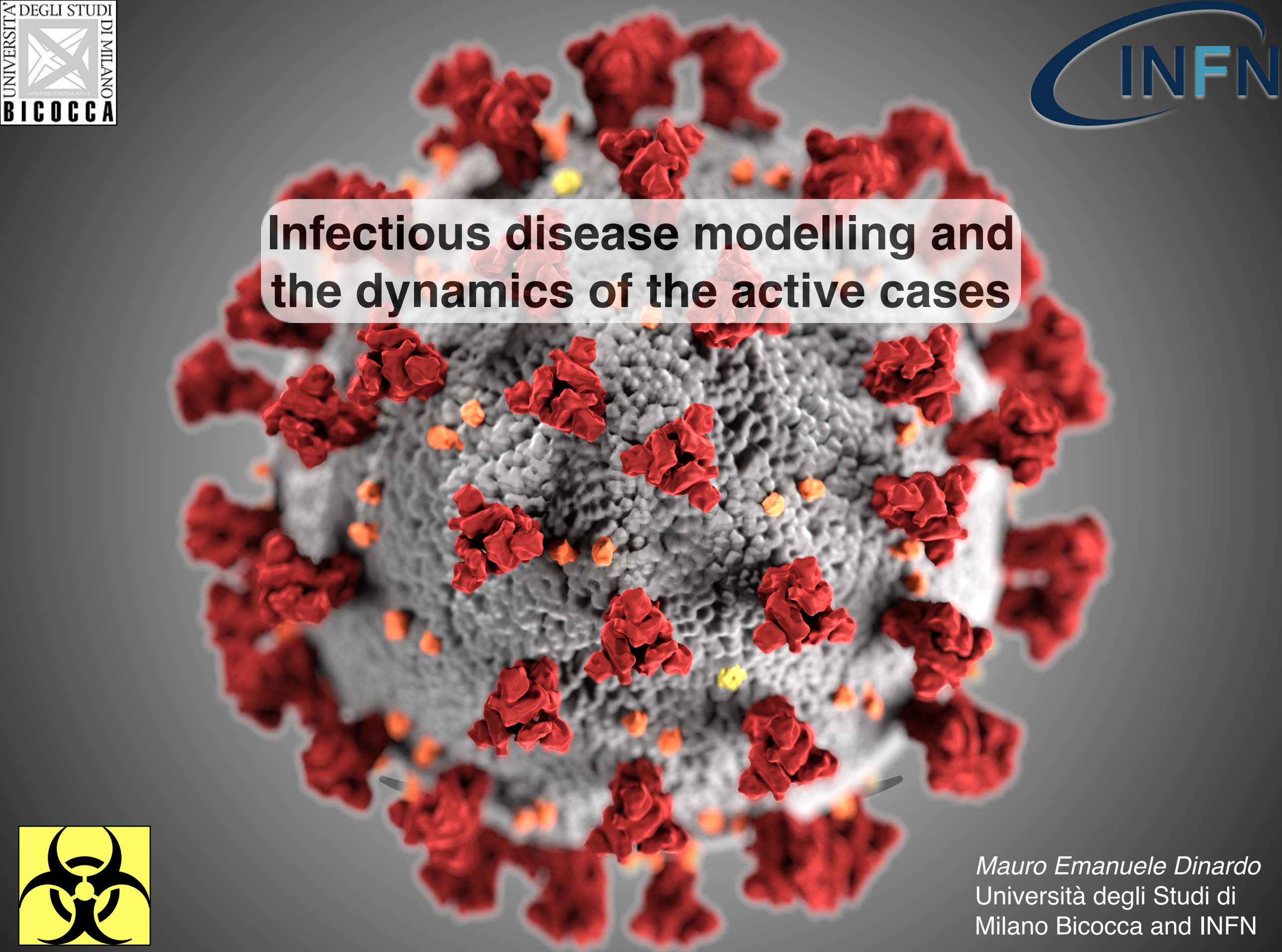
Infectious disease modelling and the dynamics of the active cases



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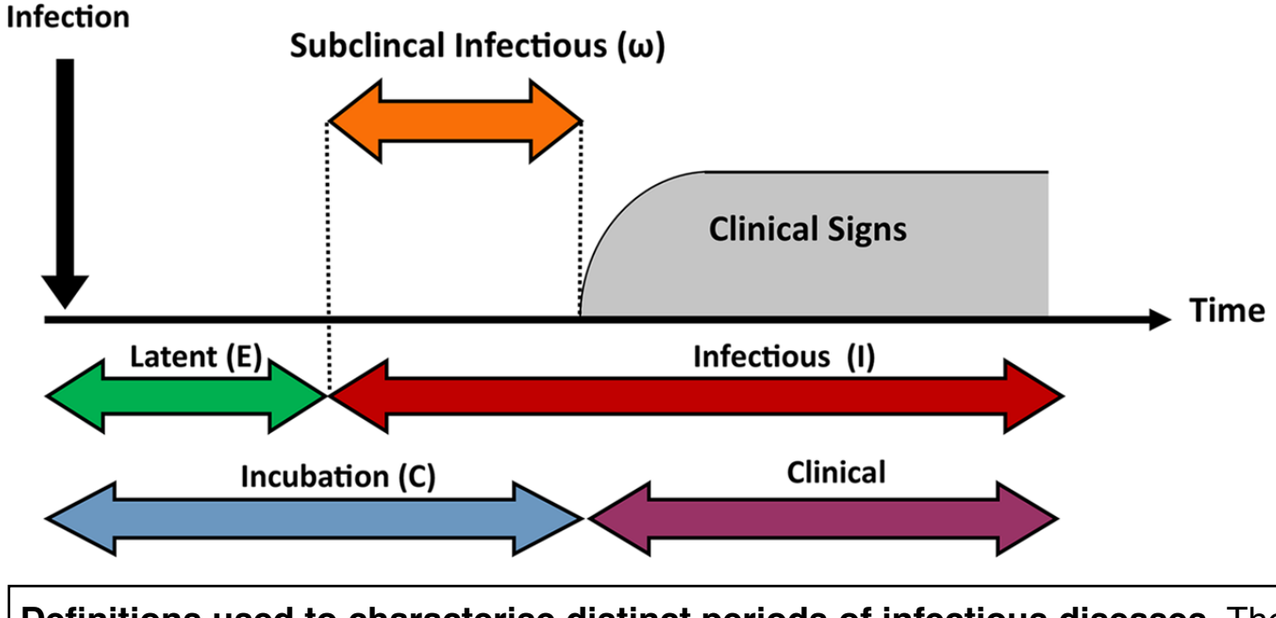
Introduction

Goal: we want to describe the dynamics of the spread of a disease among a population, in particular we are interested in the development of infected active cases

Basic assumptions:

- the disease can spread to other individuals from the infected ones
- the infected individuals can recover (either survive or die)
- recovered individuals can not become re-infected
- both symptomatic and asymptomatic cases are considered
- the system is closed (no “natural” demographic change)



Definitions used to characterise distinct periods of infectious diseases. The latent period (**E; green arrow**) begins at the time of infection and ends at the onset of the infectious period. (**I; red arrow**). The incubation period (**C; blue arrow**) starts at the time of infection and ends at the appearance of clinical signs of disease (**purple arrow**). The difference between incubation and latency is denoted by ω (omega), and can have either a positive or negative value depending on whether transition to the infectious period occurs before or after appearance of clinical signs. The ratio of transmission occurring during incubation, and transmission occurring through the total infectious period is denoted by θ (theta; not shown)

The model

The model describe the dynamics of the number of infected active cases, i.e. the total number of currently infected individuals as a function of time

Finite difference model of infected population growth:

$$N_{n+1} = N_n + \underbrace{N_n\ K\ p\ q}_{\textit{Increment}} - \underbrace{N_n\ r}_{\textit{Decrement}}$$

Definition of the different terms:

- N_n: number of active cases at time n

- K: average number of encountered people by one infected individual. Another way to interpret K is: $K = (1-Q) \times k$, where Q is the fraction of active cases which are in quarantine and k is the average number of encountered people by one infected individual

- p: probability to spread the disease from one individual to another

The model

- **q**: probability that that the new individual doesn't have already the antibodies. This probability is equal to **1** minus the probability of being infected, which can be derived from $\mathbf{N_n}$ and it's equal to:

$$\frac{N_n + r\sum_{i=0}^{n-1} N_i}{C}$$, where **C** is the carrying capacity

- **r**: recovery rate (either to survive or die) ➜ related to the average recovery time through the relation **τ = 1/r**

Final formulation of the model:

$$N_{n+1} = N_n + N_n Kp\left(1 - \frac{N_n + r\sum_{i=0}^{n-1} N_i}{C}\right) - N_n r$$

The basic reproduction number, $\mathbf{R_0}$, and the effective reproduction number, $\mathbf{R_n}$ at time n, as referred in epidemiology, are $\mathbf{R_0 = Kp/r}$ and $R_n = Kp\left(1 - \frac{N_n + r\sum_{i=0}^{n-1} N_i}{C}\right)\Big/ r$, respectively

The model

From the finite difference equation we can construct the differential equation:

$$\frac{dN(t)}{dt} = N(t)Kp\left(1 - \frac{N(t) + r\int_0^t N(t')dt'}{C}\right) - N(t)r$$

The integral-differential equation can not be solved in a closed form ➜ it has to be treated numerically (**`Kp`**, i.e. the growth rate will be denoted **`g`**)

Refining the carrying capacity

The carrying capacity, **`C`**, does not correspond to the total population of the system, **`T`**, but it's rather a subset that should evolve together with the number of infected people. In fact if the disease spreads out from a certain region, the probability that the individual encountered by an infected one doesn't have already the antibodies, **`q`**, can not be computed as the ratio of the total number of non infected individuals over **`T`**, because the encountered individual is not extracted uniformly from **`T`**, but rather from a subset which is "close" to the subset of infected individuals

The model

Final system of equations:

$$\begin{cases} N_{n+1} = N_n + N_n Kp\left(1 - \dfrac{N_n + r\sum_{i=0}^{n-1} N_i}{C_n}\right) - N_n r \\ C_{n+1} = C_n + \left(N_{n+1} - N_n(1-r)\right)K\left(1 - \dfrac{C_n}{T}\right) \end{cases}$$

Differential form:

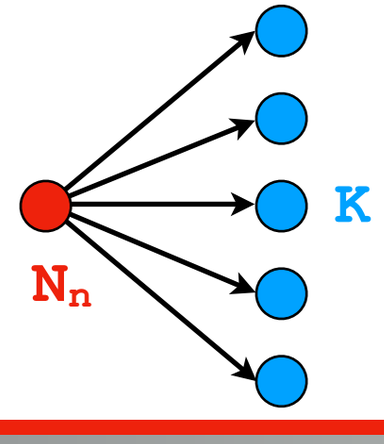
$$\begin{cases} \dfrac{dN(t)}{dt} = N(t)Kp\left(1 - \dfrac{N(t) + r\int_0^t N(t')dt'}{C(t)}\right) - N(t)r \\ \dfrac{dC(t)}{dt} = \left(\dfrac{dN(t)}{dt} + N(t)r\right)K\left(1 - \dfrac{C(t)}{T}\right) \end{cases}$$

Which derives from:

$C_{n+1} = C_n + N_n Kp\left(1 - \dfrac{N_n + r\sum_{i=0}^{n-1} N_i}{C_n}\right)K\left(1 - \dfrac{C_n}{T}\right)$, in turns the carrying capacity is the total number of encountered individuals by the infected ones, in fact the increment of the carrying capacity depends upon the new infected cases, N_n **K p q**, each of which encounter **K** number of individuals, times the probability of not being already accounted for

N.B. the term **Kp** is estimated from a fit to the data, while **p** is estimated with the following multi-period dataset optimisation criteria:

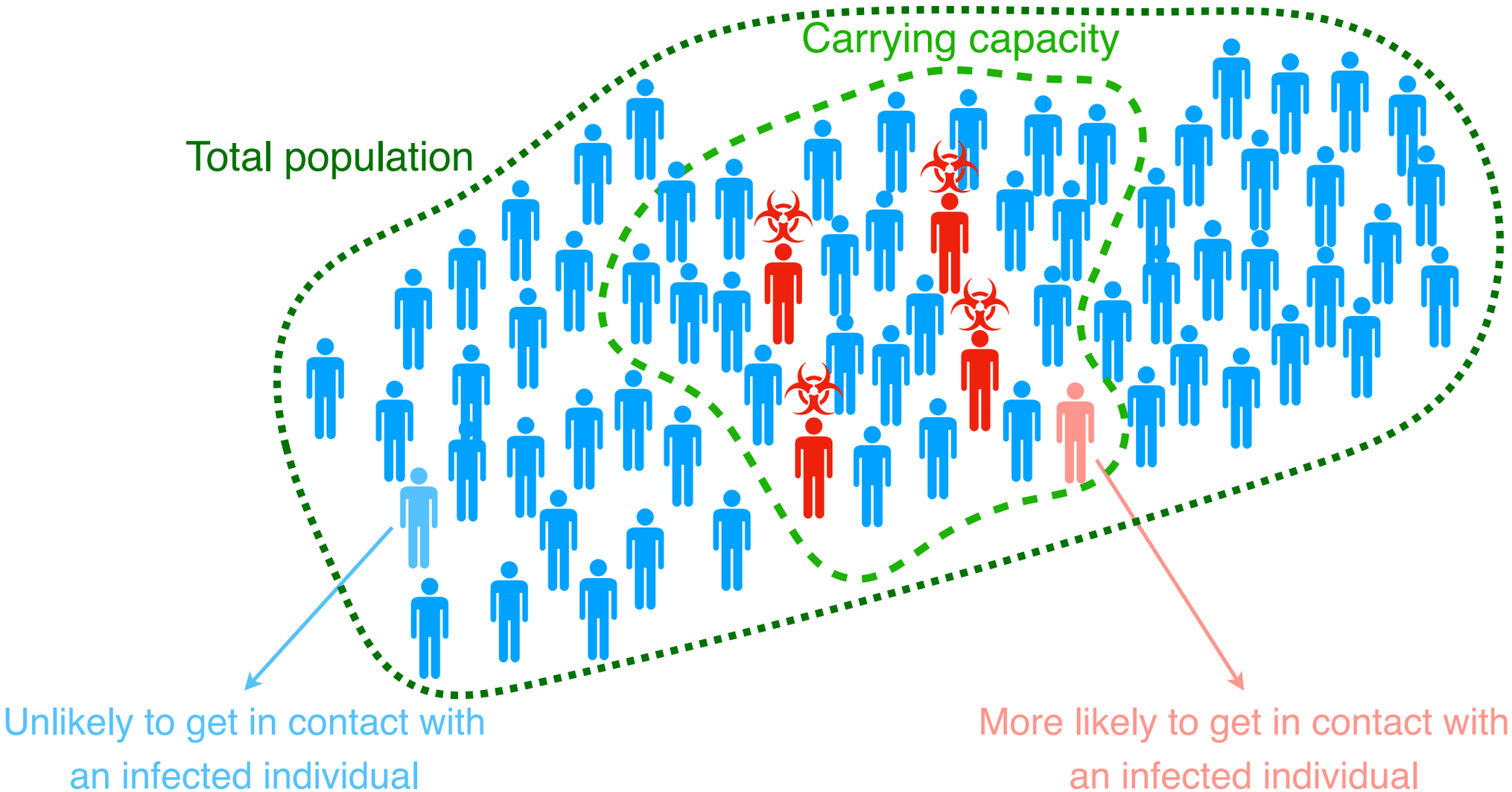
- best χ^2/d.o.f.
- coherence of carrying capacity evolution across periods



The model

Final system of equations:

$$\begin{cases} N_{n+1} = N_n + N_n Kp\left(1 - \dfrac{N_n + r\sum_{i=0}^{n-1} N_i}{C_n}\right) - N_n r \\ C_{n+1} = C_n + \left(N_{n+1} - N_n(1-r)\right)K\left(1 - \dfrac{C_n}{T}\right) \end{cases}$$

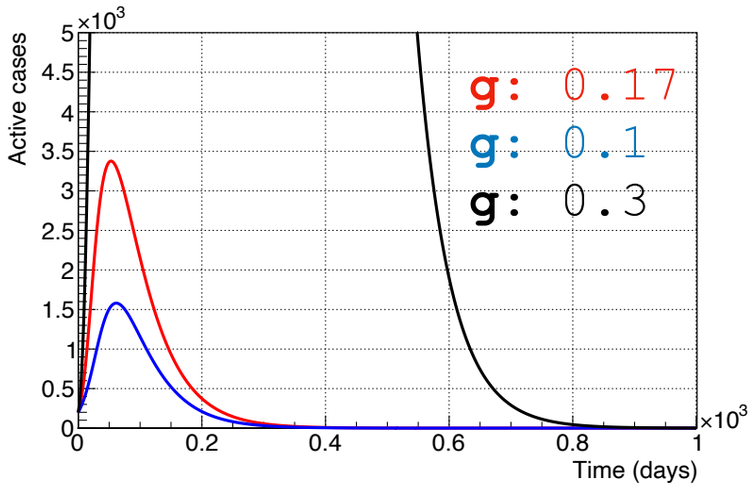


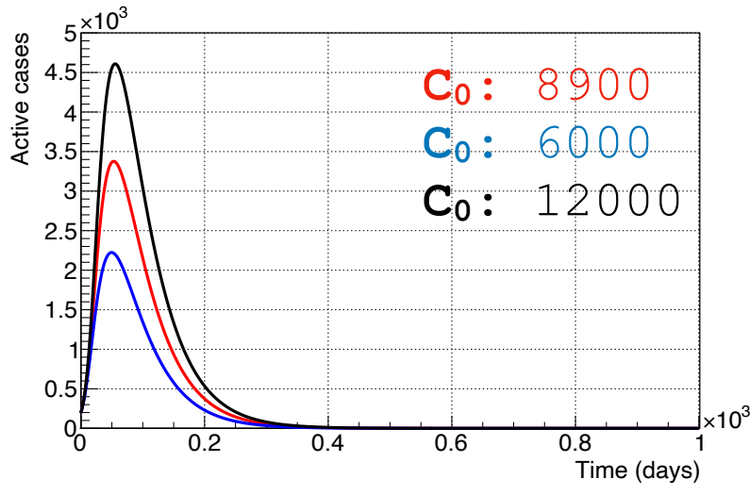
The model

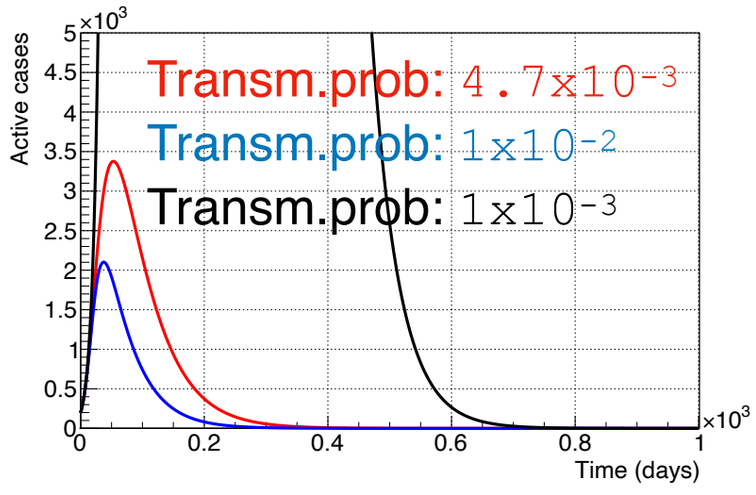
Impact of the different parameters on the model

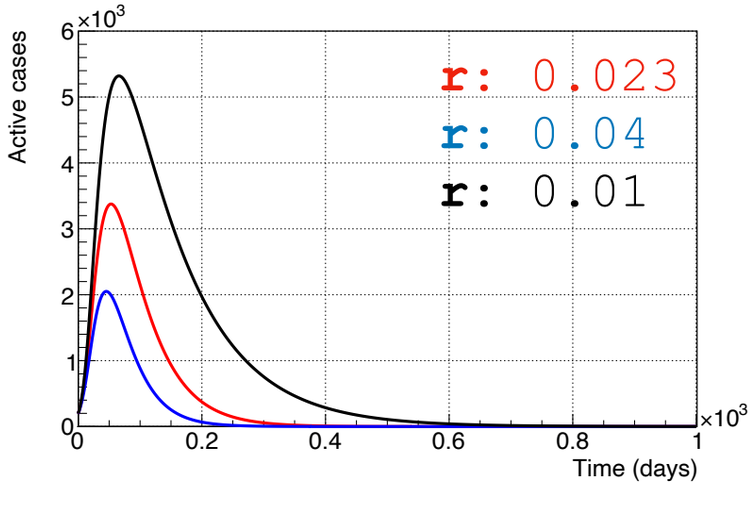
Default model parameter values:

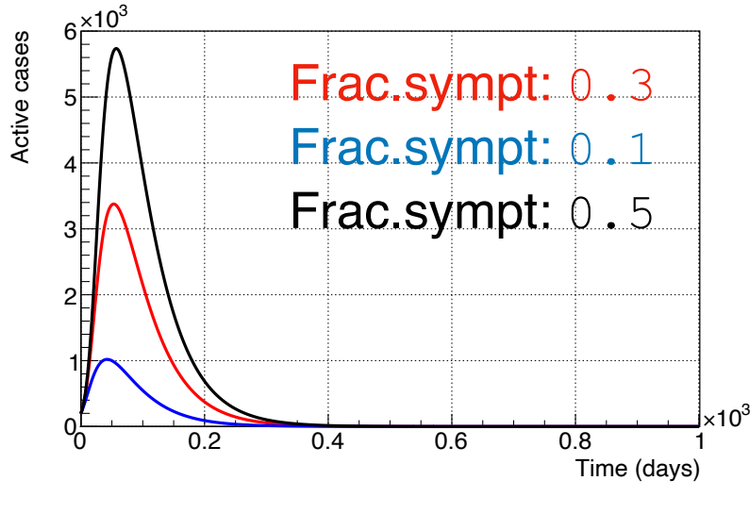
- N_0 (initial population): 200
- **g**: 0.17
- C_0: 8900
- **r**: 0.023
- **Total population**: 60×10^6
- **Frac.sympt**: 0.3
- **Transmission prob.**: 4.7×10^{-3}

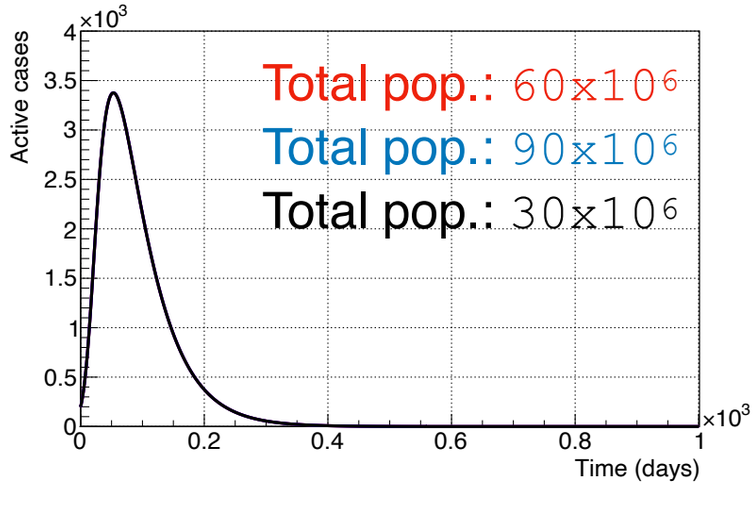












The model

The model is very similar to the S.I.R. model (**S**usceptible, **I**nfected, **R**ecovered from `Kermack` and `McKendrick, 1927`), in fact:

$$\begin{cases} \frac{dS}{dt} = -\beta \frac{IS}{N} \\ \frac{dI}{dt} = \beta \frac{IS}{N} - \gamma I \\ \frac{dR}{dt} = \gamma I \end{cases}$$

We can identify `β` with **`Kp`**, `γ` with **`r`**, `N` with **`C`**, `I(t)` with **`N(t)`**, and `S(t)` with

$$C - \left(N(t) + r \int_0^t N(t')dt' \right)$$

The key difference is that the model takes into account the non uniform spread of the disease with the equation:

$$C_{n+1} = C_n + \left(N_{n+1} - N_n(1-r) \right) K \left(1 - \frac{C_n}{T} \right)$$

Probability of being infected

Derivation of the coefficient **q** for the model of infected active cases

- The term **q** is equal to **1** minus the probability of being infected
- The probability of being infected can be derived from $\mathbf{N_n}$ and it's equal to the sum of the terms $N_i\tilde{K}$ divided by **C** (**K-tilde** is just a short writing for the product **K p q**)

$$
\begin{aligned}
&N_0 \\
&N_1 = N_0 + N_0\tilde{K} - rN_0 \\
&N_2 = N_1 + N_1\tilde{K} - rN_1 \\
&N_3 = N_2 + N_2K - rN_2 \\
&\dots
\end{aligned}
\quad\Rightarrow\quad
\begin{aligned}
&N_0 \\
&N_0\tilde{K} = N_1 - N_0 + rN_0 \\
&N_1\tilde{K} = N_2 - N_1 + rN_1 \\
&N_2K = N_3 - N_2 + rN_2 \\
&\dots
\end{aligned}
$$

Summing up all the terms and simplifying, we obtain:

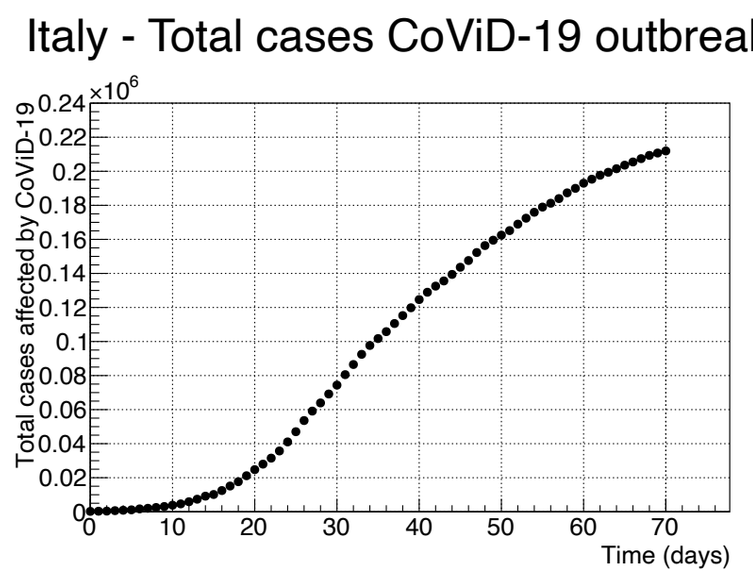
$$q = 1 - \frac{N_n + r\sum_{i=0}^{n-1} N_i}{C}$$

Terminology

Just for completeness we would like to relate the equation to typical plots shown in epidemiology

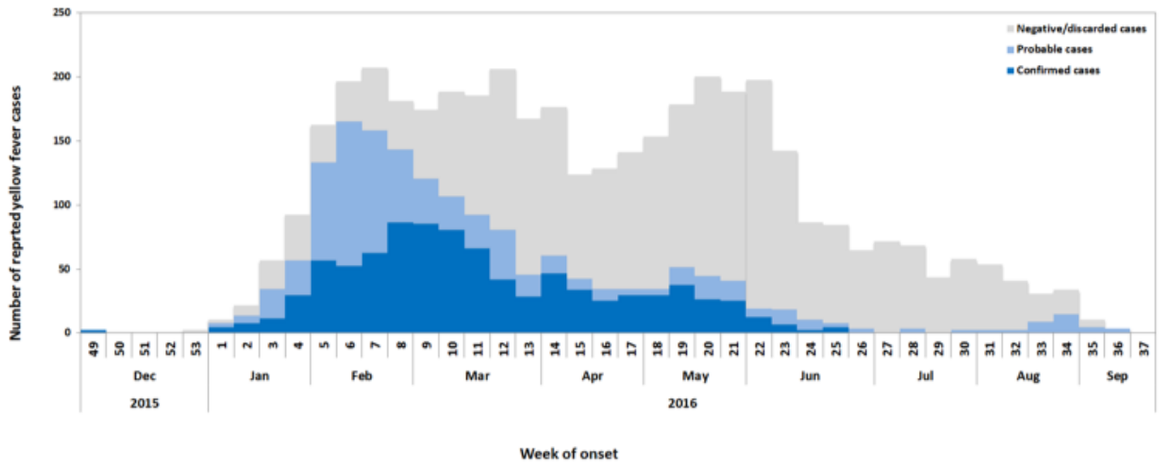
$$N_{n+1} = N_n + N_n K p q - N_n r$$

- The sum $\sum_n N_n K p q$ represent the total cases, i.e. the cumulated number of infected case as a function of time



- The derivative of the total cases, i.e. the term $N_n K p q$, represents the so called epidemic curve, i.e. the curve that shows the number of cases at the time of disease onset

- The term N_n itself instead represent the so called active cases, i.e. the total number of currently infected individuals as a function of time



Data source: Data as of 15 September 2016. Data for the past four weeks are subject to revision pending ongoing investigation and reclassification.

Model parameters

Parameter name	Symbol	Derivation
Recovery rate	**r**	Data plot Δrecovered/active cases
Growth rate	**g**, i.e. **KP**	Fit to the data
Transmission probability	**p**	χ^2/d.o.f. scan + coherence of carrying capacity evolution across periods
Fraction of symptomatic	N.A.	Obtained from literature
Total population	**T**	Demography
Initial conditions	N_0 and C_0	Fit to the data

Summary

- Three free floating parameters during the fit (**g**, N_0, C_0)
- One parameter is determined by χ^2/d.o.f. scan (**p**)
- One parameter determined from data plot (**r**)
- Two parameters determined from literature (**T**, fraction of symptomatic)

Application to data: **Italy - 3/5/2020**

We will present results obtained from different refinements of the analysis:

1. Fit to single, self-consistent, time periods
2. Fit to multiple time-periods simultaneously
3. Fit to multiple time-periods, considering also data smearing

History CoViD-19 Italy 2020

- Friday 21st February ➜ Codogno become red zone
- Monday 24th February ➜ Data recording starts
- Wednesday 4th March ➜ Lock down schools and universities
- Sunday 8th March ➜ Lombardy isolated
- Tuesday 10th March ➜ Restrictions on movements
- Monday 23rd March ➜ Total lock down

- Start period **1**
- Start period **2**
- Start period **3**
- Start period **4**

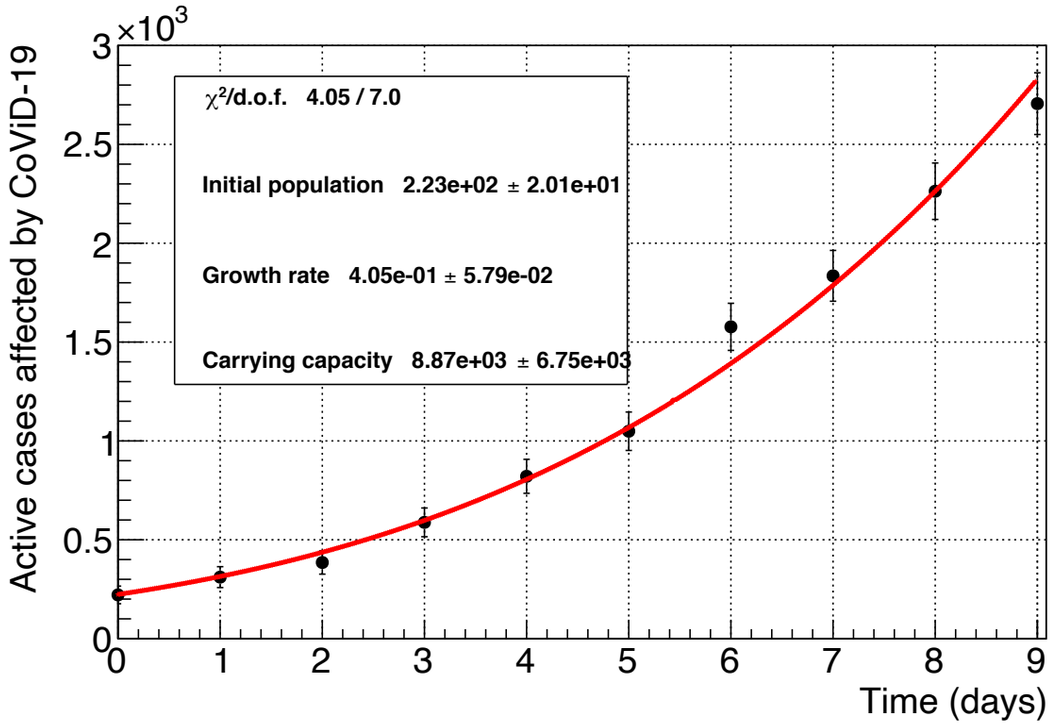
Some references:

- Fraction of asymptomatic:
  - ★ https://www.repubblica.it/salute/medicina-e-ricerca/2020/03/16/news/coronavirus_studio_il_50-75_dei_casi_a_vo_sono_asintomatici_e_molto_contagiosi-251474302/

- Latent/incubation period:
  - ★ https://www.internazionale.it/notizie/graham-lawton/2020/03/26/sintomatici-diffondono-virus

  - ★ https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30746-7/fulltext

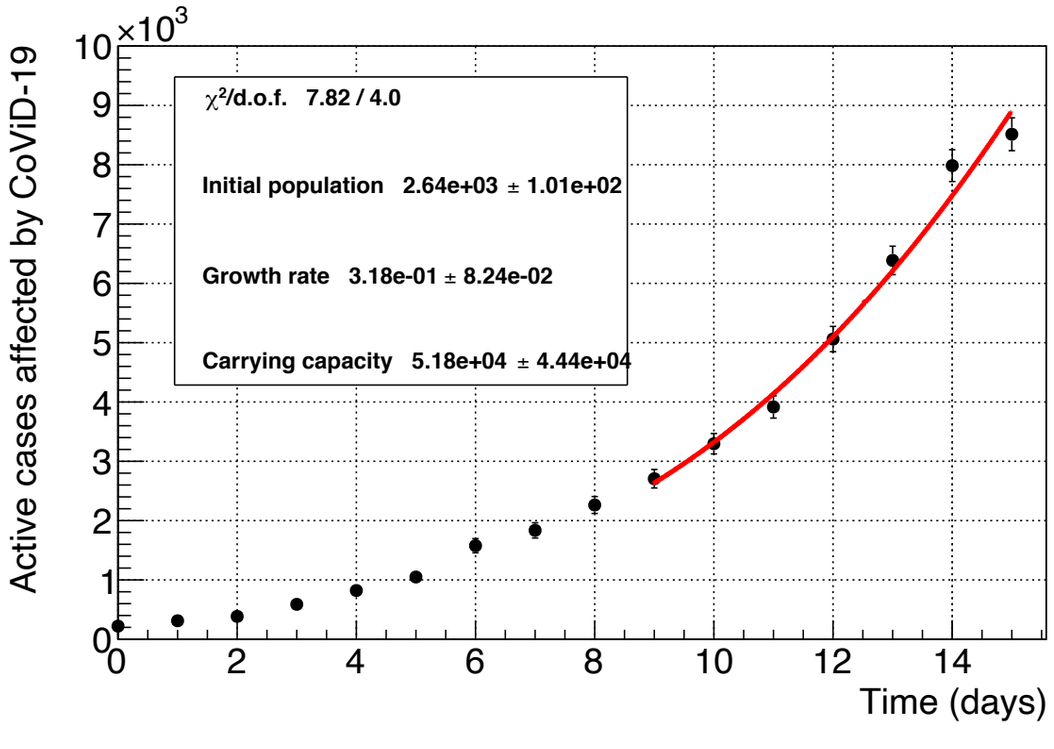
Application to data: fit to single time period



Number of <u>active</u> cases, fit data from 0th to 8th day (<u>period 1</u>):

- N_0: 223
- g: 0.405
- C_0: 8870±6750
- N_9: 2831
- C_9: 25200±19177

Compatible within errors



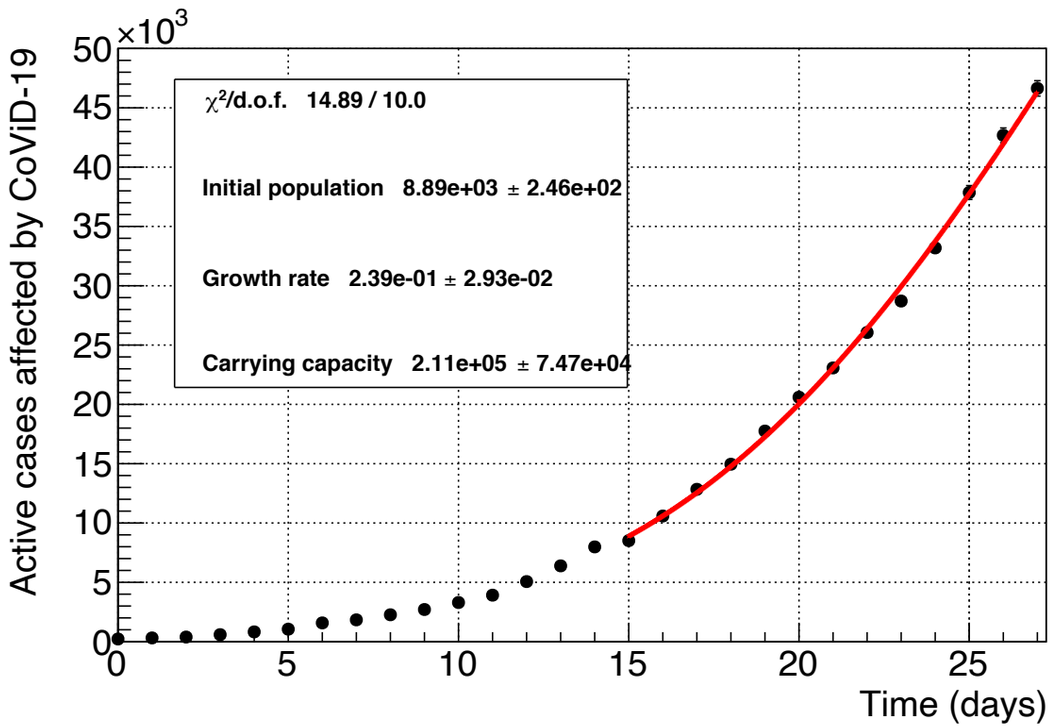
Number of <u>active</u> cases, fit data from 9th to 14th day (<u>period 2</u>):

- N_0: 2640
- g: 0.318
- C_0: 51800±44400
- N_{15}: 8909
- C_{15}: 83427±71509

Compatible within errors

- C_0: 211000±75000

Application to data: fit to single time period

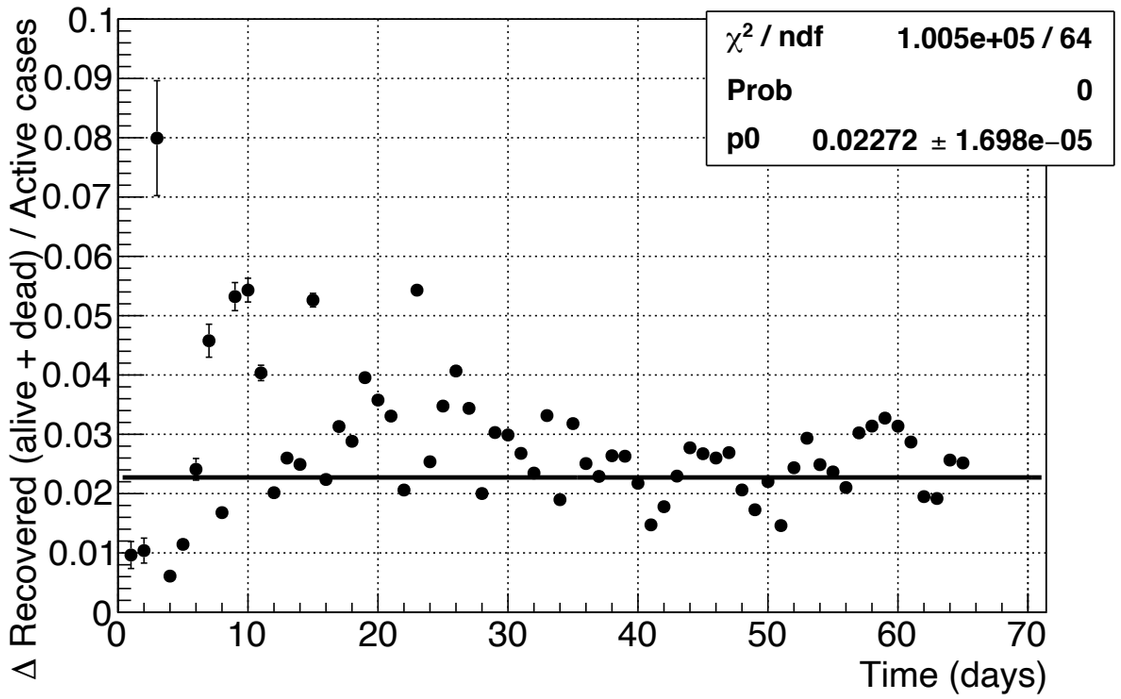


Number of active cases, fit data from 15th to 26th day (period 3):

- N_0: 8890
- g: 0.239
- C_0: 211000±75000
- N_{27}: 46346
- C_{27}: 359830±127900

Compatible within errors

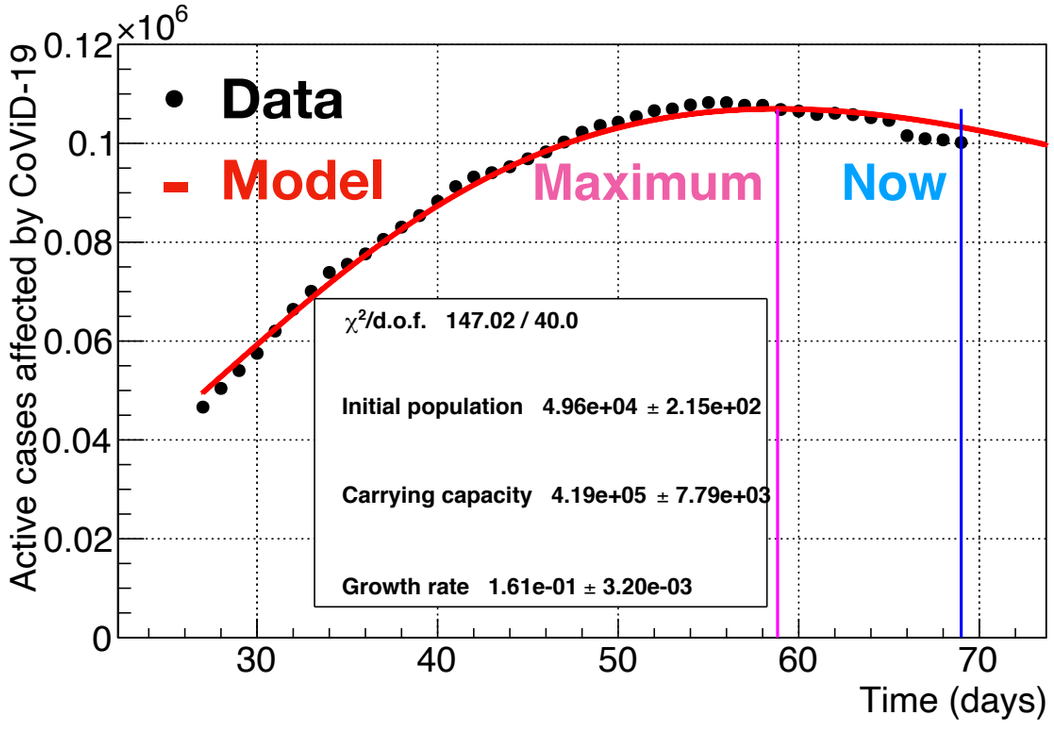
- C_0: 419000±7790

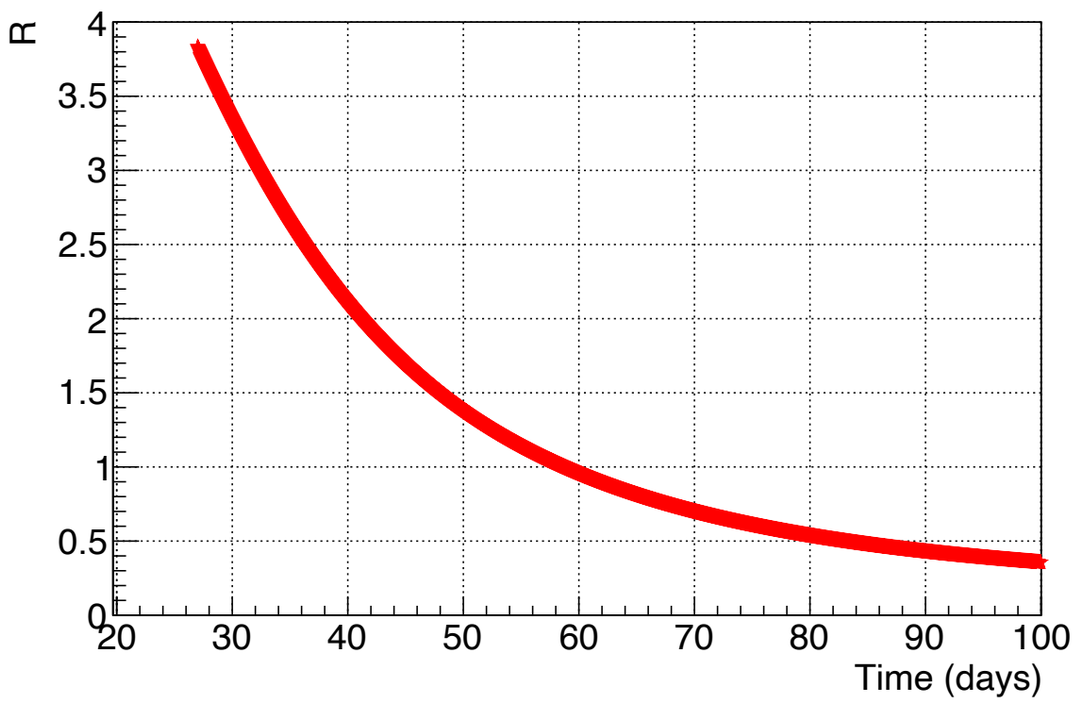


Recovery rate (r) is derived from data:

- r ~ 0.023 ➜ τ ~ 44 days

Application to data: fit to single time period





Number of <u>active</u> cases, fit data from 27th day till now (<u>period 4</u>)

<u>For all fit</u>

Errors rescaled by `x3`

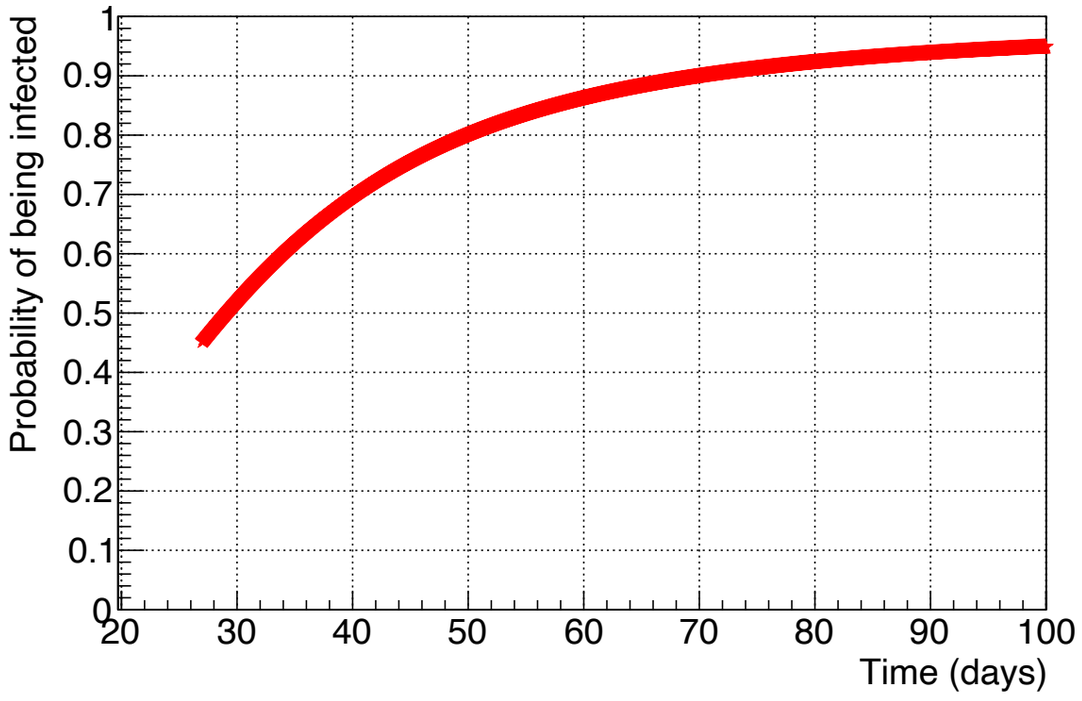
Fitted parameters:

- `Initial population (`$\mathbf{N_0}$`)`
- `Growth rate (`$\mathbf{g}$`)`
- `Carrying capacity (`$\mathbf{C_0}$`)`

Fixed parameters:

- `Recovery rate (`$\mathbf{r}$ `= 0.023)`
- `Fraction of symptomatic (`$\mathbf{0.3}$`)`
- `Transmission probability`
  `(`$\mathbf{p}$ `= 4.7x10`$^{-3}$ `- <u>see control plots</u>)`
- `Total population (`$\mathbf{T}$ `= 60x10`^{6}`)`

Application to data: fit to single time period



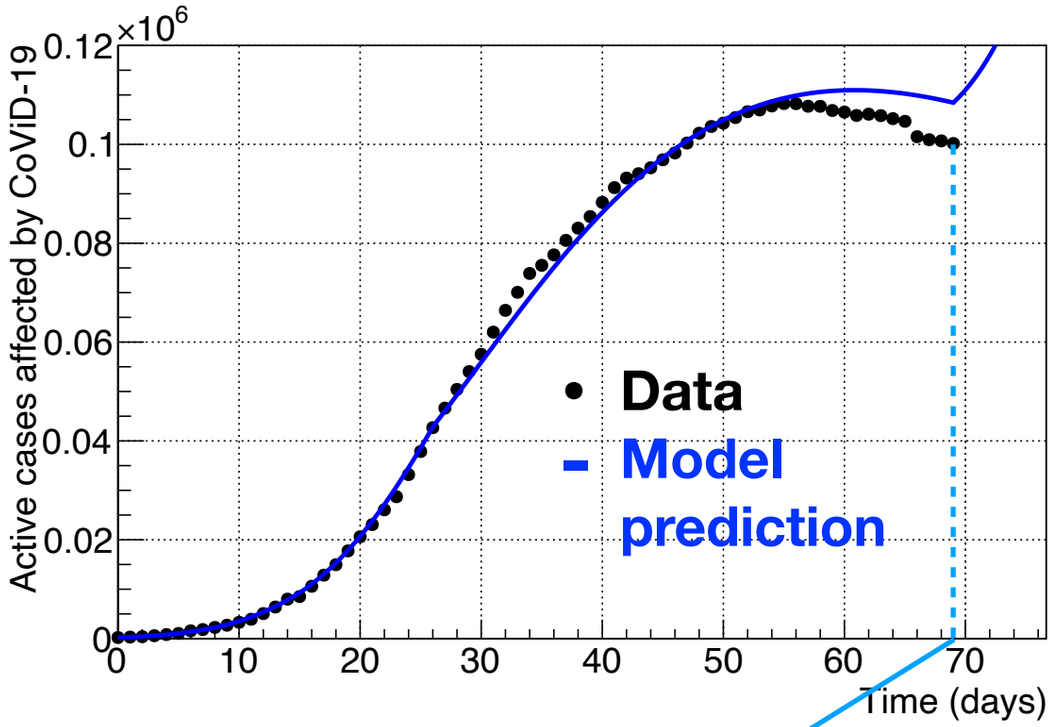
Probability of being infected, i.e. `1-q`

Parameter summary last period:

- `r = 0.023` ➜ plot Δrecovered/active
- `g = 0.161` ➜ fit
- `p = 4.7x10⁻³` ➜ χ^2/d.o.f. scan + coherence of carrying capacity evolution across periods
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography

Nuisance parameters: N_0 and C_0

Predictions: first scenario

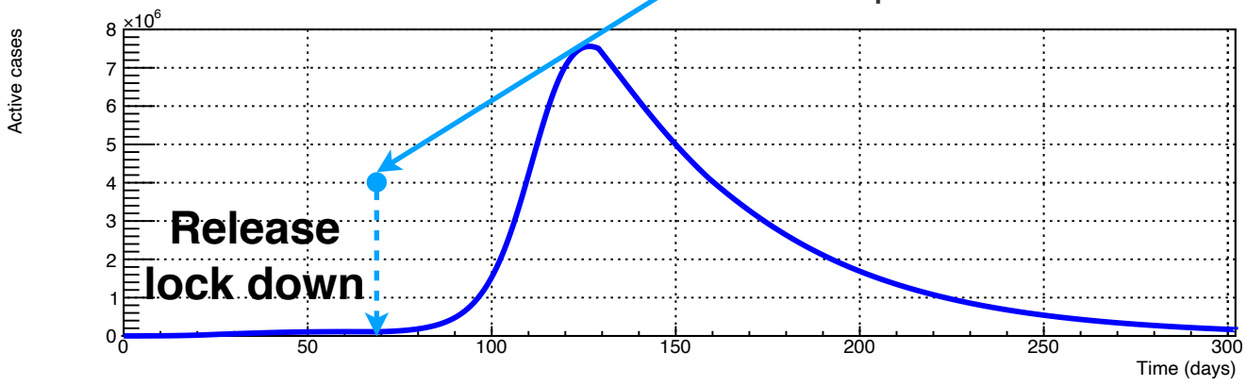


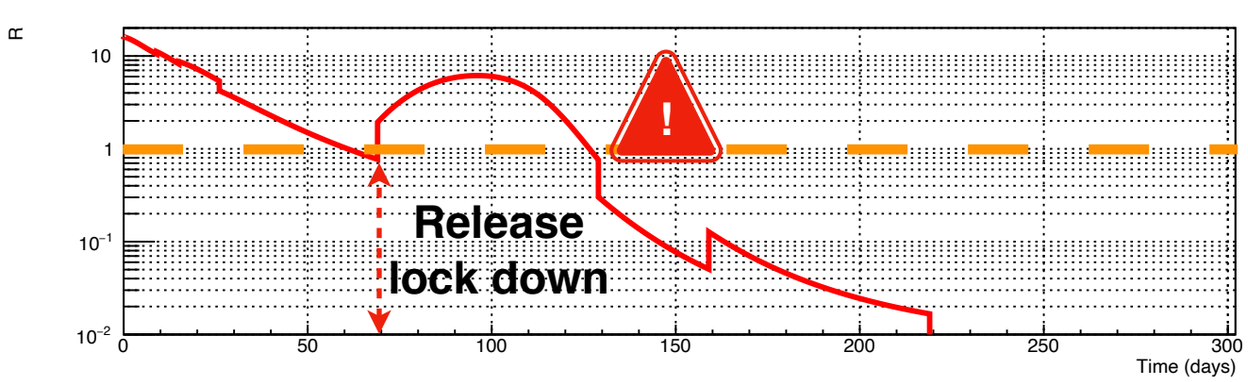
- Normal life style (g = 0.405) for 9 days
- Mild soc.distance (g = 0.318) for 6 days
- Medium soc.distance (g = 0.239) for 11 days
- Hard soc.distance (g = 0.161) for **43** days

☝ Past ☝ Future

- Normal life style (g = 0.405) for 60 days
- Hard soc.distance (g = 0.161) for 30 days
- Normal life style (g = 0.405) for 60 days
- Hard soc.distance (g = 0.161) for 120 days

Model prediction: full scale

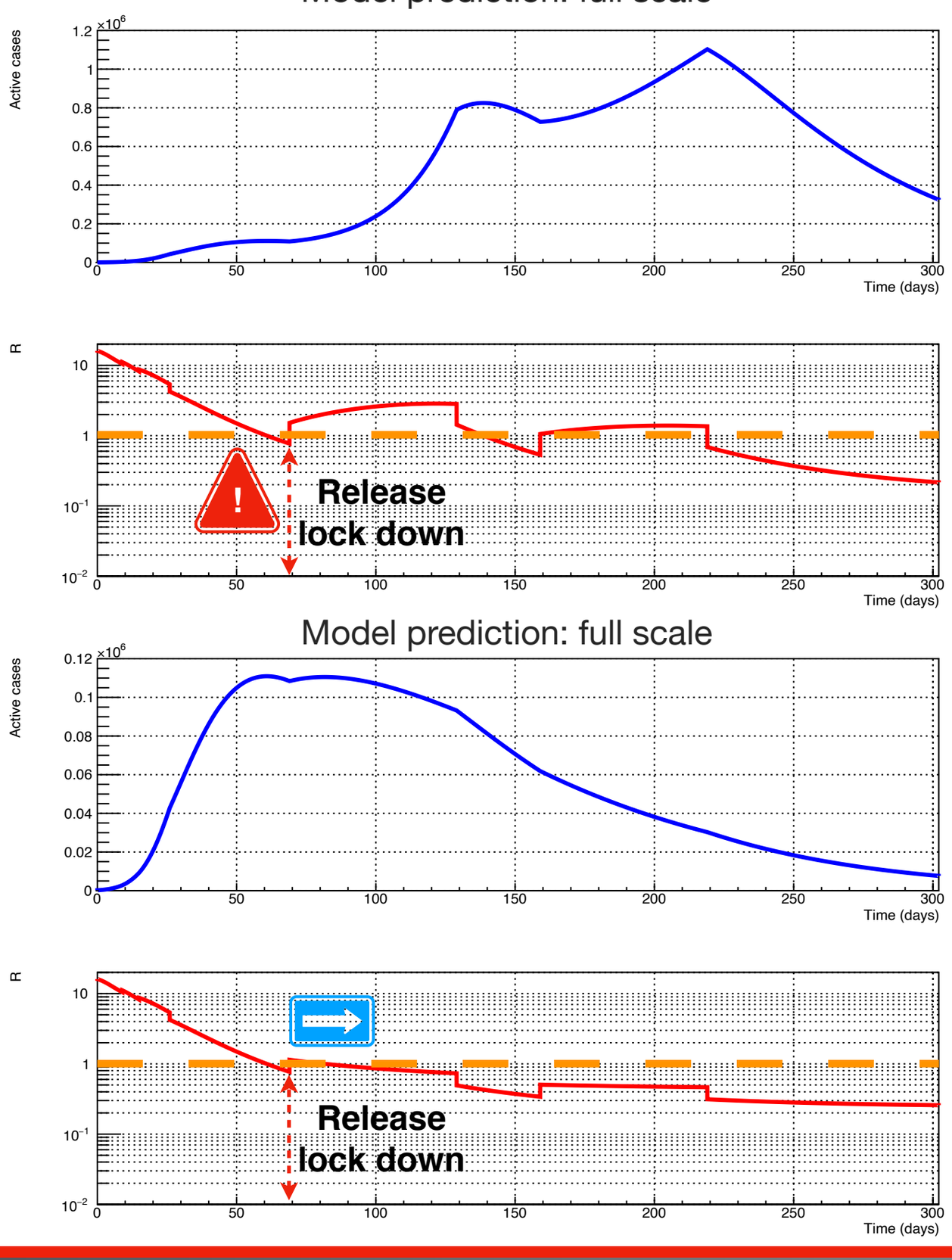




Other parameters:

- N_0: 223
- **r**: 0.023
- Symptomatic fraction: 0.3
- Transmission probability: 4.7x10^{-3}

Predictions: second and third scenarios



- Normal life style ($g = 0.405$) for 9 days
- Mild soc.distance ($g = 0.318$) for 6 days
- Medium soc.distance ($g = 0.239$) for 11 days
- Hard soc.distance ($g = 0.161$) for **43** days

Past Future

- Mild soc.distance ($g = 0.318$) for 60 days
- Hard soc.distance ($g = 0.161$) for 30 days
- Mild soc.distance ($g = 0.318$) for 60 days
- Hard soc.distance ($g = 0.161$) for 120 days

==========

- Normal life style ($g = 0.405$) for 9 days
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- Hard soc.distance ($g = 0.161$) for **43** days

Past Future

- Medium soc.distance ($g = 0.239$) for 60 days
- Hard soc.distance ($g = 0.161$) for 30 days
- Medium soc.distance ($g = 0.239$) for 60 days
- Hard soc.distance ($g = 0.161$) for 120 days

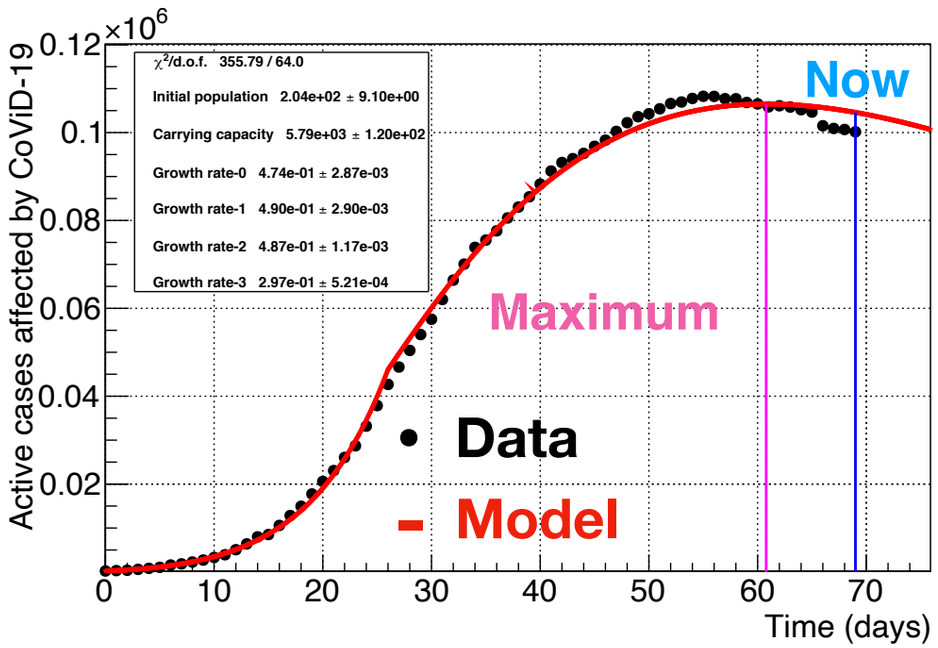
Refinements of the analysis

The model was first tested on different periods, independently, as shown in the previous slides. Then the analysis was further improved by performing:

1. a global fit, i.e. a joint fit, to multiple periods simultaneously, imposing coherence on the number of active cases ($\mathbf{N_n}$) and on the carrying capacity ($\mathbf{C_n}$) across periods, i.e. $\mathbf{N_n}$ and $\mathbf{C_n}$ at the end or period `m` must be equal to $\mathbf{N_n}$ and $\mathbf{C_n}$ at the beginning of perdio `m+1`

2. a global fit with `logNormal` smearing to take into account effects such as latent/ incubation periods or in general delays in data reporting, law enforcement, or social behaviour

Application to data: fit to multiple time-periods



Number of <u>active</u> cases, **joint fit** periods **1 + 2 + 3 + 4**

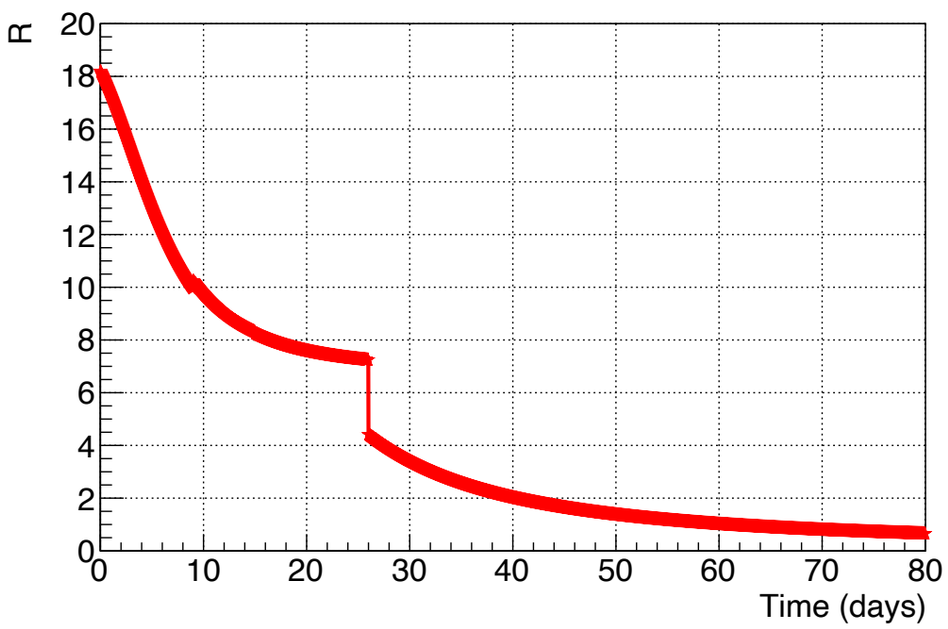
Errors rescaled by x3

Fitted parameters:

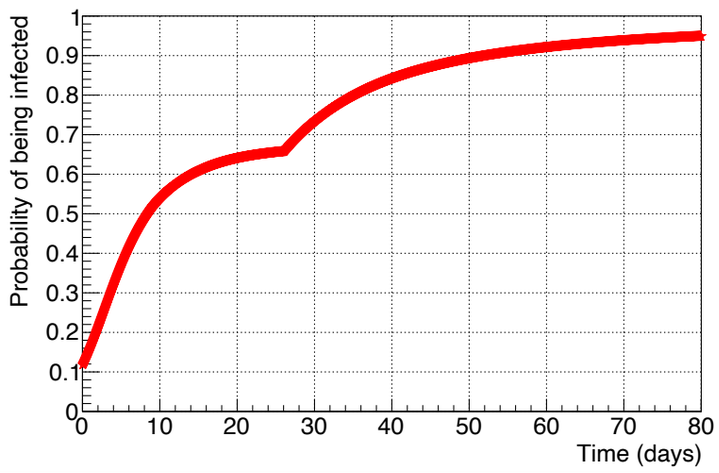
- Initial population ($\mathbf{N_0}$)
- Growth rates periods 1, 2, 3, 4 ($\mathbf{g}$)
- Carrying capacity ($\mathbf{C_0}$)

Fixed parameters:

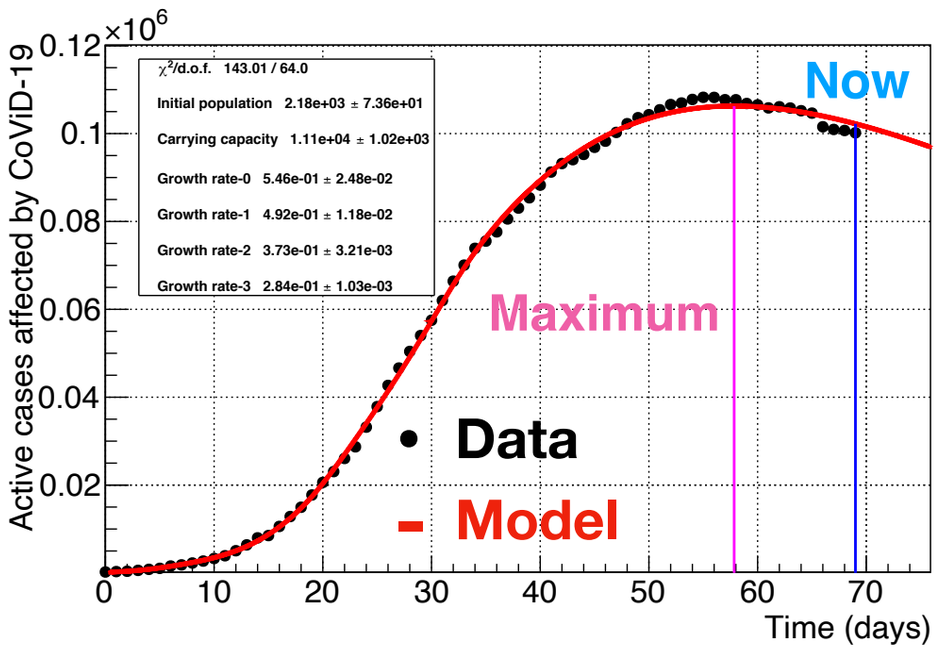
- Recovery rate ($\mathbf{r}$ = 0.023)
- Fraction of symptomatic (0.3)
- Transmission probability ($\mathbf{p}$ = 6.5×10^{-3} - <u>see control plots</u>)
- Total population ($\mathbf{T}$ = 60×10^6)



Probability of being infected, i.e. **1-q**



Application to data: fit to multiple time-periods



Number of <u>active</u> cases, **joint fit** periods **1 + 2 + 3 + 4** with **`logNormal`** ($\mu = 2, \sigma = 0.3$) smearing, i.e. convolution, to mimic effects such as latent/incubation periods (`logNormal` is used to preserve causality)

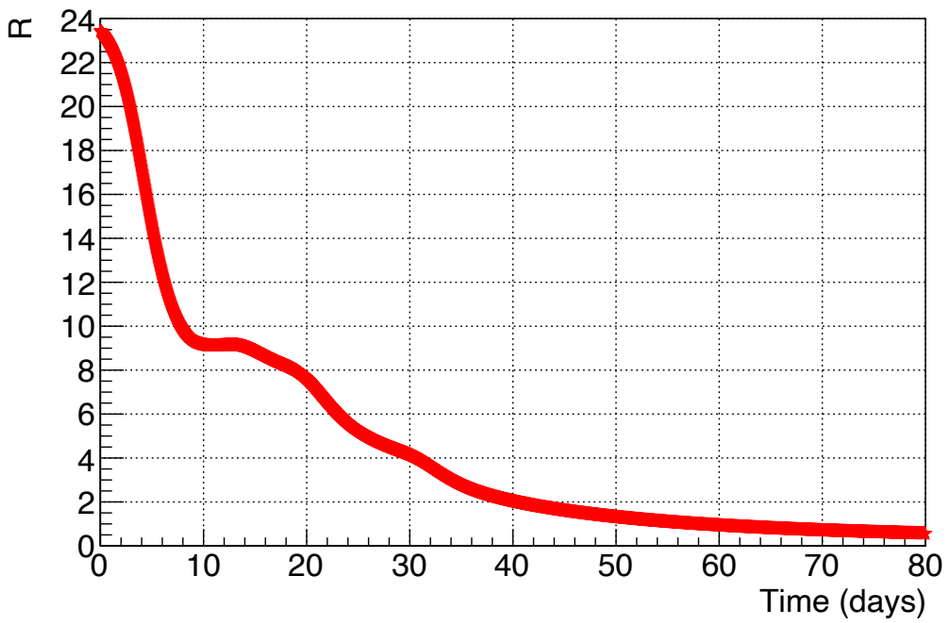
Errors rescaled by `x3`

Fitted parameters:

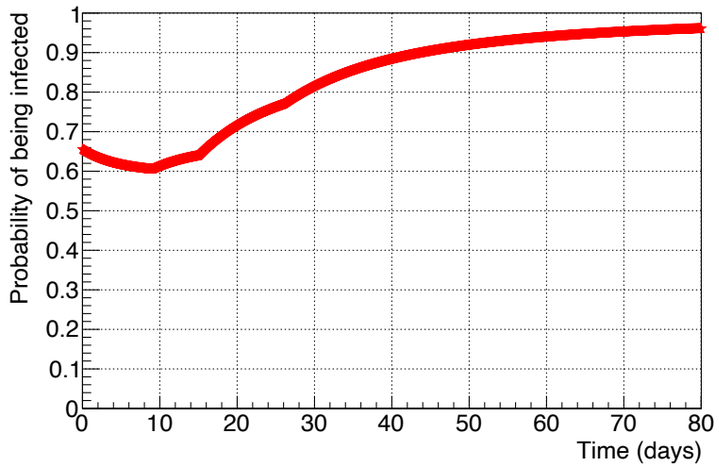
- `Initial population` (**N_0**)
- `Growth rates periods 1, 2, 3, 4` (**`g`**)
- `Carrying capacity` (**C_0**)

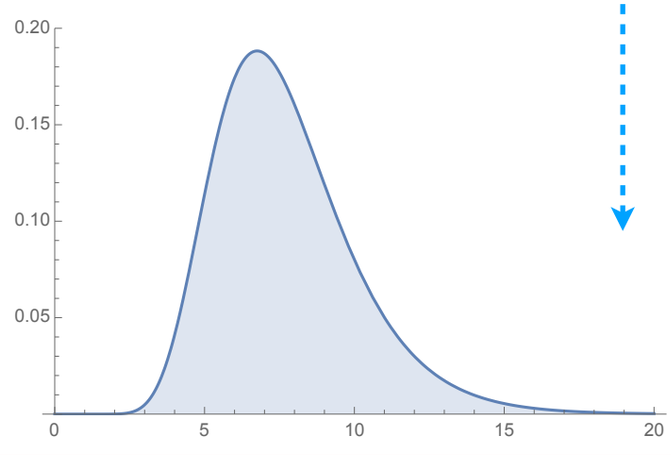
Fixed parameters:

- `Recovery rate` (**`r`** = 0.023)
- `Fraction of symptomatic` (**0.3**)
- `Transmission probability` (**`p`** = 6.5×10^{-3} - <u>see control plots</u>)
- `Total population` (**`T`** = 60×10^6)

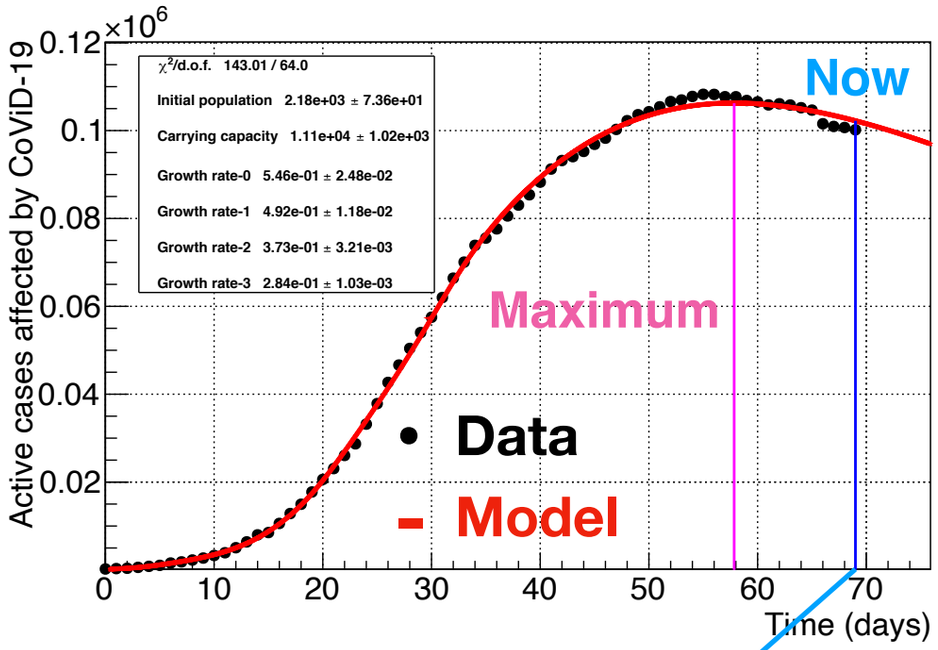


Probability of being infected, i.e. **`1-q`**





Predictions

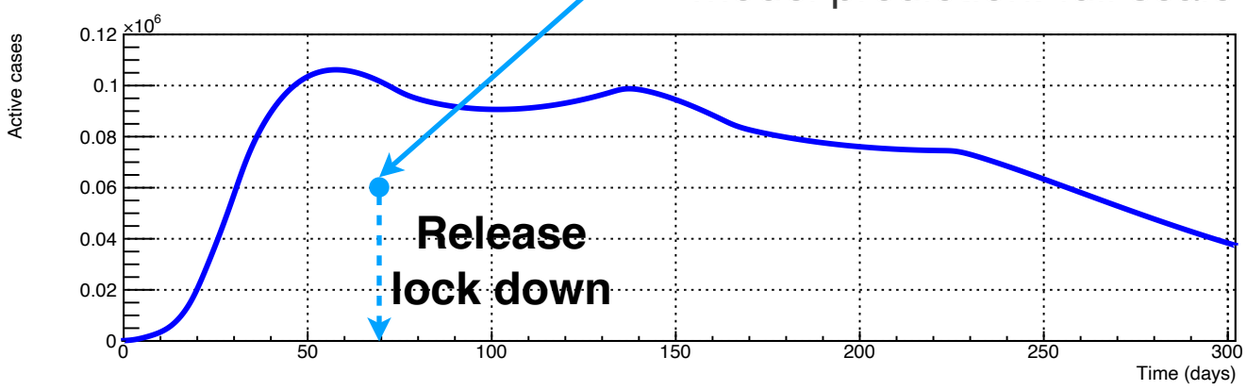


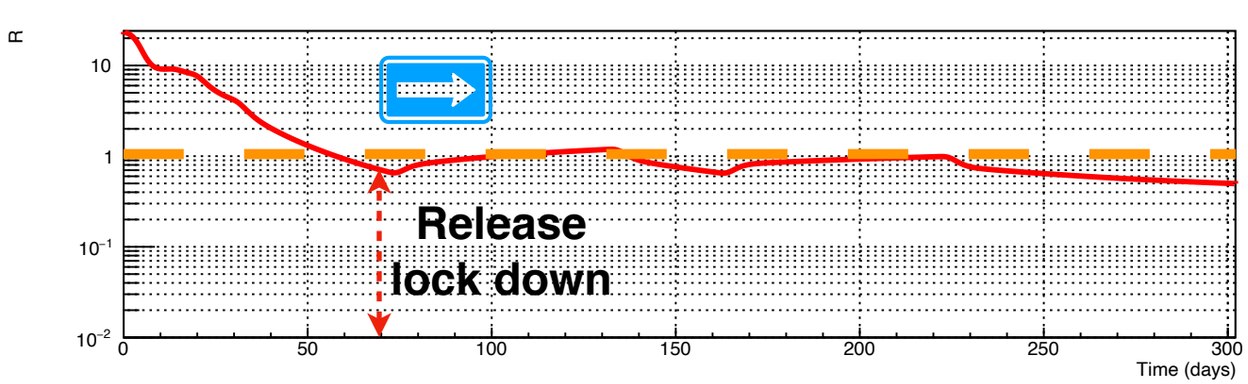
- Normal life style ($g = 0.546$) for 9 days
- Mild soc.distance ($g = 0.492$) for 6 days
- Medium soc.distance ($g = 0.373$) for 11 days
- Hard soc.distance ($g = 0.284$) for **43** days

Past Future

- Normal life style ($g = 0.373$) for 60 days
- Hard soc.distance ($g = 0.284$) for 30 days
- Normal life style ($g = 0.373$) for 60 days
- Hard soc.distance ($g = 0.284$) for 120 days

Model prediction: full scale





Other parameters:

- N_0: 223
- **r**: 0.023
- Symptomatic fraction: 0.3
- Transmission probability: 6.5×10^{-3}

Considerations

The model has in total 7 parameters:

- recovery rate **r** ➜ obtained from data plot Δrecovered/active
- growth rate **g** ➜ obtained from fit to the data
- transmission probability **p** ➜ obtained from χ^2/d.o.f. scan + coherence of carrying capacity evolution across periods
- fraction of symptomatic ➜ obtained from literature
- total population **T** ➜ demography
- initial conditions N_0 and C_0 ➜ obtained from fit to the data

We extracted as much information as possible from the available data and we tried to avoid any a priori assumption, though the model unavoidably rely on a couple of tacit assumptions:

- the different periods are well defined, this of course might not be entirely realistic especially for those practices, e.g. wearing a mask, which were not dictated by law, and because the model doesn't take into account the latent/incubation periods, though the smearing with `logNormal` does not show significative effects

- possible differences/variations, region-by-region, double/under counting, etc…, in the criteria of measuring the data, are averaged out

Considerations

Even so the model seems to reasonably describe the data and therefore we tried to project possible evolutions of the disease in the future by exploring three different scenarios:

1. normal life style
2. lock down schools and universities: “mild soc.distance”
3. mild soc.distance + restrictions on movements: “medium soc.distance”

➜ only the third scenario is capable of keeping the effective reproduction below **1**

- All other scenarios will unavoidably bring **R > 1** with the consequence of clogging the hospitals, even though **R** will no longer reach values as high as at the beginning of the contagion (**~20**)

- Most likely we will get back to normal life thanks to the herd immunity

By any means this work pretend to describe the true dynamic of the infection spread, though it’s interesting to notice that with just few parameters, and reasonable assumptions, the model is able to follow the evolution of the active cases

How to act …

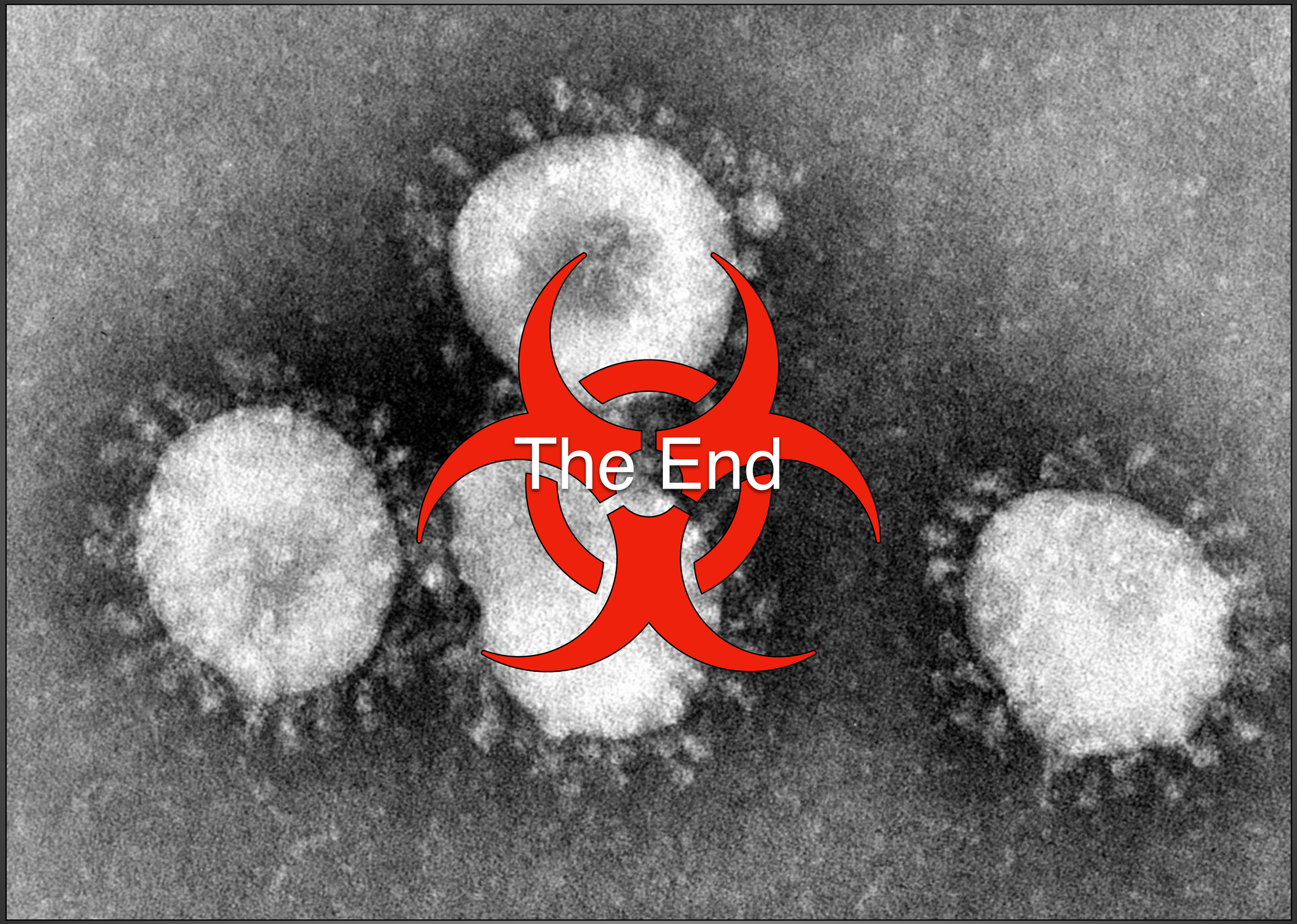
How to act in order to dump the spread of the disease:

1. Decrease the factor **p** (probability to spread the disease from one individual to another): adopt masks, gloves, disinfections, etc…

2. Decrease factor **k** (average number of encountered people by one individual): enforce social distancing

3. Increase factor **Q** (fraction of active cases which are in quarantine): quickly discover the new infected cases and put them in quarantine

4. Increase factor **r** (recovery rate): develop a vaccine

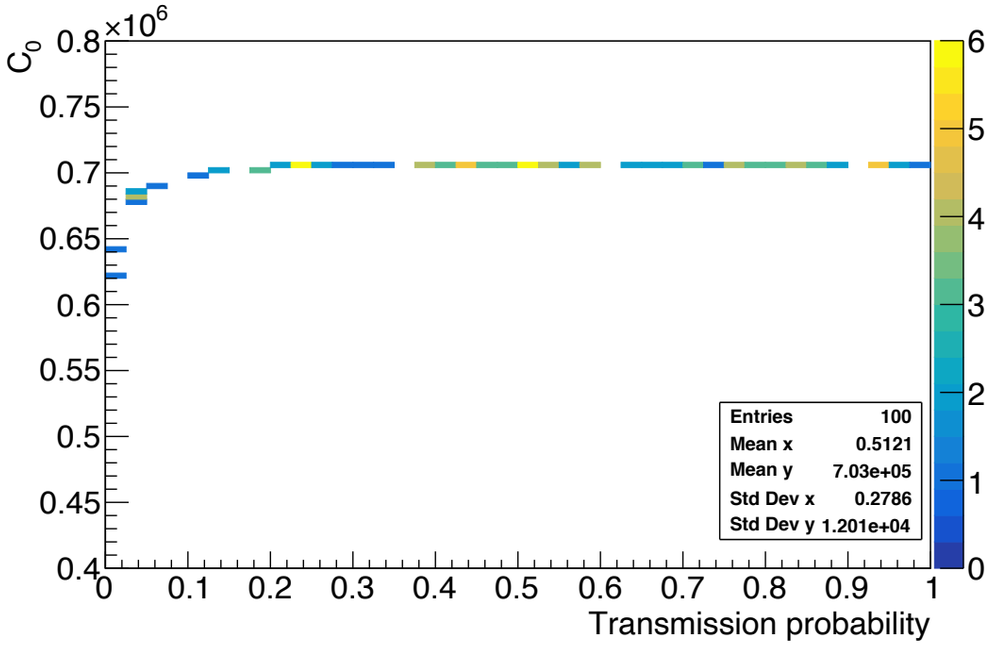

The End

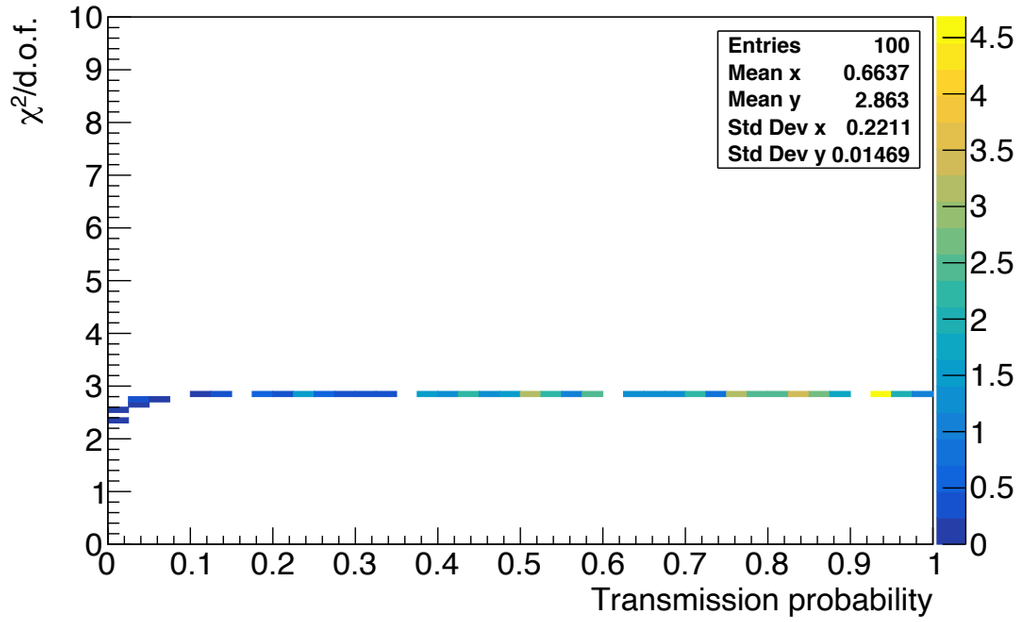
Control plots

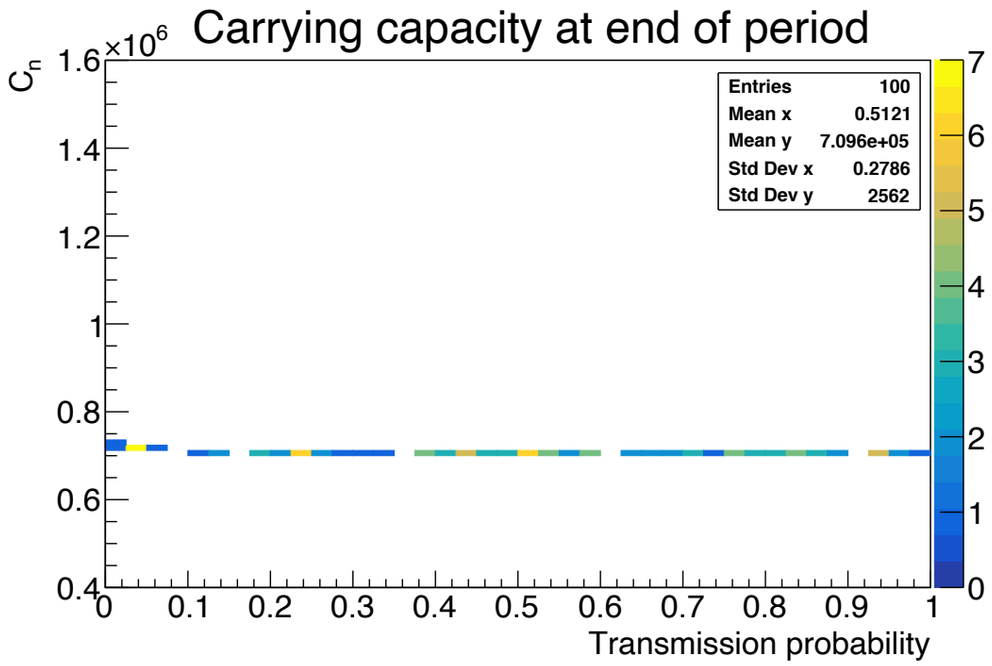
Model ameliorations/extensions:

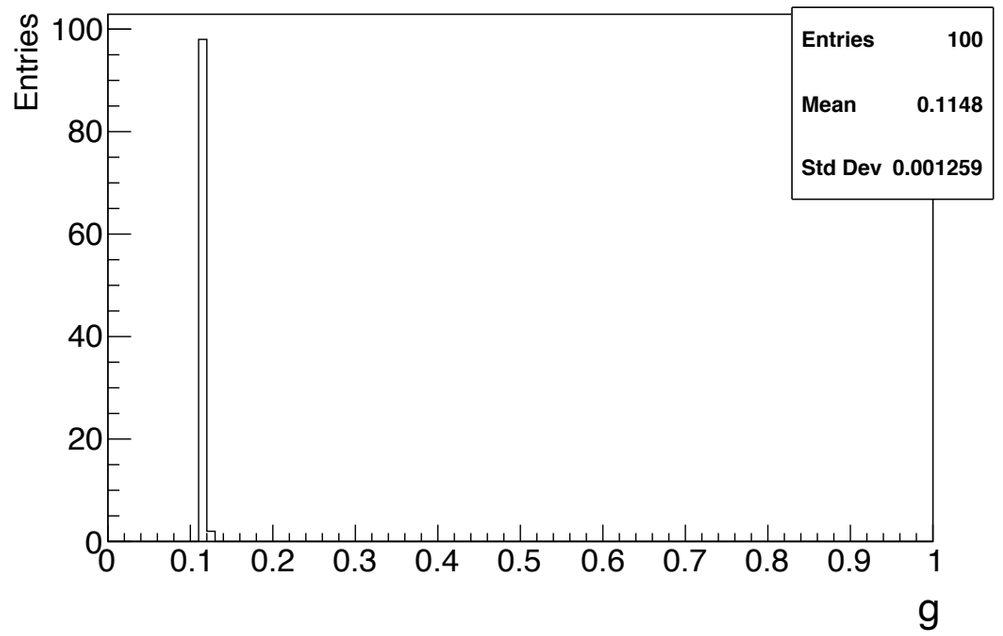
- Compute in how much time we will reach the herd immunity
- Take into account natural demographic change

Application to data: fit to single time period









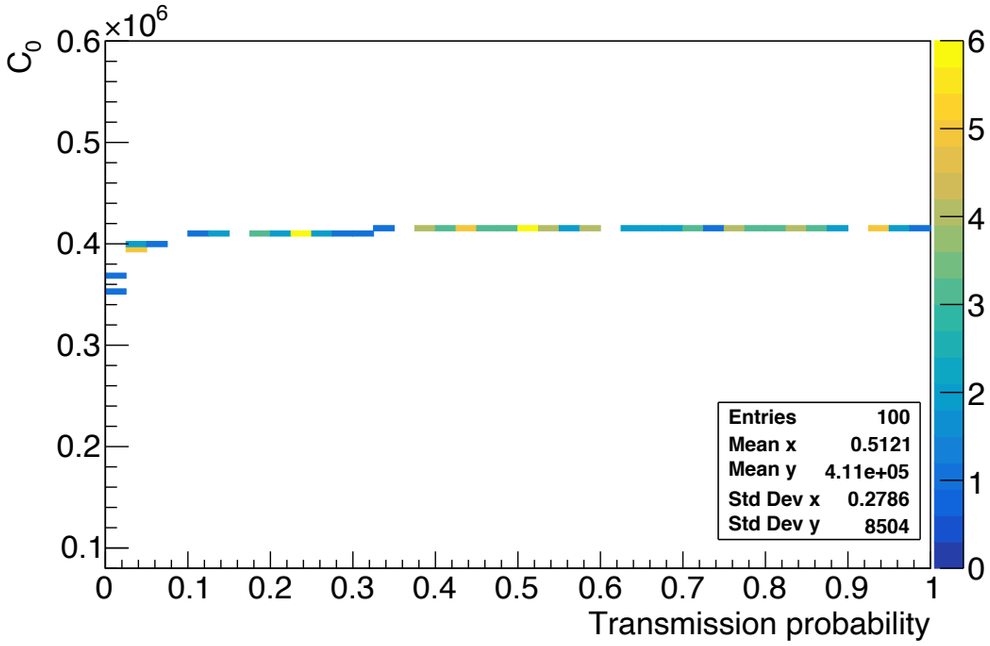
Fit data from 27th day to now (period 4)

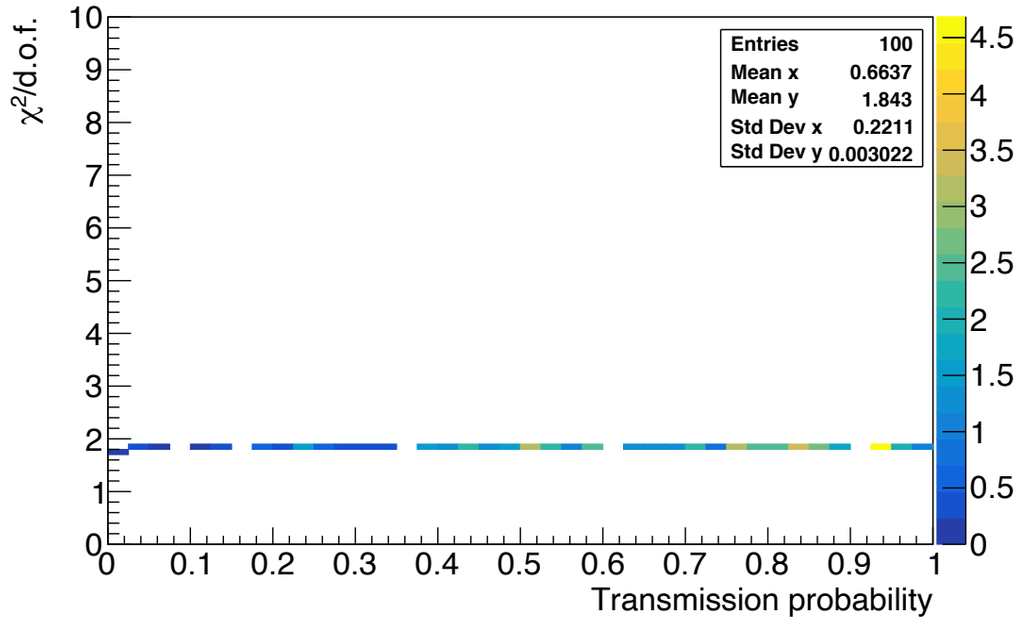
- `N = 100` extractions of transmission probability, `p`

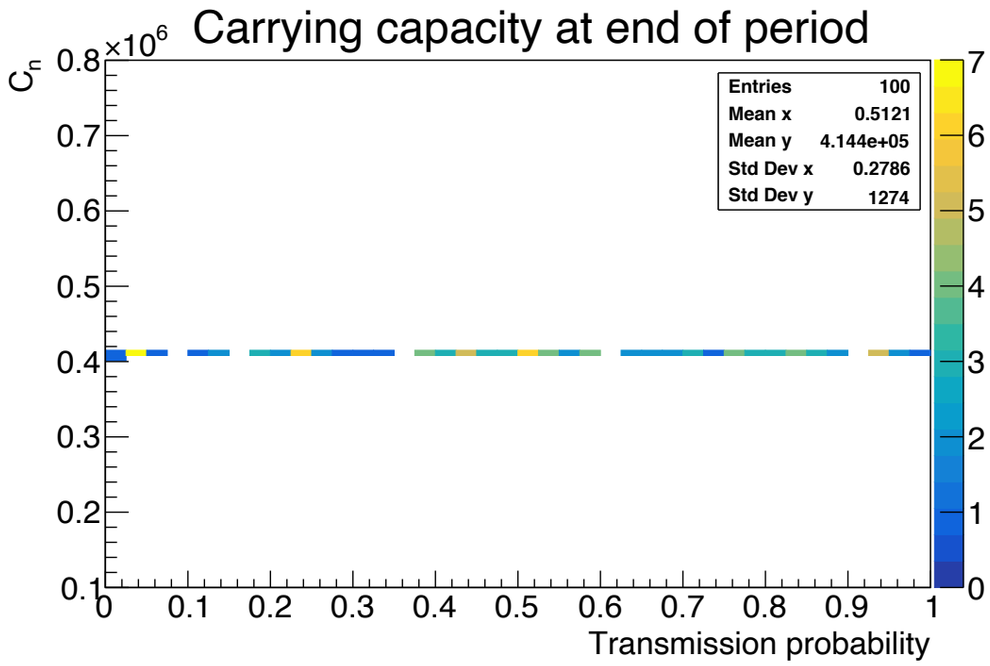
Fixed parameters:

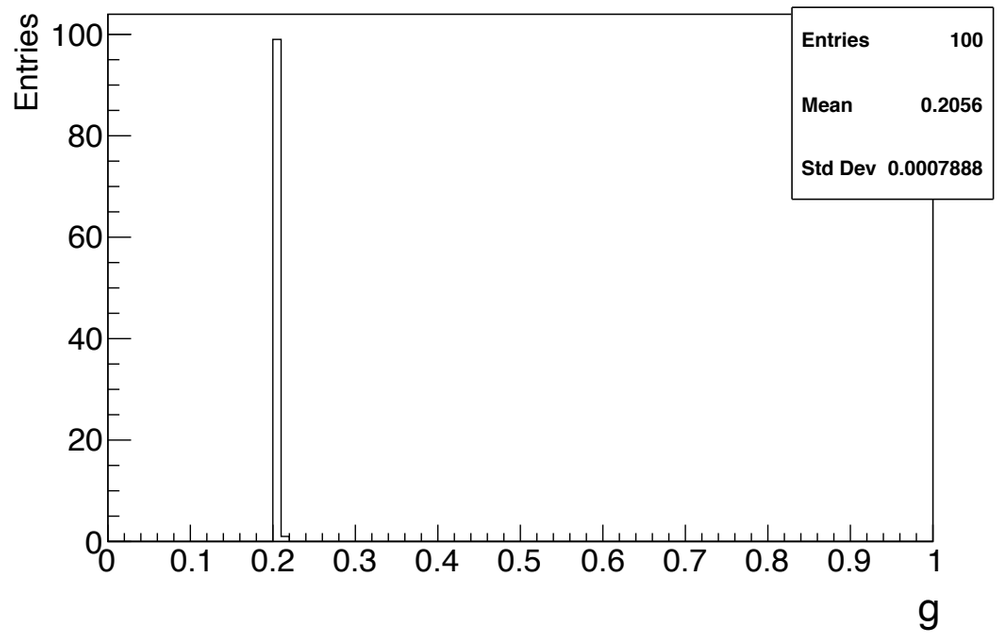
- `r = 0.023` ➜ plot Δrecovered/active
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography

Application to data: fit to single time period









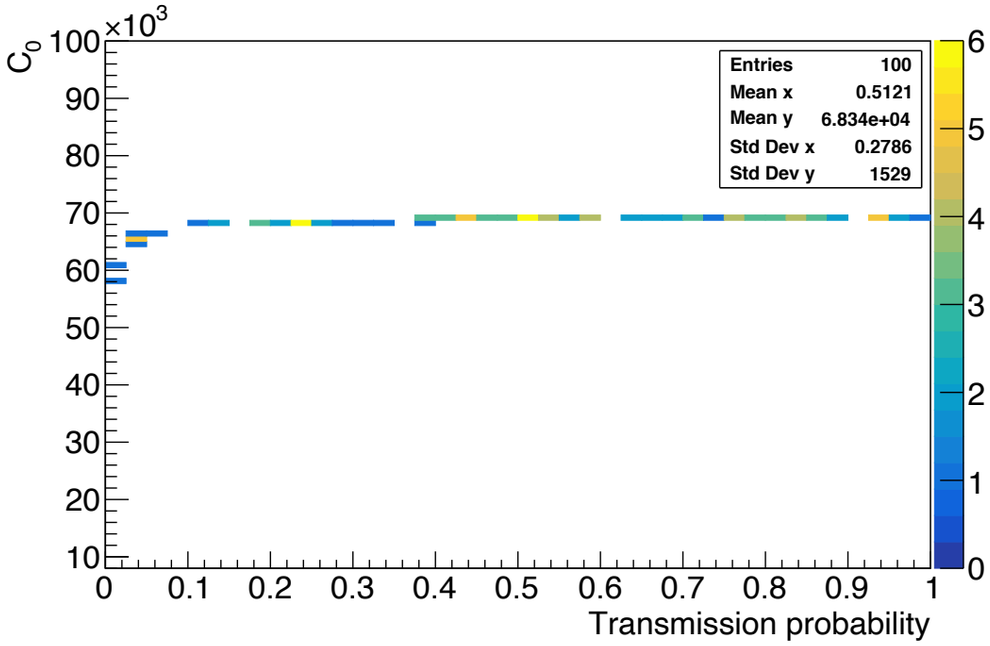
Fit data from 15th to 26th day (period 3)

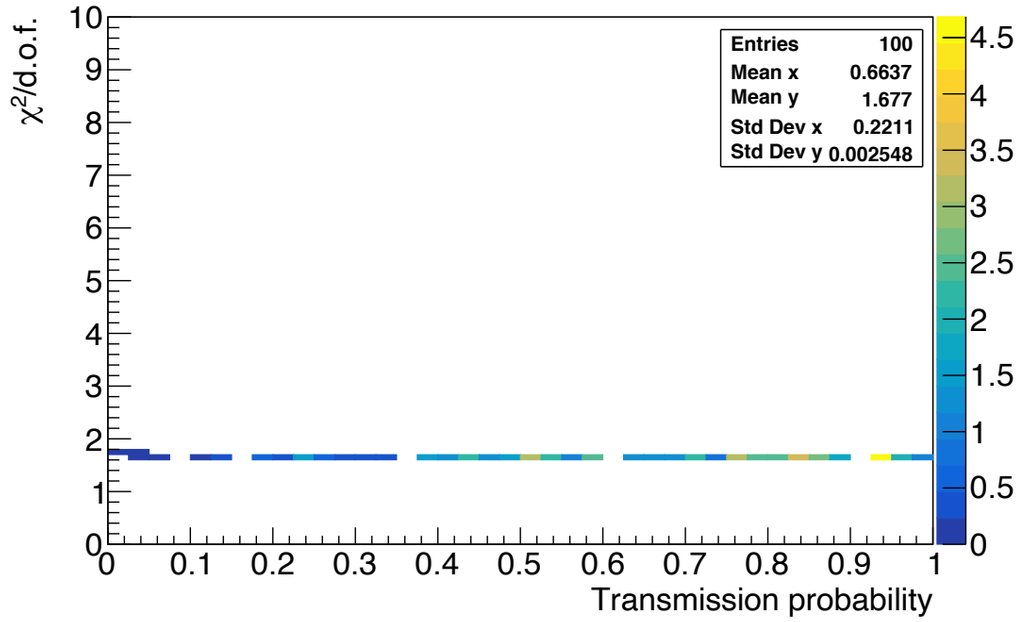
- `N = 100` extractions of transmission probability, `p`

Fixed parameters:

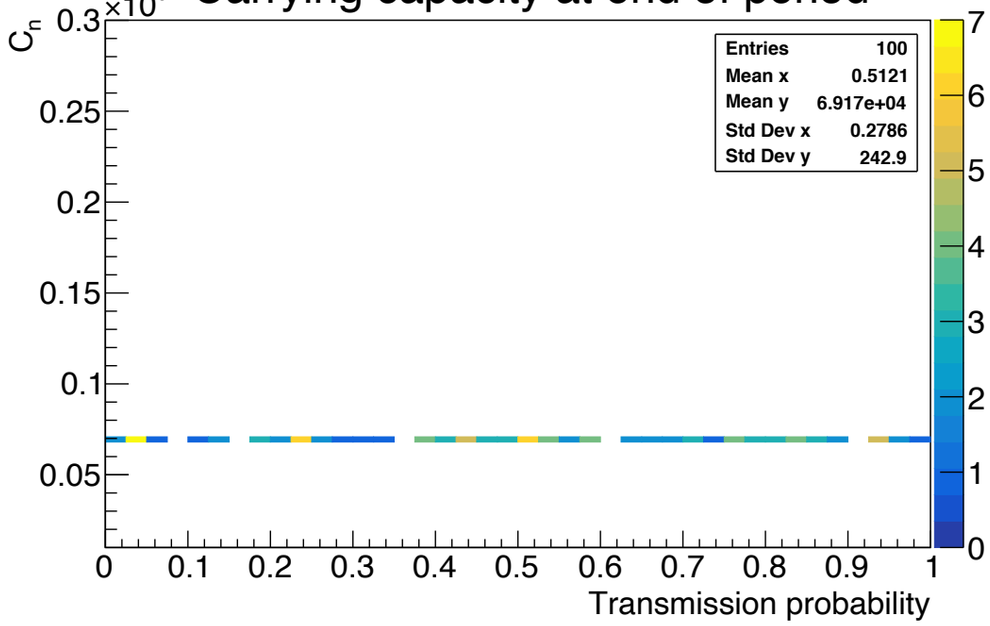
- `r = 0.023` ➜ plot Δrecovered/active
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography

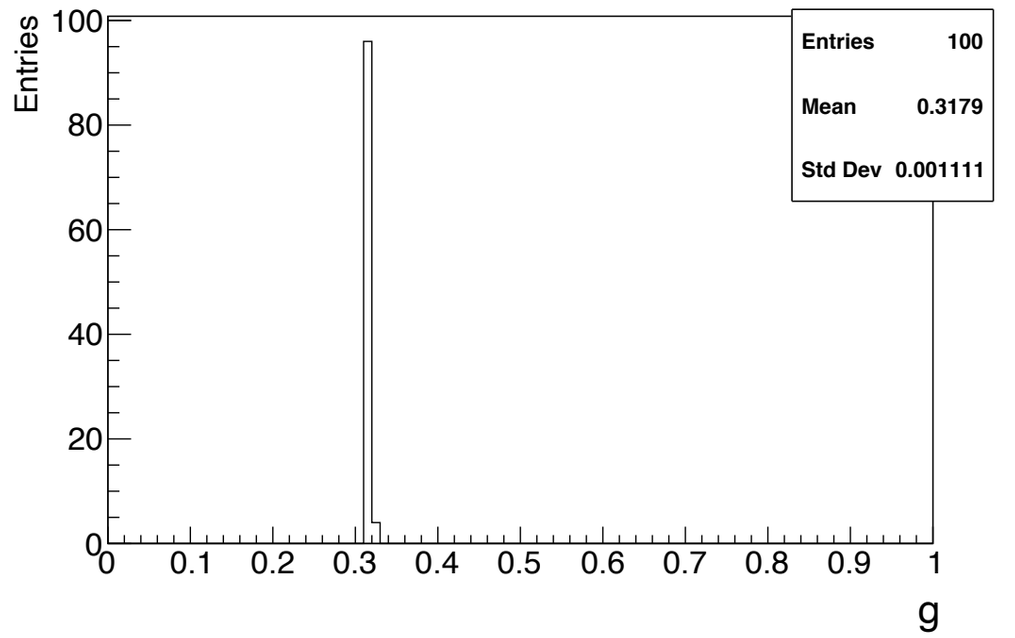
Application to data: fit to single time period





Carrying capacity at end of period





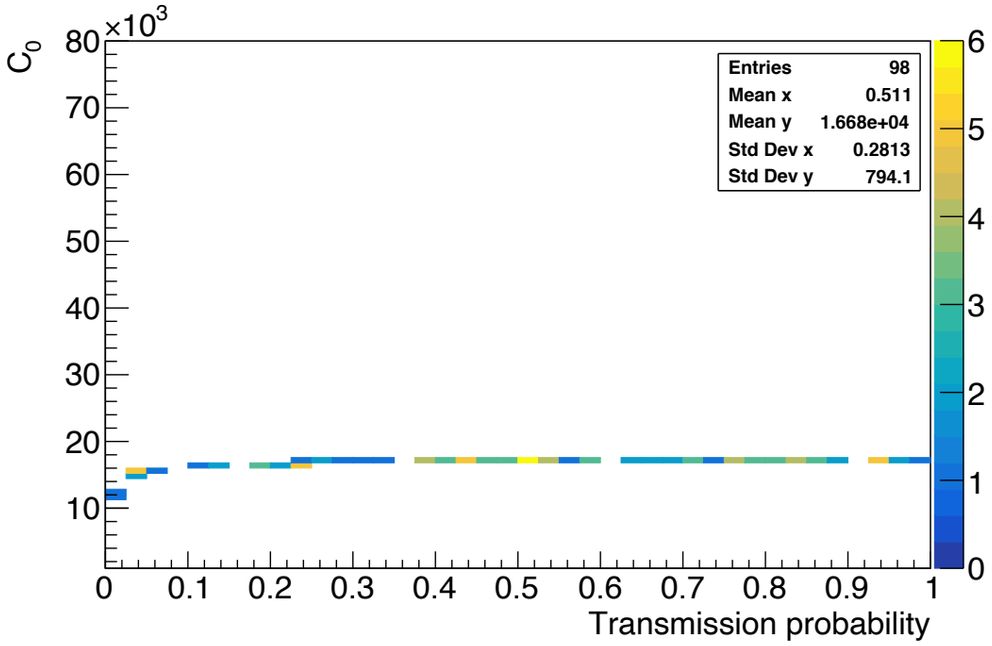
Fit data from 9th to 14th day (period 2)

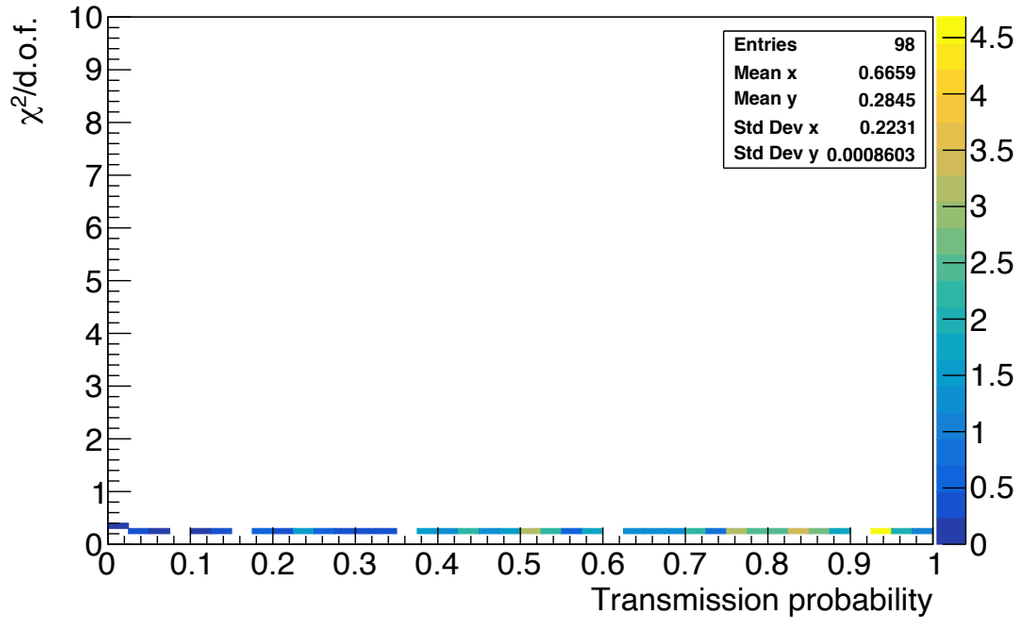
- `N = 100` extractions of transmission probability, `p`

Fixed parameters:

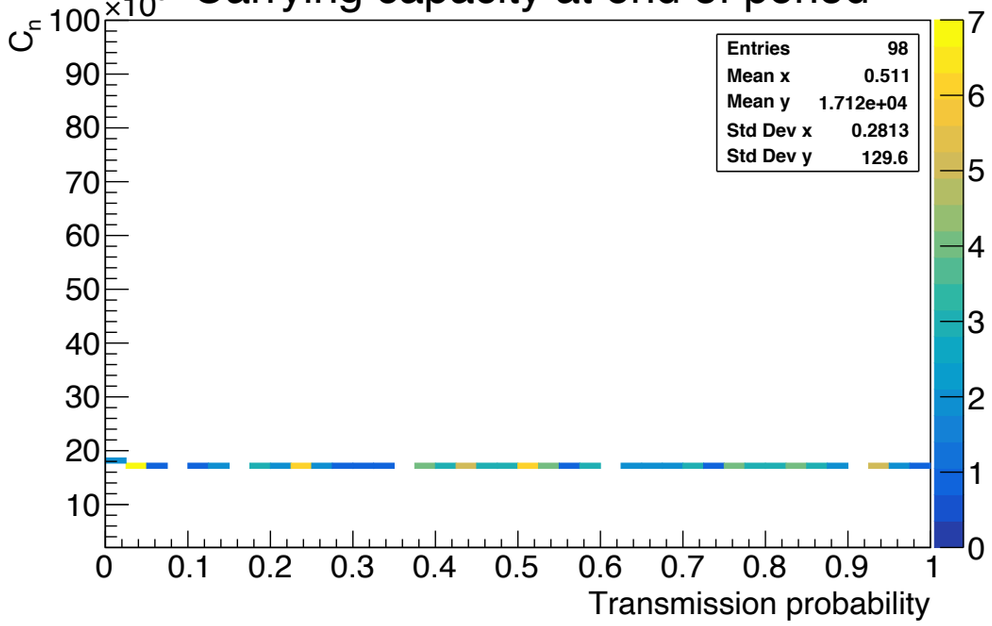
- `r = 0.023` ➜ plot Δrecovered/active
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography

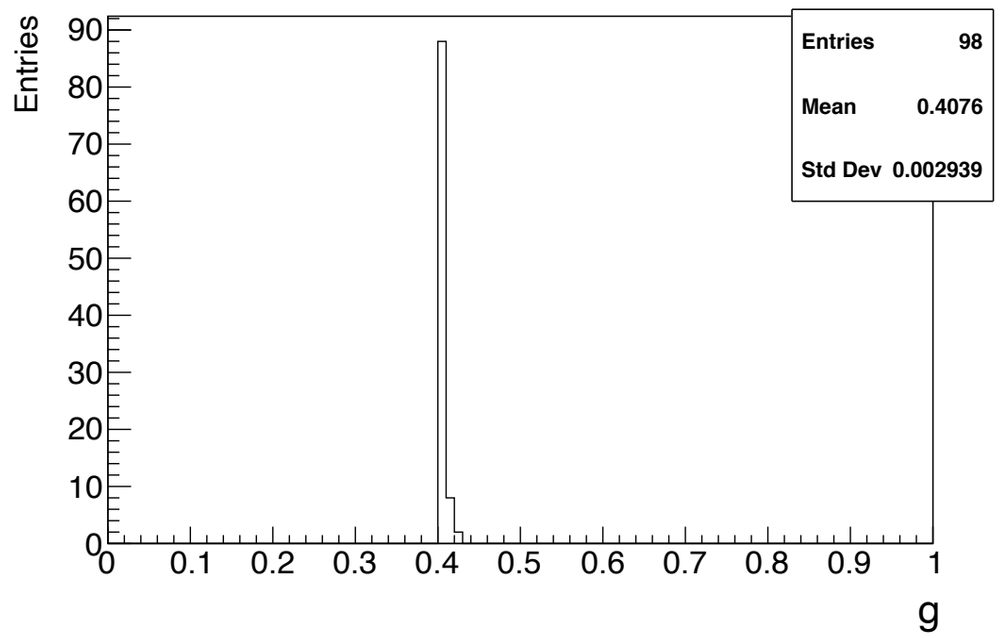
Application to data: fit to single time period





Carrying capacity at end of period





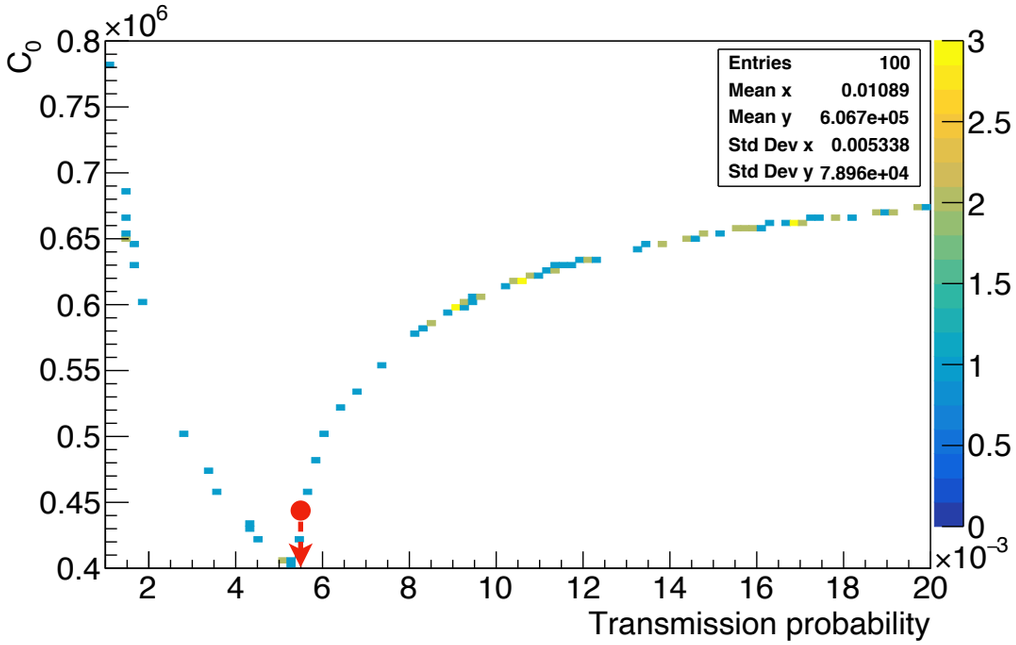
Fit data from 0th to 8th day (period 1)

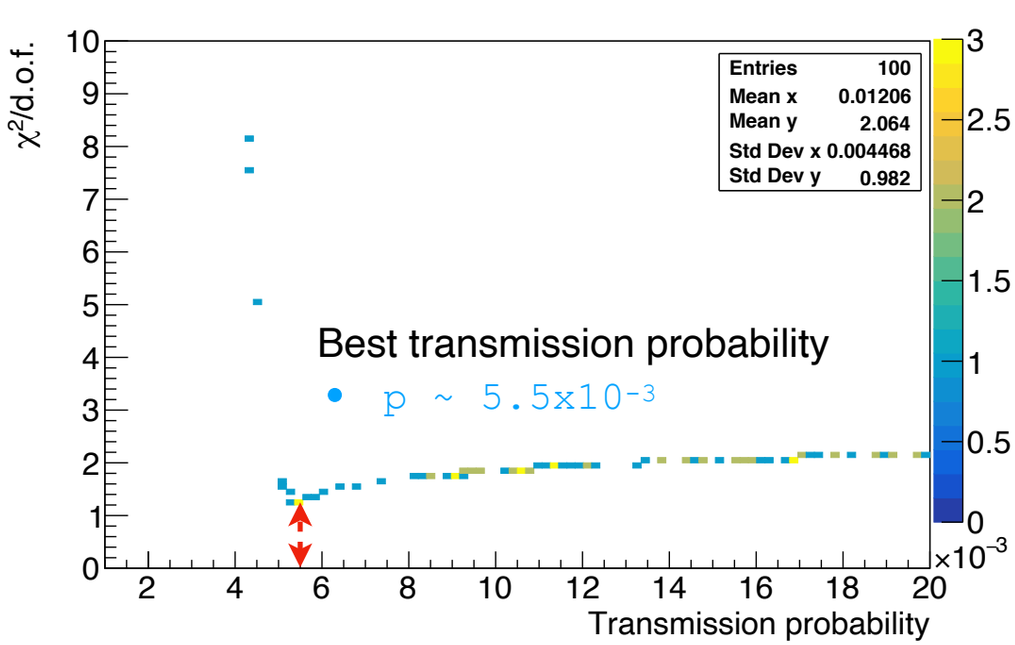
- `N = 100` extractions of transmission probability, `p`

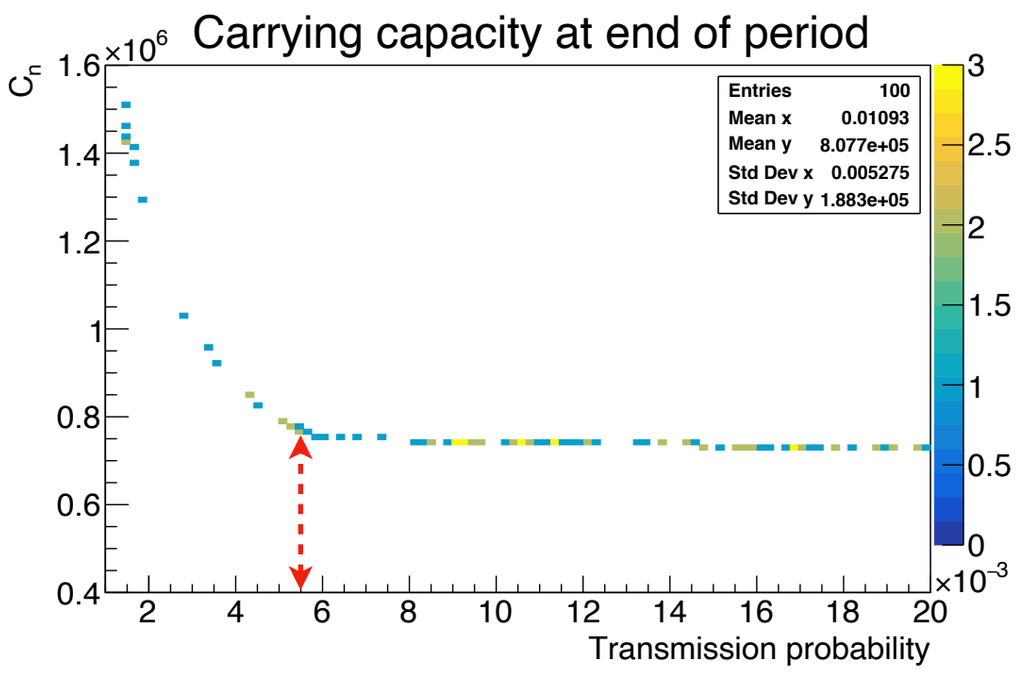
Fixed parameters:

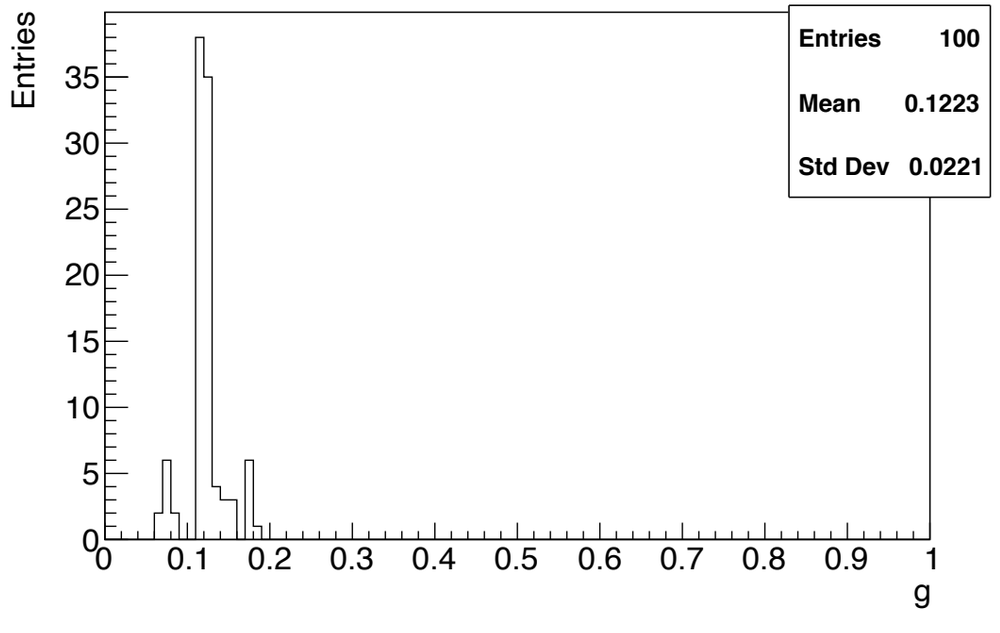
- `r = 0.023` ➜ plot Δrecovered/active
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography

Application to data: fit to single time period









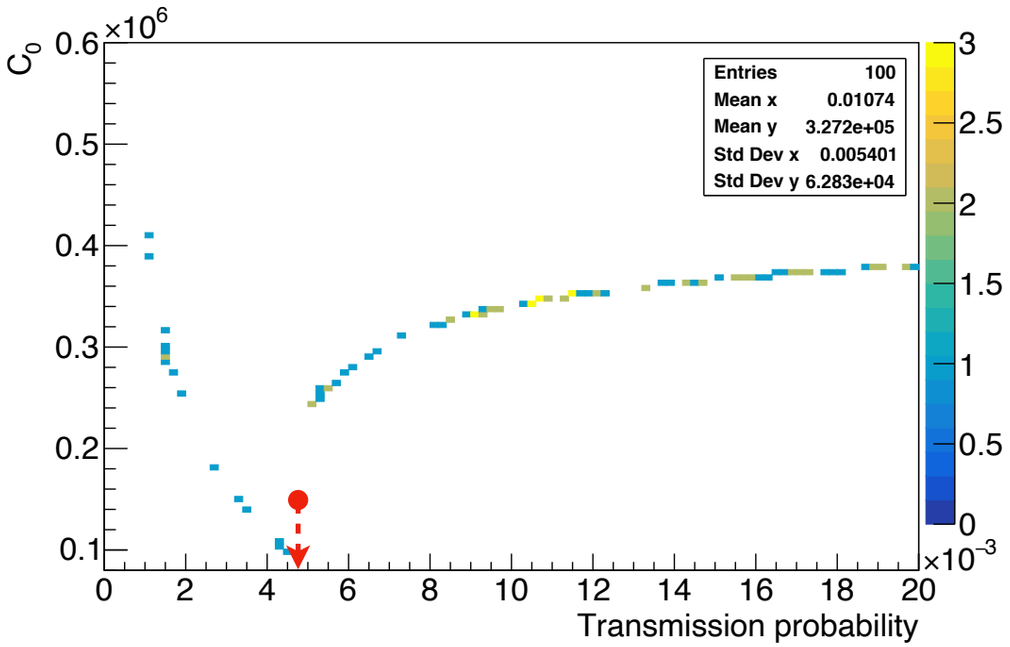
Fit data from 27th day till now (period 4)

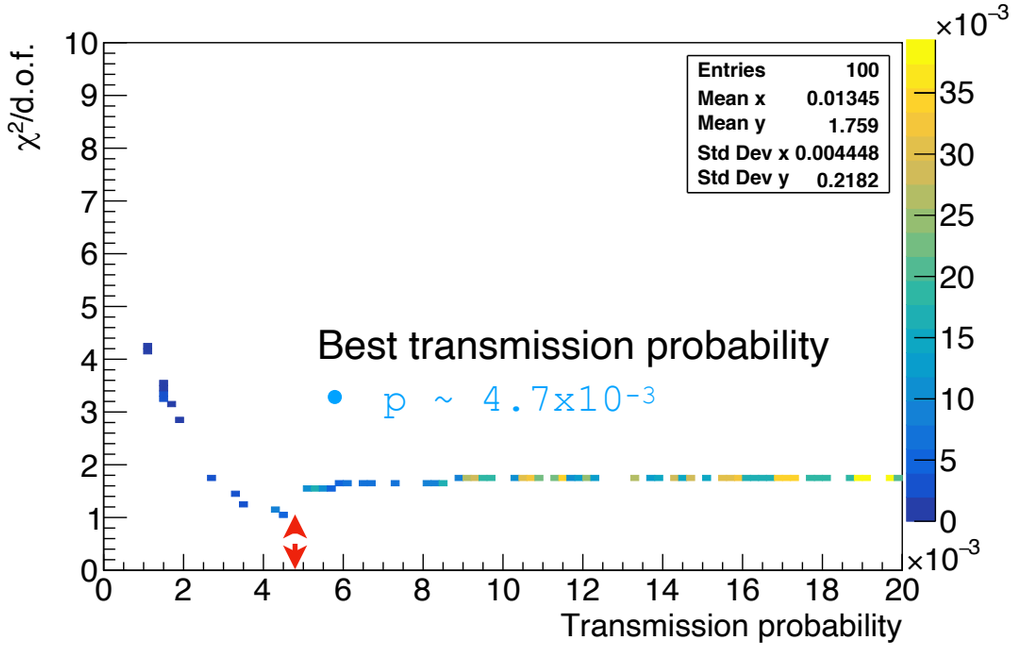
- `N = 100` extractions of transmission probability, `p`

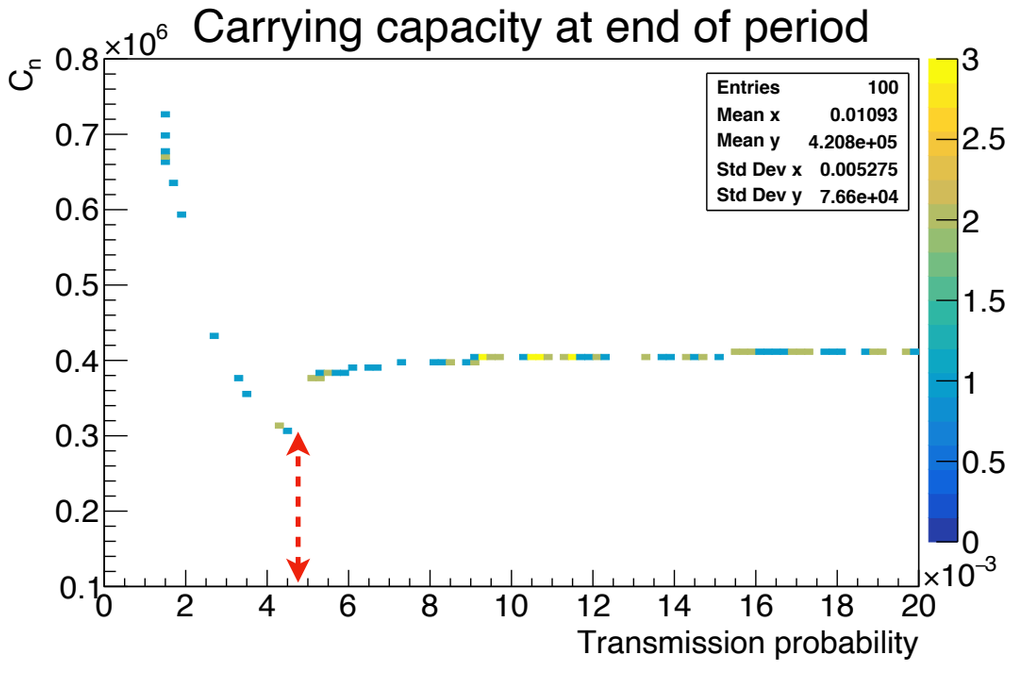
Fixed parameters:

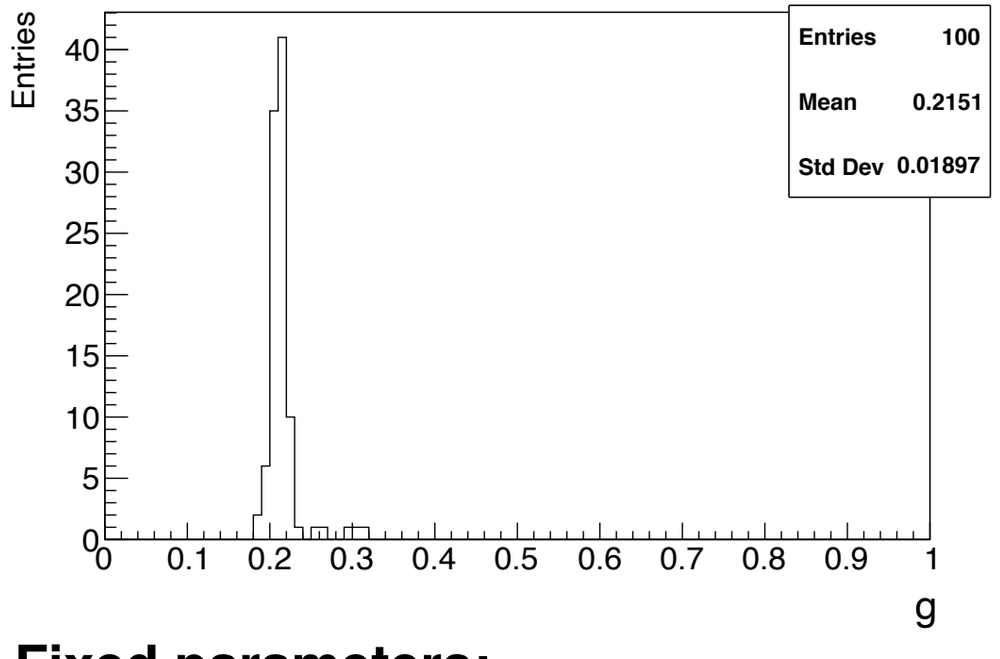
- `r = 0.023` ➜ plot Δrecovered/active
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography

Application to data: fit to single time period









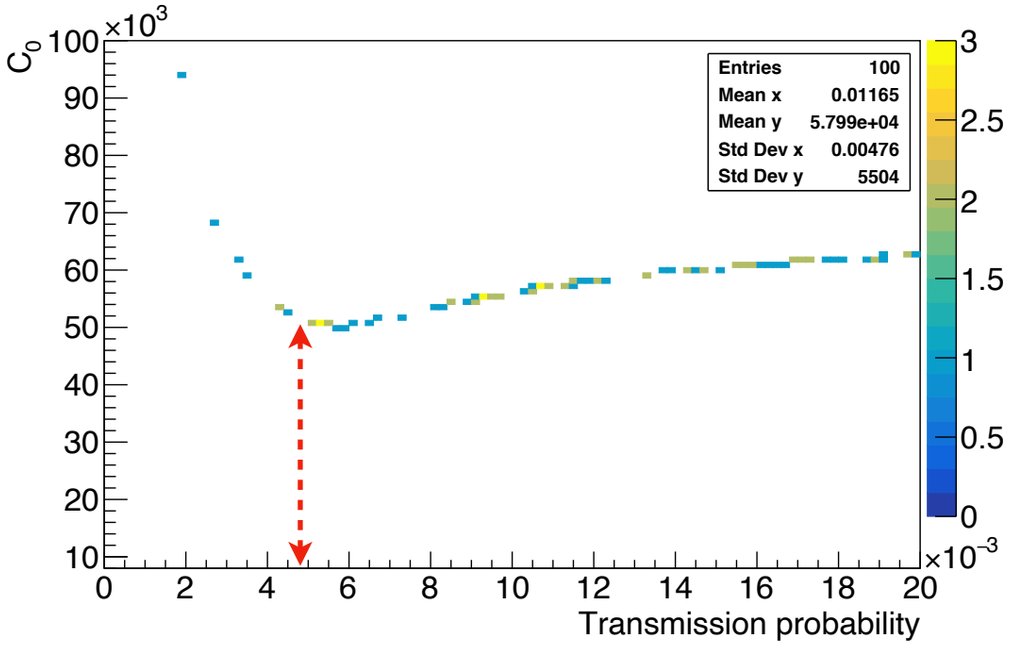
Fit data from 15th to 26th day (period 3)

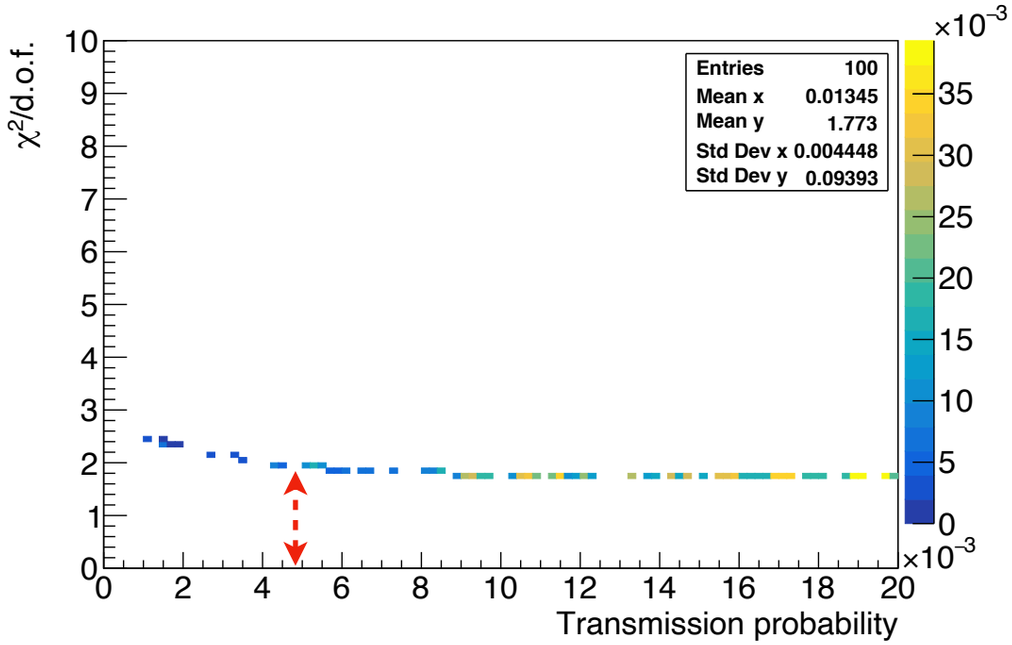
- `N = 100` extractions of transmission probability, `p`

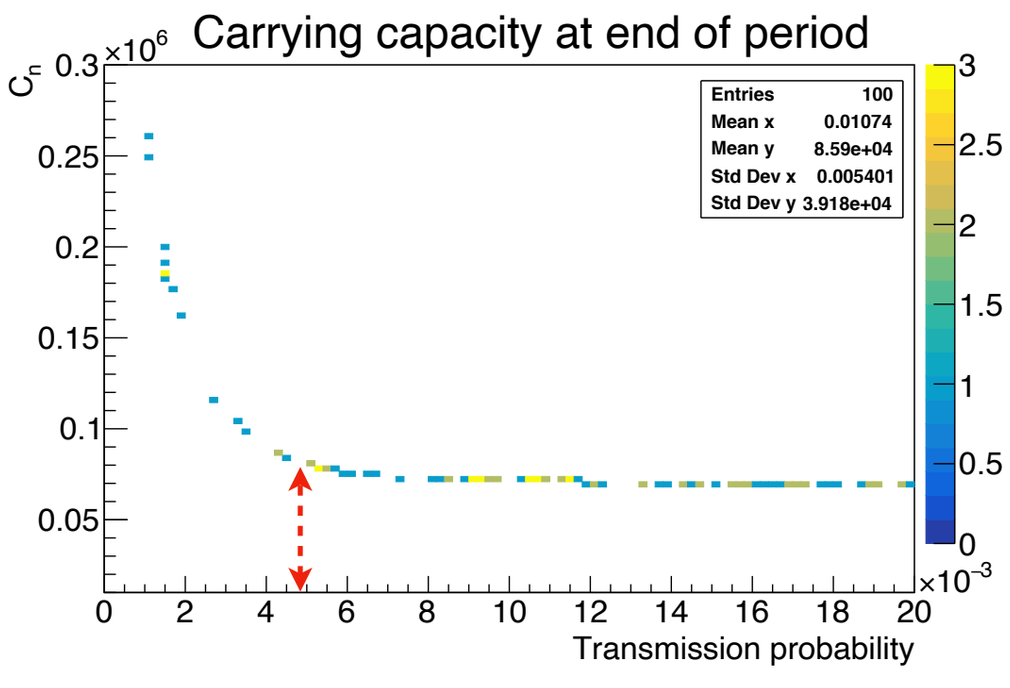
Fixed parameters:

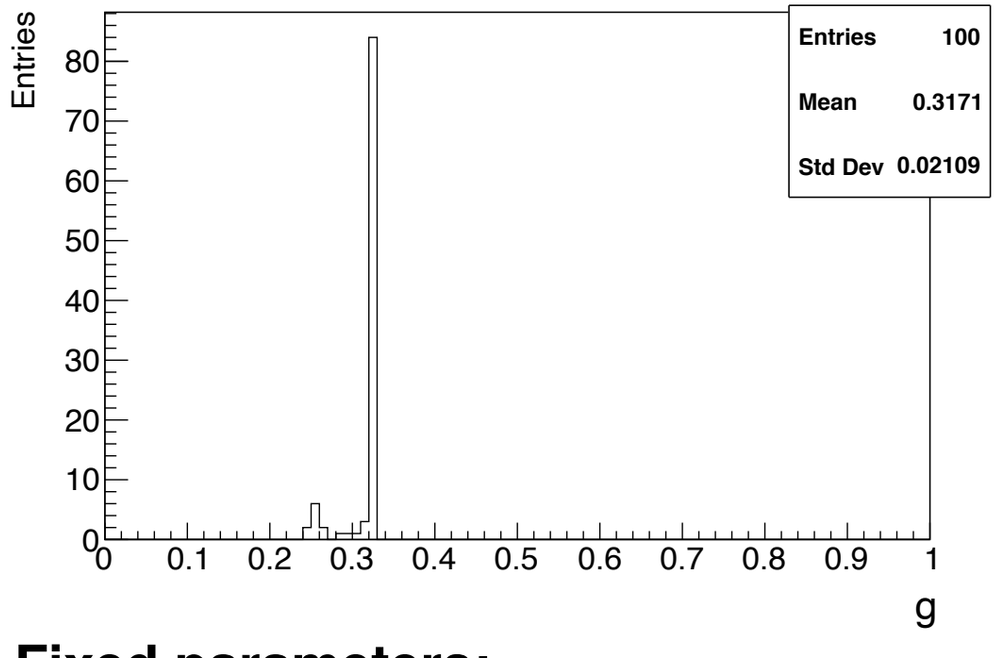
- `r = 0.023` ➜ plot Δrecovered/active
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography

Application to data: fit to single time period









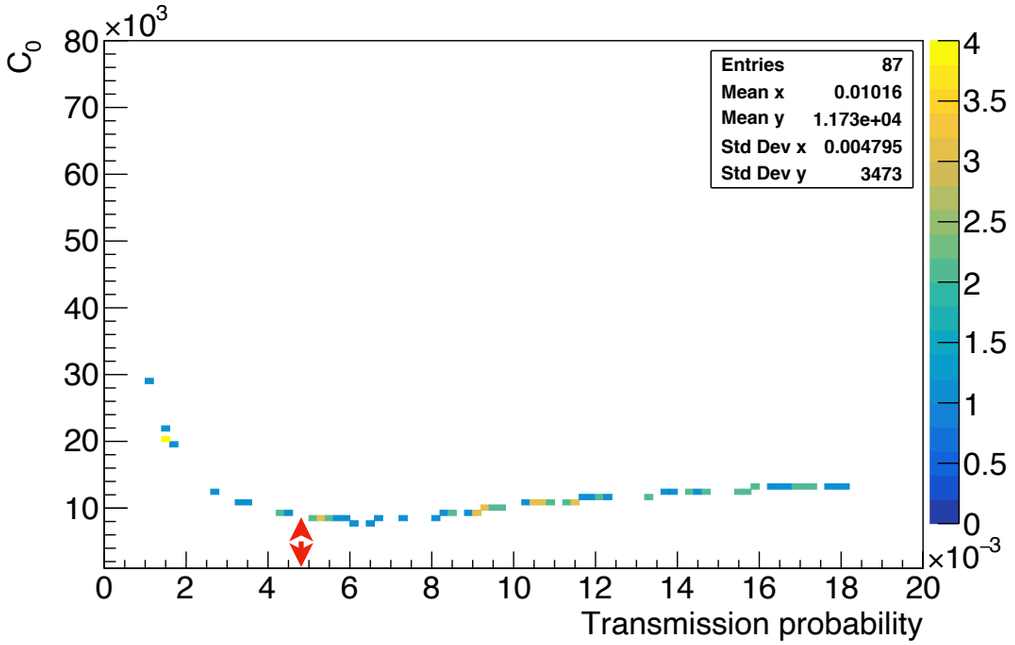
Fit data from 9th to 14th day (period 2)

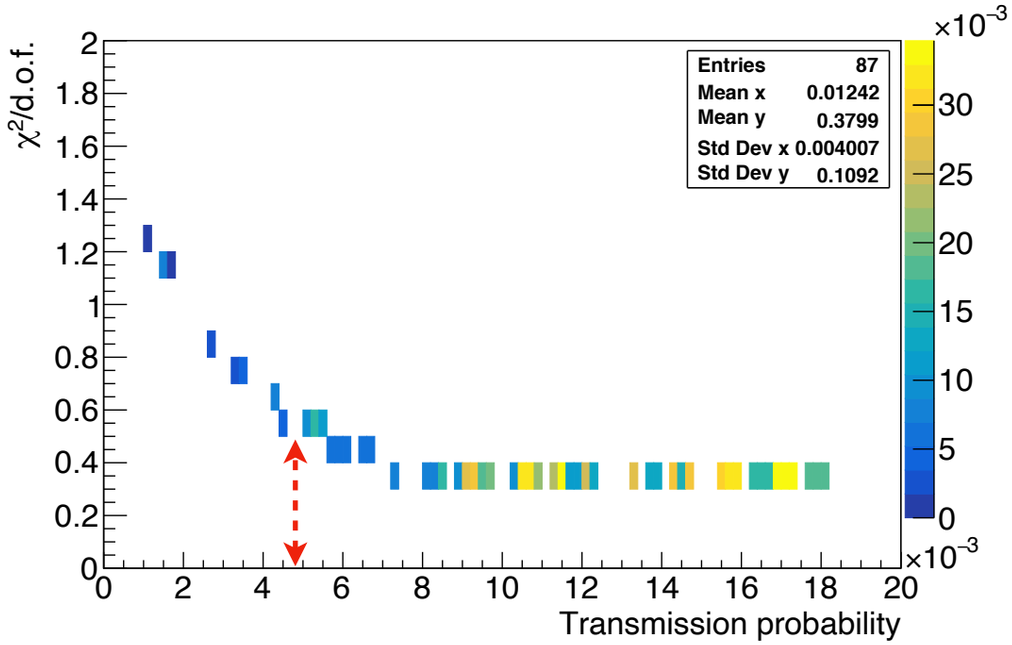
- `N = 100` extractions of transmission probability, `p`

Fixed parameters:

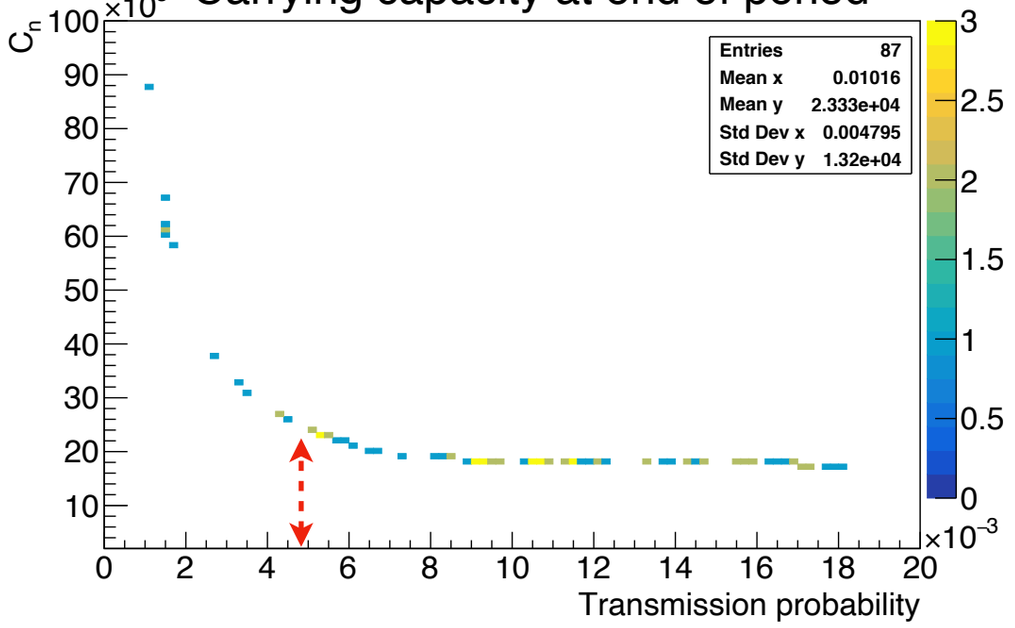
- `r = 0.023` ➜ plot Δrecovered/active
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography

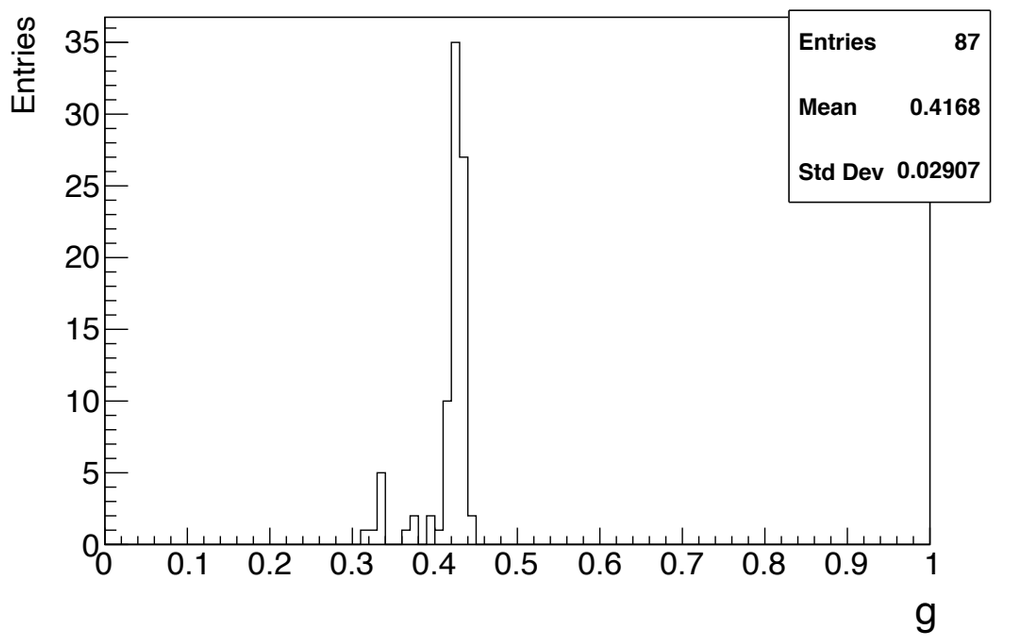
Application to data: fit to single time period





Carrying capacity at end of period





Fit data from 0th to 8th day (period 1)

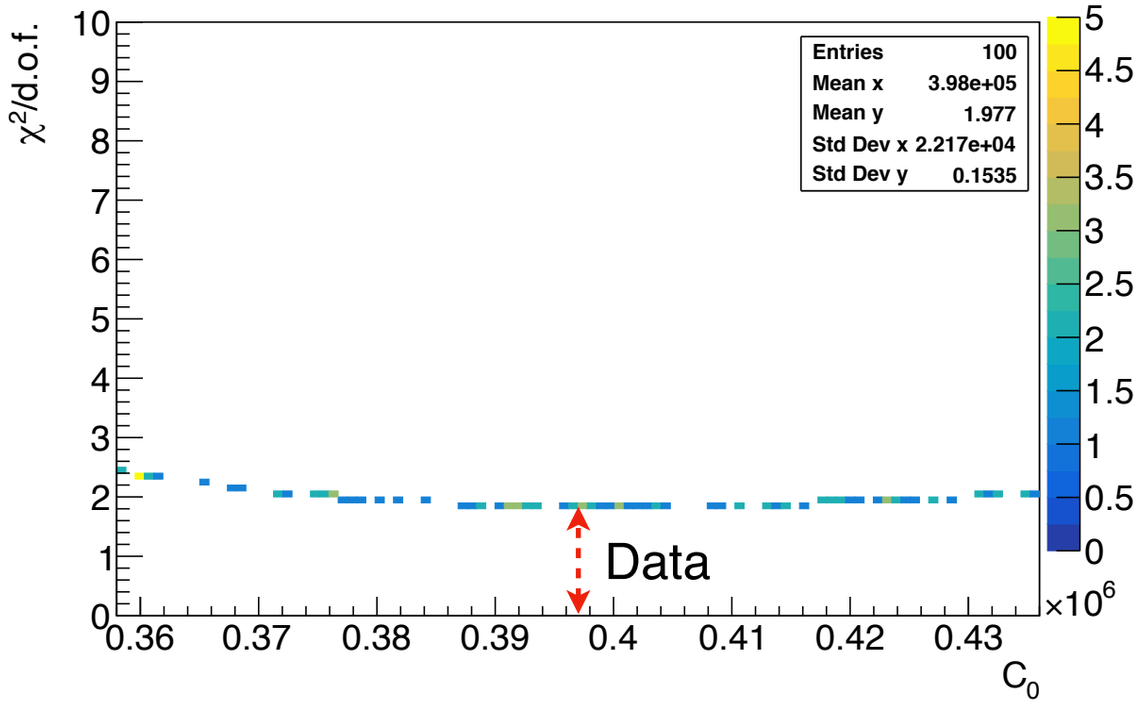
- `N = 100` extractions of transmission probability, **`p`**

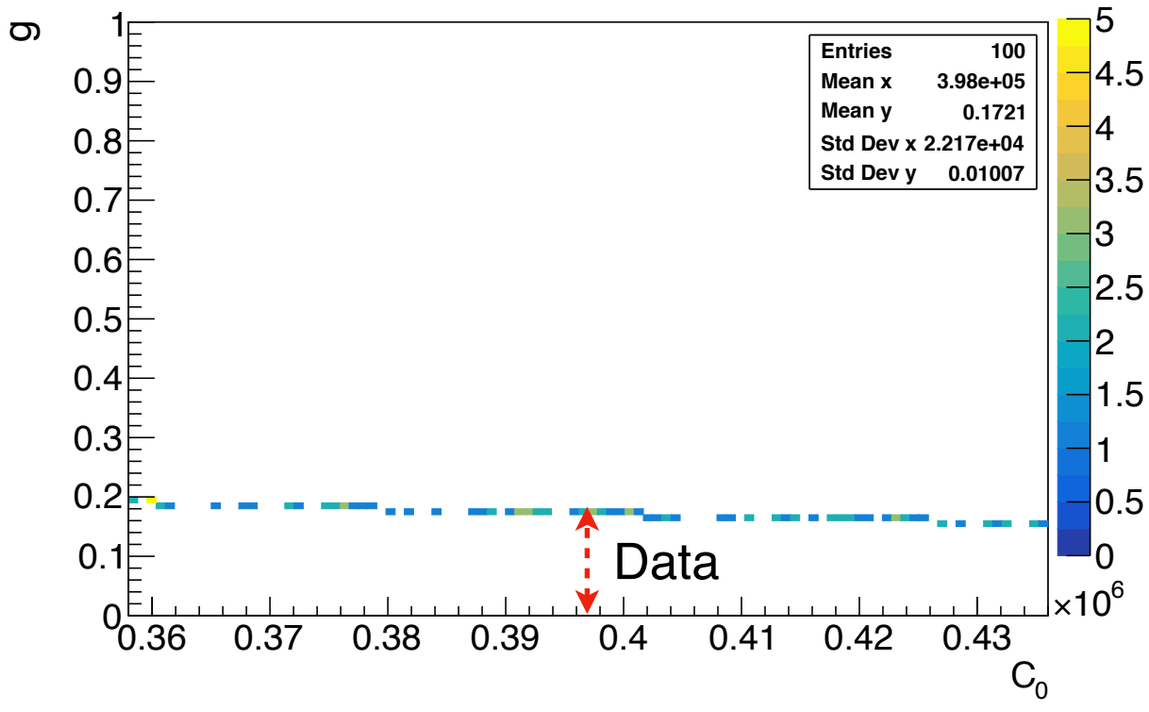
Period 3 and 4 have slightly different transmission probability, we choose

- **`p ~ 4.7x10`$^{-3}$**

for compatibility of $\mathbf{N_n}$ and $\mathbf{C_n}$ across periods

Application to data: fit to single time period





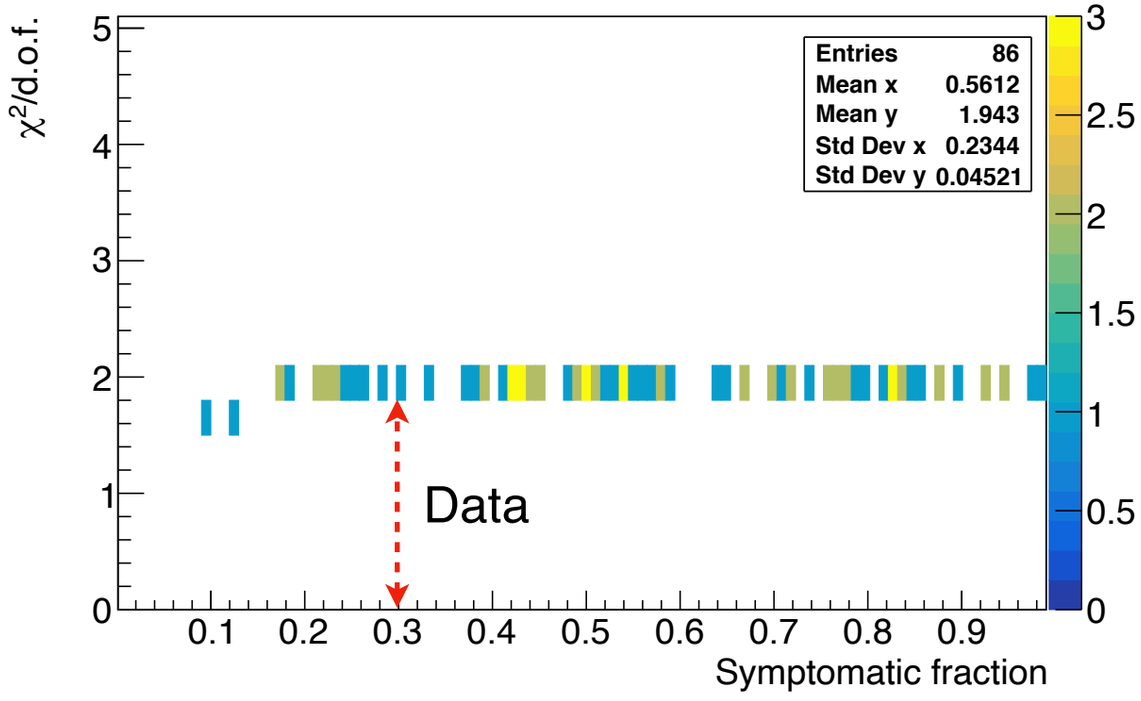
Fit data from 27th day to now (period 4)

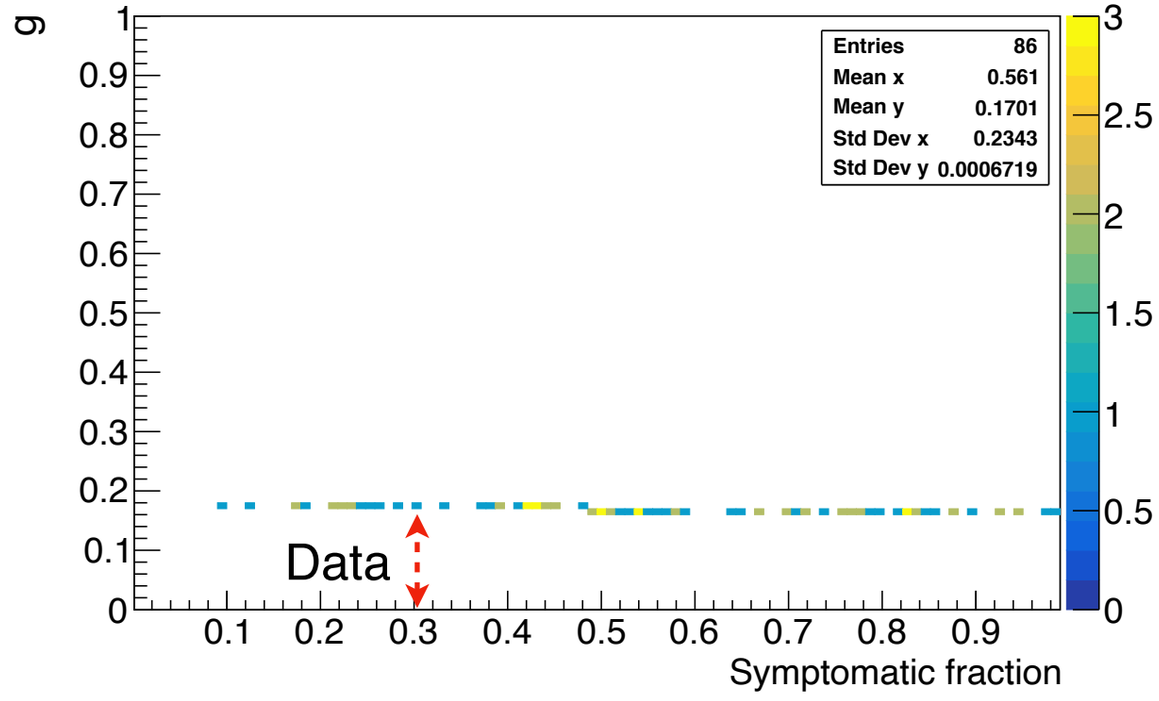
- `N = 100` extractions of C_0

Fixed parameters:

- `r = 0.023` ➜ plot Δrecovered/active
- `p = 4.7x10-3`
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography

Application to data: fit to single time period





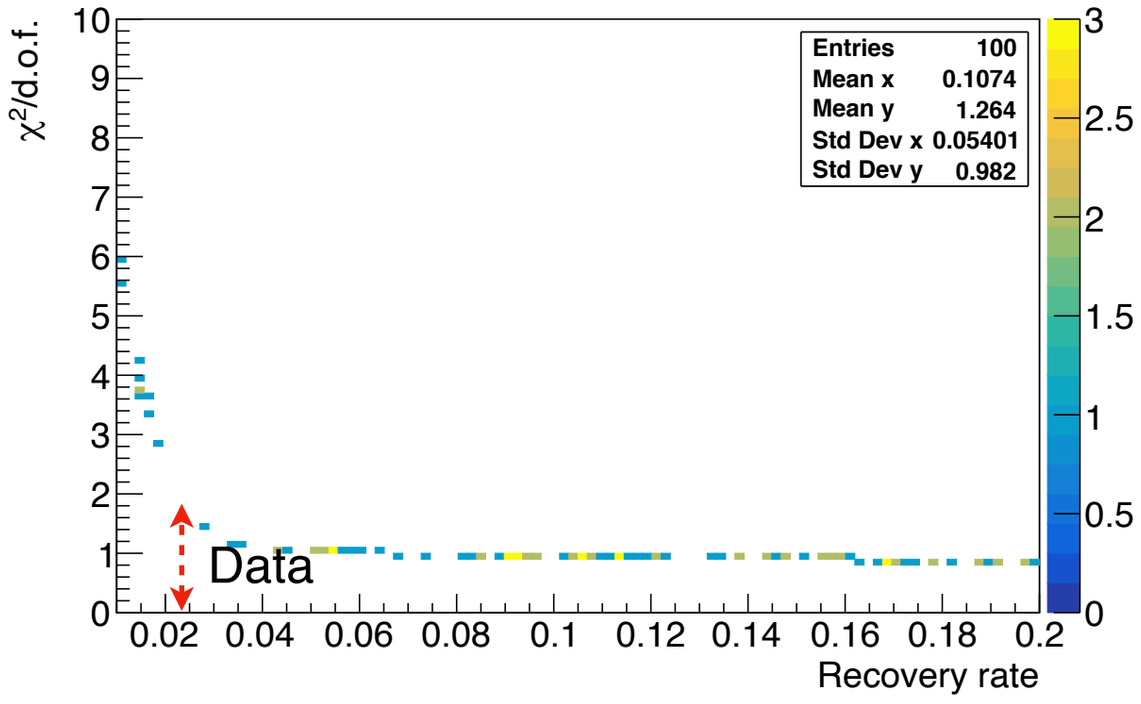
Fit data from 27th day to now (period 4)

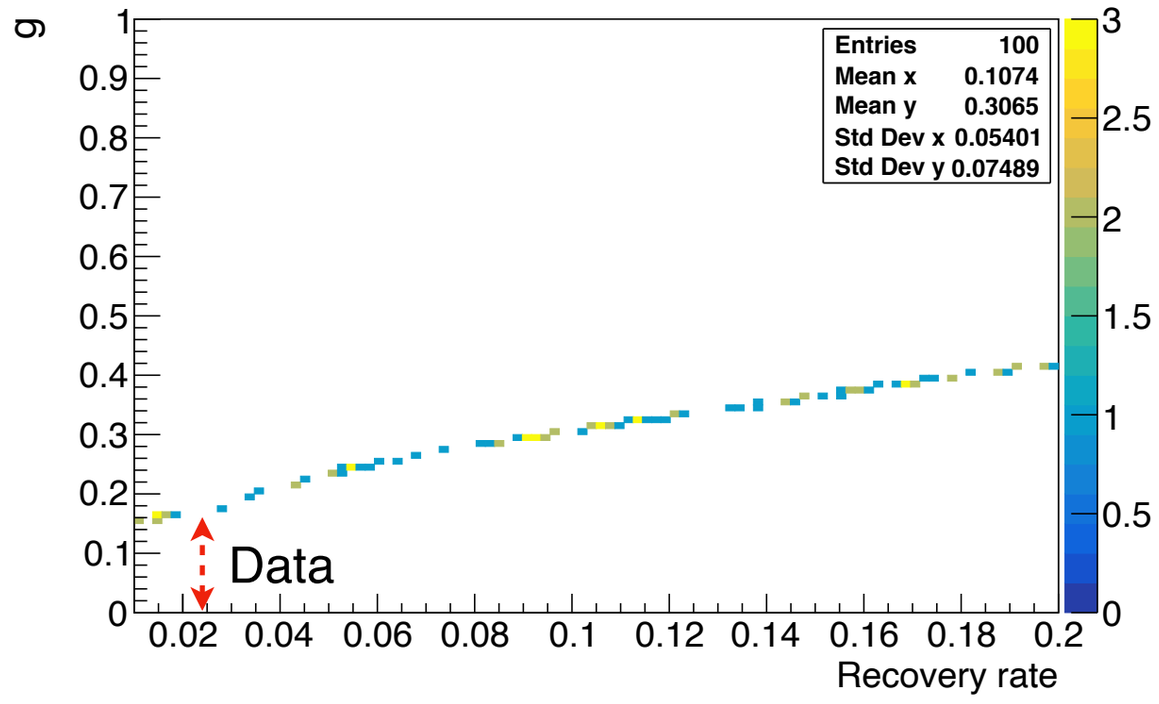
- `N = 100` extractions of symptomatic fraction

Fixed parameters:

- `r = 0.023` ➜ plot Δrecovered/active
- `p = 4.7x10⁻³`
- `T = 60x10⁶` ➜ demography

Application to data: fit to single time period





Fit data from 27th day to now (period 4)

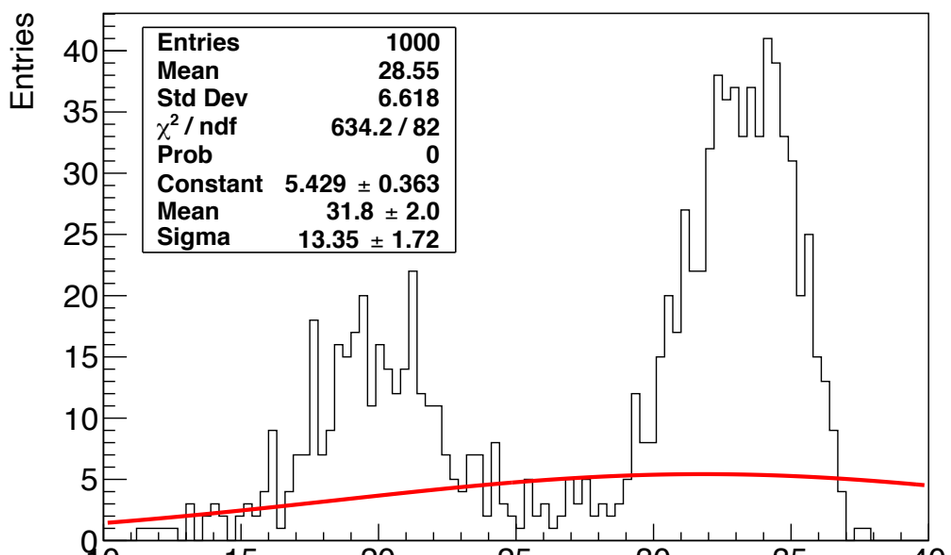
- `N = 100` extractions of **`r`**

Fixed parameters:

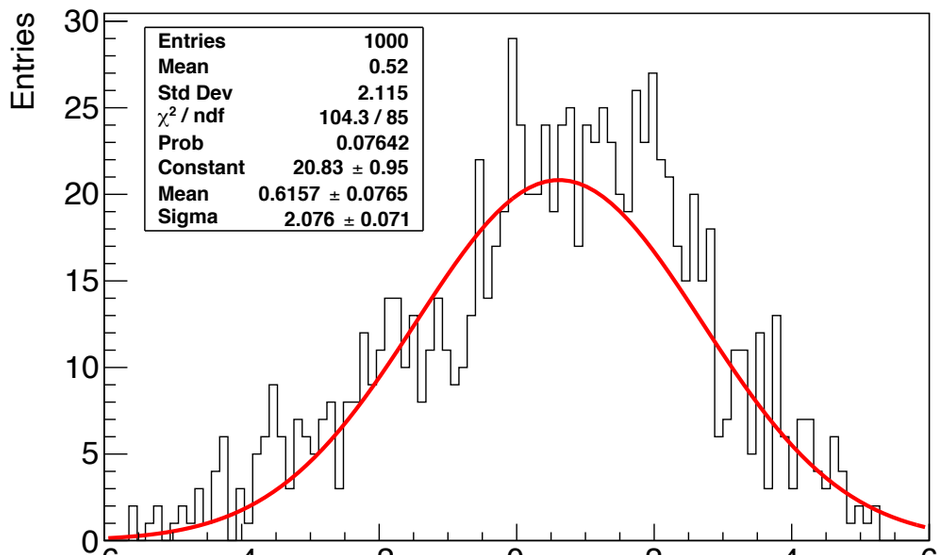
- **`p = 4.7x10⁻³`**
- Symptomatic fraction **`= 0.3`** ➜ literature
- **`T = 60x10⁶`** ➜ demography

Pseudo experiment studies

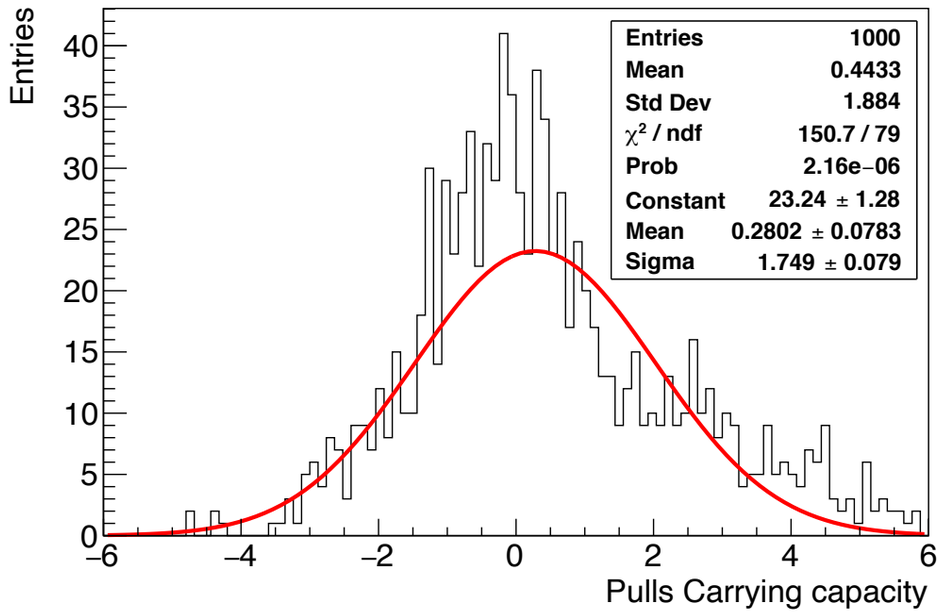
Generated 1000 pseudo experiments of period 4, and re-fit them in order to check stability of the fit procedure



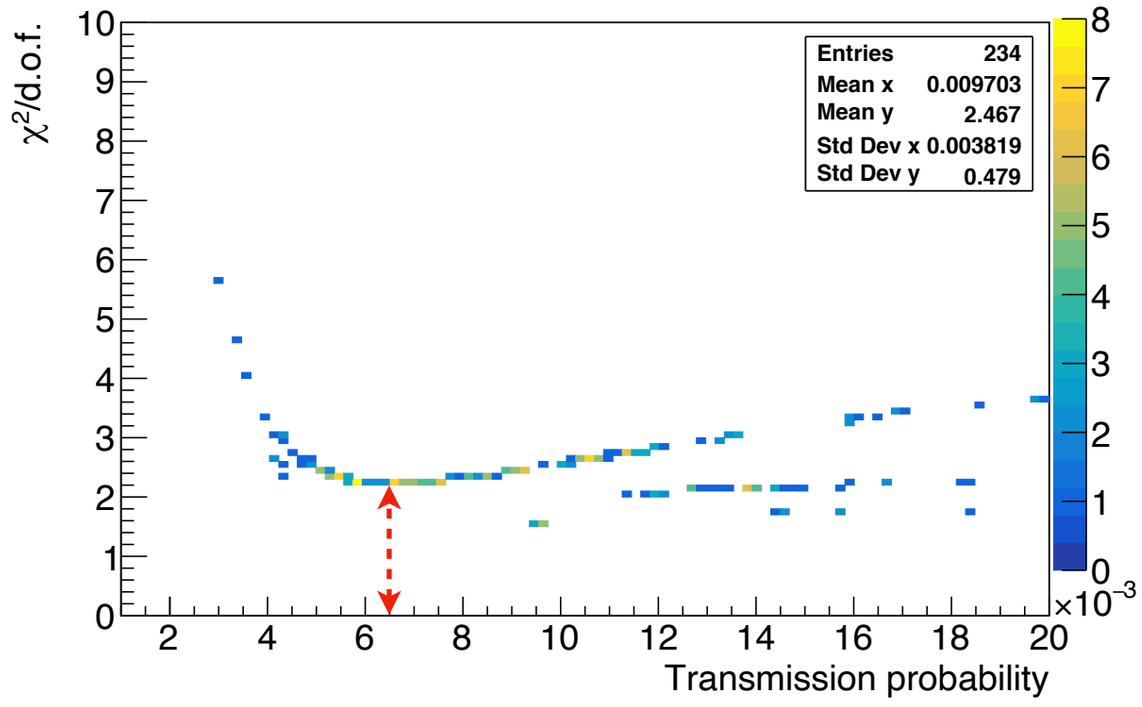
Pulls Initial population



Pulls Growth rate



Application to data: fit to multiple time-periods

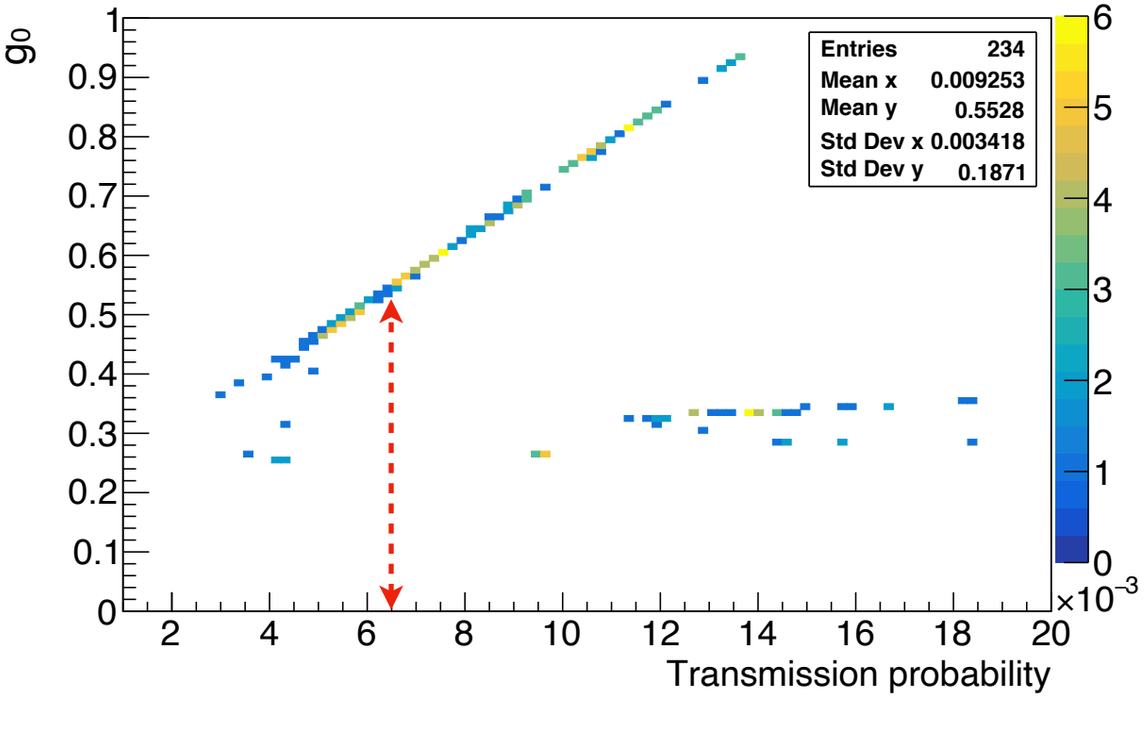


Joint fit periods **1 + 2 + 3 + 4**, with smearing

- `N = 400` extractions of transmission probability, `p`

Fixed parameters:

- `r = 0.023` ➜ plot Δrecovered/active
- Symptomatic fraction `= 0.3` ➜ literature
- `T = 60x10⁶` ➜ demography



Best transmission probability

- `p ~ 6.5x10⁻³`