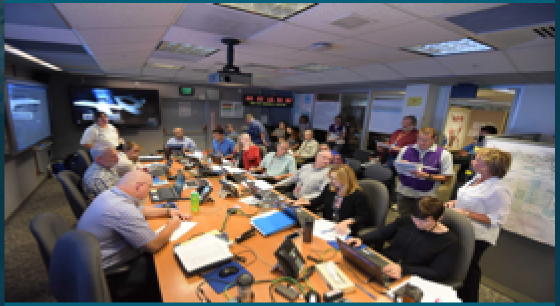
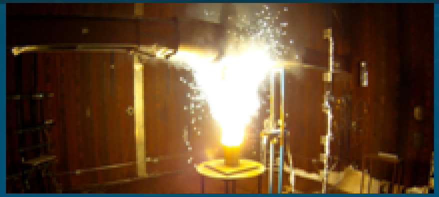
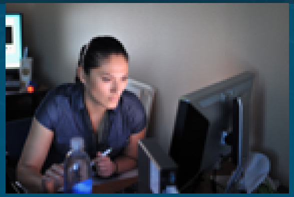
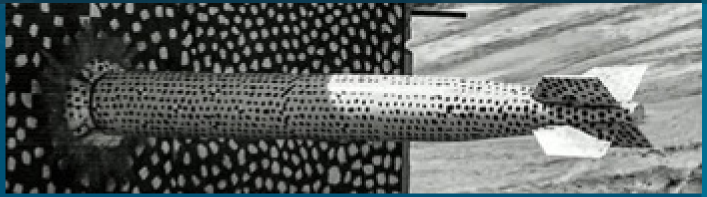
SAND2021-4179PE

# Mathematical Modeling and Analysis for Emerging Infectious Diseases









*PRESENTED BY*

Erin C.S. Acquesta

Presented to: UNM Health and Environmental Communication

April 8th, 2021

Material is derived from collaborations with

SNL:Walt Beyeler, Haedi Deangelis, Pat Finley, Kate Klise, Monear Makvandi, Teresa Portone, Jaideep Ray, Cosmin Safta, and many others. MIT: Raj Dandekar, Chris Rackauckas

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# Outline

- Introduction to Epidemiology
- Epi Modeling Paradigms
- Compartmental Model System Analysis
- Modeling Mitigation Strategies

# Epidemiology

The study of the distribution and determinants of health-related states or events in *specified populations*, and the application of this study to the control of health problems [Last, 2001]

For more details, please reference the CDC's *Introduction to Epidemiology*:
https://www.cdc.gov/csels/dsepd/ss1978/Lesson1/Section1.html#_ref1

# Infectious Disease Nomenclature

*Pathology* of the Virus:

Viruses are named based on their genetic structure to facilitate the development of diagnostic tests, vaccines and medicines.

*Epidemiology* of the Disease:

Diseases are named to enable discussion on disease prevent, spread, transmissibility, severity and treatment.

| **Virus** | **Disease** |
|---|---|
| Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) | COronaVIrus Disease, 2019 (COVID-19) |

[WHO, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it ]

# Epidemiology Nomenclature

**Doubling Time, $T_d$**

The expected amount of time for the number of cumulative infections to double.

**Basic Reproduction Number, $R_0$**

The expected number of infections from one infected individual introduced into a population of 100% susceptible individuals.

**Replacement Number, $R(\text{t})$**

After the early stages of an epidemic has passed, the number of secondary infections is expected to go down as the number of susceptible individuals goes down.

**Herd Immunity, $\Psi$**

Implies the susceptible population is small enough, either through vaccination or immunity due to infection and recovery, that the effective secondary infection rate is less than 1.

**Non-Pharmaceutical Interventions**

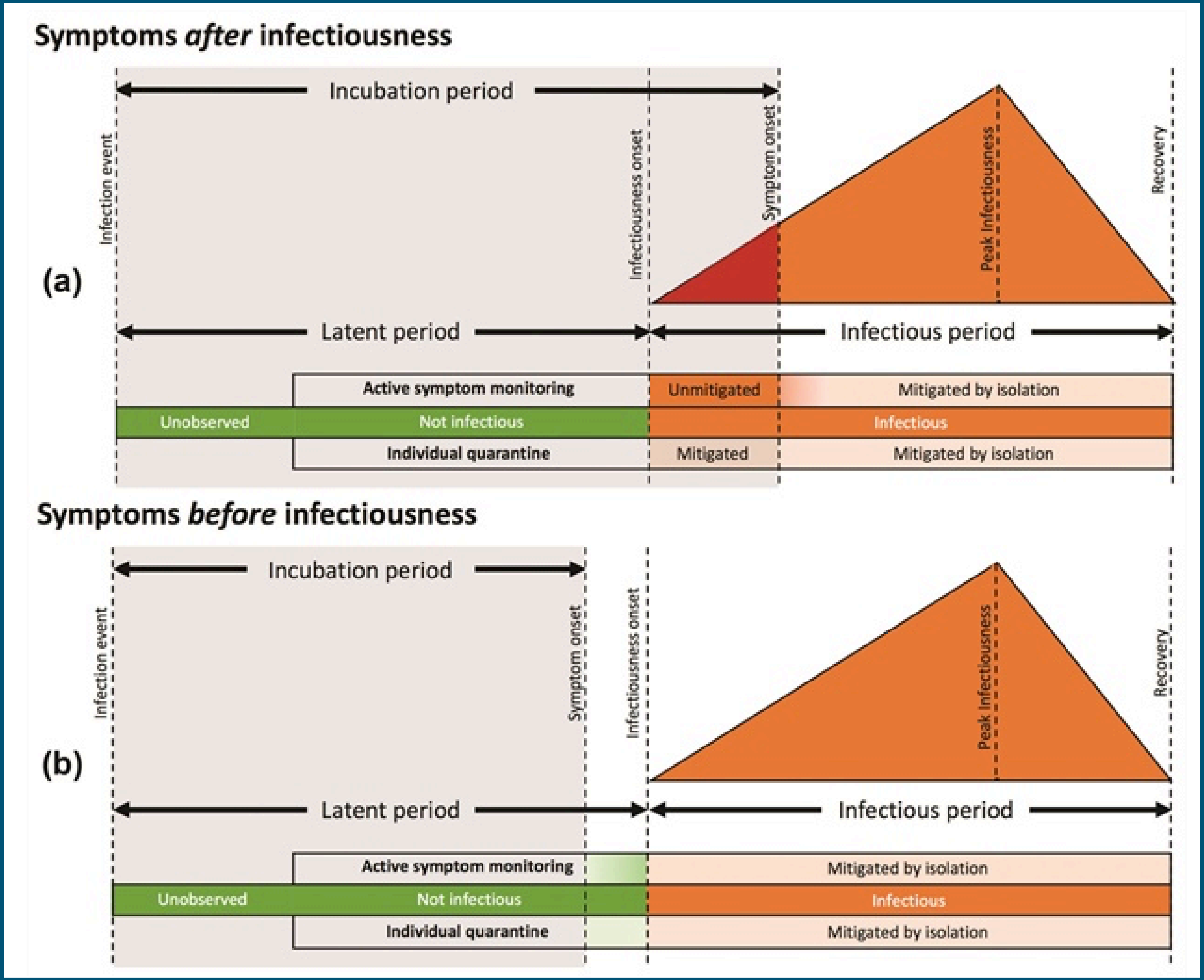
Social distancing, business & school closures, face masks, isolation, and quarantine.

**Pharmaceutical Interventions**

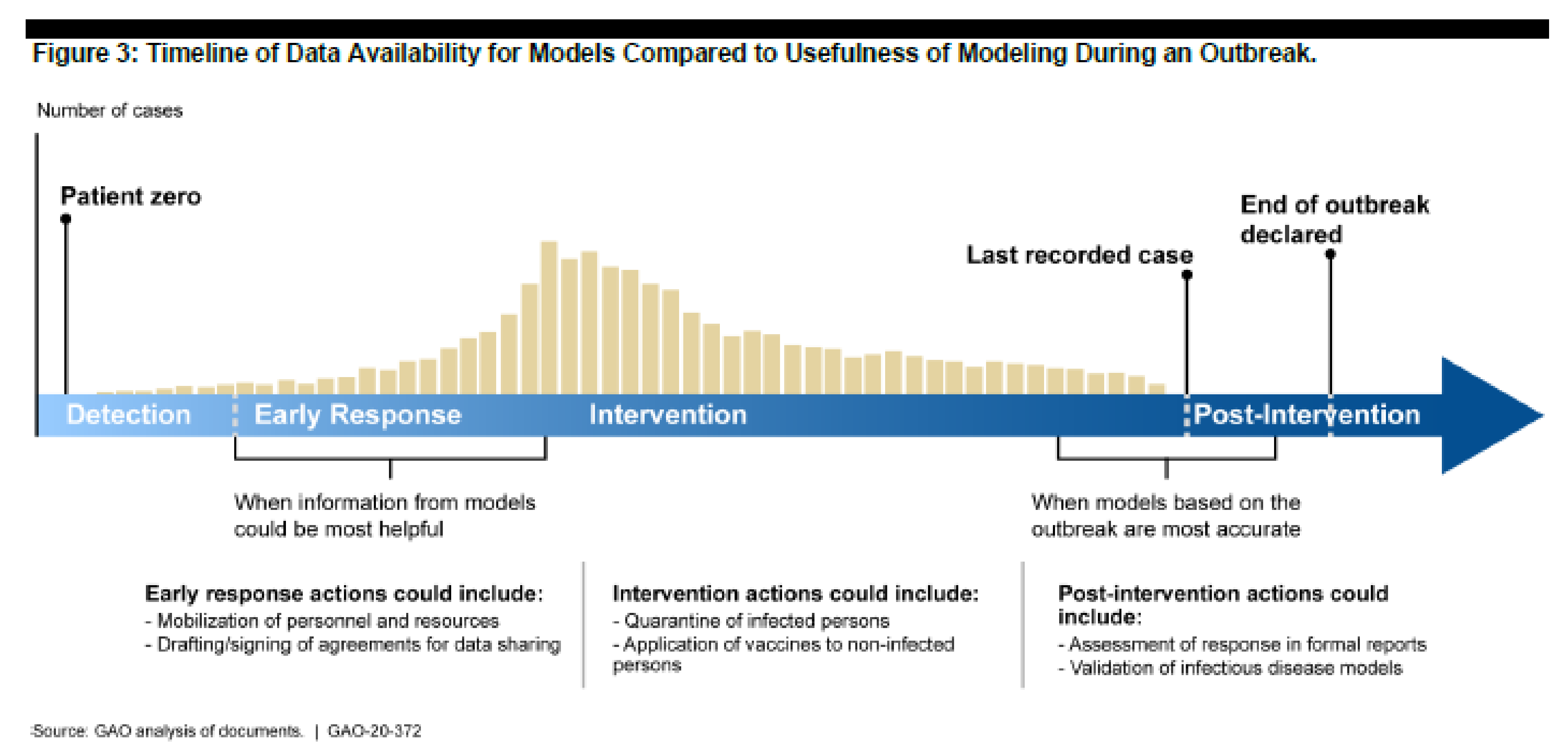
Vaccinations for the susceptible populations and/or therapeutics for the infected population.

# Infection to Infectious Timeline

[Childs, 2020]



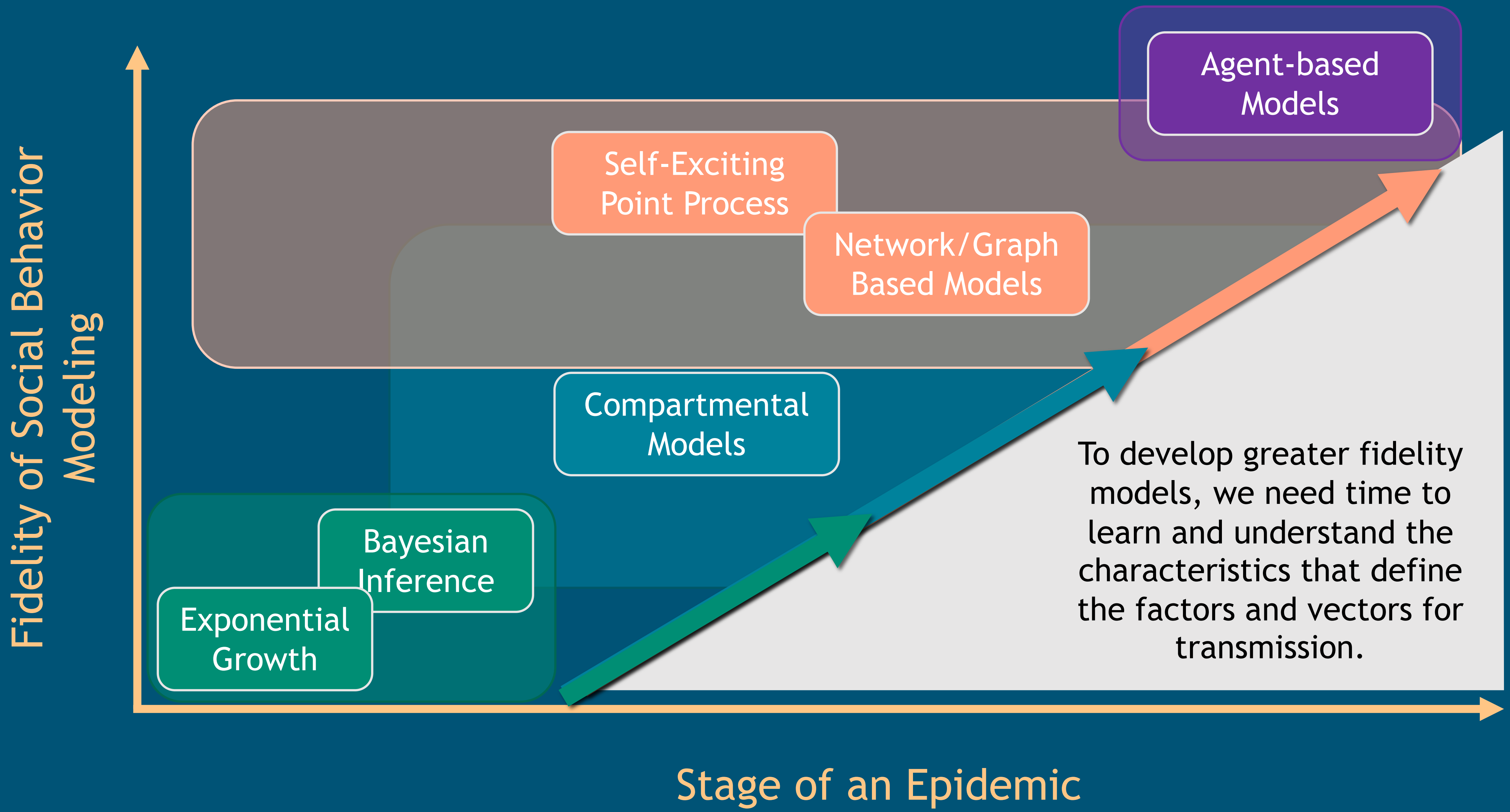
# Timeline of Data Availability and Model Usefulness



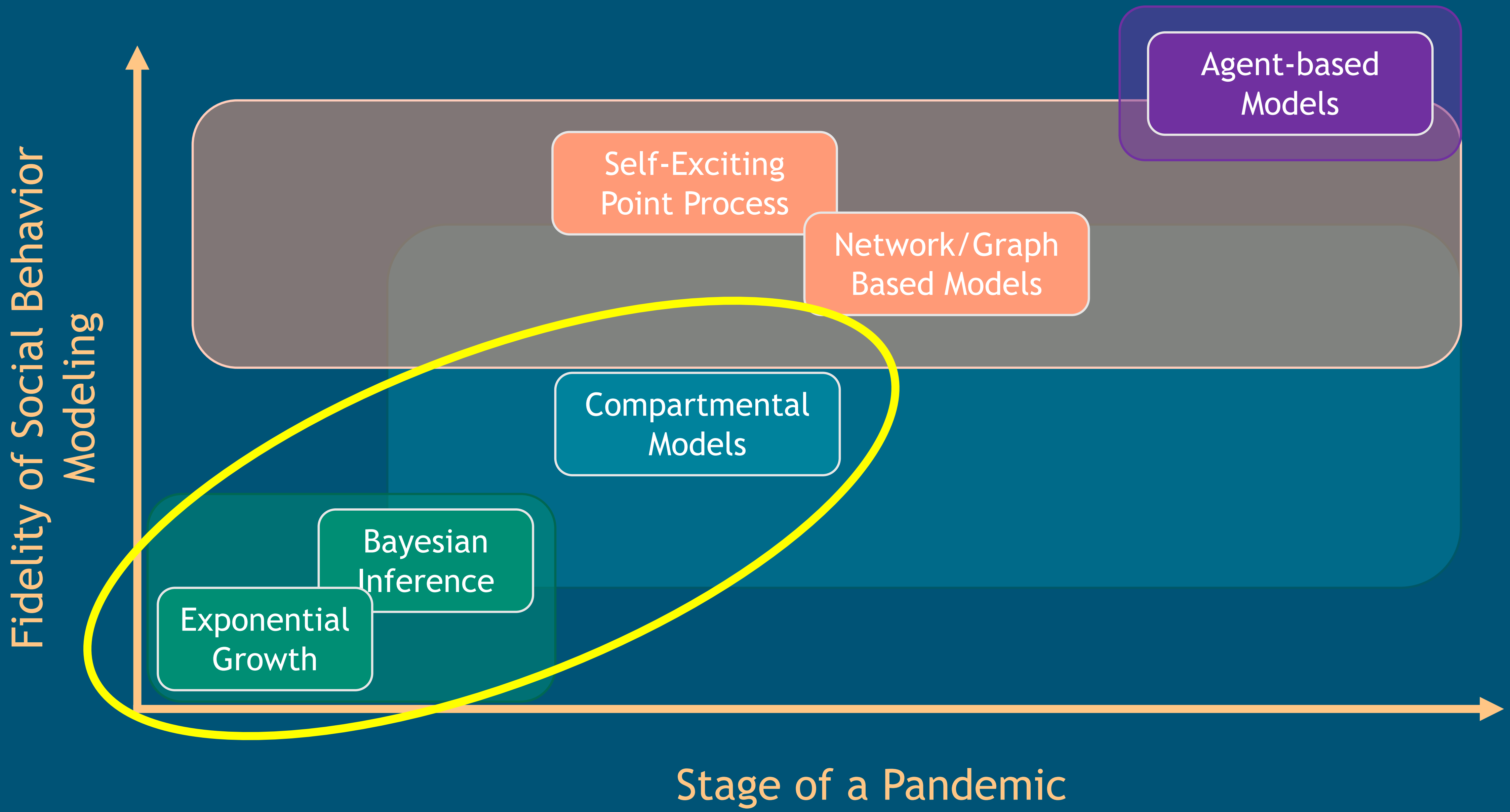

[U.S. Government Accountability Office, https://www.gao.gov/products/gao-20-372]

# Outline

# Epidemiology Modeling Paradigms



# Epidemiology Modeling Paradigms



# Exponential Growth

As an early stage model, these models are typically used to derive the secondary infection rate, $R_0$, for an emerging epidemic.

$T_d$ (Doubling Time) is observable from the case counts

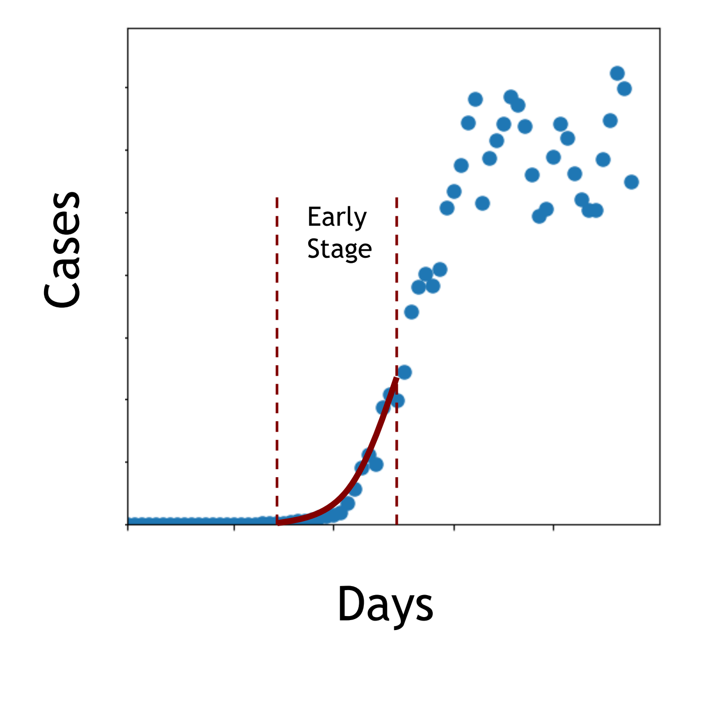
$$\Downarrow$$

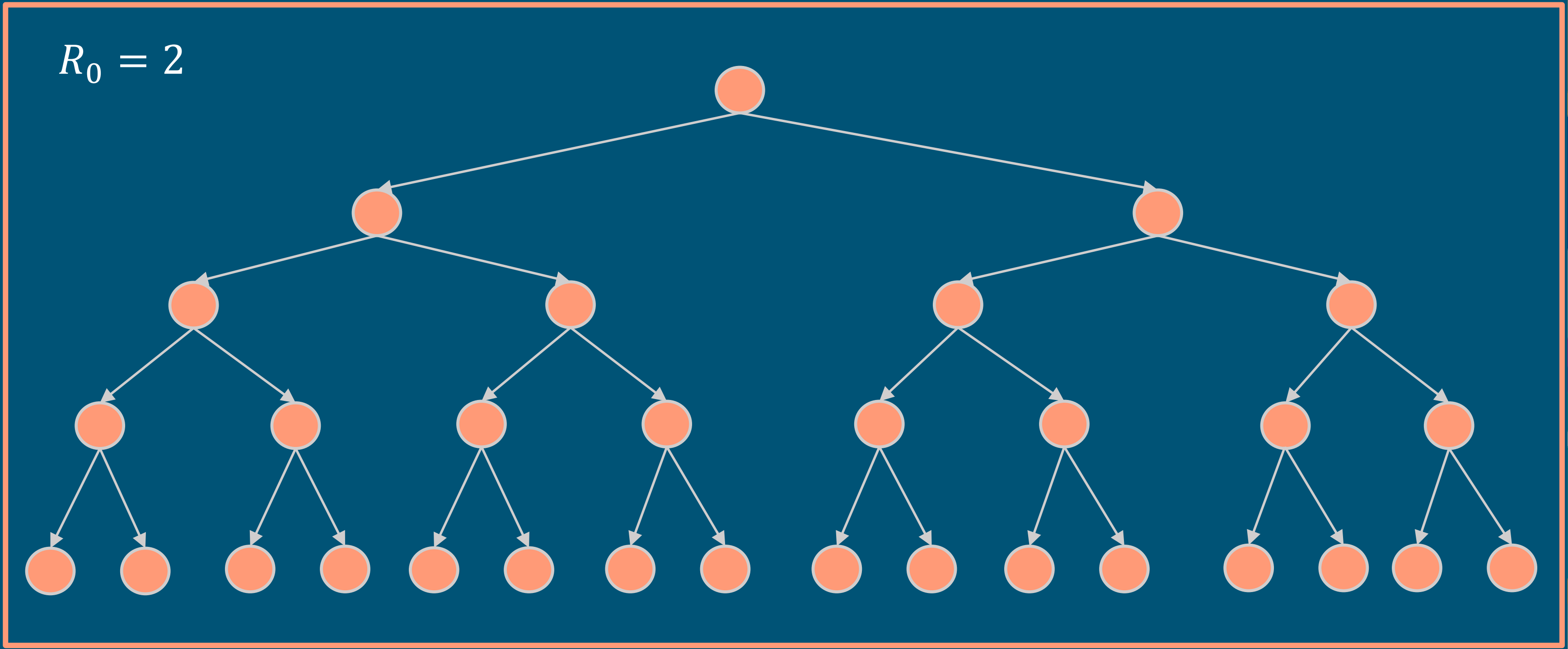
$$R_0 = \ln(2)\,/T_d$$

$$\Downarrow$$

$$I(t) = I_0 e^{R_0 t}$$

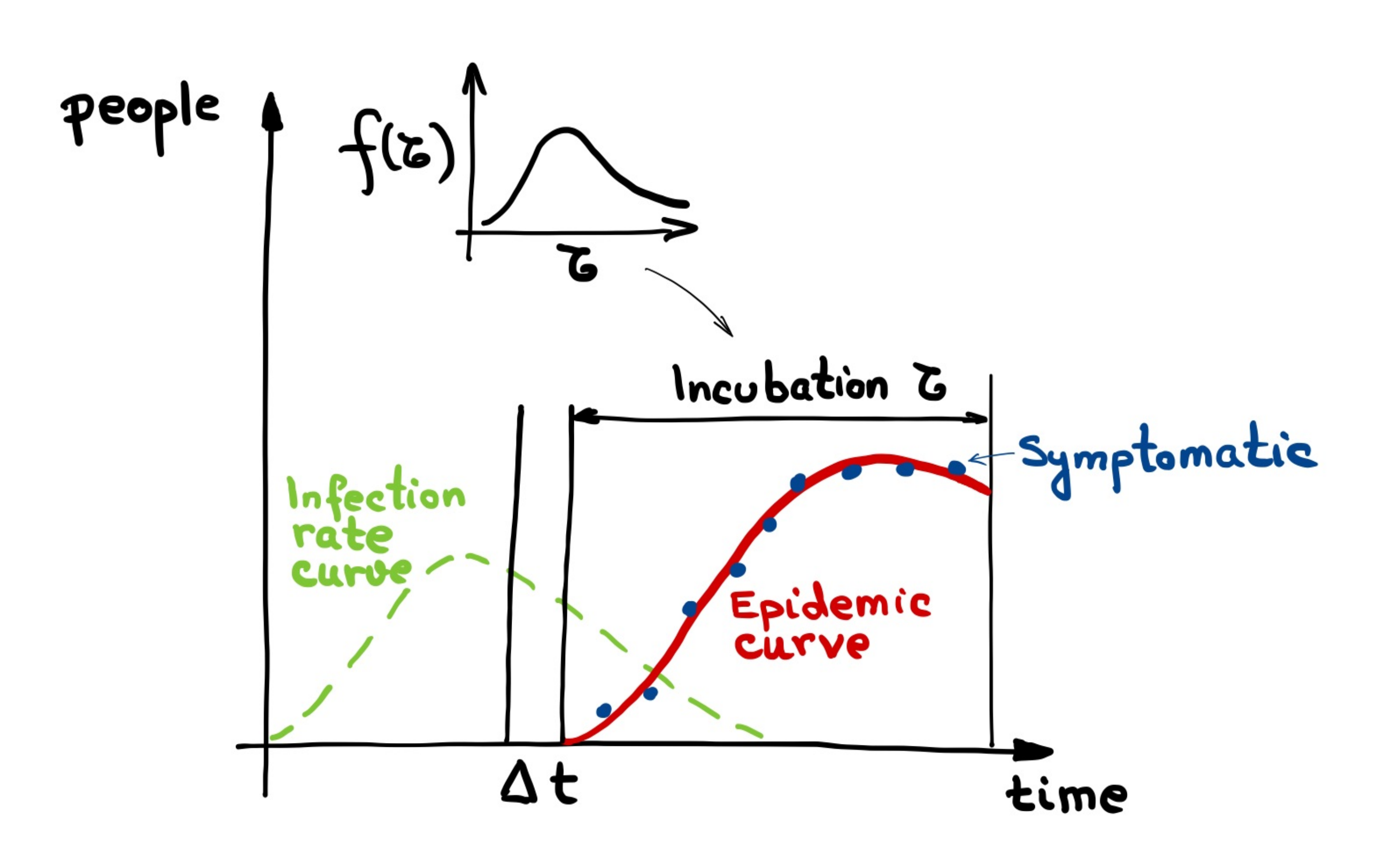
[Bertozzi, 2020]



# Bayesian Inference

From observable reported new cases, Bayesian models infer the infection rate curve (i.e. variable replacement number $R$) then push forward a predictive epidemic curve.




[Safta et al, 2011]

- Infection Rate curve modeled as a Gamma distribution with unknown shape ($k$) and scale ($\theta$) parameters

$$\mathrm{InfR}(\mathrm{t}-\mathrm{t}_0) \sim \Gamma(k, 1/\theta)$$

- The incubation rate is modeled using a log-normal distribution with parameters based on published results [Lauer, 2020]

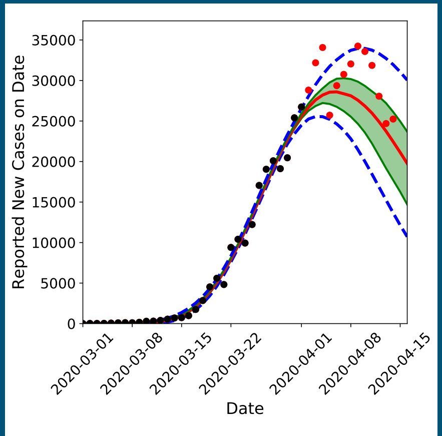
$$\mathrm{IncR} \sim \mathrm{Lognormal}(\mu(\xi_1), \sigma(\xi_2)^2)$$

# Bayesian Inference

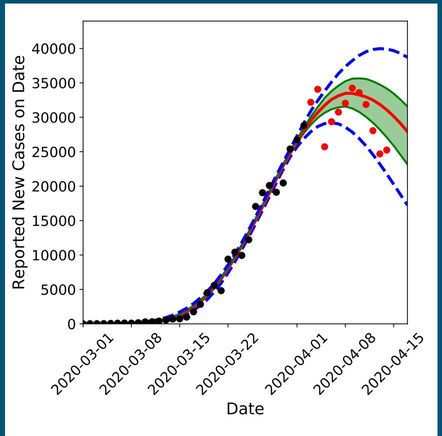
## We can now learn the bend in the curve, when we start to move away from exponential growth.

Example: COVID-19 Reported Cases in U.S. from April 1st – April 14th 2020

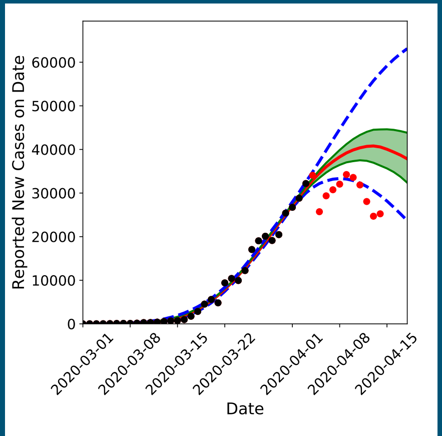
April 1



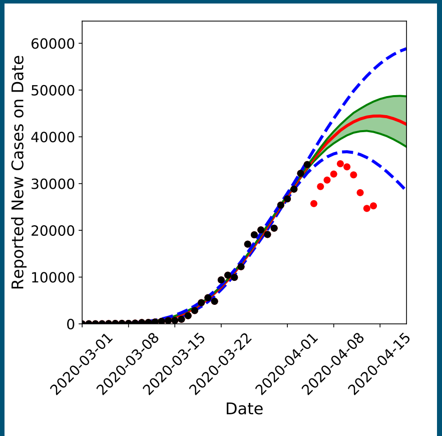

April 2



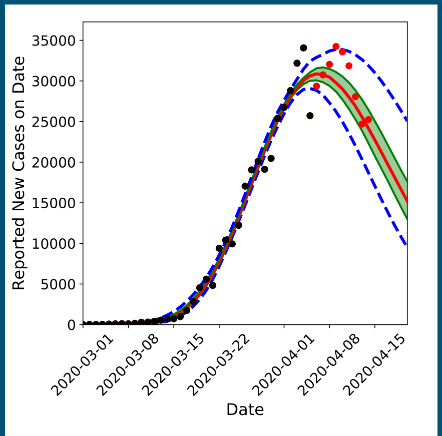

April 3



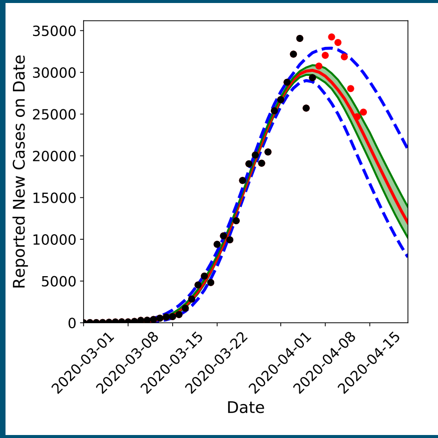

April 4



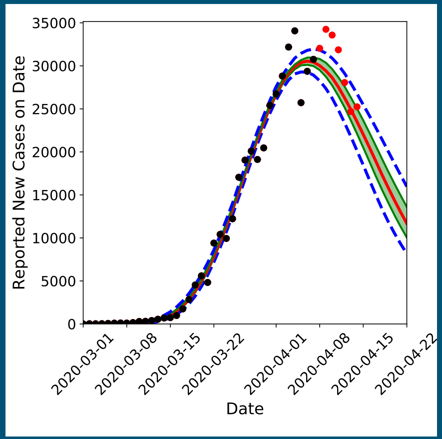

April 5



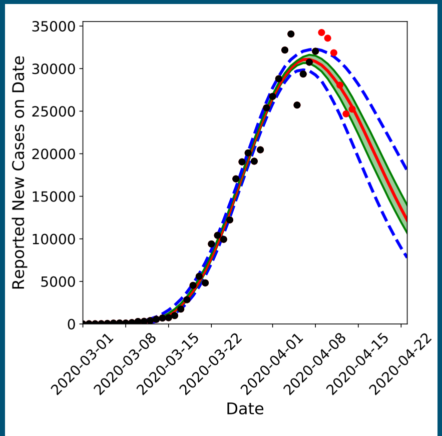

April 6



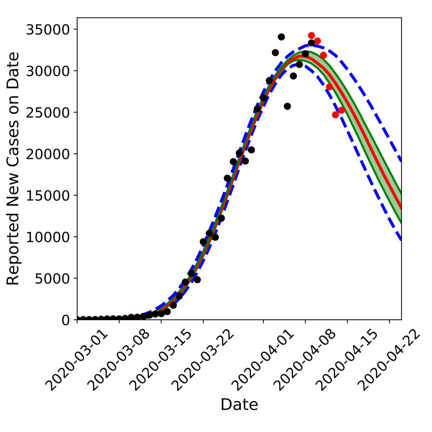

April 7



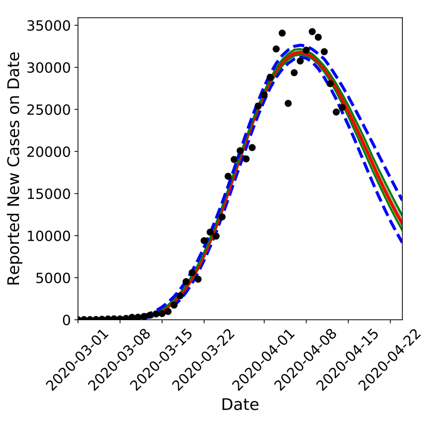

April 8




April 9




April 14




- Black symbols show data used for model inference and to generate forecasts
- Red symbols display data observed after the forecast was produced

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# Compartmental Model: Classic SEIR

[Hethcote, 2000]

Susceptible-Exposed-Infected-Recovered

System of ordinary differential equations (ODEs):

$$\dot{S}(t) = -\beta \frac{I(t)}{N(t)} S(t)$$

$$\dot{E}(t) = \beta \frac{I(t)}{N(t)} S(t) - \xi E(t)$$

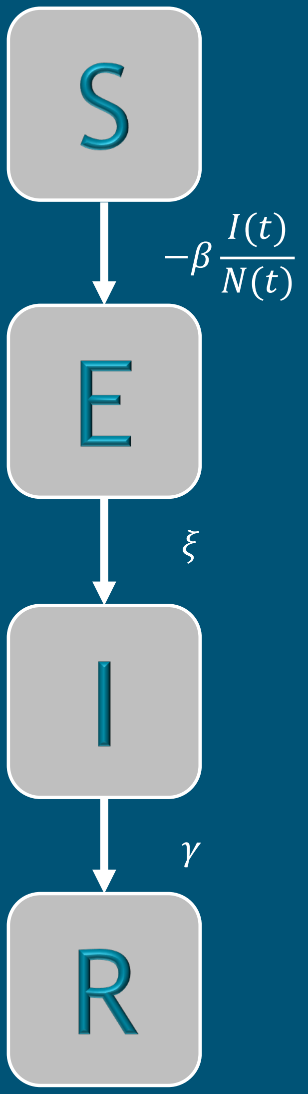
$$\dot{I}(t) = \xi E(t) - \gamma I(t)$$

$$\dot{R}(t) = \gamma I(t)$$

Force of Infection Function: $\lambda(t) \coloneqq \beta \frac{I(t)}{N(t)}$

Average Incubation Period: $\frac{1}{\xi}$

Average Infectious Period: $\frac{1}{\gamma}$




$$N(t) = S(t) + E(t) + I(t) + R(t)$$

# Compartmental Model: Classic SEIR

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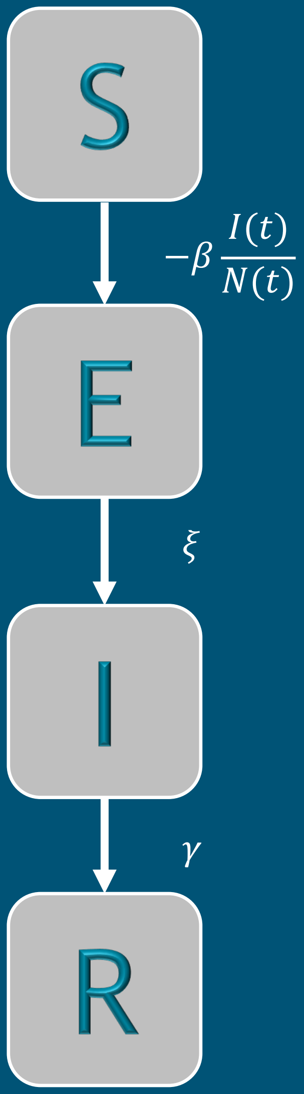
$$\dot{R}(t) = \gamma I(t)$$

Model $R_0 = \beta \frac{1}{\gamma}$




$$N(t) = S(t) + E(t) + I(t) + R(t)$$

Force of Infection Function: $\lambda(t) := \beta \frac{I(t)}{N(t)}$

Average Incubation Period: $\frac{1}{\xi}$

Average Infectious Period: $\frac{1}{\gamma}$

# Compartmental Model: a little more detailed

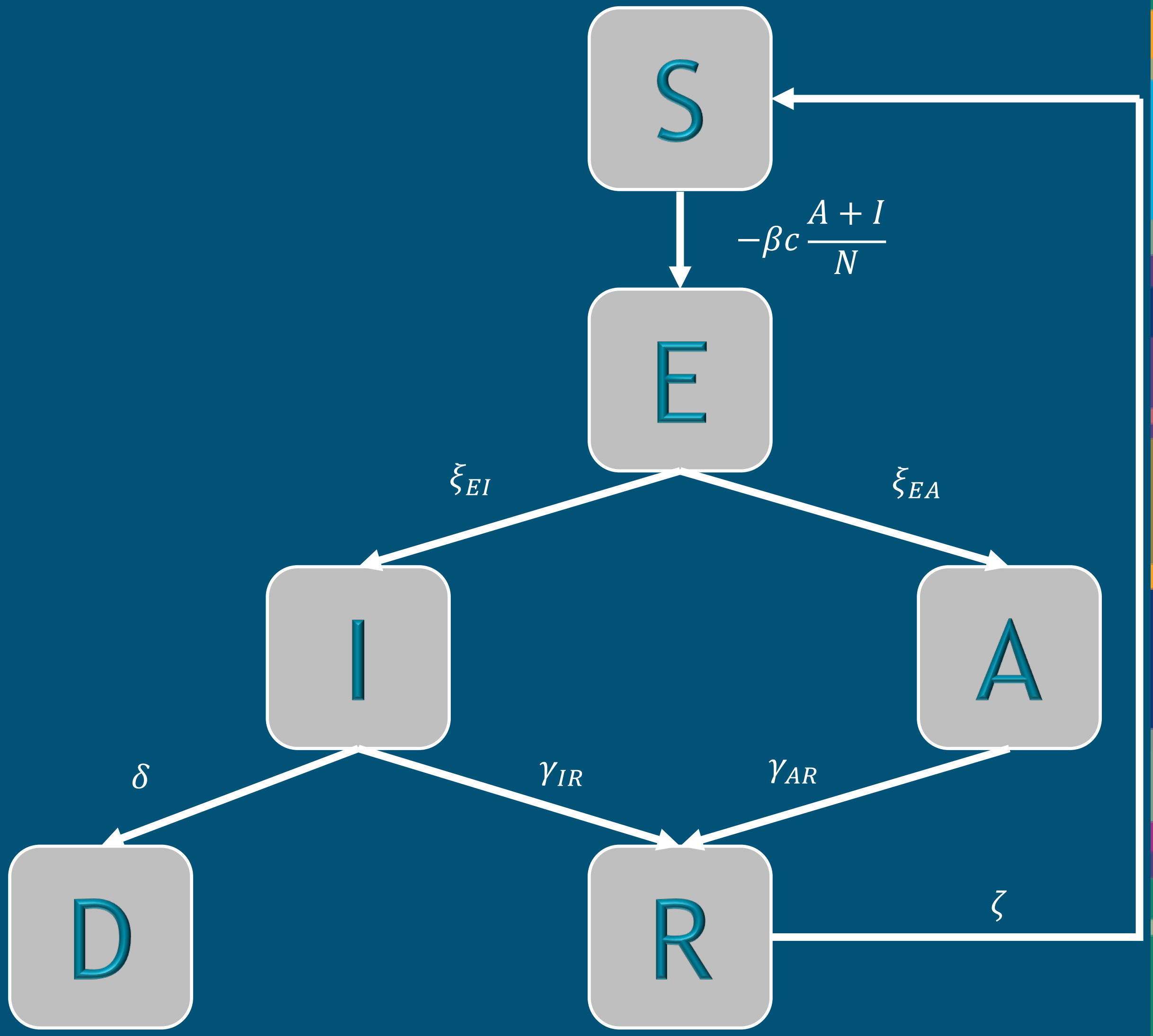
[Hethcote, 2000]

Susceptible-Exposed-Infected(Asymptomatic)
-Infected(Symptomatic)-Recovered

System of ordinary differential equations (ODEs):
[Note: at times we drop the state dependence on time, for simplified notation]

$$\dot{S} = -\beta c \frac{A+I}{N} S + \zeta R$$
$$\dot{E} = \beta c \frac{A+I}{N} S - (\xi_{EA} + \xi_{EI}) E$$
$$\dot{A} = \xi_{EA} E - \gamma_{AR} A$$
$$\dot{I} = \xi_{EI} E - \gamma_{IR} I - \delta I$$
$$\dot{R} = \gamma_{AR} A + \gamma_{RI} I - \zeta R$$
$$\dot{D} = \delta I$$

Model $R_0 = ??$




$$N = S + E + A + I + R$$

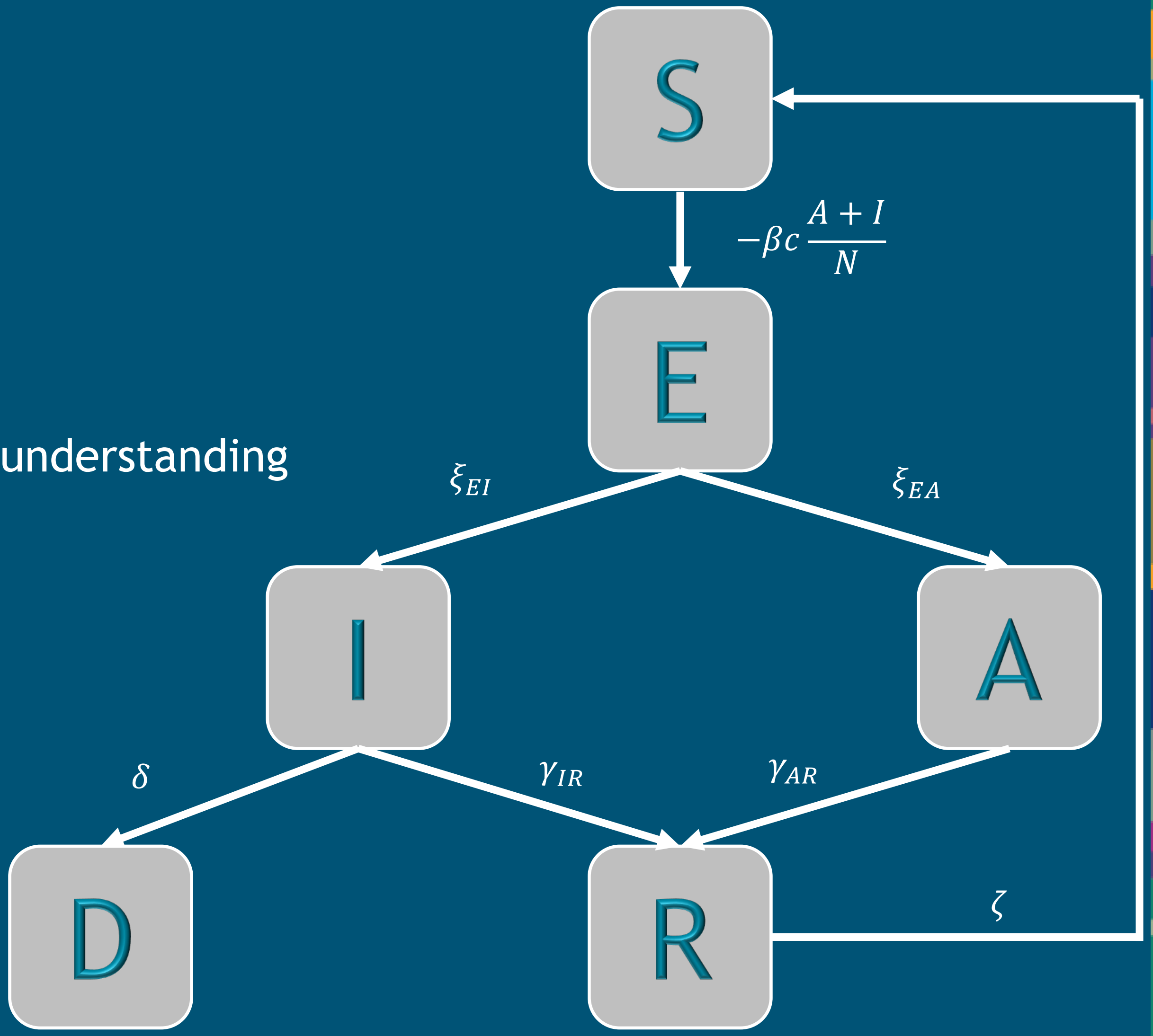
# Model $R_0$: An intuition based assessment

Practical Assessment:

- When $R_0 > 1$, we expect the disease to persist and spread throughout the population
- When $R_0 < 1$, we expect the disease to die out

Force of Infection Function: $\lambda(t) \coloneqq \beta c \frac{A(t)+I(t)}{N(t)}$

- the force of infection function can help guide us in understanding the model $R_0$



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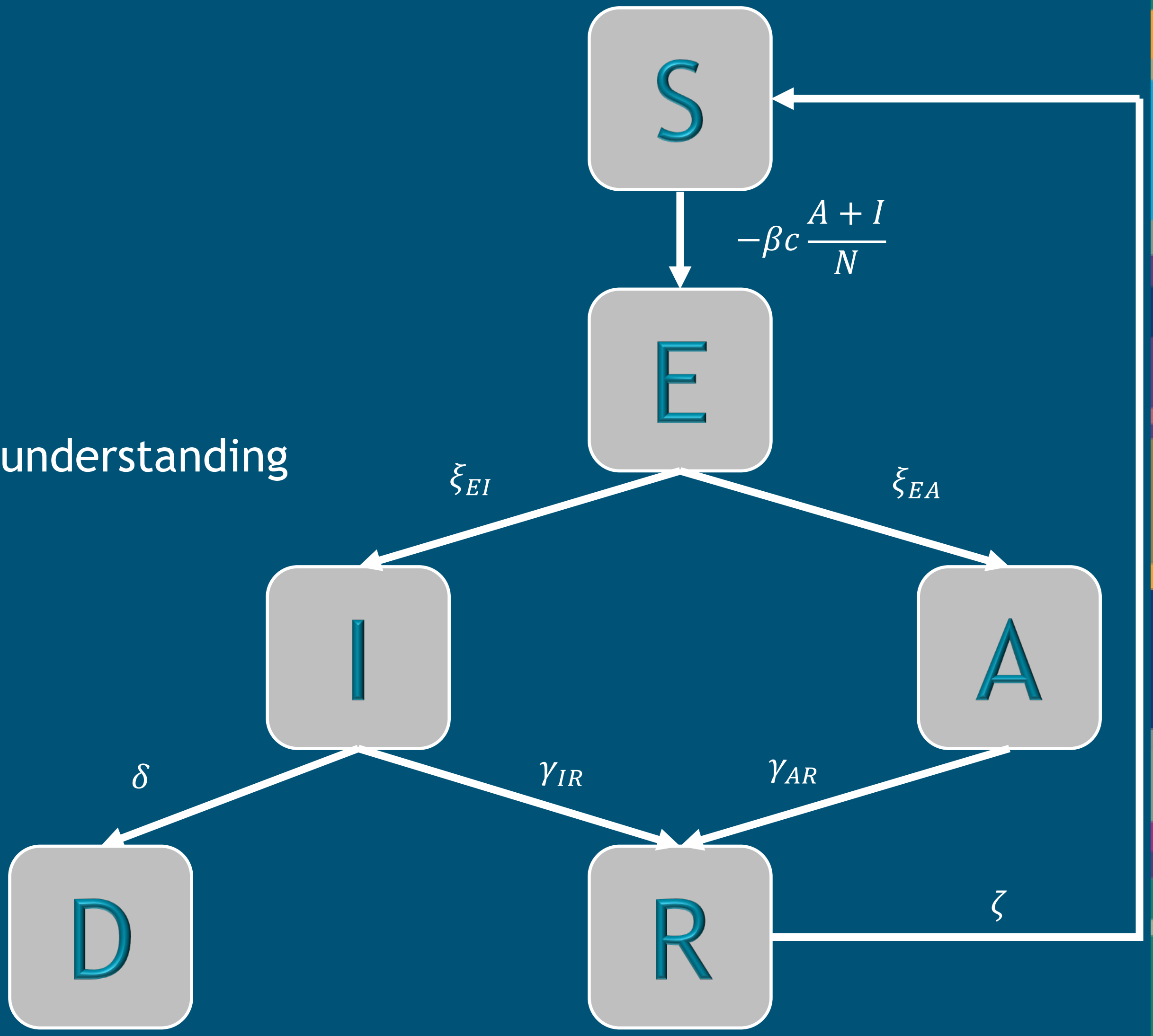
- the force of infection function can help guide us in understanding the model $R_0$

Recall when $\lambda(t) \coloneqq \beta \frac{I(t)}{N(t)}$, the SEIR model $R_0 = \beta\left(\frac{1}{\gamma}\right)$

Qualitatively, this implies:

$$R_0 = (\text{“}infection\ rate\text{”})\times(\text{“}average\ infectious\ period\text{”})$$



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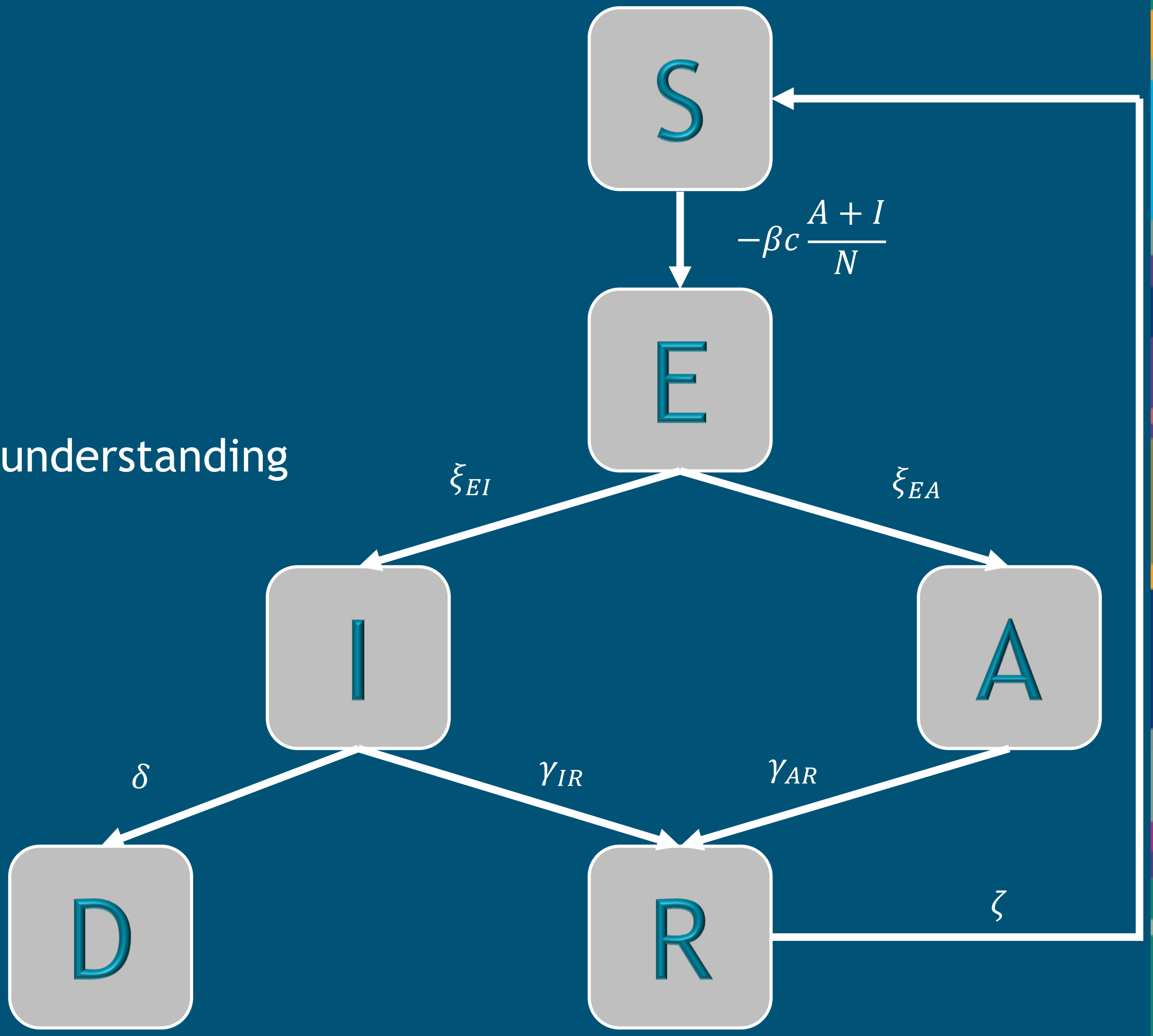
BUT… our new force of infection function also has:

- $c$: average number of daily contacts
- $A(t)$: Asymptomatic-Infectious population



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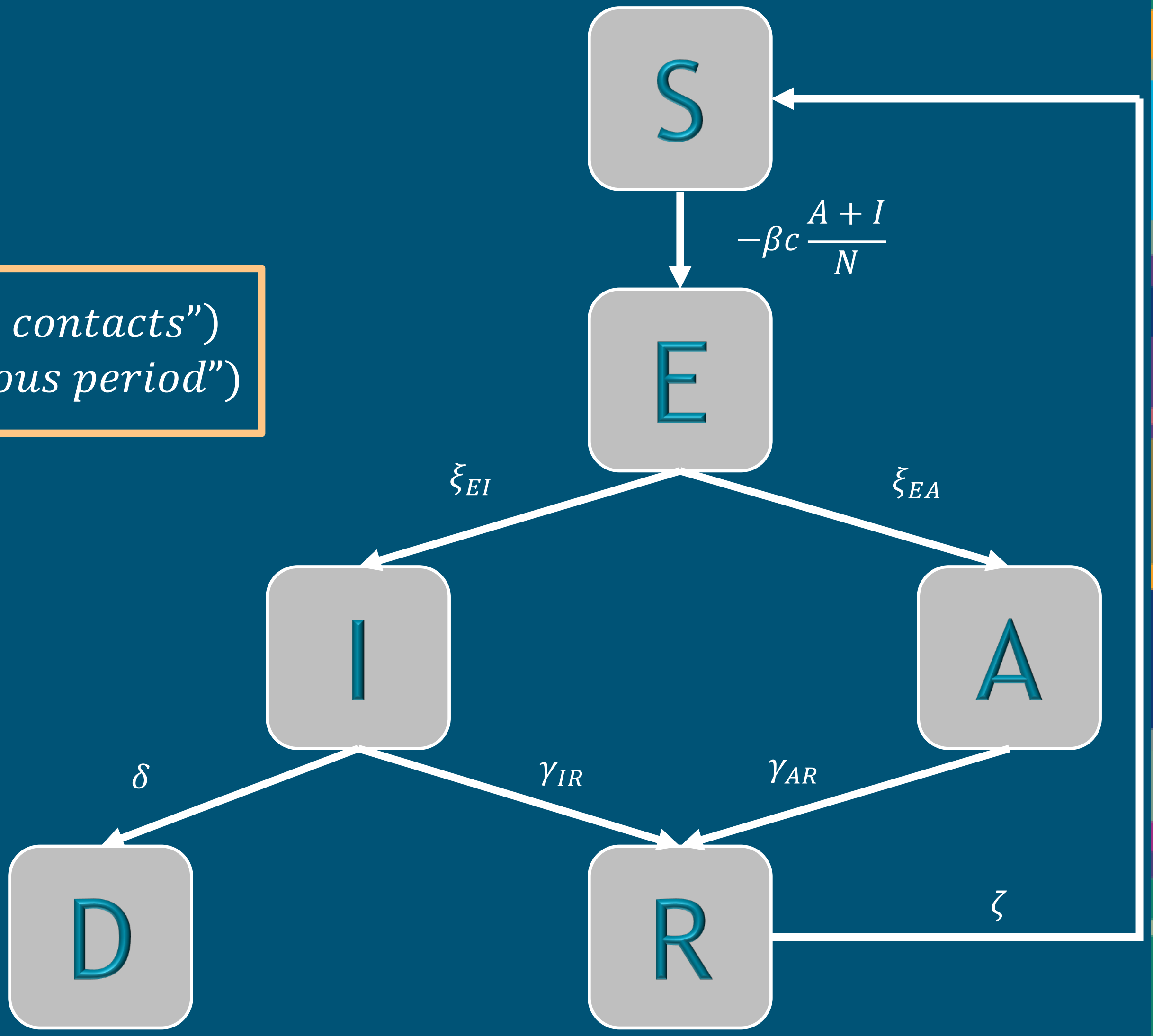

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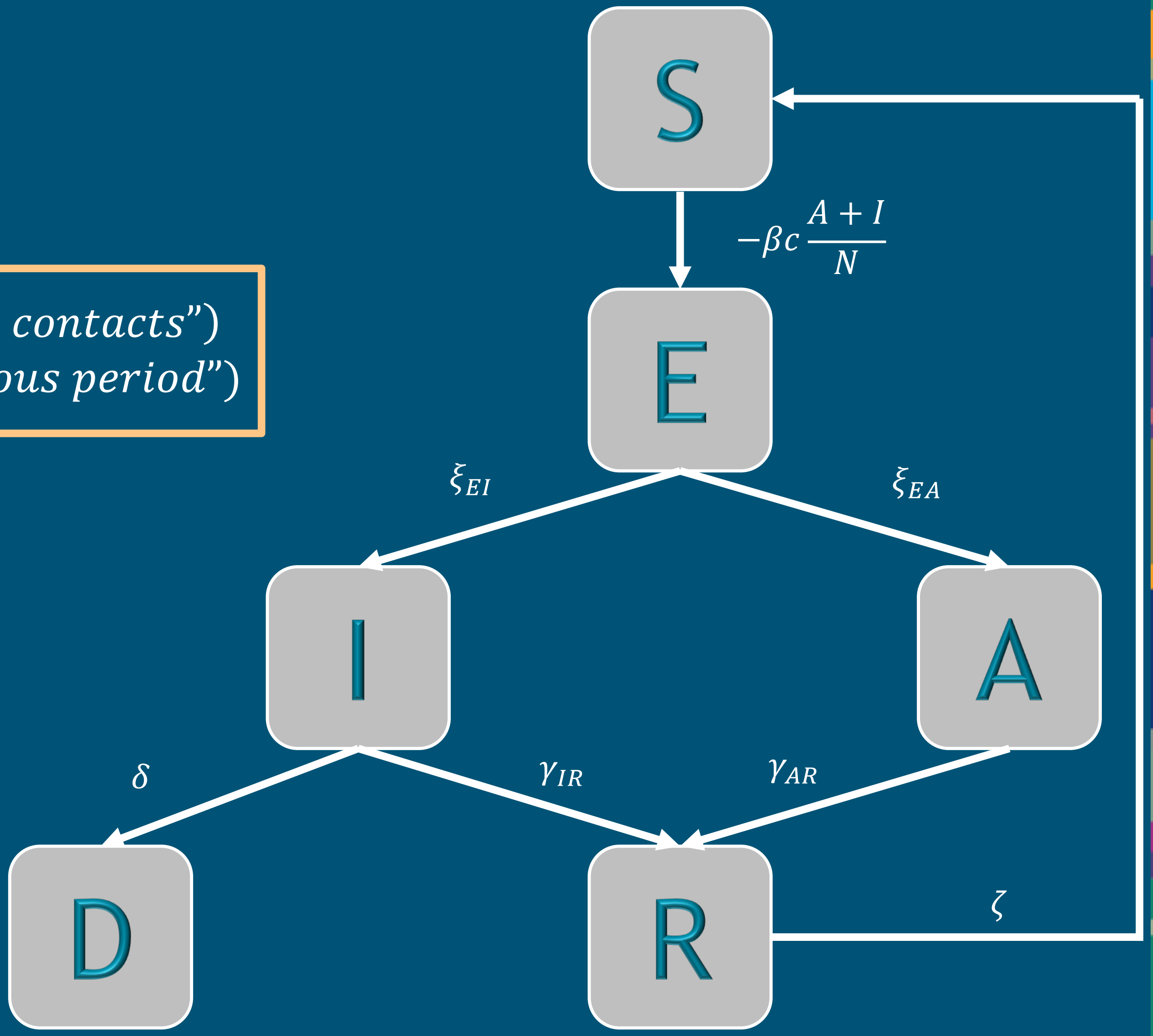
So what is the “average infectious period”?

We need to first understand

- Residence Time and
- Population Flow Fractions.



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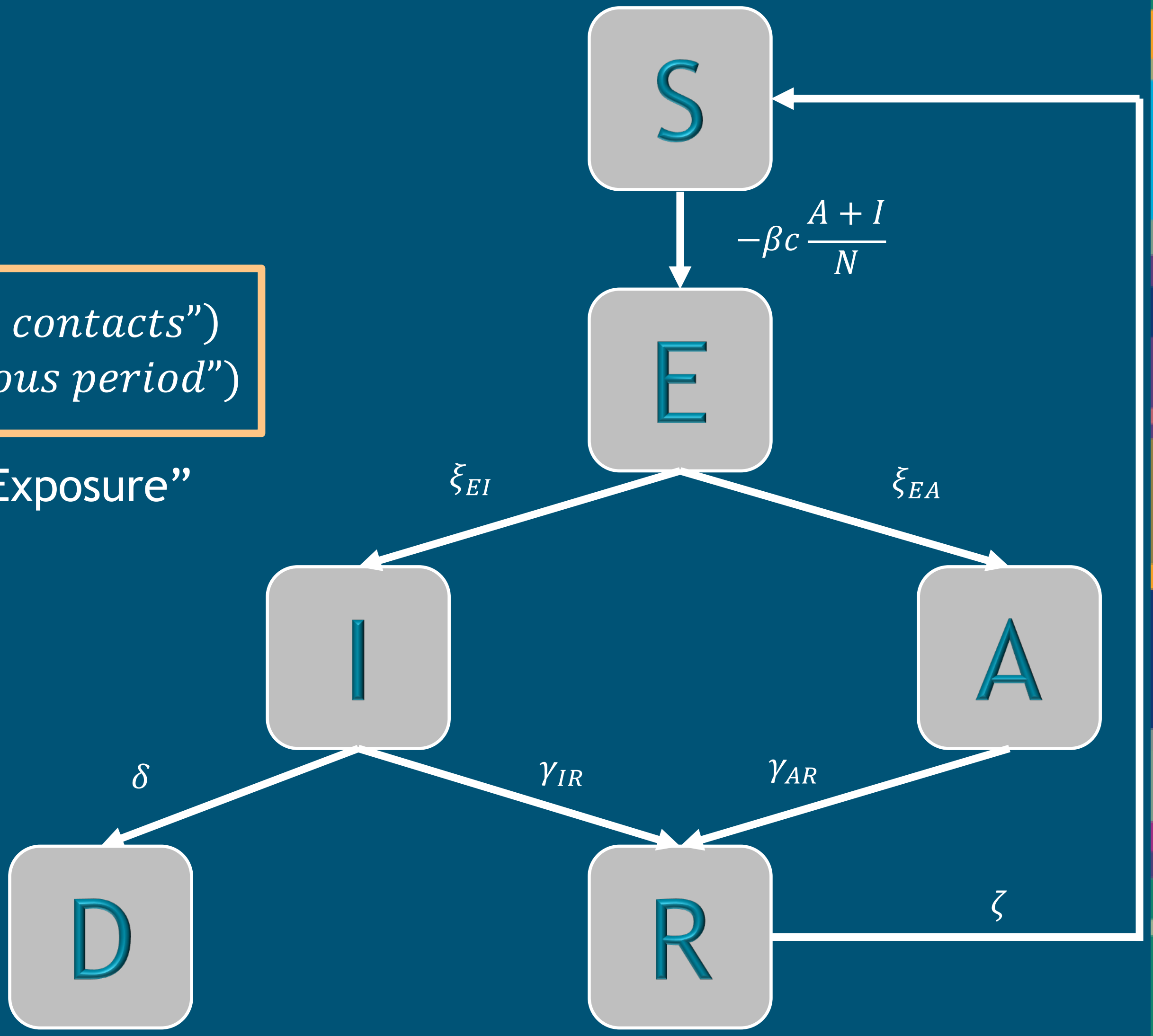
Residence Time and Population Flow Fraction through “Exposure”

- Residence time in “Exposure”: $\frac{1}{\xi_{EI}+\xi_{EA}}$
- Fraction “Symptomatic Population” :
$$f_I = \frac{\xi_{EI}}{\xi_{EI}+\xi_{EA}}$$
- Fraction “Asymptomatic Population” :
$$(1-f_I) = \frac{\xi_{EA}}{\xi_{EI}+\xi_{EA}}$$



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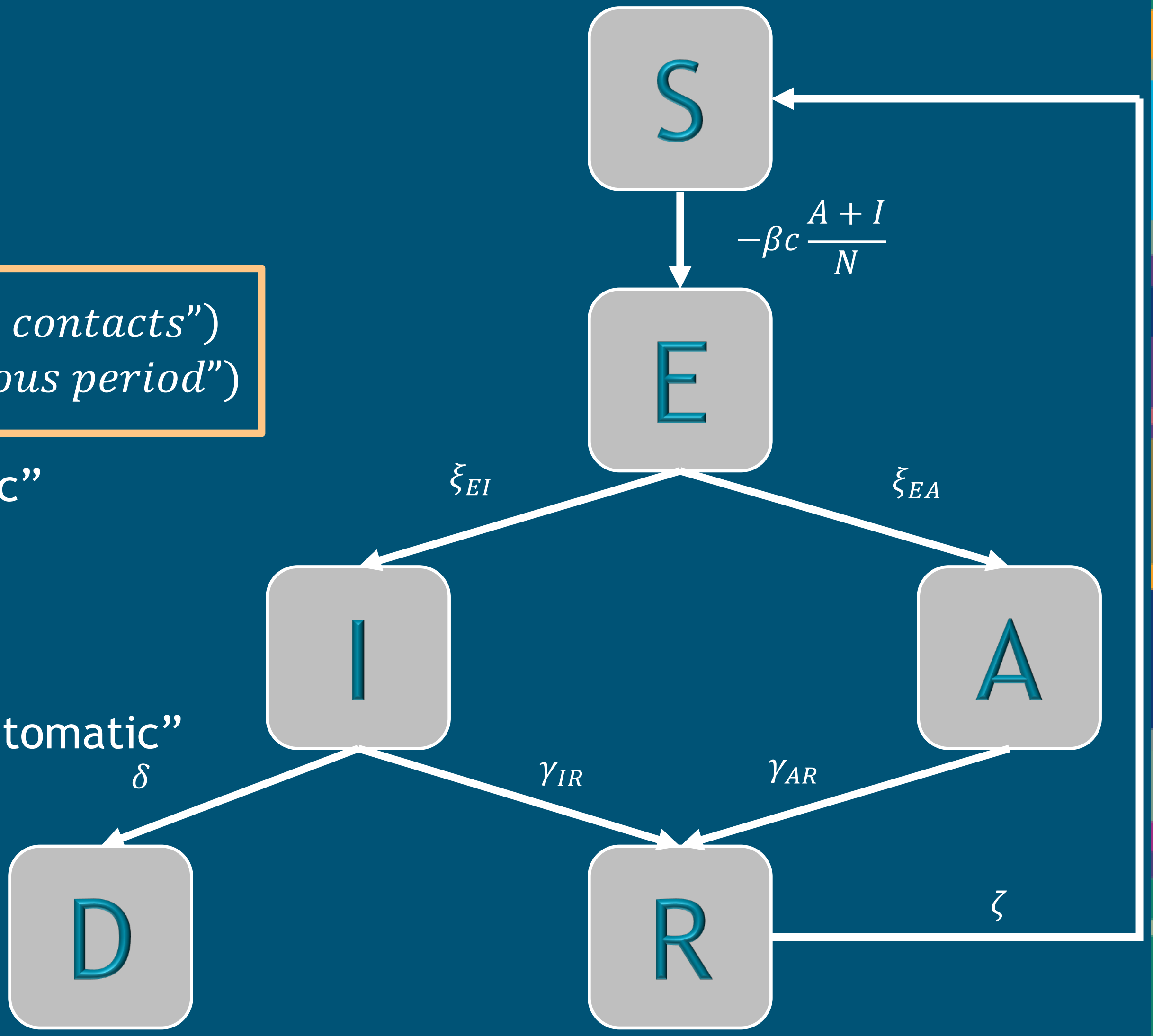
$f_I$: Fraction of the population that become “Symptomatic”

- Residence time “Symptomatic”: $\frac{1}{\delta+\gamma_{IR}}$

$(1 - f_I)$: Fraction of the population that become “Asymptomatic”

- Residence time “Asymptomatic”: $\frac{1}{\gamma_{AR}}$



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$f_I$: Fraction of the population that become “Symptomatic”

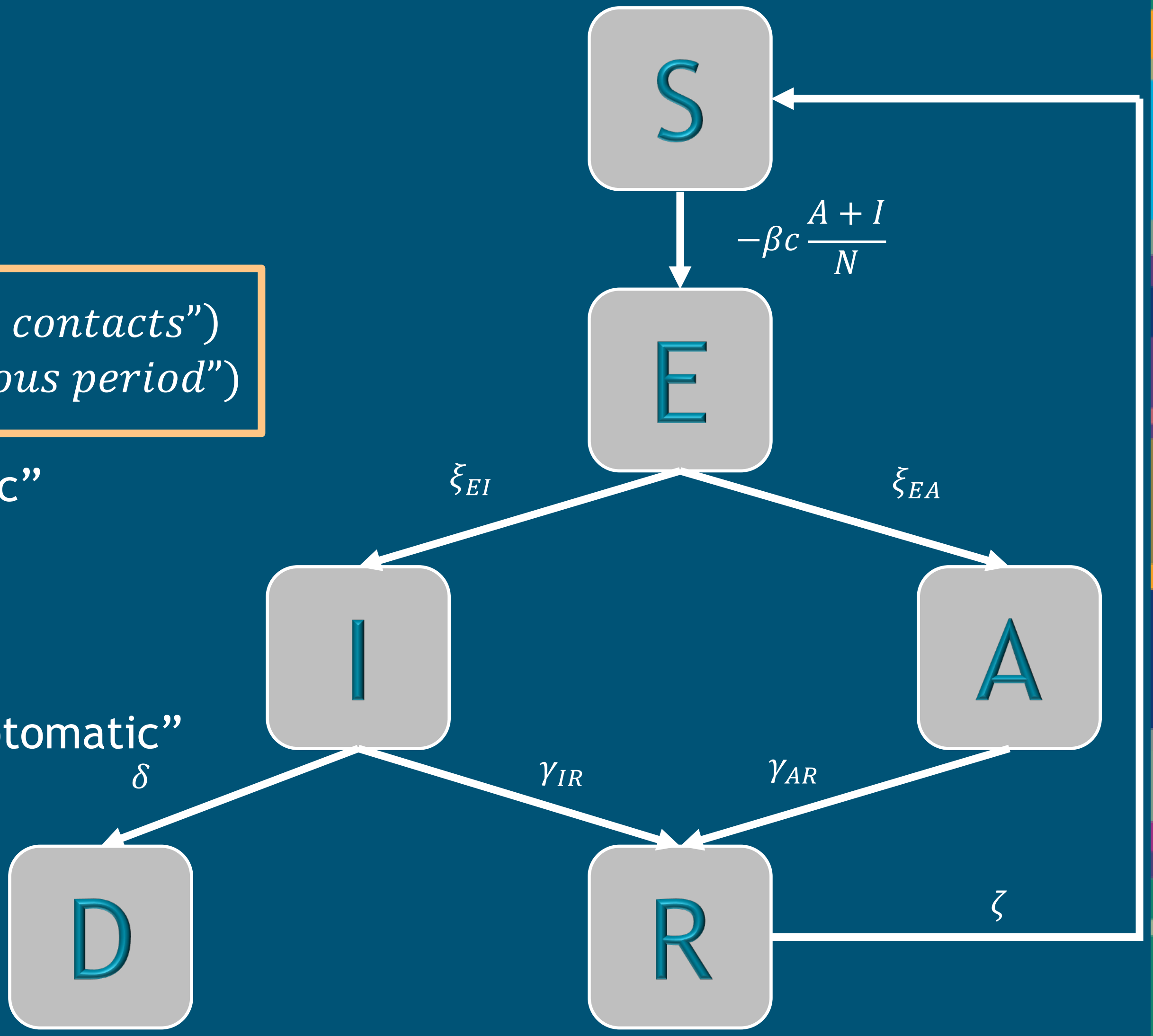
- Residence time “Symptomatic”: $\frac{1}{\delta+\gamma_{IR}}$

$(1 - f_I)$: Fraction of the population that become “Asymptomatic”

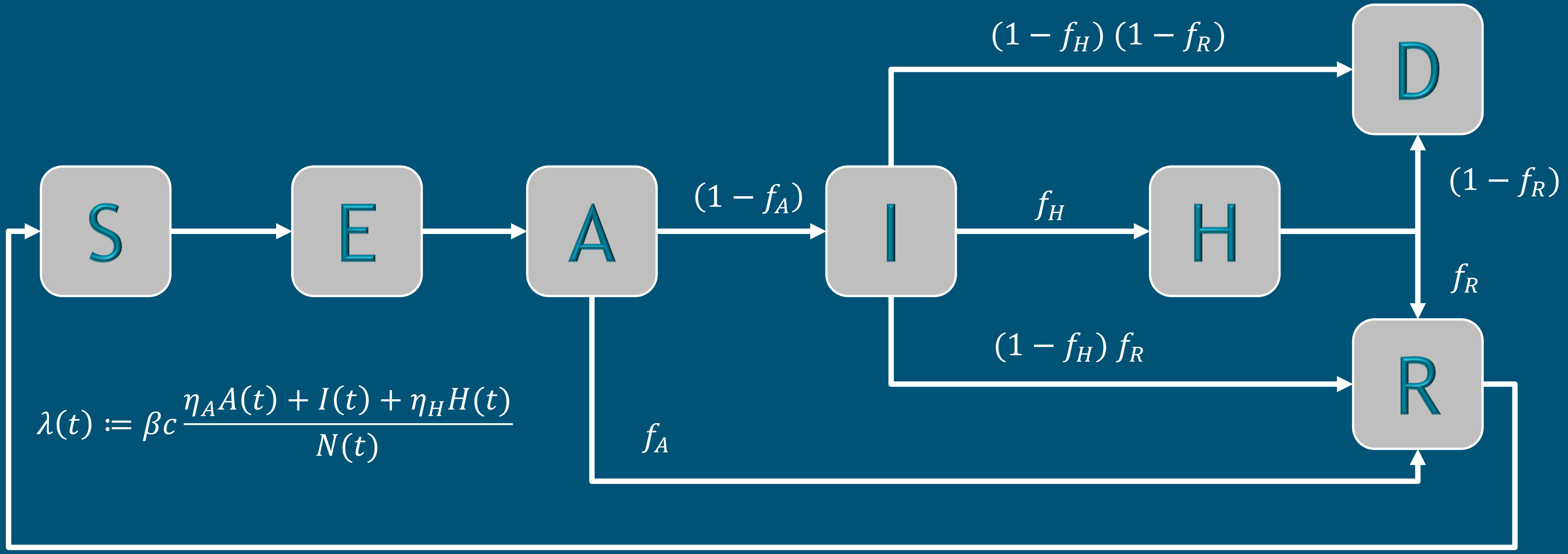
- Residence time “Asymptomatic”: $\frac{1}{\gamma_{AR}}$

THEN…

$$R_0 = \beta c \left( f_I \left( \frac{1}{\delta + \gamma_{IR}} \right) + (1 - f_I) \left( \frac{1}{\gamma_{AR}} \right) \right)$$



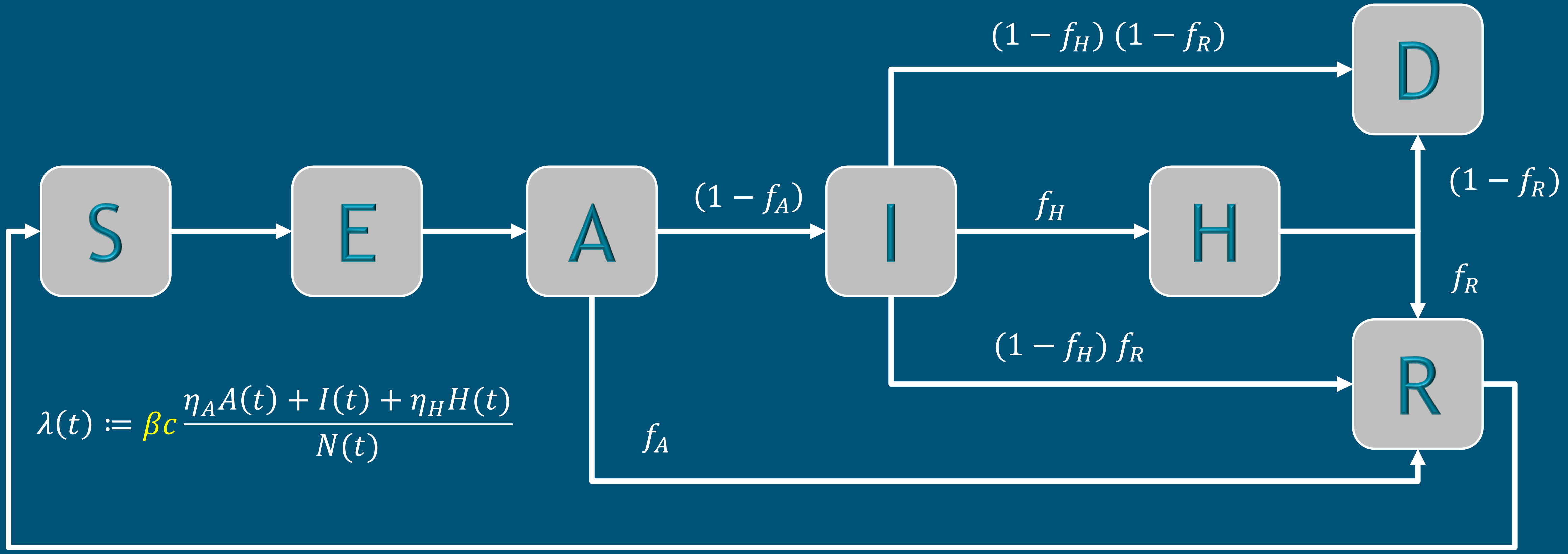
# Compartmental Model: As a Tree with Residence Time




$$R_0 = \beta c(f_A\eta_A T_A + (1-f_A)(1-f_H)(\eta_A T_A + T_I) + (1-f_A)f_H(\eta_A T_A + T_I + \eta_H T_H))$$

Where $T_\star$ represents the residence time for each respective state.

# Compartmental Model: As a Tree with Residence Time




$$\lambda(t) := \beta c \frac{\eta_A A(t) + I(t) + \eta_H H(t)}{N(t)}$$

$$R_0 = \beta c(f_A \eta_A T_A + (1 - f_A)(1 - f_H)(\eta_A T_A + T_I) + (1 - f_A) f_H (\eta_A T_A + T_I + \eta_H T_H))$$

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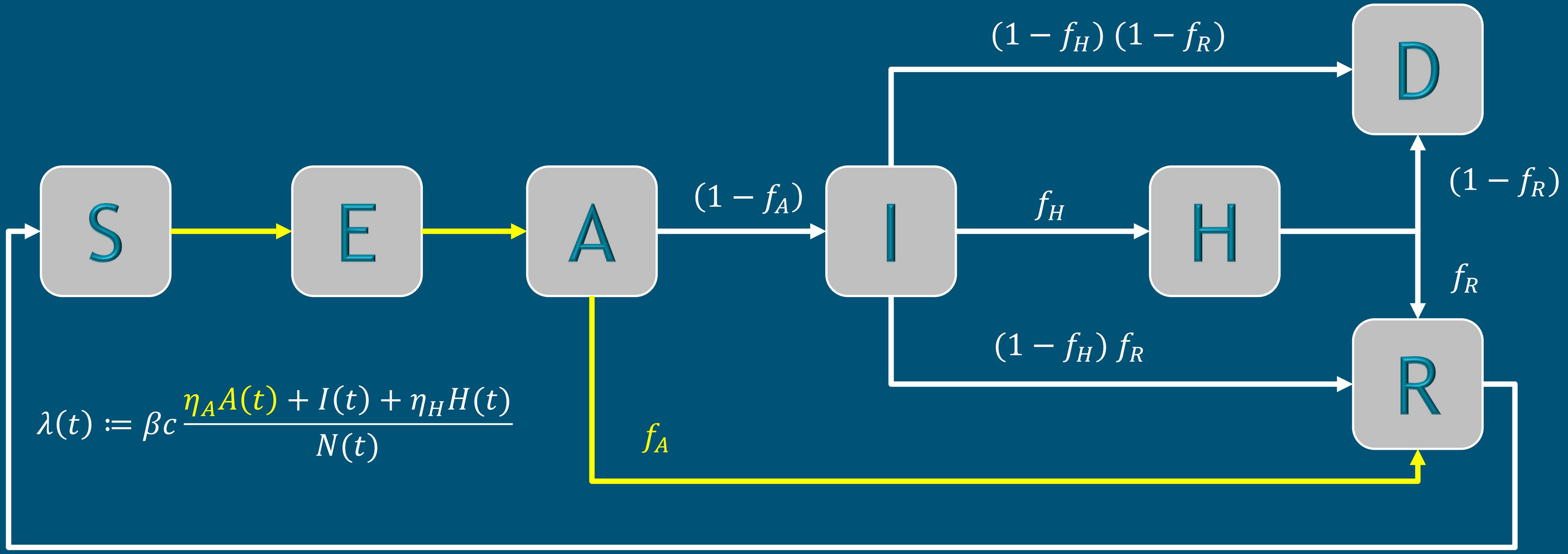


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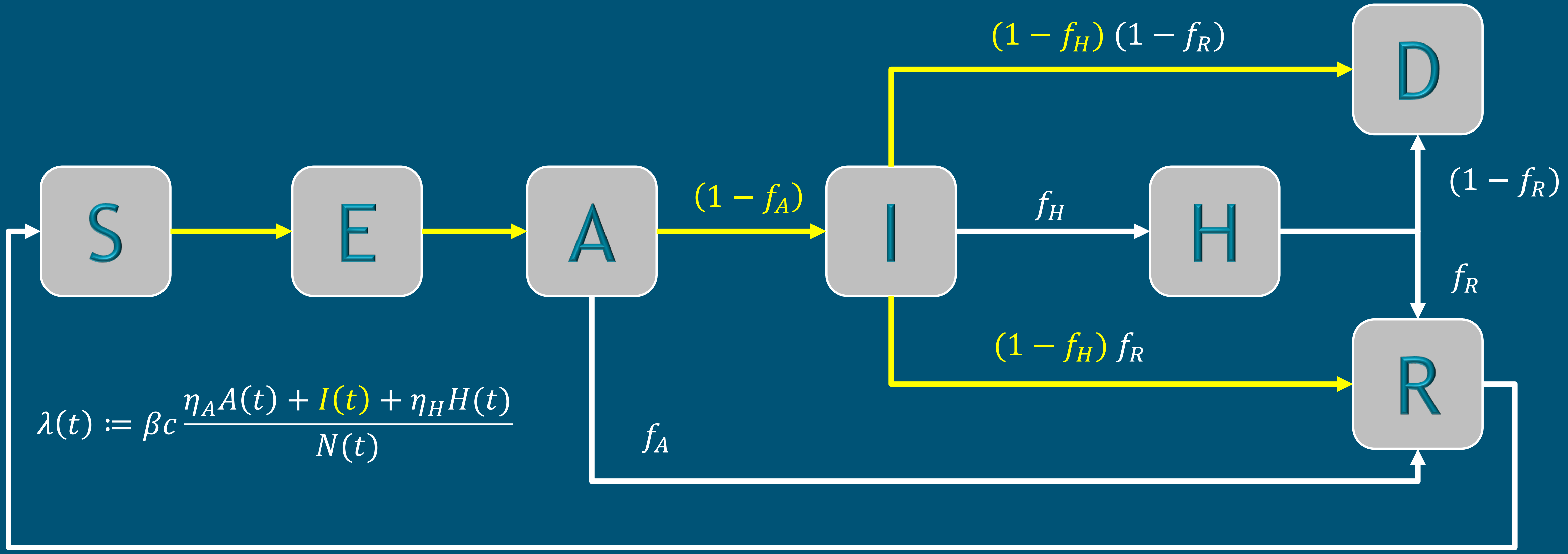


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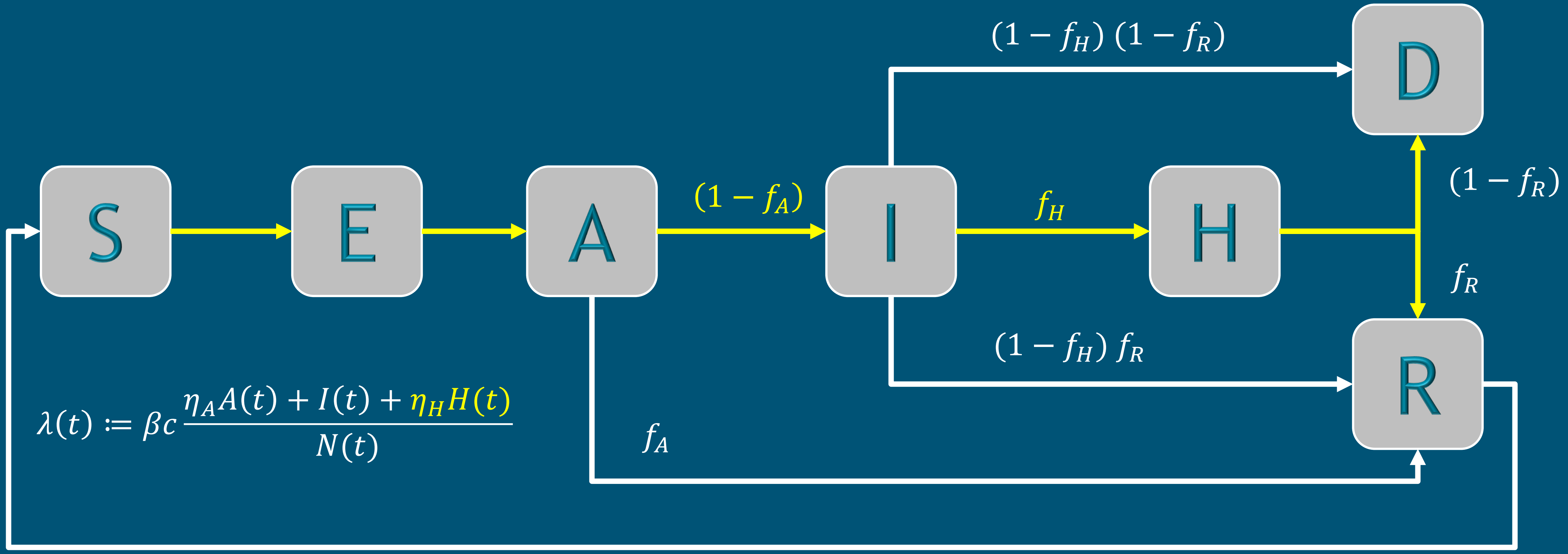



$$R_0 = \beta c\left(f_A \eta_A T_A + (1-f_A)(1-f_H)(\eta_A T_A + T_I) + (1-f_A) f_H (\eta_A T_A + T_I + \eta_H T_H)\right)$$

Where $T_\star$ represents the residence time for each respective state.

# Notional Results: $S - E - A - I - R - H - D$

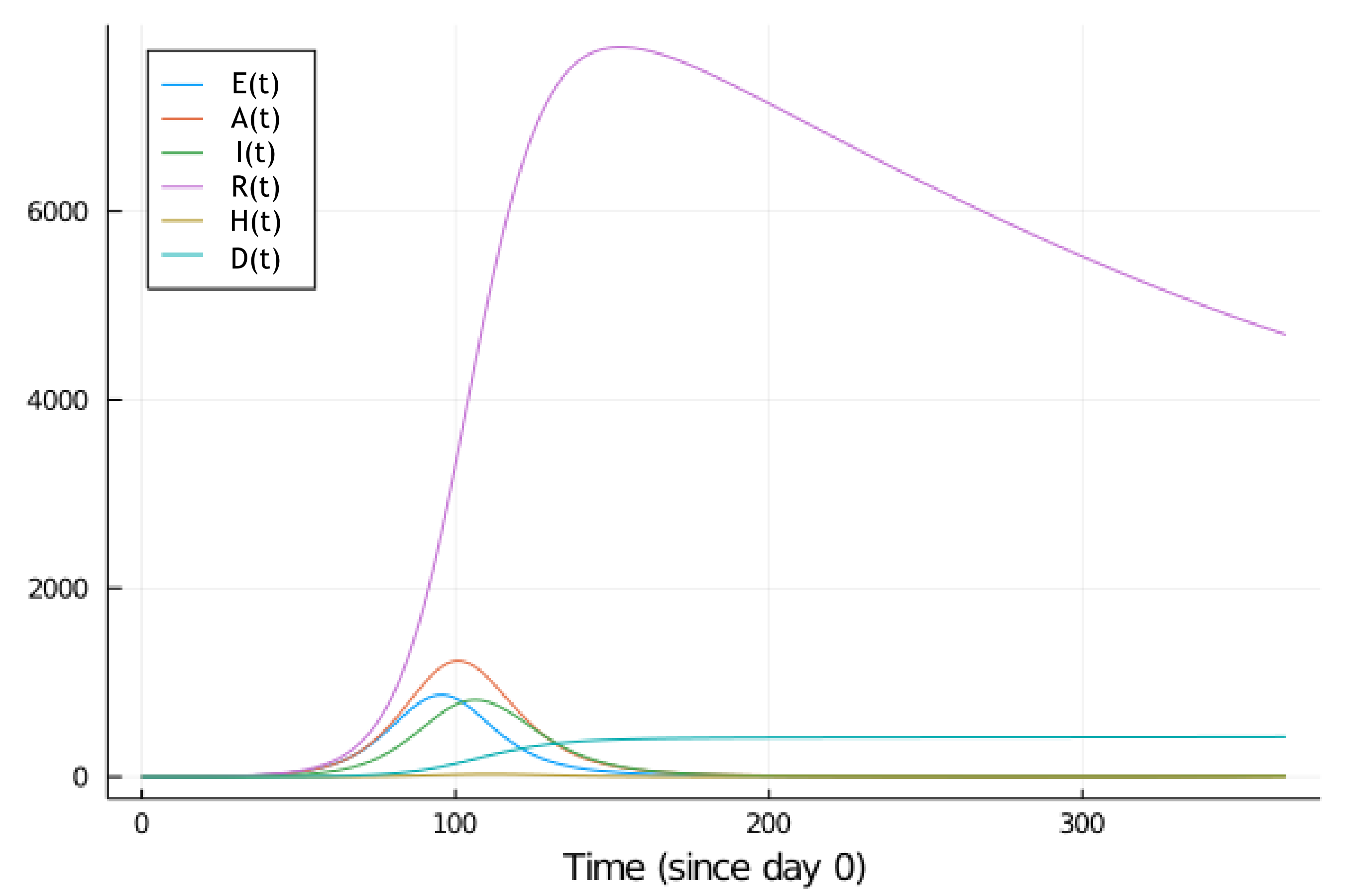
## Nominal Parameter Values:

| | | | | | |
|---|---|---|---|---|---|
| $\beta$ | 0.08 | $\rho_E$ | 0.6 | $\rho_P$ | 0.7 |
| $c$ | 5 | $T_E$ | 4 | | |
| $\eta_A$ | 0.75 | $T_A$ | 6 | $f_A$ | 0.3 |
| | | $T_I$ | 6 | | |
| $\eta_H$ | 0.01 | $T_H$ | 5 | $f_H$ | 0.04 |
| | | $T_R$ | 365 | $f_R$ | 0.94 |

| | |
|---|---|
| $N_0$ | 10,000 |
| $I_0$ | 1 |
| Time Horizon | [0, 365] |

$R_0$ for this parameterization is 2.0187248

## State Trajectories:



# Notional Results: $S - E - A - I - R - H - D$

## Nominal Parameter Values:

| | | | | | |
|---|---|---|---|---|---|
| $\beta$ | 0.08 | $\rho_E$ | 0.6 | $\rho_P$ | 0.7 |
| $c$ | 5 | $T_E$ | 4 | | |
| $\eta_A$ | 0.75 | $T_A$ | 6 | $f_A$ | 0.3 |
| | | $T_I$ | 6 | | |
| $\eta_H$ | 0.01 | $T_H$ | 5 | $f_H$ | 0.04 |
| | | $T_R$ | 365 | $f_R$ | 0.94 |

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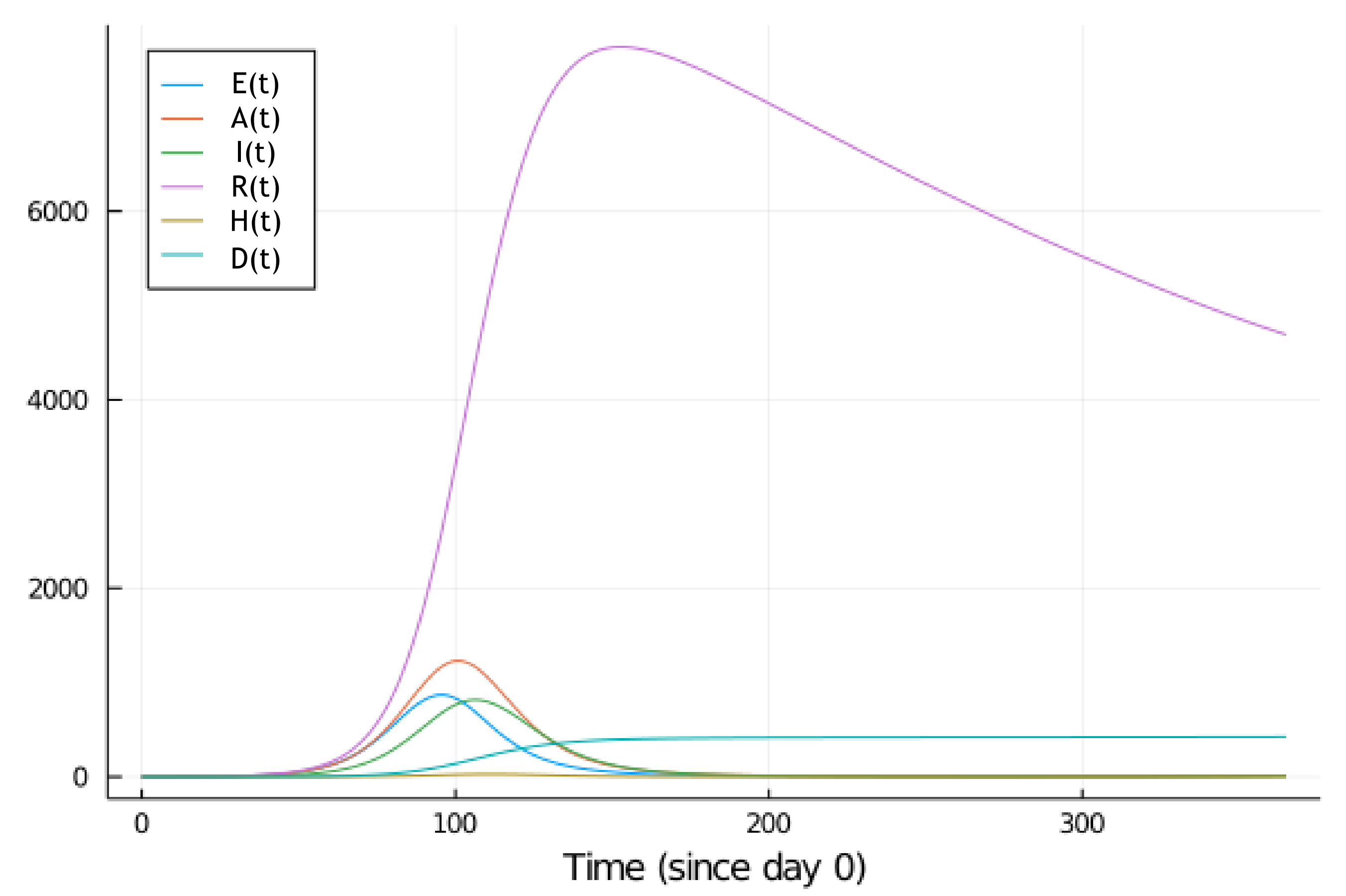

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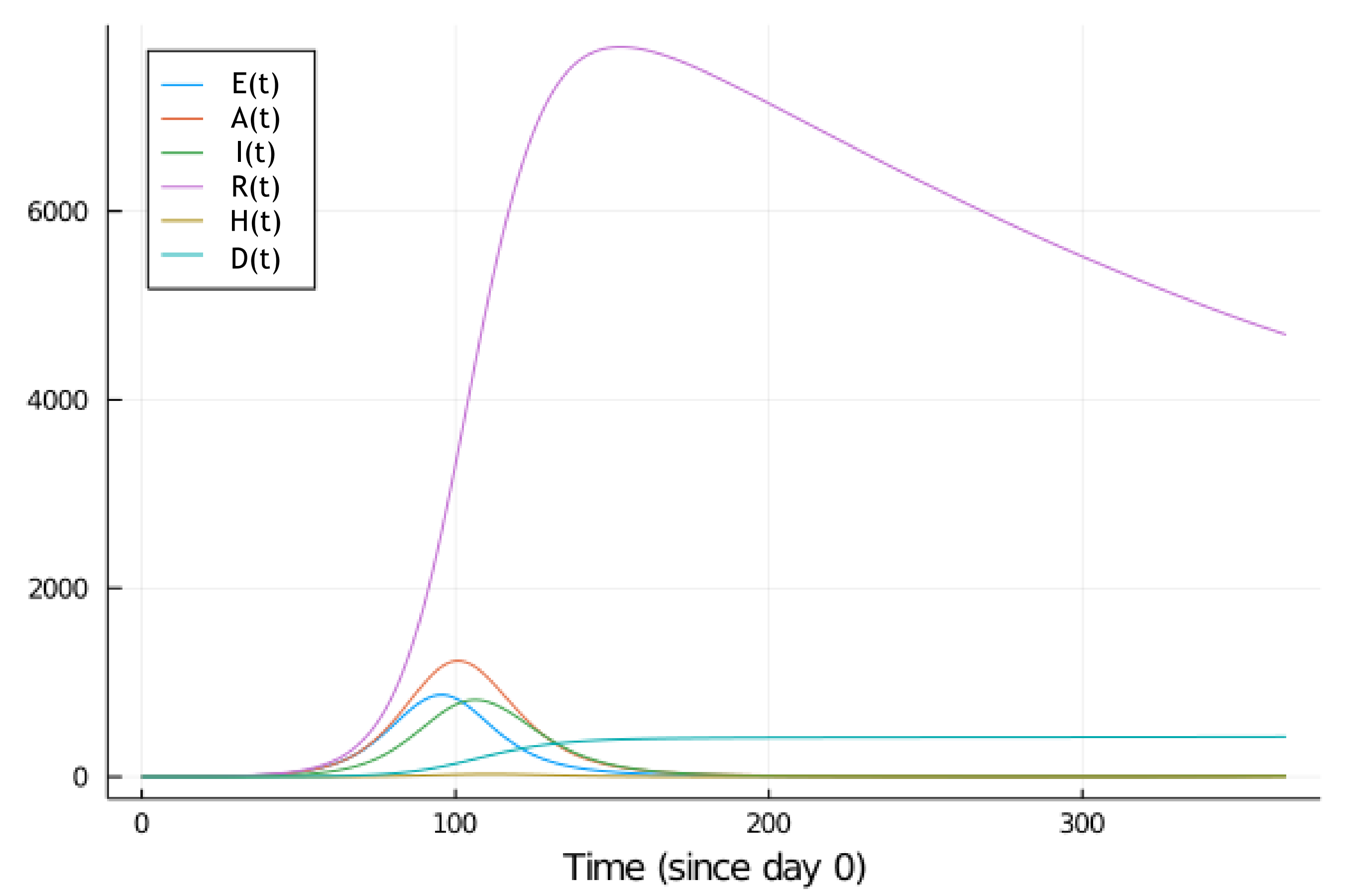

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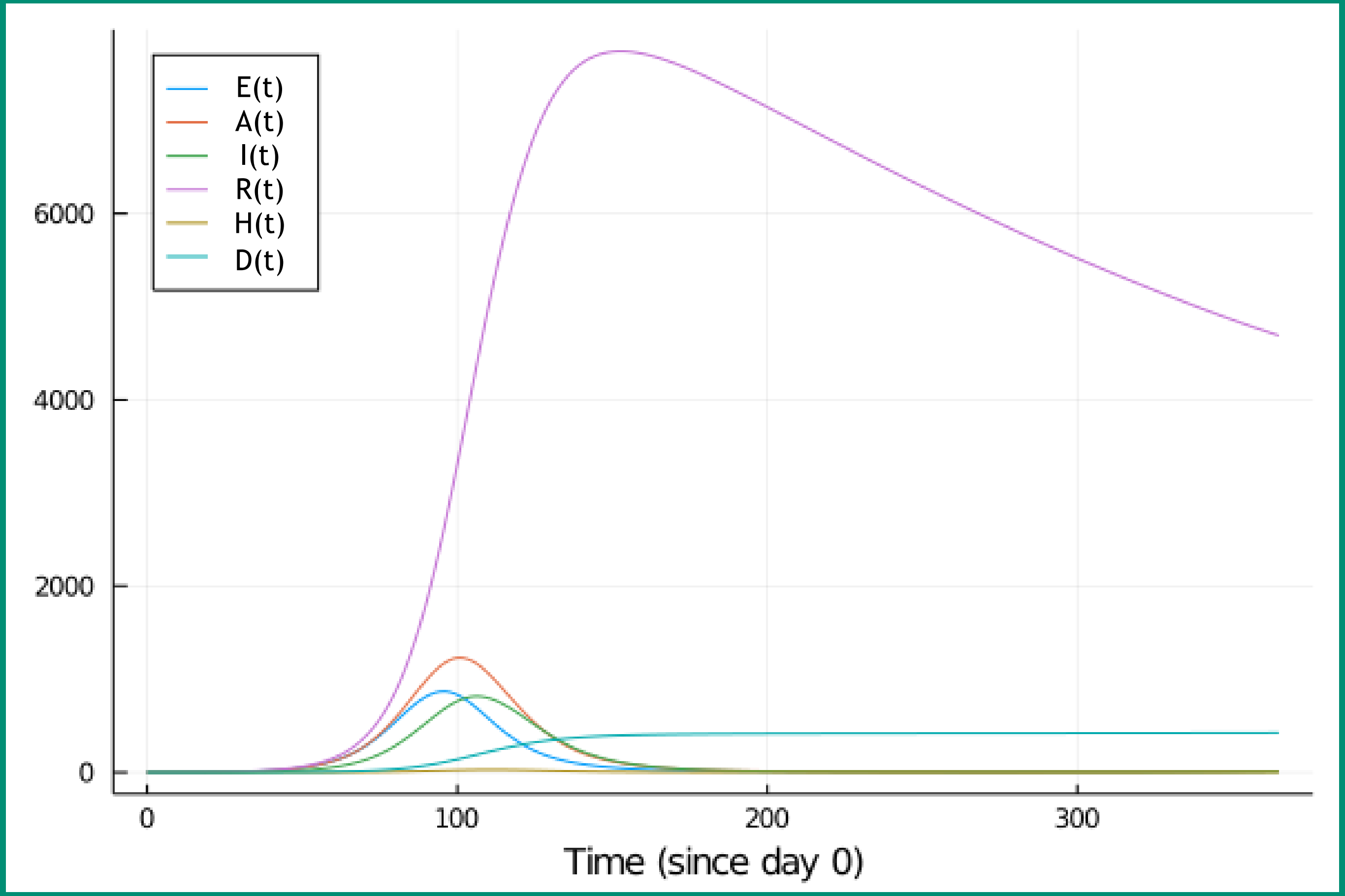

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| | | | | | |
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| $\beta$ | 0.08 | $\rho_E$ | 0.6 | $\rho_P$ | 0.7 |
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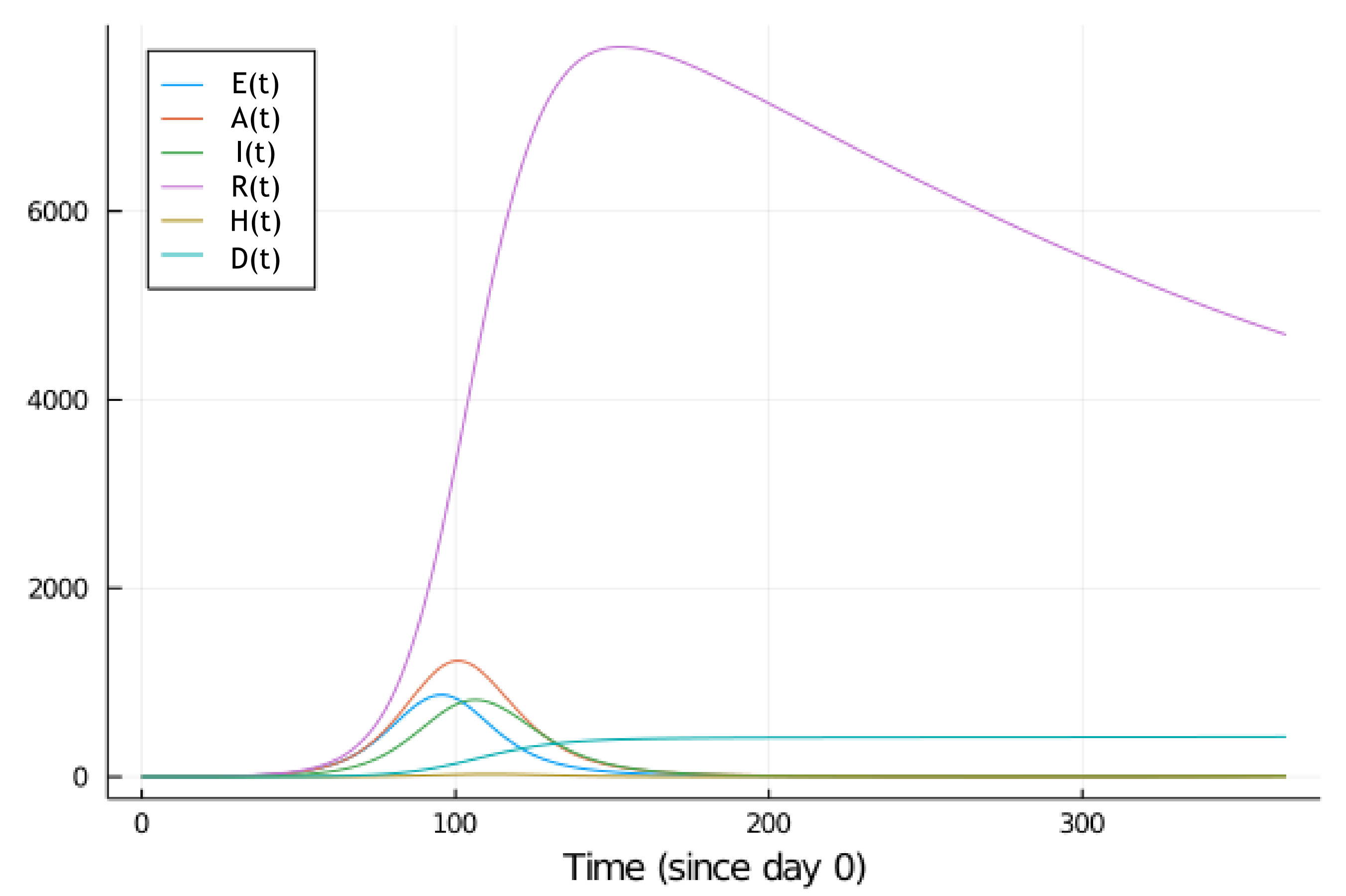


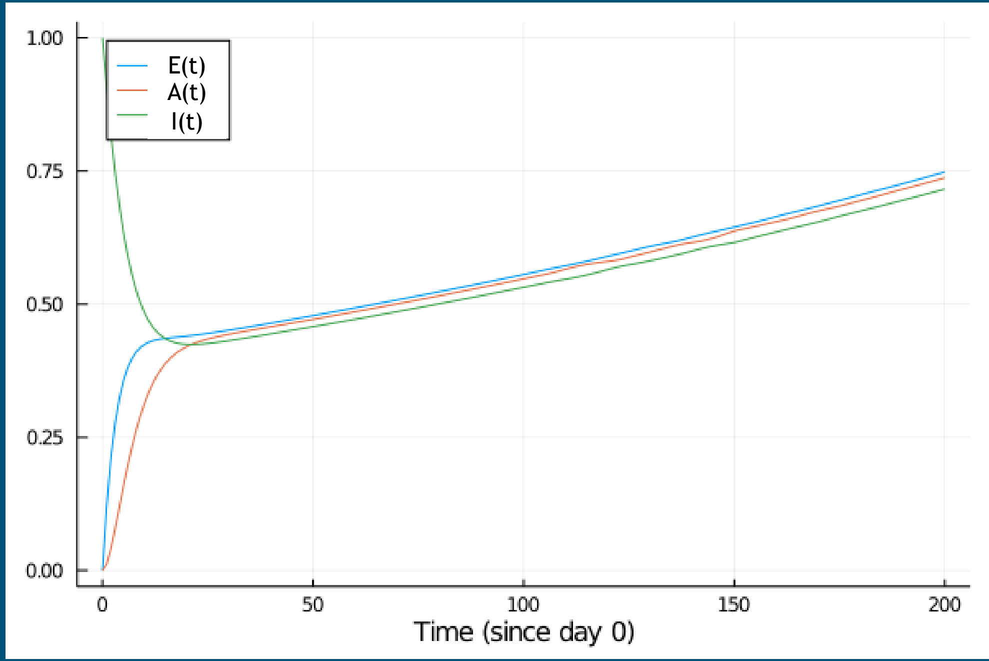

How Do We Know We Have Derived the Correct Model $R_0$??

# Model $R_0$ Verification: $S - E - A - I - R - H - D$

When $R_0 > 1$, we expect the disease to persist

Parameter Changes:

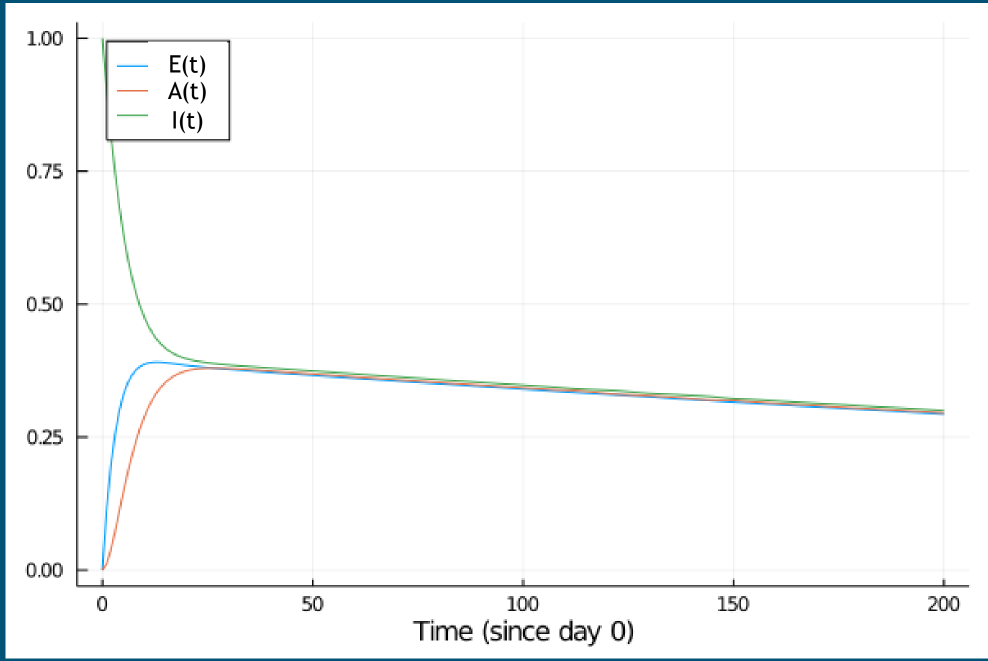
| | |
|---|---|
| $\beta$ | 0.07 |
| $c$ | 3 |
| $R_0$ | 1.05983 |




When $R_0 < 1$, we expect the disease to die out

Parameter Changes:

| | |
|---|---|
| $\beta$ | 0.065 |
| $c$ | 3 |
| $R_0$ | 0.984128 |



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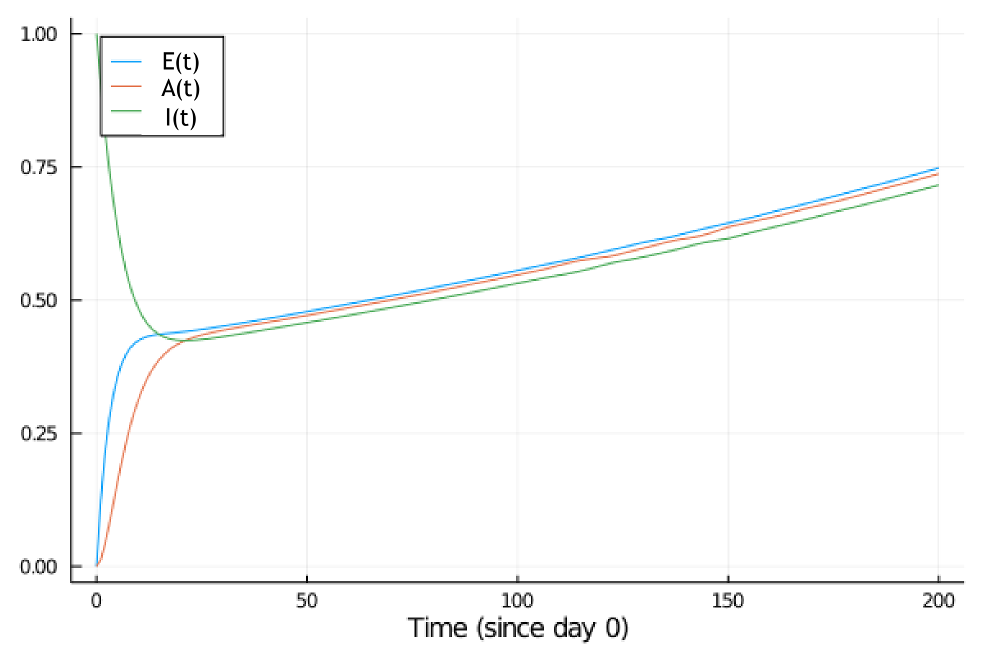


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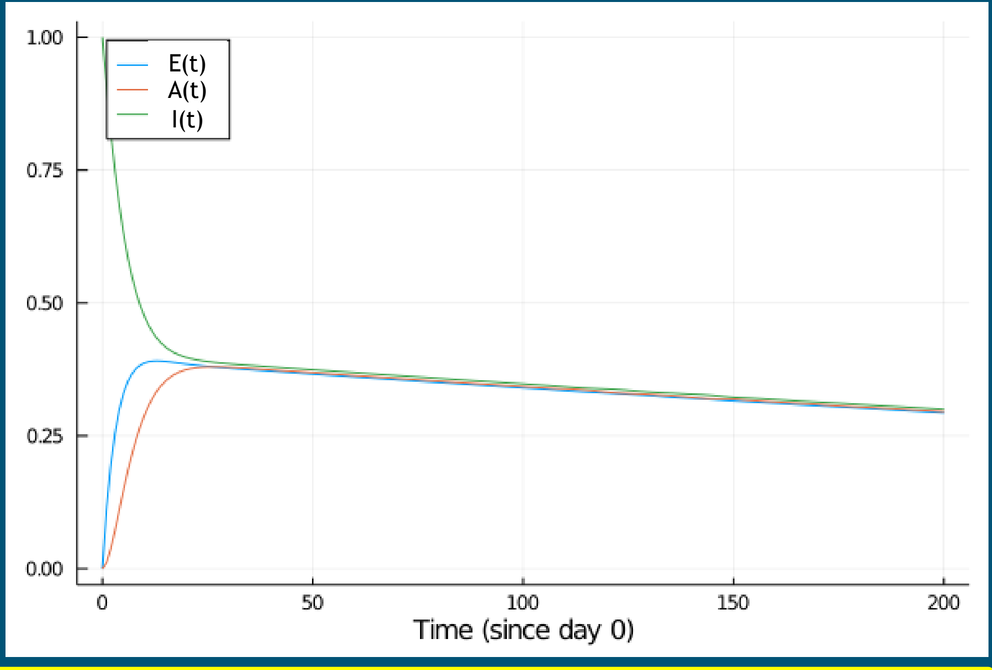



A subtle change in $\beta$ alone can make all the difference in whether or not we simulate a persistent disease or a controlled disease

# Uncertainty Quantification (UQ) and Global Sensitivity Analysis (GSA)

Quantity of Interest (QoI):

Our analysis needs to target a particular output of our model (e.g. $R_0$, $\max(H(t))$)

Forward Uncertainty Quantification:

With a measured uncertainty coming from the nominal values in our parameterizations, we want to measure the uncertainty of our QoI.

Uncertainty in our context is measured by the variance in our model inputs (parameters) and outputs (QoIs)

Global Sensitivity Analysis:

When the uncertainty of our QoI is high, it is often the case that we want to determine what sources of uncertainty are the most influential.

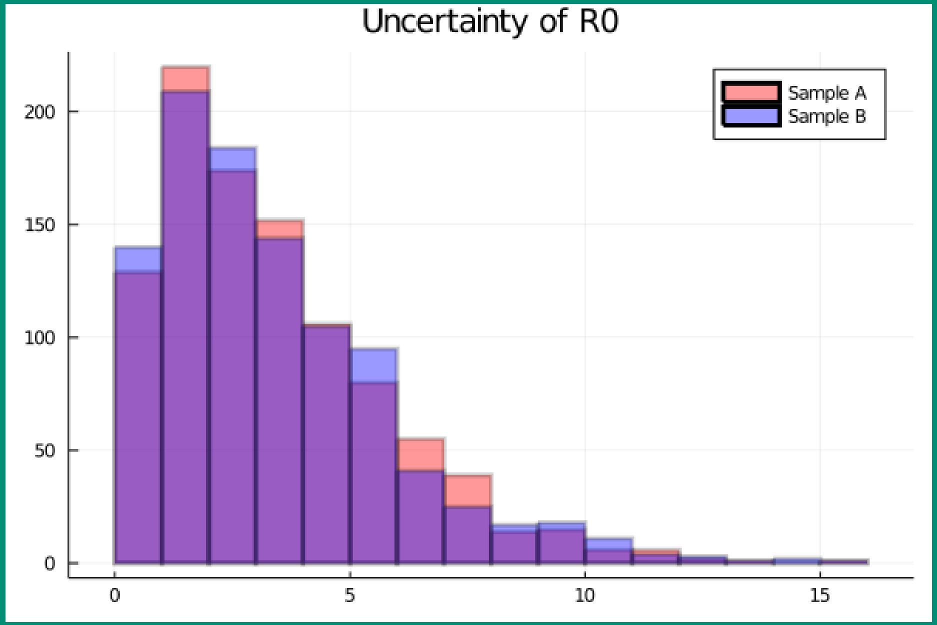
What is the sensitivity of our QoI with respect to the parameter uncertainties.

# UQ/GSA for $R_0$

## Parameter Uniform Uncertainties:

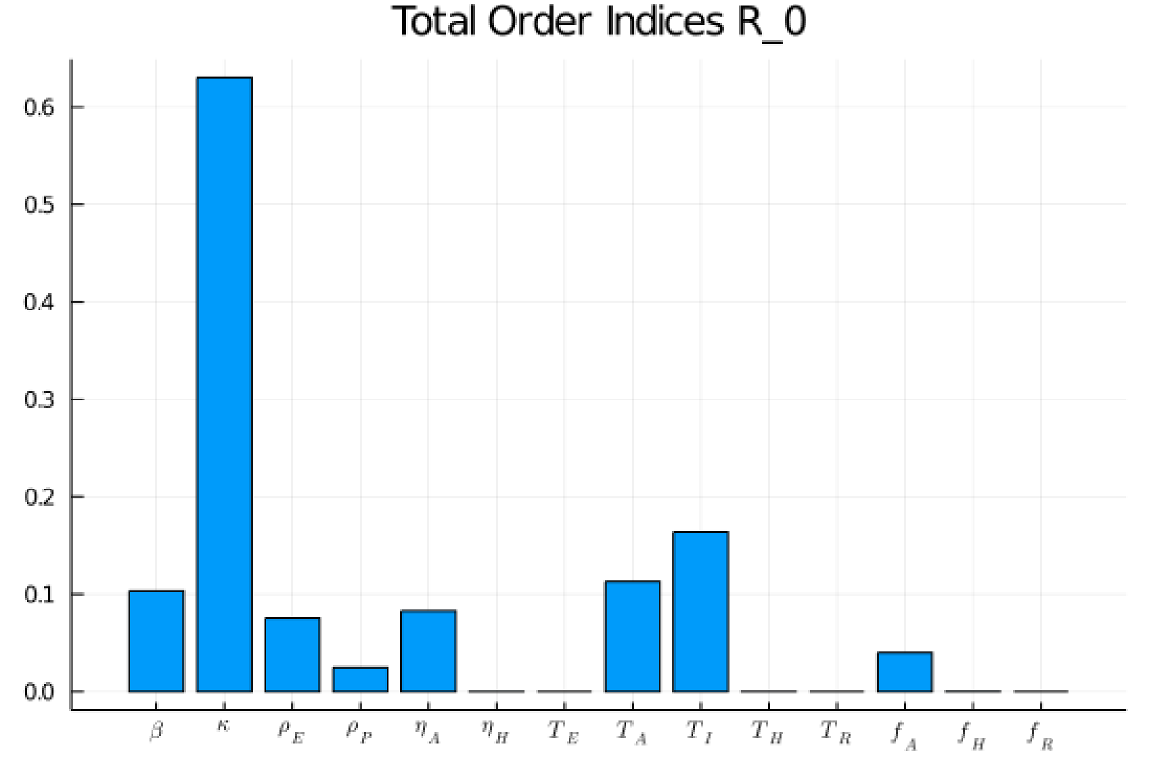
| | | | | | |
|---|---|---|---|---|---|
| $\beta$ | $[0.06, 0.12]$ | $T_E$ | $[3, 5]$ | | |
| $\eta_A$ | $[0.25, 1.0]$ | $T_A$ | $[2, 14]$ | $f_A$ | $[0.15, 0.5]$ |
| $c$ | $[0.5, 7.5]$ | $T_I$ | $[5, 20]$ | | |
| $\eta_H$ | $[0.005, 0.1]$ | $T_H$ | $[2, 25]$ | $f_H$ | $[0.01, 0.07]$ |
| $\rho_E$ | $[0.2, 0.8]$ | $\rho_P$ | $[0.4, 0.85]$ | | |
| | | $T_R$ | $[210, 600]$ | $f_R$ | $[0.9, 0.99]$ |

## $R_0$ Uncertainty:




Quasi-Monte Carlo Simulations were run to measure forward UQ

## Parameter Influence* on $R_0$ Uncertainty:




Sobol' indices were derived using Julia implementation of numerical methods for variance based decomposition

# UQ/GSA for $\max(H(t))$

## Parameter Uniform Uncertainties:

| | | | | | |
|---|---|---|---|---|---|
| $\beta$ | $[0.06, 0.12]$ | $T_E$ | $[3, 5]$ | | |
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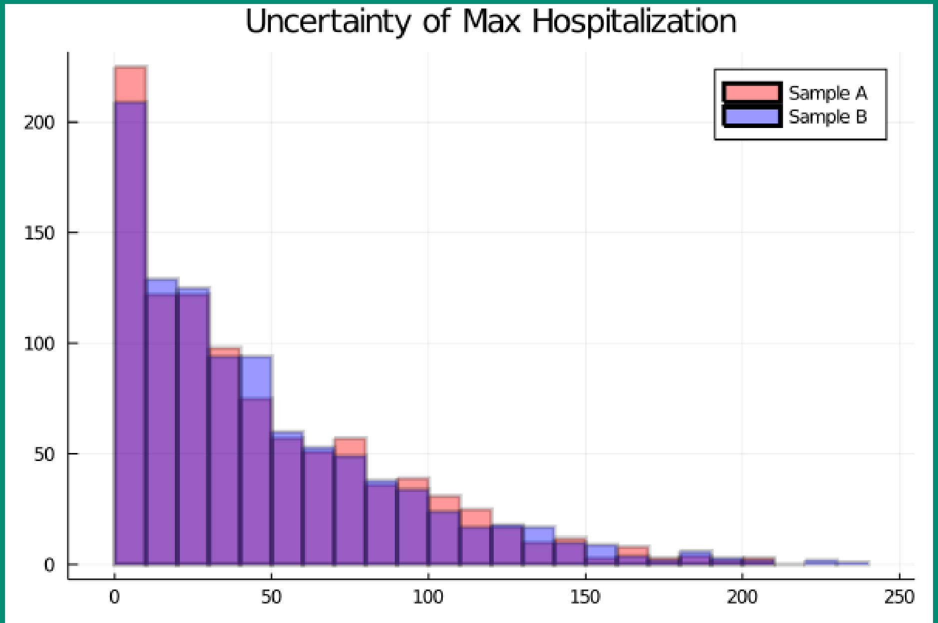
## $\max(H(t))$ Uncertainty:

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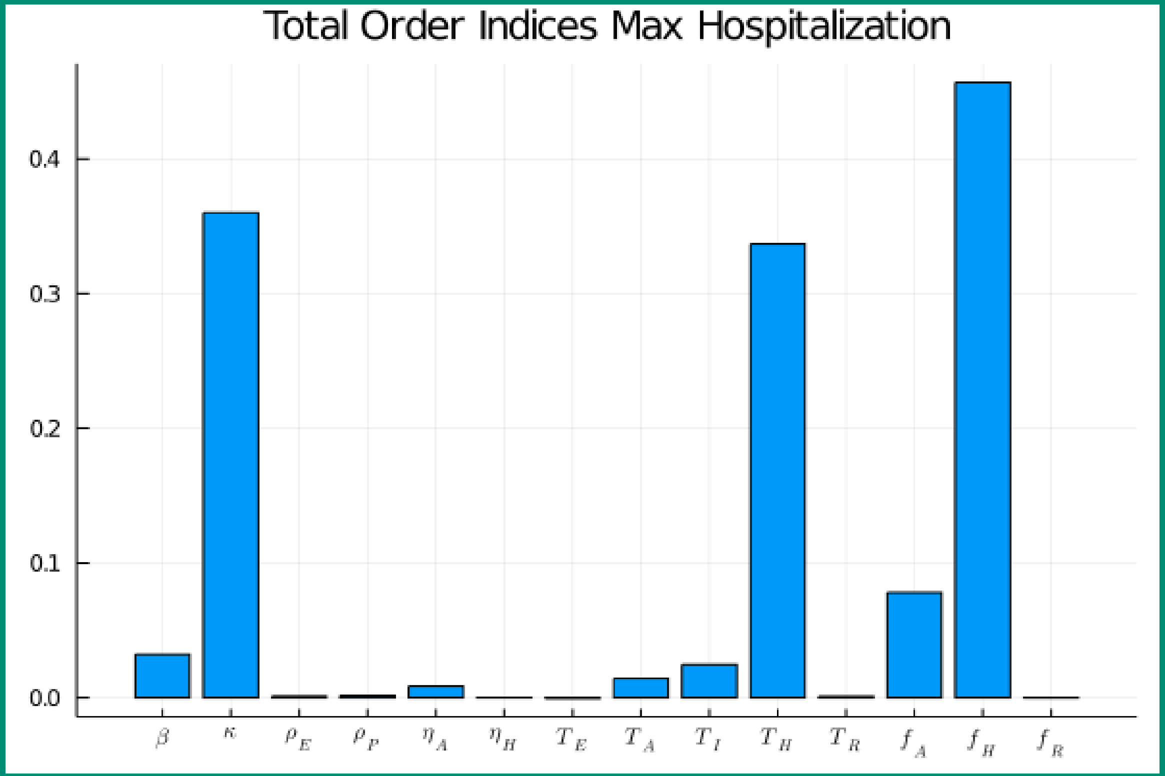
## Parameter Influence on $\max(H(t))$ Uncertainty:

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# Notional Results: $S - E - A - I - R - H - D$

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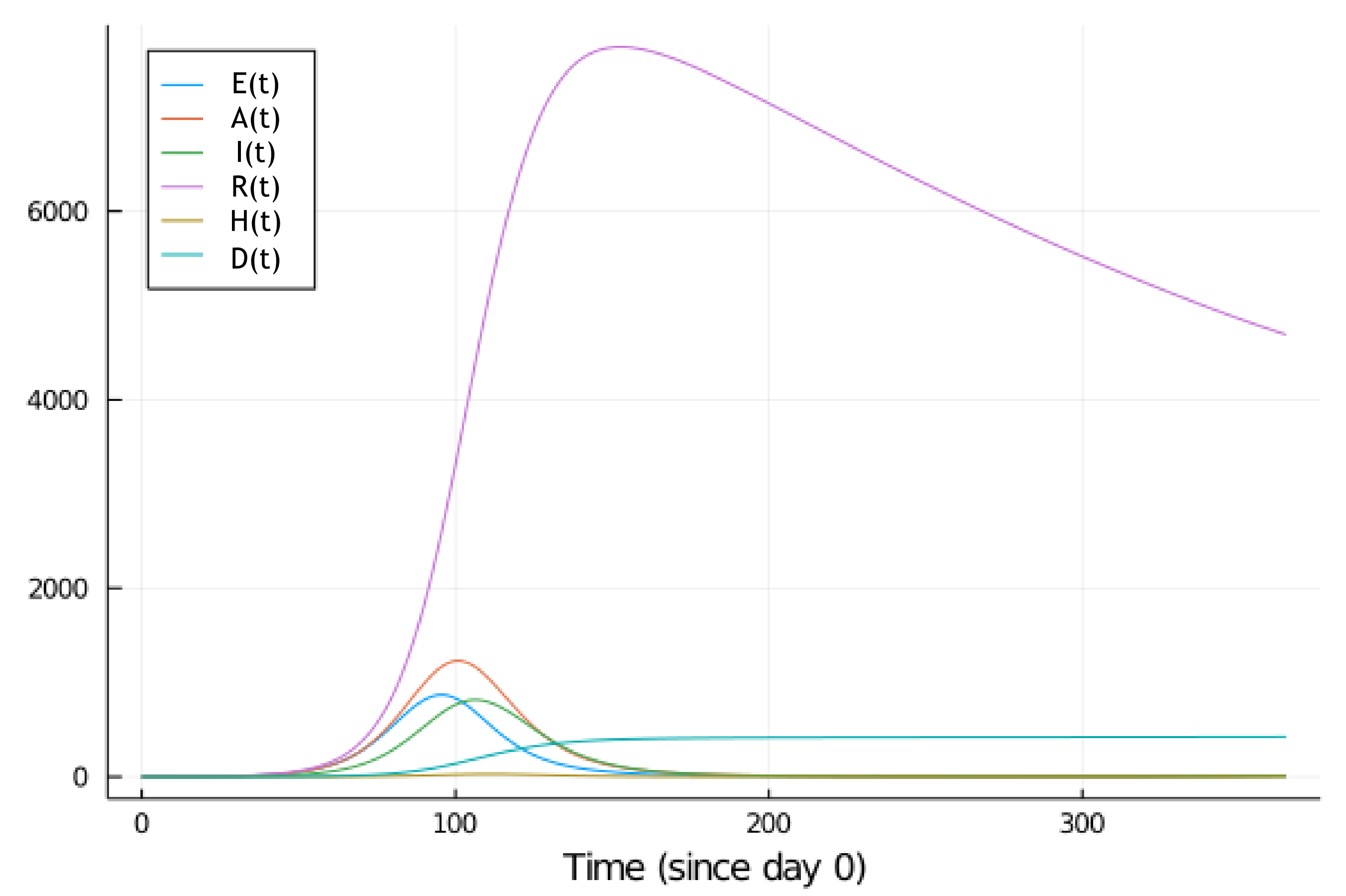
$R_0$ for this parameterization is 2.0187248

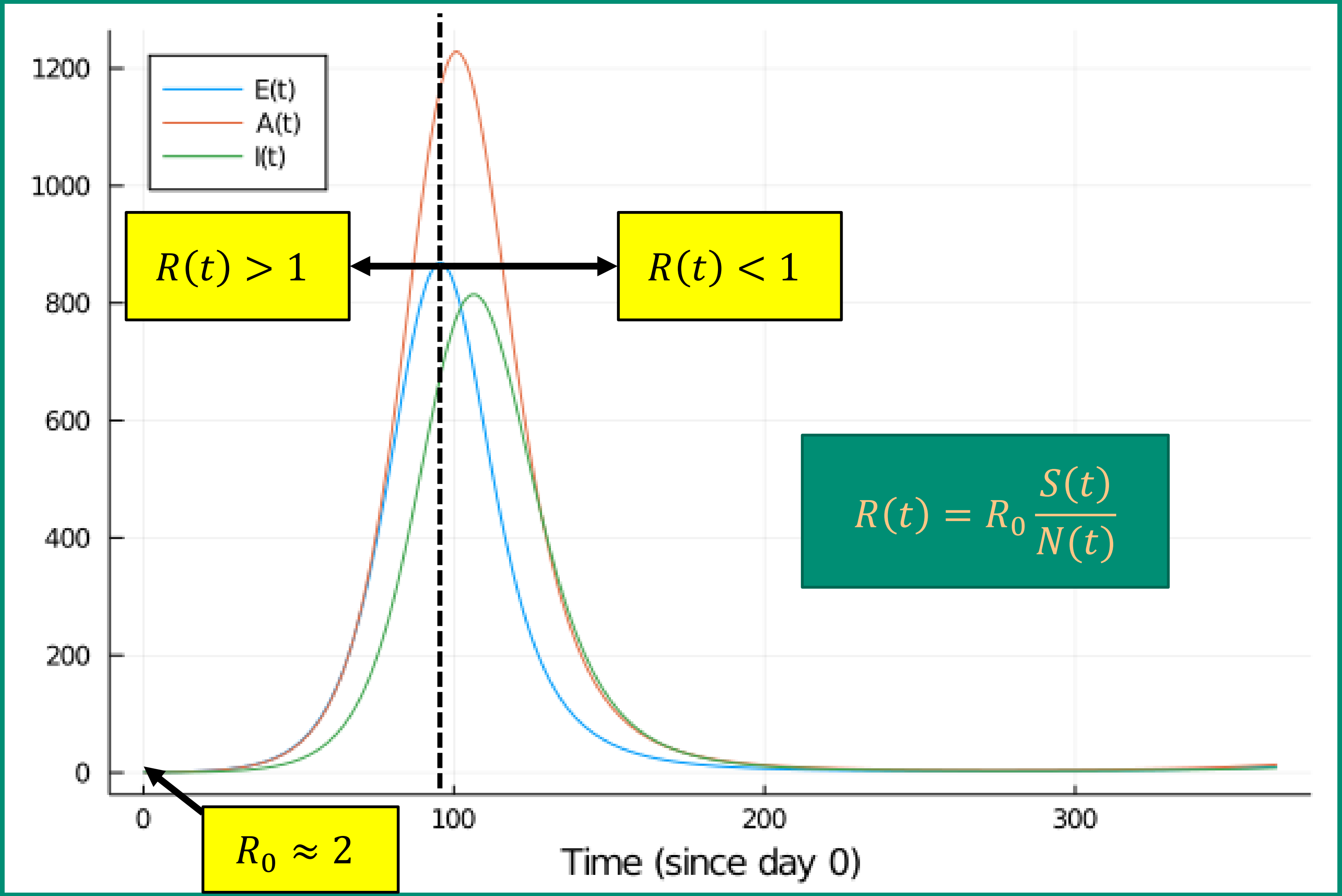
## State Trajectories:




What is the difference between $R_0$ and replacement number $R(t)$??

# $R_0$ Versus $R(t)$

## Infected State Trajectories:




## What to Know:

$R(t) \approx R_0$ at time $t = 0$

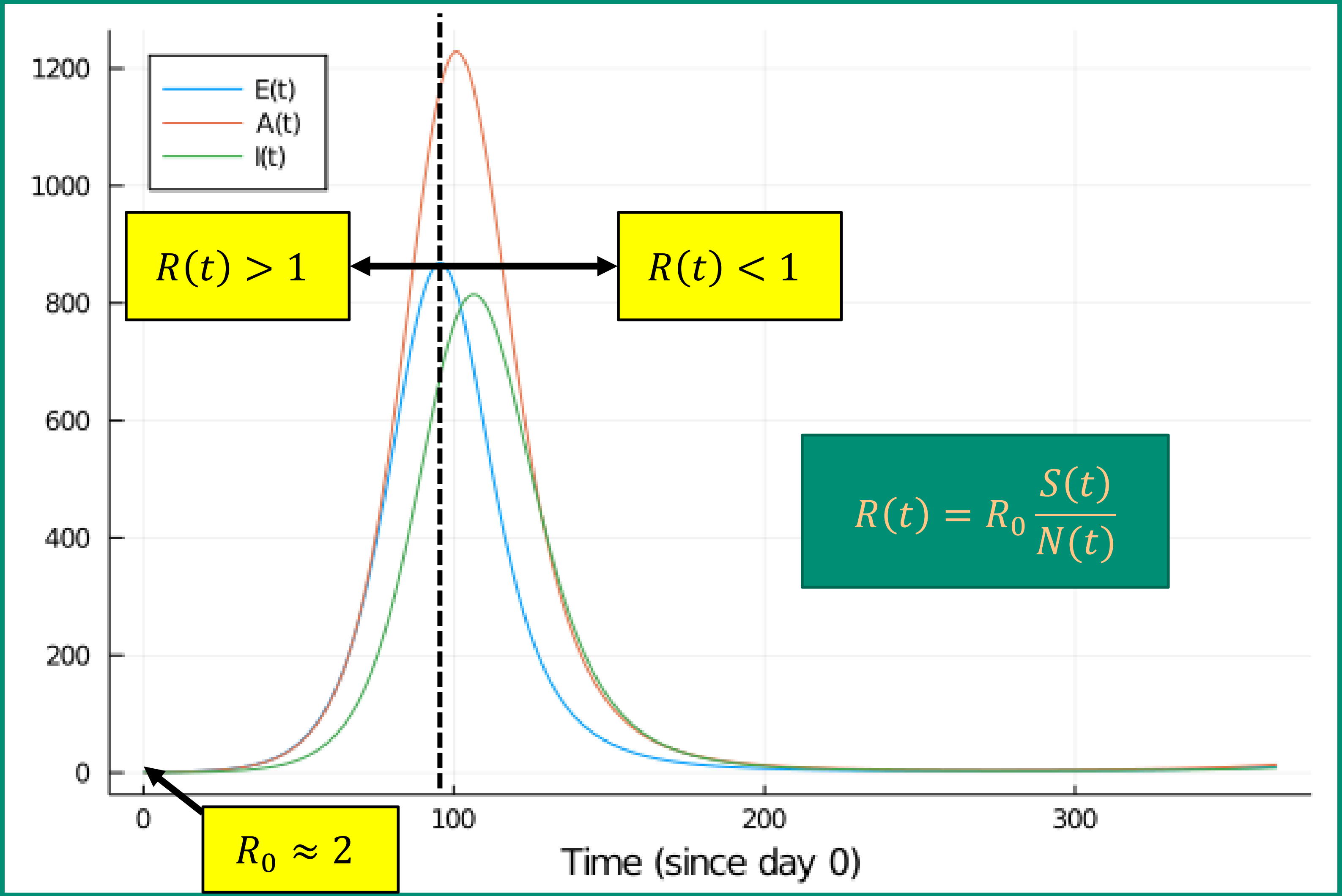
- $t = 0$ is when the first infected is introduced to a fully susceptible population.

$R(t) \approx 1$ at time $t = 95$ (specific to this example)

- Implying that we can reach herd immunity on day 95 (after the first infected is introduced)

# Herd Immunity in terms of $R_0$ and $R(t)$

Infected State Trajectories:




What to Know:

$R(t) \approx R_0$ at time $t = 0$

$R(t) \approx 1$ at time $t = 95$

Herd Immunity $:= \Psi = 1 - \left(\frac{1}{R_0}\right)$

- When $R_0 = 2$, then $\Psi = 0.5$
- $S(t) < 0.5N(t)$ is needed to control the spread

$N(t) = 10{,}000$

At time $t = 95$

- $S(95) \approx 4854$
- $\mathrm{R}(95) \approx 0.98 < 1$

# Outline

Introduction to Epidemiology

Epi Modeling Paradigms

Compartmental Model System Analysis

Modeling Mitigation Strategies

# Non-Pharmaceutical Interventions (NPI)

### Personal Protective Equipment (PPE)

- Face masks

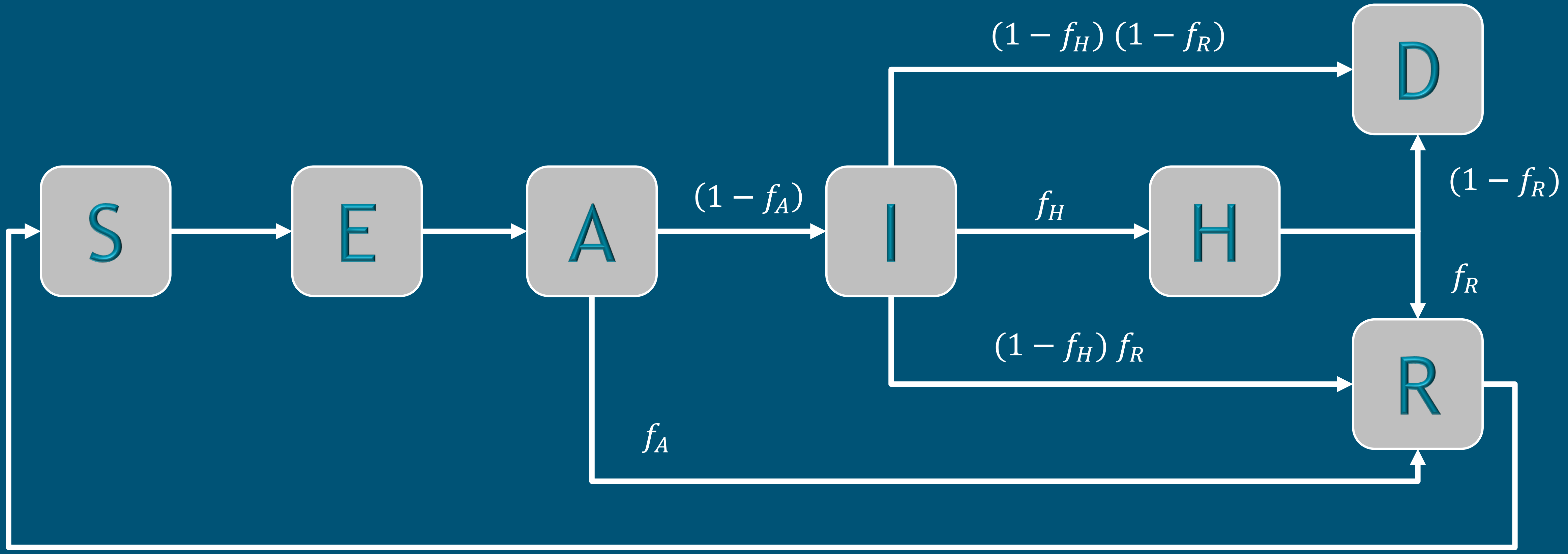
### Isolation

- Identified infected individuals only.
- Those who have a positive test result, indicating that they have been infected by the virus.

### Quarantine

- Contacts of an infected individual in isolation.
- Identification and quarantine of presumptive positive cases is most critical to infectious diseases where infectious onset occurs before symptom onset.

# Compartmental Model: NPI Intervention (Face Masks)




$$\lambda(t) \coloneqq \beta c (1 - \rho_E \times \rho_P) \frac{\eta_A A(t) + I(t) + \eta_H H(t)}{N(t)}$$

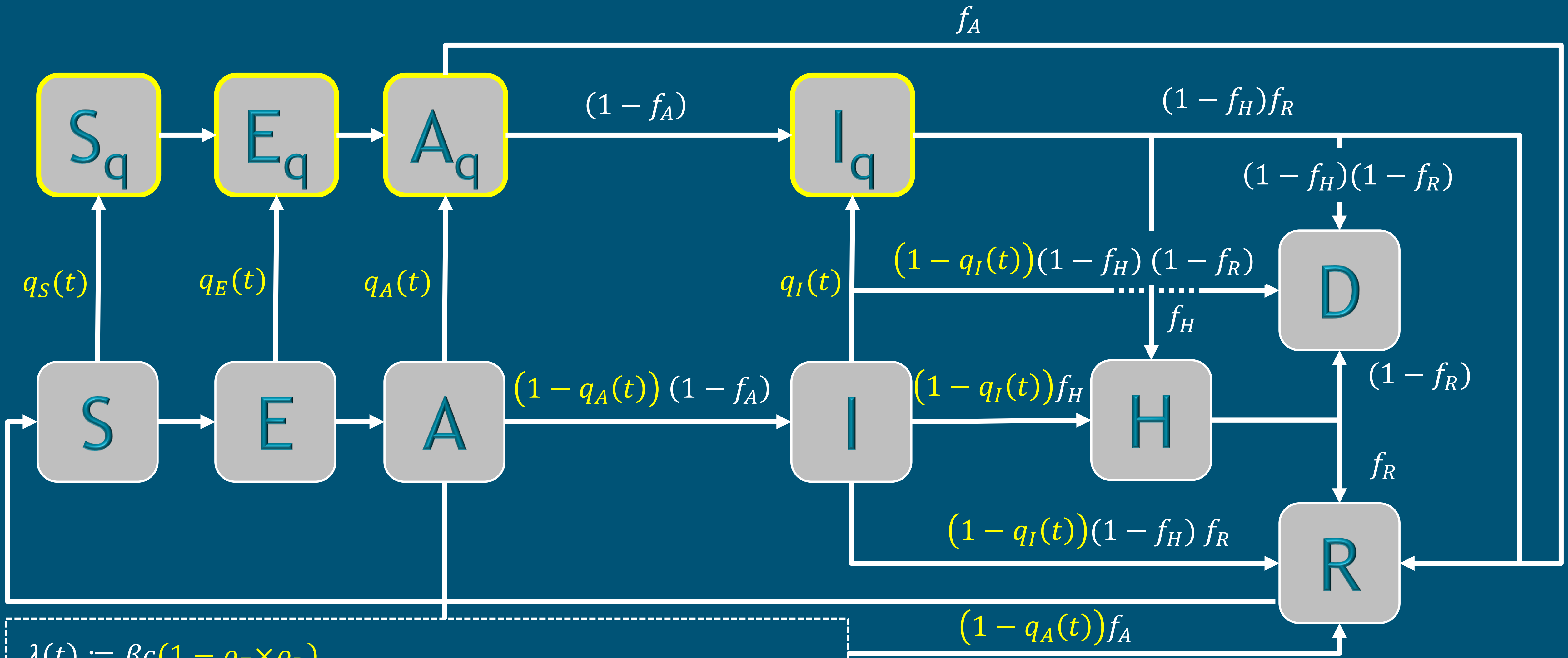
$\rho_E$ : Effectiveness of Face Masks
$\rho_P$ : Probability the interaction between two individuals is protected by Face Masks

# Face Mask $R_0$

$$\lambda(t) \coloneqq \beta c(1 - \rho_E \times \rho_P)\frac{\eta_A A(t) + I(t) + \eta_H H(t)}{N(t)}$$

$$R_0 = \beta c(1 - \rho_E \times \rho_P) \times (f_A \eta_A T_A + (1 - f_A)(1 - f_H)(\eta_A T_A + T_I) + (1 - f_A) f_H (\eta_A T_A + T_I + \eta_H T_H))$$

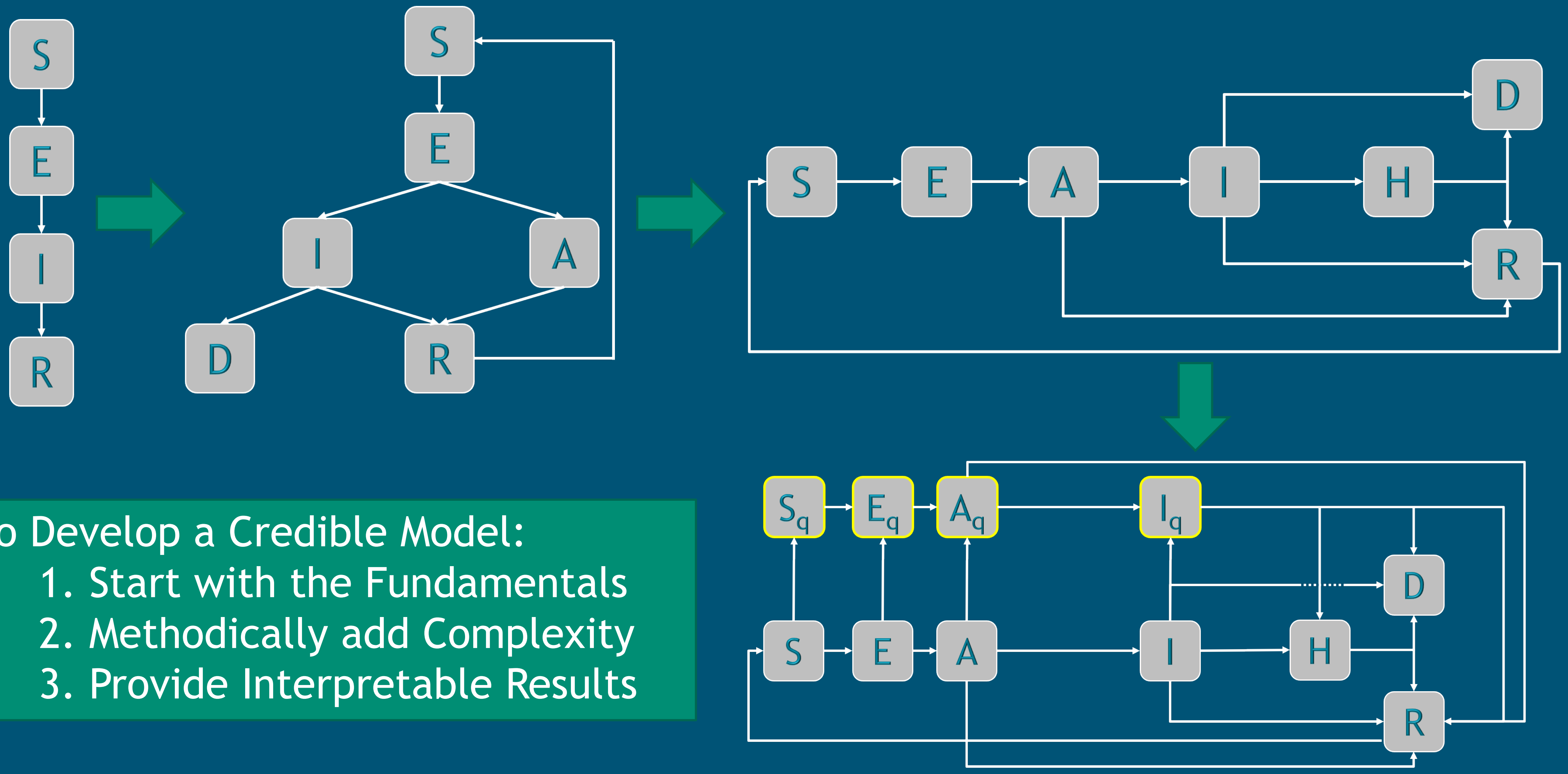
# Compartmental Model: NPI Intervention (Isolation & Quarantine)




$$\lambda(t) := \beta c(1 - \rho_E \times \rho_P) \times \frac{\eta_A A(t) + I(t) + \eta_H H(t) + (1 - \theta_q)(\eta_A A_q(t) + I_i(t))}{N(t)}$$

$\theta_q$ : Effectiveness of Quarantine & Isolation

# Evolution of Compartmental Model Complexity




To Develop a Credible Model:

1. Start with the Fundamentals
2. Methodically add Complexity
3. Provide Interpretable Results

# References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