

```
function [ka,k,Vd_F]=get_params()

[t_data,Cp_data]=get_data();
% Dose is given.
D=100;

% Create an anonymous function handle to the MATLAB file.
f = @(x)mycost(x);

% Initial guess - ka,k,Vd_F
x0 = [2,0.1,20];

lb=[0,0, 0];
ub=[10,10,200];

options = optimoptions('fmincon','Display','iter');
[x, fval] = fmincon(f,x0,[],[],[],[],lb,ub,[],options);

ka=x(1);
k=x(2);
Vd_F=x(3);

t=0:0.01:t_data(end);
Cp_model=(ka/(ka-k))*(D/Vd_F)*(exp(-k*t)-exp(-ka*t));
plot(t,Cp_model,t_data,Cp_data,'o')
drawnow
```

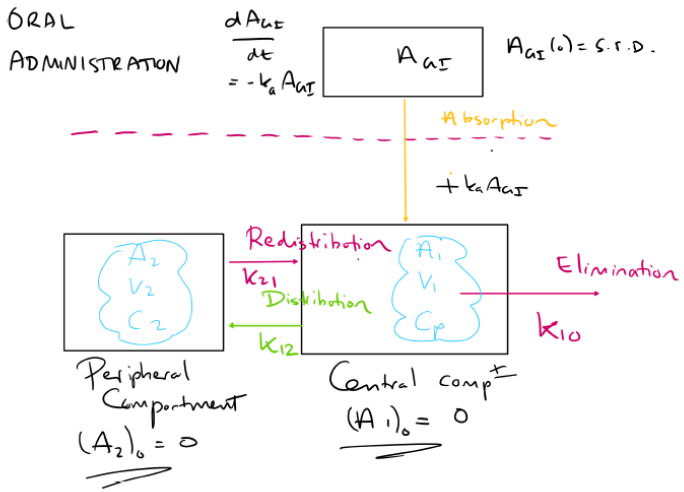
Results

The results are good and enable estimation of the PK parameters.

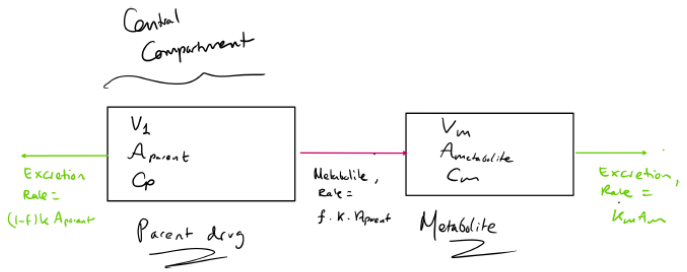


Parameter	Value
k_a	$1.50\,\text{hours}^{-1}$
k	$0.23\,\text{hours}^{-1}$
V_d/F	$20.0\,\text{L}$

Other models we will look at:

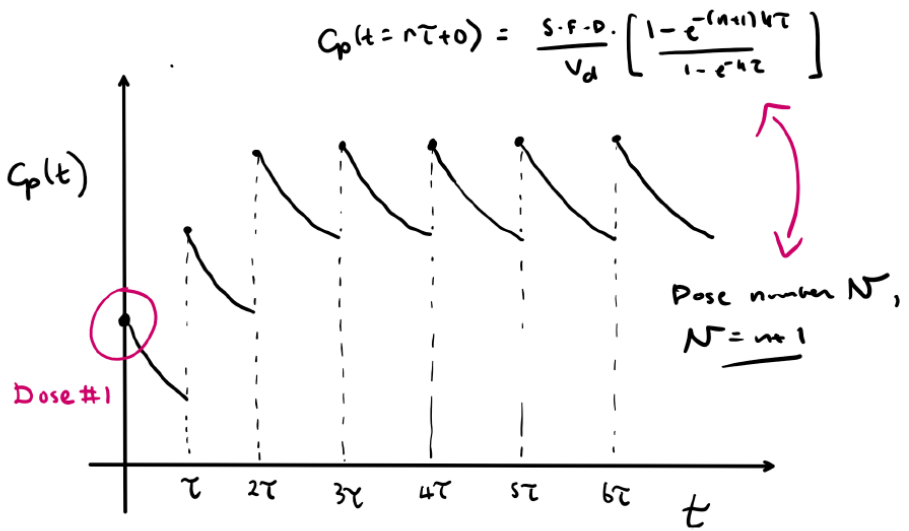


Mass balances for the two-compartment model (oral administration)



Mass balances for the metabolite model (IV administration)

$$\frac{\mathrm{d}A_{parent}}{\mathrm{d}t} = -kA_{parent},$$
$$\frac{\mathrm{d}A_{metabolite}}{\mathrm{d}t} = fkA_{parent} - k_m A_{metabolite}.$$



Main Projects:

- To main projects on Epi and two main projects on PK.
- All main projects start with the typed lecture notes:
  - Follow notes.
  - Follow recorded lectures.
- Two main project son Epi:
  - Initial tasks involve theoretical analysis of models;
  - Final task involves applying the models to a dataset.
- The same concept for the main projects on PK.
- All materials on module website:

  https://maths.ucd.ie/∼onaraigh/CSMM.html