Investigating the Structural and Practical Identifiability of Adult-Child Compartment Epidemic Models

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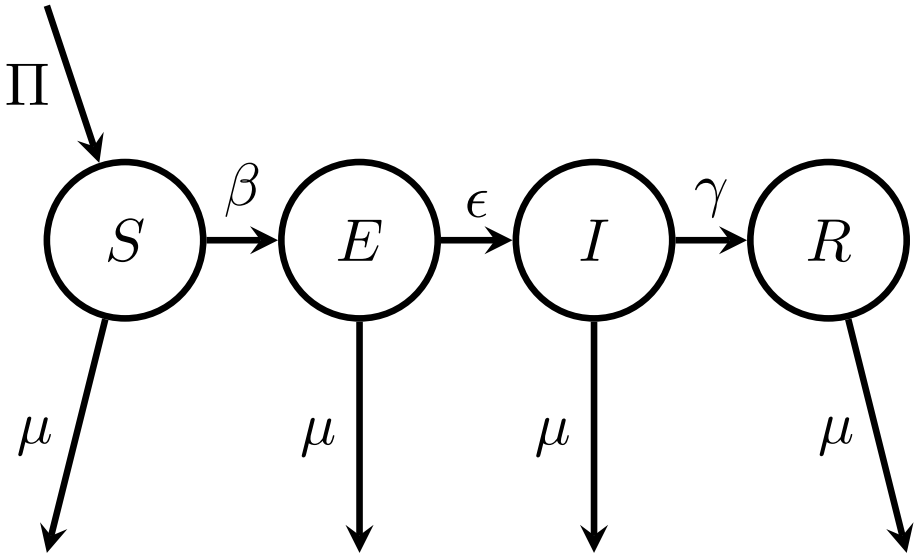
Epidemic Modeling and the SIR/SEIR Models

2 Main Ideas for Modeling:

- Given data about number of cases, can we retroactively understand information about the disease?
- Given biological information about a disease, can we predict the severity and future outcome of an epidemic?

SEIR Model

$$\frac{dS}{dt} = -\beta SI + \Pi N - \mu S$$
$$\frac{dE}{dt} = \beta SI - \epsilon E - \mu E$$
$$\frac{dI}{dt} = \epsilon E - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$

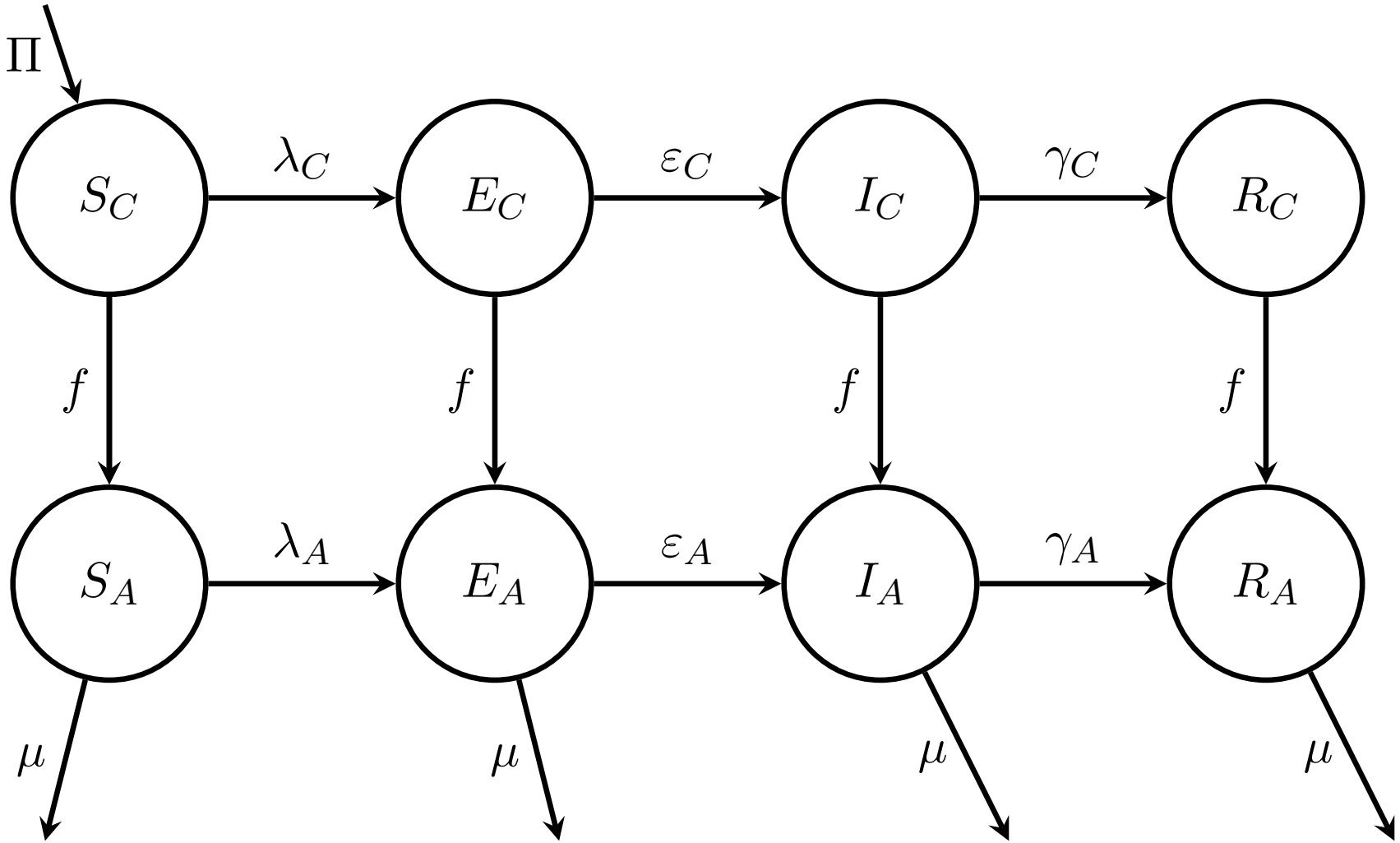


Where $\Pi = \mu$

Age-Dependent Model

- $S_{C/A}$: the number of susceptible people, assuming that everyone is susceptible at t=0.
- $E_{C/A}$: the number of exposed people who made successful contact with an infected person but do not have symptoms.
- $I_{C/A}$: the number of infected people.
- $R_{C/A}$: the number of recovered people, assuming that recovery grants immunity

Age-Dependent Model



Our Known and Unknown Parameters

While most of our parameters are constants, here, λ is a function of I_C, I_A, E_C, E_A.
Children are frequency dependent while adults are density dependent.

- $\lambda_C(I_C, I_A, E_C, E_A) = \beta_{CC}\frac{I_C}{N_C} + \beta_{AC}\frac{I_A}{N_A} + \xi_{CC}\frac{E_C}{N_C} + \xi_{AC}\frac{E_A}{N_A}$
- $\lambda_A(I_C, I_A, E_C, E_A) = \beta_{AA}I_A + \beta_{CA}I_C + \xi_{AA}E_A + \xi_{CA}E_C$

The Model Equations

- $\frac{dS_C}{dt} = \Pi N_A - fS_C - \lambda_C S_C$
- $\frac{dS_A}{dt} = fS_C - \lambda_A S_A - \mu S_A$
- $\frac{dE_C}{dt} = \lambda_C S_C - \epsilon_C E_C - fE_C$
- $\frac{dE_A}{dt} = \lambda_A S_A + fE_C - \epsilon_A E_A - \mu E_A$
- $\frac{dI_C}{dt} = \epsilon_C E_C - fI_C - \gamma_C I_C$
- $\frac{dI_A}{dt} = fI_C + \epsilon_A E_A - \gamma_A I_A - \mu I_A$
- $\frac{dR_C}{dt} = \gamma_C I_C - fR_C$
- $\frac{dR_A}{dt} = \gamma_A I_A + fR_C - \mu R_A$

Where $\Pi = \mu$

Parameter Values

Parameter	Range	Reasoning
β_{CC}	$[0.1, 1.0]$	Estimated from reasonable R_0
β_{AC}	$[.05, 1.0]$	Estimated from reasonable R_0
β_{AA}	$[5 \times 10^{-7}, 2 \times 10^{-5}]$	Estimated from reasonable R_0
β_{CA}	$[1 \times 10^{-8}, 5 \times 10^{-7}]$	Estimated from reasonable R_0
γ_C	$[0.02, 1]$	Infectious from 1 to 50 days
γ_A	$[0.01, 1]$	Infectious from 1 day to 100 days
μ	$[4 \times 10^{-5}, 8 \times 10^{-5}]$	Adult age from 35 to 70
f	$[1 \times 10^{-4}, 5 \times 10^{-4}]$	Child age from 5.5 to 27
ϵ_C	$[0.04, 1]$	Incubation from 1 and 25 days
ϵ_A	$[0.02, 1]$	Incubation from 1 to 50 days

Basic Reproduction Number

Definition

R_0 is the number of new infections that can come from one infected individual in a totally susceptible population

- $R_0 < 1$ will not create an epidemic
- $R_0 > 1$ might create an epidemic

We use the next generation matrix method to compute our R_0

Next Generation Matrix Method

Approach: calculate a matrix whose ij-th term represents the average number of infections in the ith compartment created by individuals in the jth compartment

1. Identify diseased compartments
2. Identify $\mathcal{F}$ (new secondary infections) and $\mathcal{V}$ (movement **out** of compartments)

Linearize at the Disease Free Equilibrium and find F (the Jacobian of $\mathcal{F}$) and V (the Jacobian of $\mathcal{V}$)

Calculating R_0 for the Adult-Child Model

The R_0 of our Adult-Child compartment depends on:

$$A = \frac{\xi_{CC}}{(\epsilon_C + f)} + \frac{\beta_{CC}\epsilon_C}{(\epsilon_C + f)(f + \gamma_C)} + \frac{N_C f \xi_{AC}}{N_A(\epsilon_C + f)(\epsilon_A + \mu)}$$

$$+ \frac{N_C \beta_{AC}(\epsilon_A f^2 + \epsilon_A \epsilon_C f + \epsilon_A f \gamma_C + \epsilon_C f \mu)}{N_A(\epsilon_C + f)(f + \gamma_C)(\epsilon_A + \mu)(\gamma_A + \mu)}$$

$$\text{B} = \frac{N_C \xi_{AC}}{N_A(\epsilon_A + \mu)} + \frac{N_C \beta_{AC}\epsilon_A}{N_A(\epsilon_A + \mu)(\gamma_A + \mu)}$$

$$\text{E} = \frac{N_A \xi_{CA}}{\epsilon_C + f} + \frac{N_A \beta_{CA}\epsilon_C}{(\epsilon_C + f)(f + \gamma_C)} + \frac{N_A f \xi_{AA}}{(\epsilon_C + f)(\epsilon_A + mu)} +$$

$$\frac{N_A \beta_{AA}(\epsilon_A f^2 + \epsilon_A \epsilon_C f + \epsilon_A f \gamma_C + \epsilon_C f \mu)}{(\epsilon_C + f)(f + \gamma_C)(\epsilon_A + \mu)(\gamma_A + \mu)}$$

$$\text{F} = \frac{N_A \xi_{AA}}{\epsilon_A + \mu} + \frac{N_A \beta_{AA}\epsilon_A}{(\epsilon_A + \mu)(\gamma_A + \mu)}$$

Relating SEIR Model to Adult-Child Model

- Goal: compare simple SEIR to SEIR Adult-Child
- How do we relate β to β_{AA},β_{CC},β_{AC}, and β_{CA}?
- How do ϵ and γ relate to ϵ_C, ϵ_A, γ_C, and γ_A?

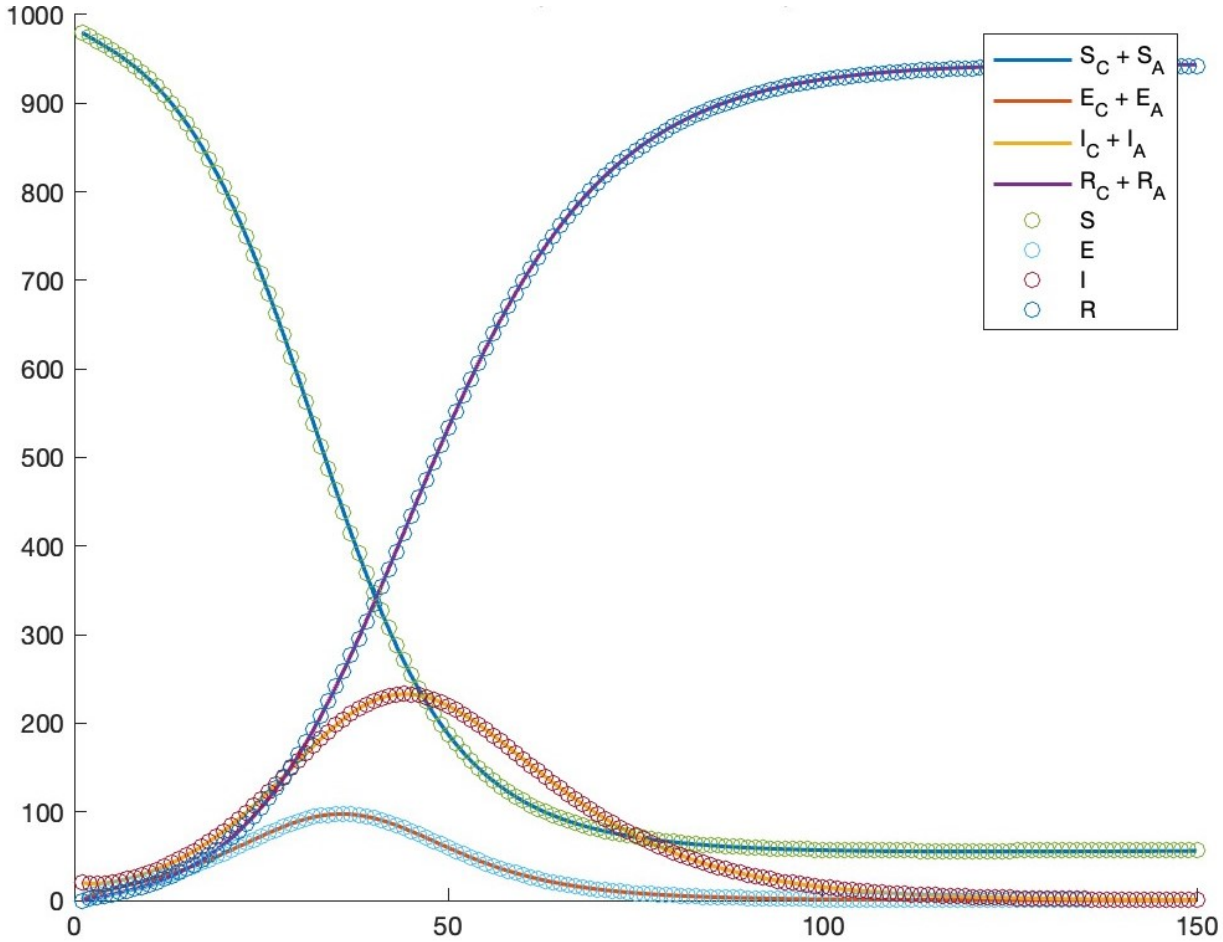
Base Case

- Begin with a base case where Child values = Adult values
- Account for frequency and density dependent β values

Adult-Child	**Relation**	**Adult-Child**	**Relation**
β_{AA}	β	β_{CC}	βN_C
β_{CA}	β	β_{AC}	βN_A
ϵ_C	ϵ	ϵ_A	ϵ
γ_C	γ	γ_A	γ
$N_C = 250$	$N - N_A$	$N_A = 750$	$N - N_C$

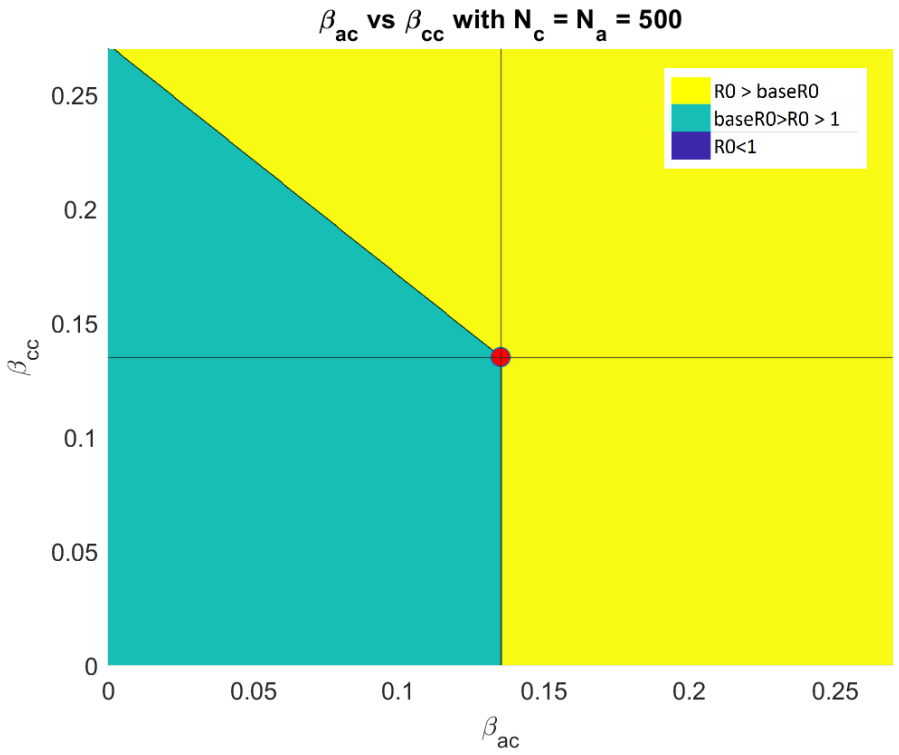
$\beta \approx 0.00027$, $\epsilon = 0.25$, $\gamma = 0.087$

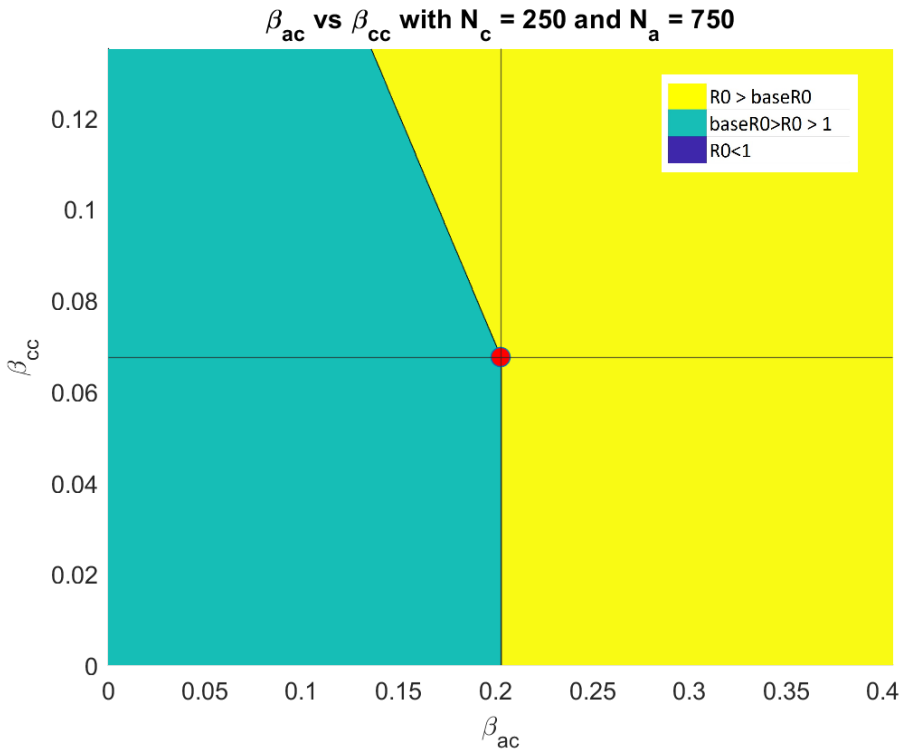
Base Case



Adult Child SEIR $R_0 = 3.1$ and base case SEIR $R_0 = 3.1$

Comparing R_0 : Adult to Child vs Child to Child





Isolated Child Populations

When our β values are not identical, what happens if we just look at one isolated population (just adults or just children)?

Standard SEIR	**Adult-Child Model**	**Value**
β	$\frac{\beta_{CC}}{N_C}$	0.00000108
ϵ	ϵ_C	0.3
γ	γ_C	0.1

How do we account for population size and the number of people interacting?

Comparing Infectious Results: Child Infections

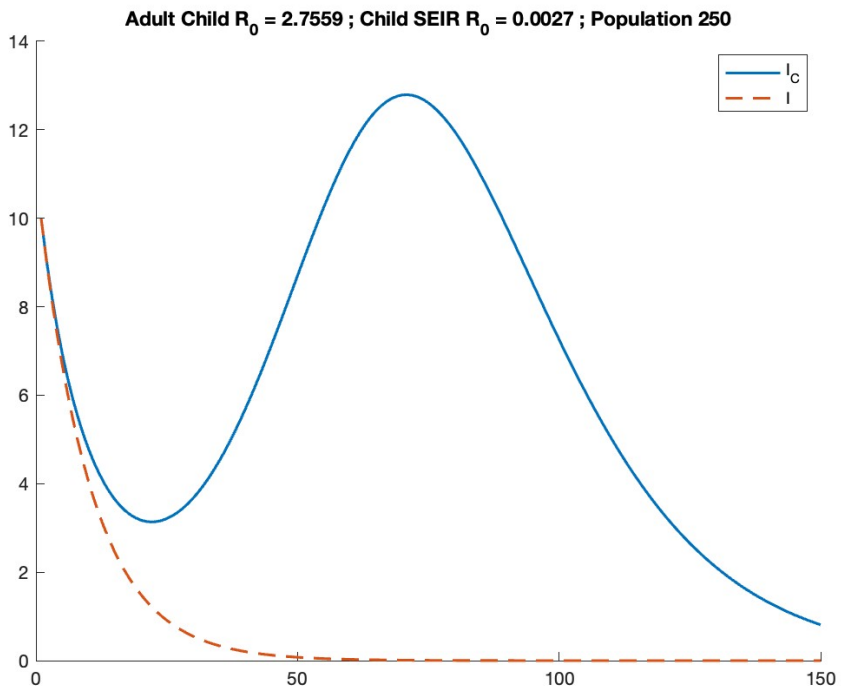


Figure: SEIR: $I(0) = 250$, SEIR-CA: $I_A(0) = 750, I_C(0) = 250$

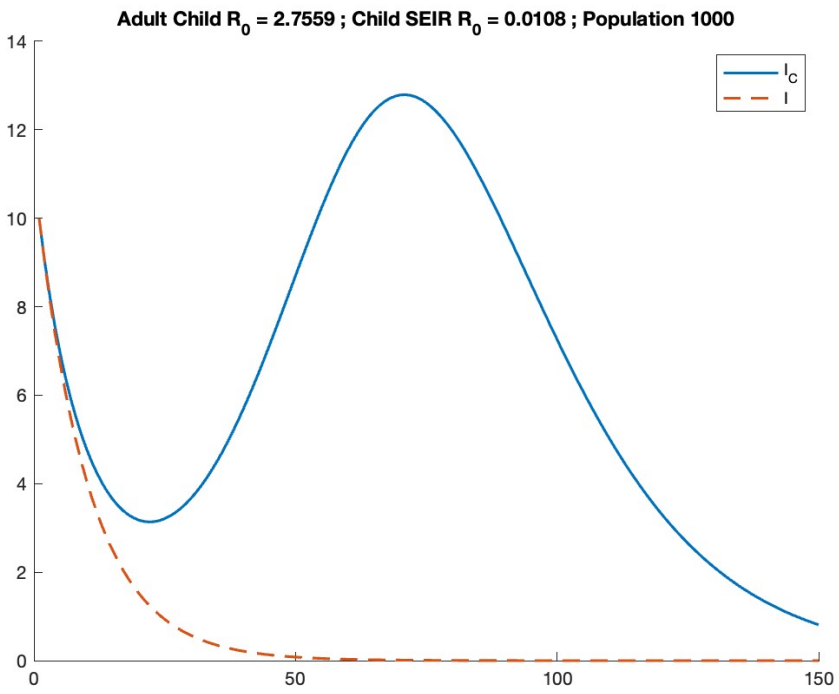


Figure: SEIR: $I(0) = 1000$, SEIR-CA: $I_A(0) = 750, I_C(0) = 250$

What is Identifiability?

Given data, we can create and fit any model. But can we use a model to predict data and understand a disease? If we ask a question, will the model give us multiple different answers or one true value?

Structural and Practical Identifiability

- **Structural Identifiability:** A model is structurally identifiable if the model parameters can be uniquely determined based on the model formulation with continuous data and no noise.
- **Practical Identifiability:** A model is practically identifiable if we can recover *reasonable* model parameters given incomplete or imperfect data.

Computing Structural Identifiability

We compute structural identifiability using **Identifiability Analysis** in Mathematica.

- works by computing a non-linear algebraic system, whose rank of the Jacobian determines the identifiability of the system.
- reduces computational complexity by directly computing the entries of the Jacobian matrix and by performing all calculations modulo a large prime number.
- uses local algebraic identifiabilty to produce a Boolean output where true means all parameters in the parameter set p are locally identifiable, while false means one or more parameters in the parameter set p are not locally identifiable.

Structural Identifiability Results

output vector	fixed parameters	identifiable parameters	non-identifiable
I_C, I_A	f, μ, β_{CC}	All	None
I_C, I_A	$f, \mu, \beta_{CC}, \beta_{CA}$	All	None
I_C, I_A	$f, \mu, \gamma_C, \gamma_A, \epsilon_C, \epsilon_A$	All	None

Table: Structural Identifiability of SEIR Parameters Non-Infectious E

output vector	fixed parameters	identifiable parameters	non-identifiable
I_C, I_A	f, μ	All	None
$I_C + I_A$	f, μ	All	None
R_C, R_A	f, μ	All	None
$R_C + R_A$	f, μ	All	None
C_C, C_A	f, μ	None	All
$C_C + R_C, C_A + R_A$	f, μ	All	None
$C_C + C_A, R_C + R_A$	f, μ	All	None

Table: Structural Identifiability of SEIR Parameters: Infectious E

Practical Identifiability Motivation

- A model could be structurally identifiable, but it still could be practically unidentifiable due to quality of data, which often needs to be addressed in model parameter estimation.
- We focus on practical identifiability given prevalence data I_C, I_A
- Method: Monte Carlo Simulation
- Practical identifiability is a very local behavior, so we fix our true parameters at COVID specific values in our investigation.

Parameter	Value	Parameter	Value
μ	0.00008	f	0.0005
β_{CC}	0.01	β_{AA}	0.00027
β_{CA}	0.00005	β_{AC}	0.01
γ_C	0.1	γ_A	0.074
ϵ_C	0.3	ϵ_A	0.2

Parameter	Value
ξ_{AA}	0.0002
ξ_{CC}	0.0067
ξ_{CA}	0.000033
ξ_{AC}	0.0067

Practical Identifiability Motivation

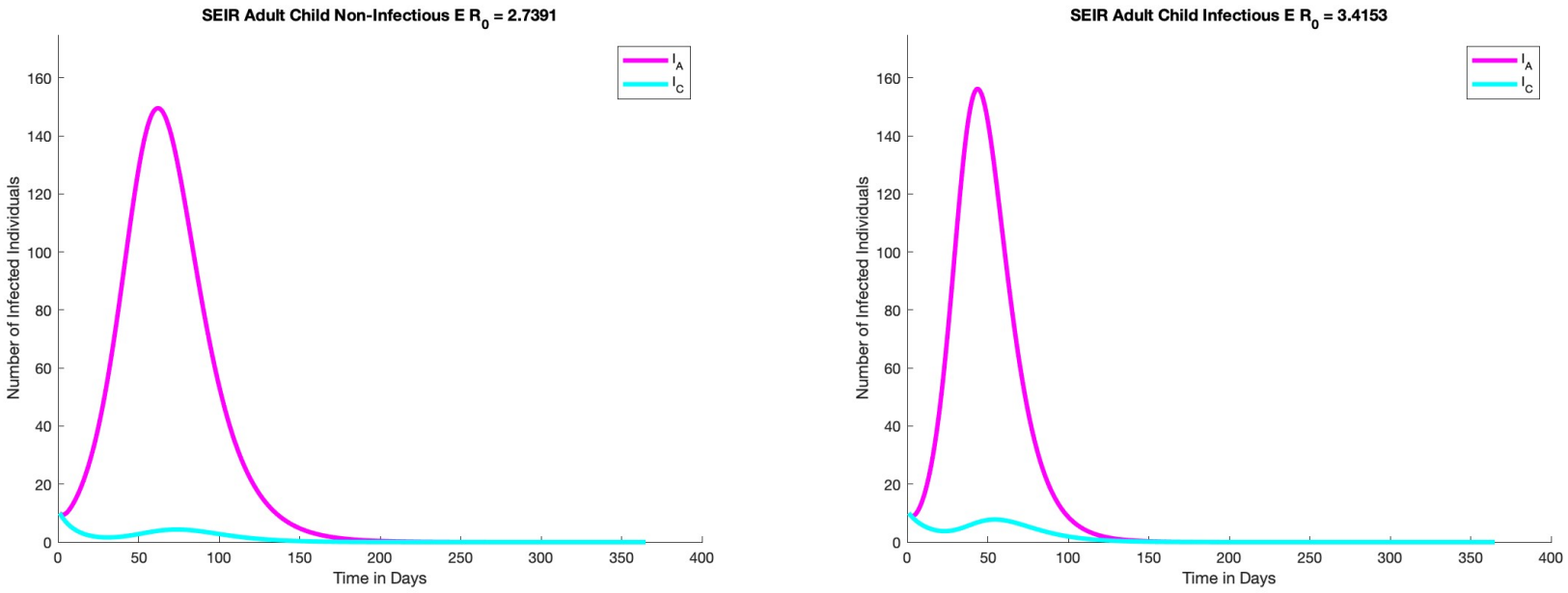


Figure: Infectious and non-infectious E SEIR adult child model dynamics with initial conditions $S_{C0} = 240$, $S_{A0} = 740$, $E_{C0} = 0$, $E_{A0} = 0$, $R_{C0} = 0$, and $R_{A0} = 0$.

Note: We adjust the time scale in our calculations to account for the differences in dynamics.

Computing Practical Identifiability

Algorithm 1 Monte Carlo Simulation

$t_j = 1, 2, \ldots, T$
Let p denote true parameter value.

for $\sigma = 0\%, 1\%, 5\%, 10\%, 20\%, 30\%$ **do**
  for $i = 1, 2, \ldots, 100$ **do**
    $\hat{I}_{iC}(t_j, p) = I_C(t_j, p) + \alpha_C$
    $\hat{I}_{iA}(t_j, p) = I_A(t_j, p) + \alpha_A$
    α_C follows $N(I_C(t_j, p), I_C(t_j, p)\sigma)$
    α_A follows $N(I_A(t_j, p), I_A(t_j, p)\sigma)$

    Optimize error function:
    error $= \sum(\frac{1}{I_{iC}(t_j)^2}(I_{iC}(t_j) - \hat{I}_{iC}(t_j))^2) + \sum(\frac{1}{I_{iA}(t_j)^2}(I_{iA}(t_j)$
    $-\hat{I}_{iA}(t_j))^2)$
    $\hat{p}_i(\sigma)$ is the optimal set of parameter values for the ith generated data set.
  end for

  Compute ARE
  Let k be the number of estimated parameters
  for $n = 1, 2, \ldots, k$ **do**
    $ARE(p_\sigma^{(k)}) = 100\% \times \frac{1}{100} \sum_{i=1}^{100} \frac{p^{(k)} - \hat{p}_{\sigma i}^{(k)}}{p^{(k)}}$
  end for
end for

Def: A parameter set p is practically identifiable if $ARE(p_\sigma^{(k)}) \leq \sigma$ for all σ.

Identifiability of Adult-Child Non-Infectious E SEIR Model

σ	β_{AA}	β_{CC}	β_{AC}	β_{CA}
0	0.0000	0.0000	0.0000	0.0000
1	0.0141	0.0771	0.0127	0.0860
5	0.1368	7.4768	0.7954	2.2646
10	0.4139	39.1975	1.9703	9.3628
20	1.8227	97.3919	3.8395	39.5859
30	5.0465	168.6005	6.2050	80.4438
σ	γ_A	γ_C	ϵ_C	ϵ_A
0	0.0000	0.0000	0.0000	0.0000
1	0.0159	0.0169	0.0130	0.0401
5	0.2317	0.9040	0.4418	0.4982
10	0.8576	4.1867	1.7974	1.6478
20	2.9308	10.0851	5.1290	6.5954
30	6.0575	15.9486	9.2823	15.4116

Figure: For 365 days using (time of peak infection for children is at day 1 and time of peak infection for adults is at day 62)

Identifiability of Adult-Child Non-Infectious E Beta Dependencies

Parameter	Dependency	Parameter	Dependency
β_{AA}	β	$\frac{\beta_{CC}}{N_{C0}}$	0.1434β
β_{CA}	0.1912β	$\frac{\beta_{AC}}{N_{A0}}$	0.1667β

Figure: COVID specific infection rate dependencies

- Scale the contact rate and probability of infection for the other three according to their relationships to β_{AA}.
- β_{AA} is the the largest followed by β_{CA}, $\dfrac{\beta_{AC}}{N_A(0)}$, and $\dfrac{\beta_{CC}}{N_C(0)}$.

Identifiability of Adult-Child Non-Infectious E Beta Dependencies Continued

σ	β	γ_A	γ_C	ϵ_C	ϵ_A
0	0.0000	0.0000	0.0000	0.0000	0.0000
1	0.0203	0.0242	0.0188	0.0142	0.0676
5	0.1681	0.2574	0.1733	0.5270	0.6985
10	0.3988	0.7500	0.4012	1.1210	1.6238
20	1.0902	2.7449	0.8450	3.3212	4.1651
30	2.6538	5.8913	1.7347	10.1056	9.1182

Figure: For 365 days (time of peak infection for children is at day 71 and time of peak infection for adults is at day 62)

Conclusions

- Differentiating between adults and children allows us to determine unique disease dynamics for the respective groups.
- Interactions between populations significantly change infection peaks and can create secondary infection peaks
- Isolated, non-infectious populations may still experience an epidemic after interacting with a more infectious population
- Cumulative outputs are not structurally identifiable.
- Including relevant β and ξ dependencies produce a full set of practically identifiable parameters.
- Age-based model captures additional disease dynamics without losing identifiability properties.

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