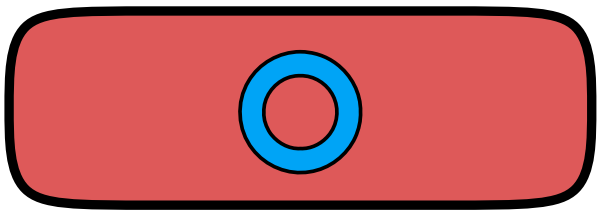
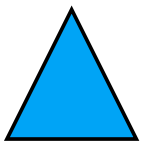
Schematic overview

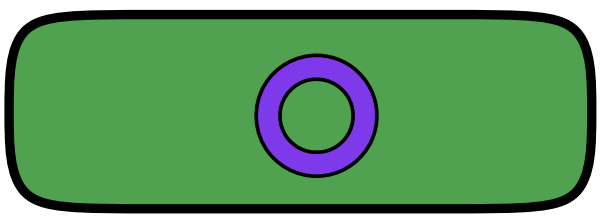


Salmonella Thphimurium (ST)

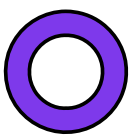
CTX-M-15
Cefotaxime resistance



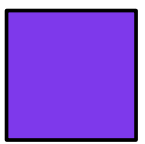
Cefotaxime



E. coli Nissle (EcN)

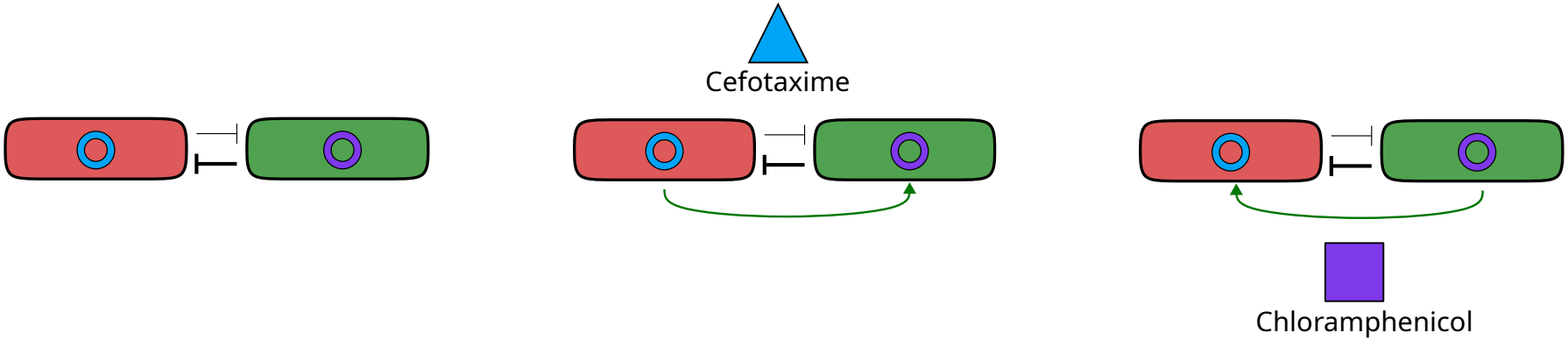


CAT
Chloramphenicol



Chloramphenicol

Interactions

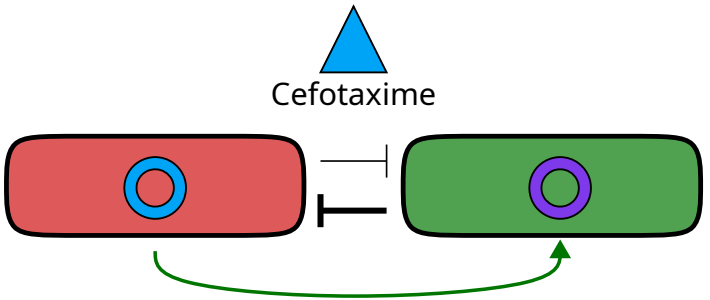


- No antibiotics
- *E. coli* excludes *ST*

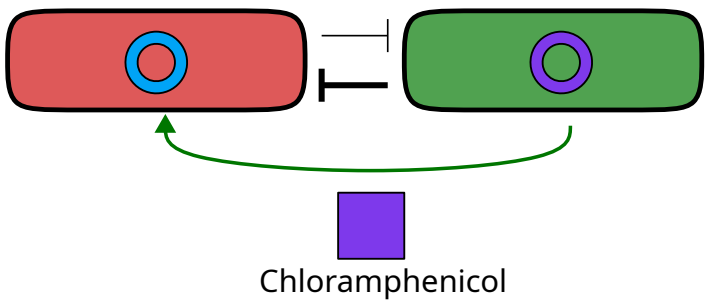
- *ST* protects *E. coli*
- Co-existence

- *E. coli* protects *ST*
- *E. coli* excludes *ST*

One-sided protection

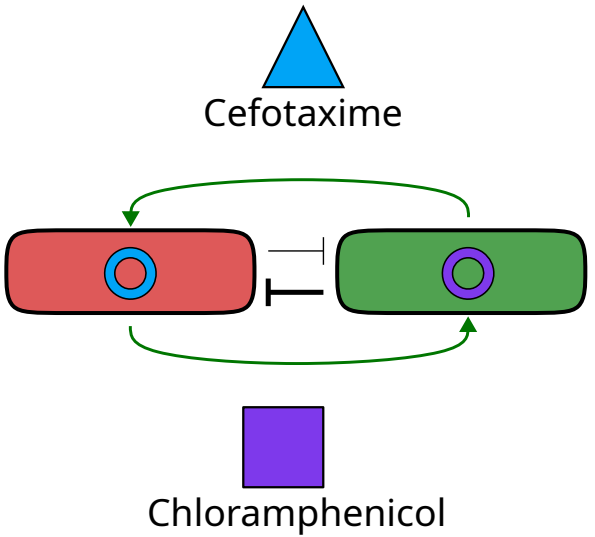


- Opposing signs (co-existence):
  - *E. coli* relies on partner species for protection
  - Can not exclude partner



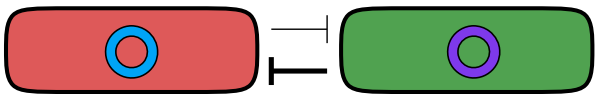
- Matching signs (exclusion):
  - Even if *E. coli* fully detoxifies the environment the negative interaction causes extinction of *ST*

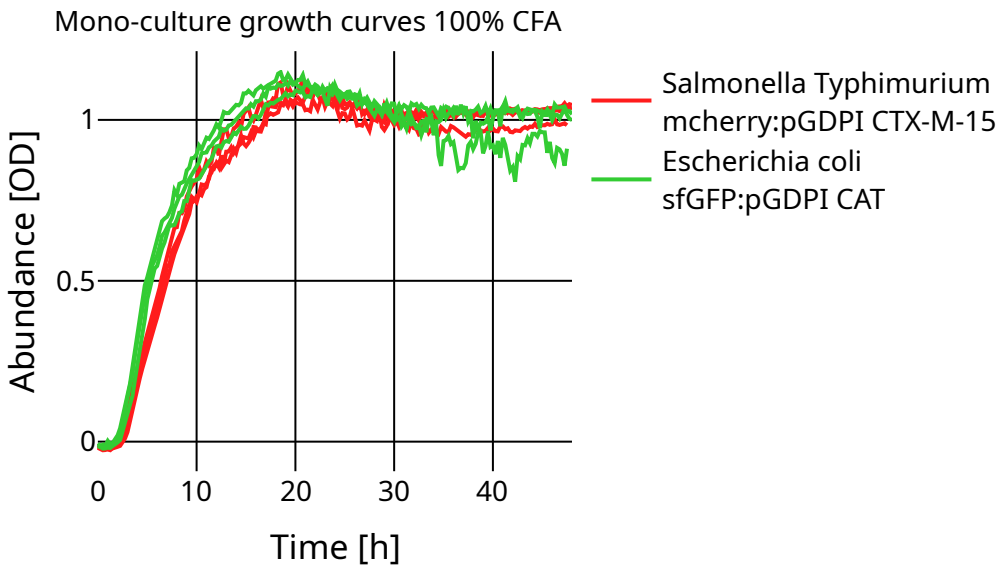
Two sided protection



- *ST* protects *E. coli*
- *E. coli* protects *ST*
- Both species go extinct

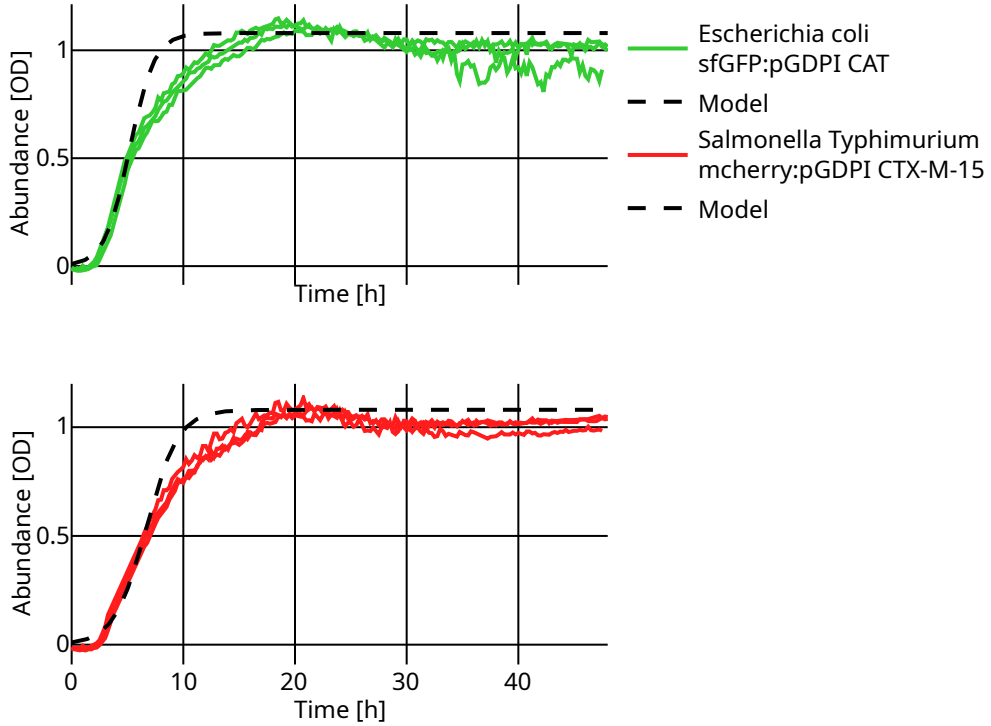
No antibiotics – Exclusion of *ST*





- Mechanism of exclusion unknown
- Fran created growth curves across CFA gradient for all strains
  - All curves look very similar
- Modeling interactions as resource competition not suitable

Growth model



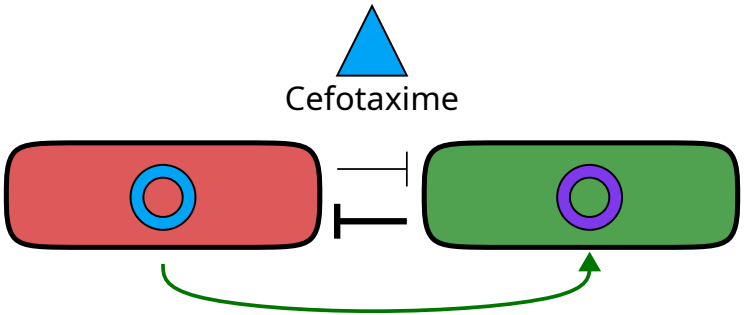
$$\frac{dN}{dt} = \mu N$$

$$\frac{dN}{dt} = r\left(1 - \frac{N}{K}\right) N$$

μ : *Per capita growth rate*
N : *Species*
r : *Maximum growth rate*
K : *Carrying capacity*

	E. coli	*St*
r [1/h]	0.9	0.7
K [OD]	1.1	1.1

One-sided protection - opposing signs

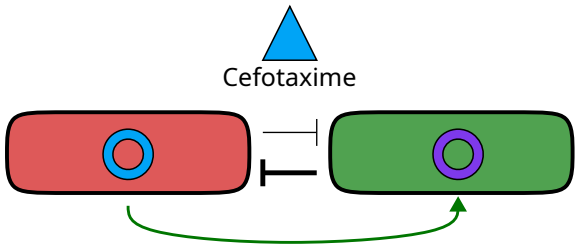


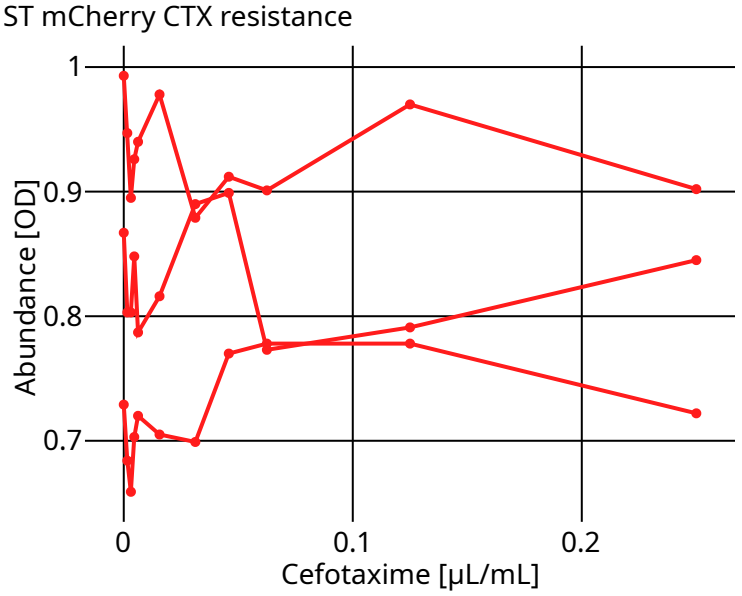
$$\frac{dN}{dt} = \left(\mu - \frac{JCf}{Cf + IC50}\right) N$$

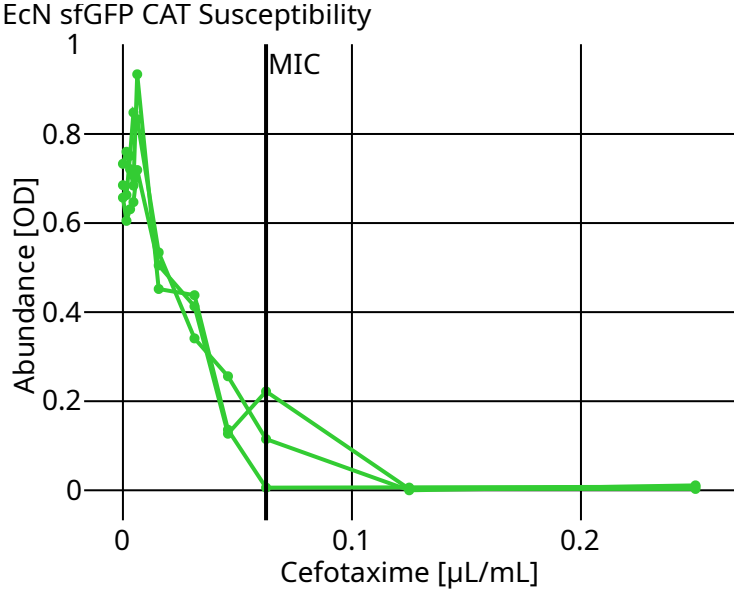
N : *Abundance E . coli*
μ : *Per capita growth rate*
J : *Maximum death rate*
Cf : *Cefotaxime*
$IC50$: *Half − maximal inhibitory concentration*

- Co-existence observed
- Cefotaxime is bactericidal
- Fran did dose response curves to measure the IC50
- Also did a kill curve to measure the maximum death rate J

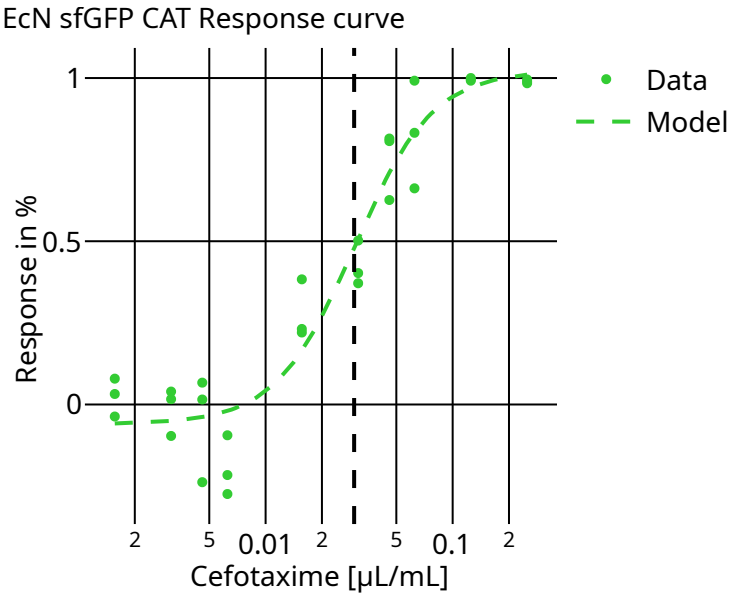
ST is resistant against Cefotaxime, *E. coli susceptible*







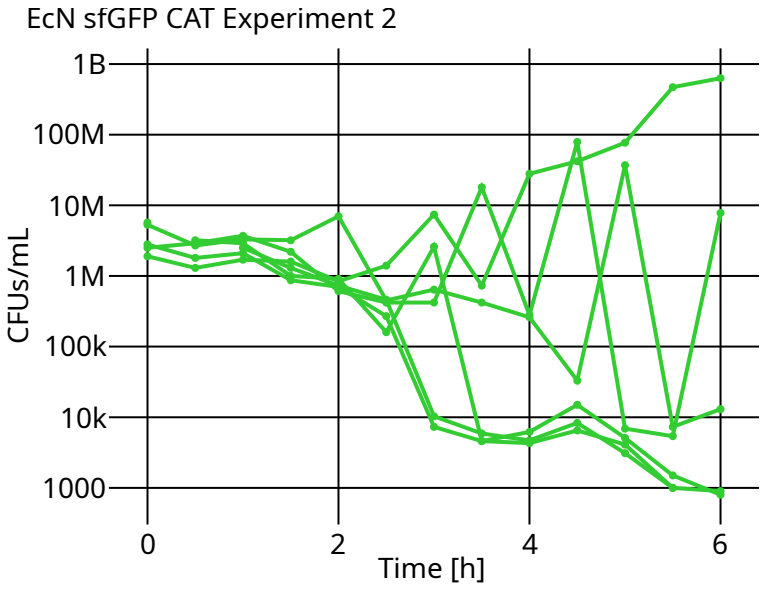
IC50 for *E. coli*



- IC50: How much drug is needed to inhibit half of a biological process
- Fitted sigmoid model
- IC50: 0.03 µg/mL
- MIC: 0.0625 µg/mL

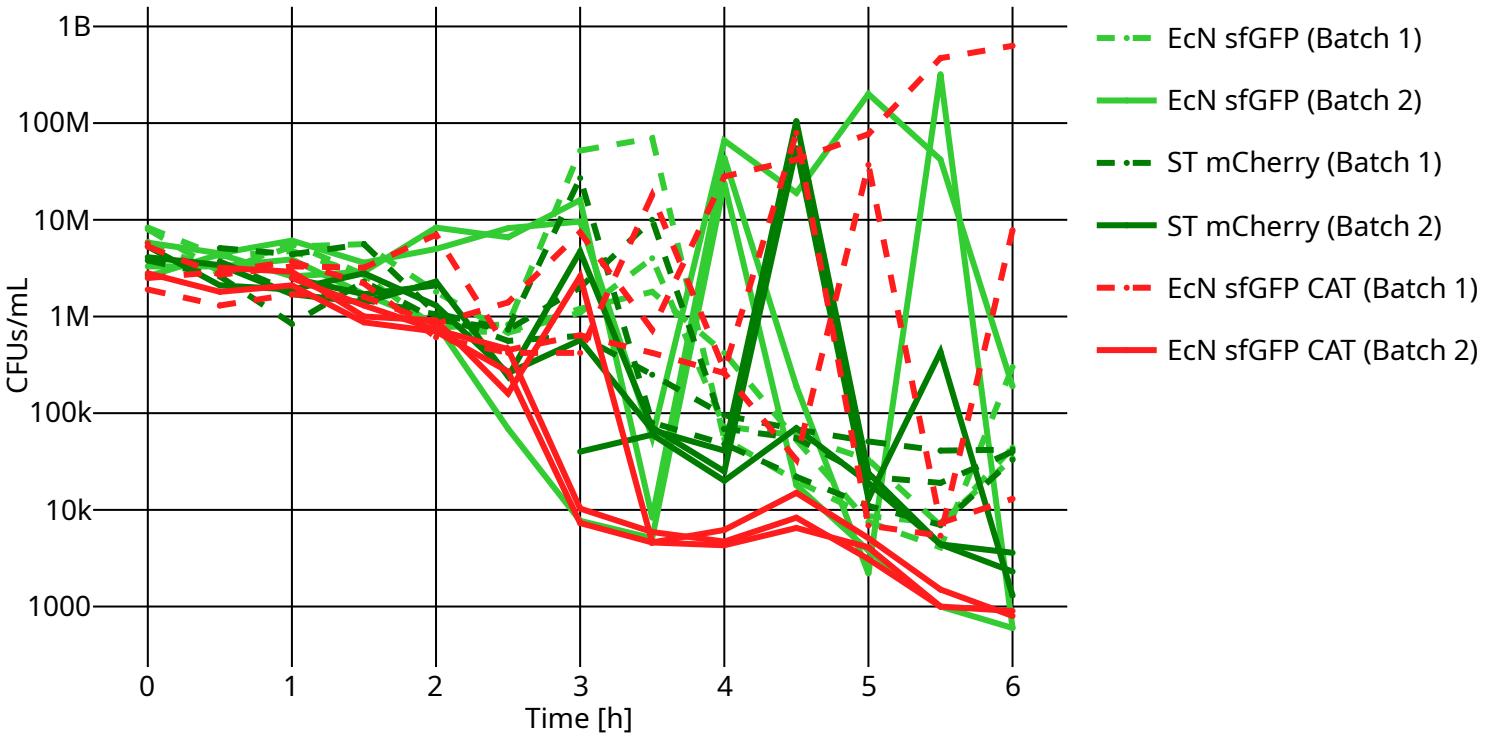
$$\frac{dN}{dt} = \left(\mu - \frac{JCf}{Cf + IC\,50}\right) N$$

Maximum death rate

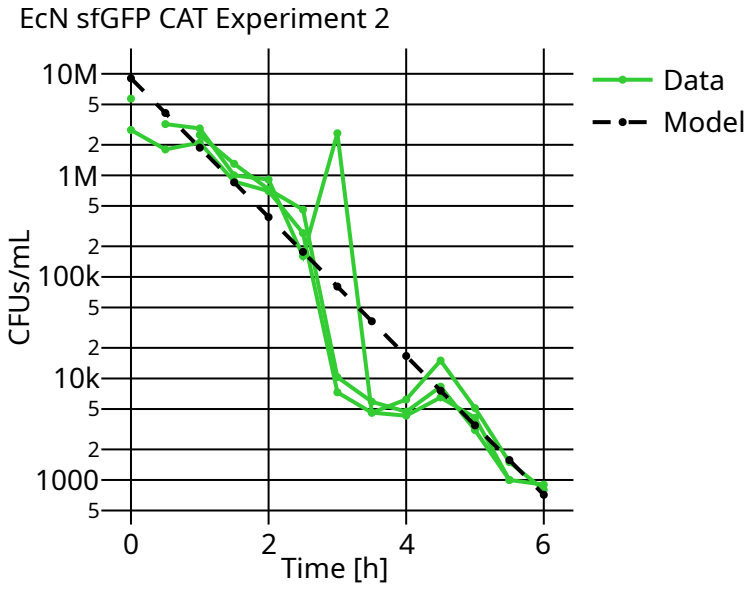


- 4x MIC of Cefotaxime was added after 2 hours
- Variety in repeats
  - In some repeats population manages to resist
- Standing variation:
  - Mutations that are present before treatment

Death rates all strains



Maximum death rate



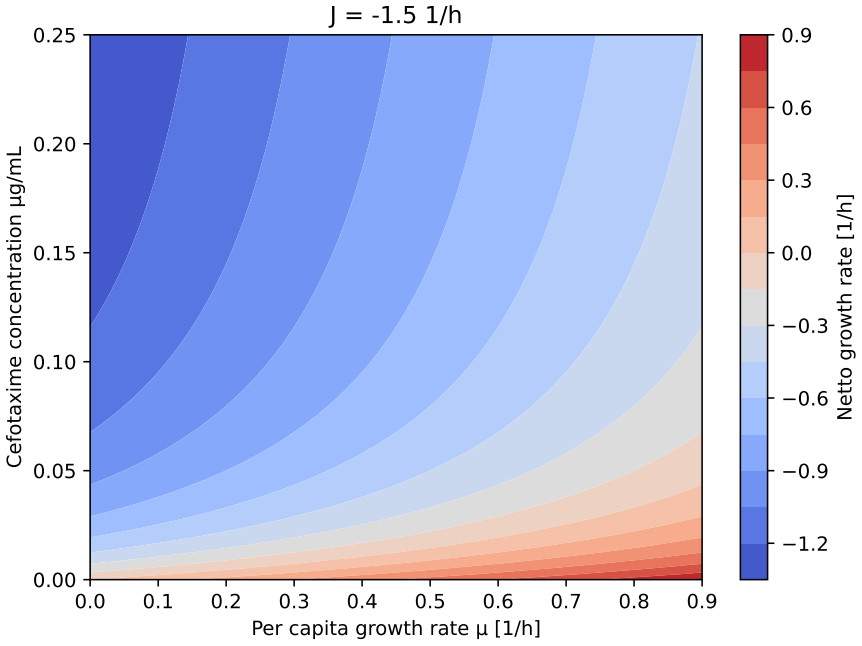
- Maximum death rate J = -1.57 1/h for repeats that are killed by Cefotaxime
- Part of the population that does not go extinct could be important for co-existence
  - Only little detoxification needed

Variation affects netto growth rate

netto growth rate

$$\frac{dN}{dt} = \left(\mu - \frac{JCf}{Cf + IC50}\right) N$$

N : *Abundance E . coli*
μ : *Per capita growth rate*
J : *Maximum death rate*
Cf : *Cefotaxime*
$IC50$: *Half − maximal inhibitory concentration*

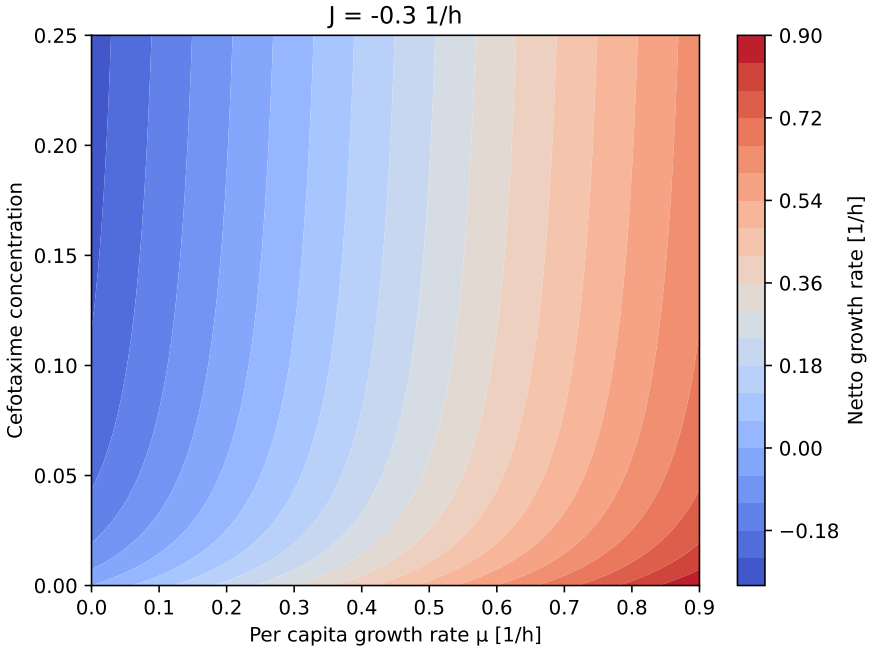


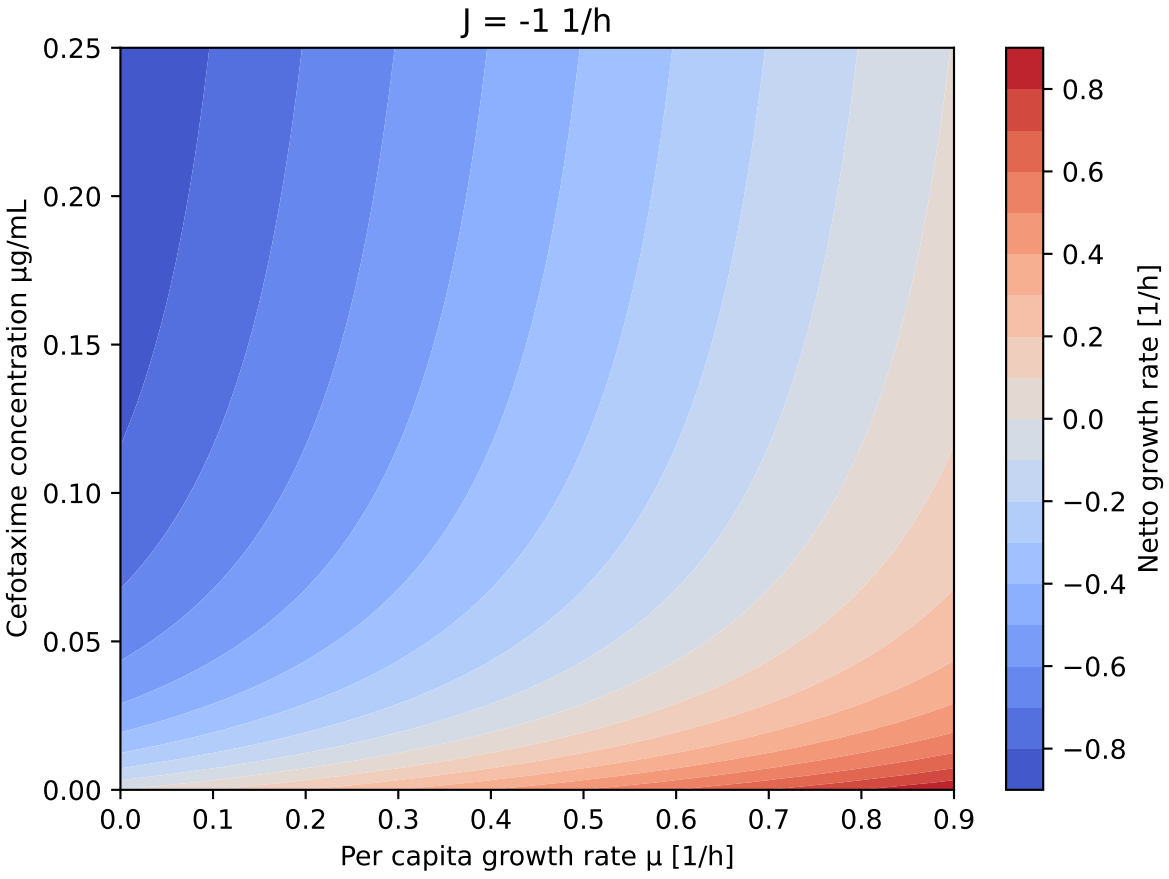
Variation affects netto growth rate

netto growth rate

$$\frac{dN}{dt} = \left(\mu - \frac{JCf}{Cf + IC50}\right) N$$

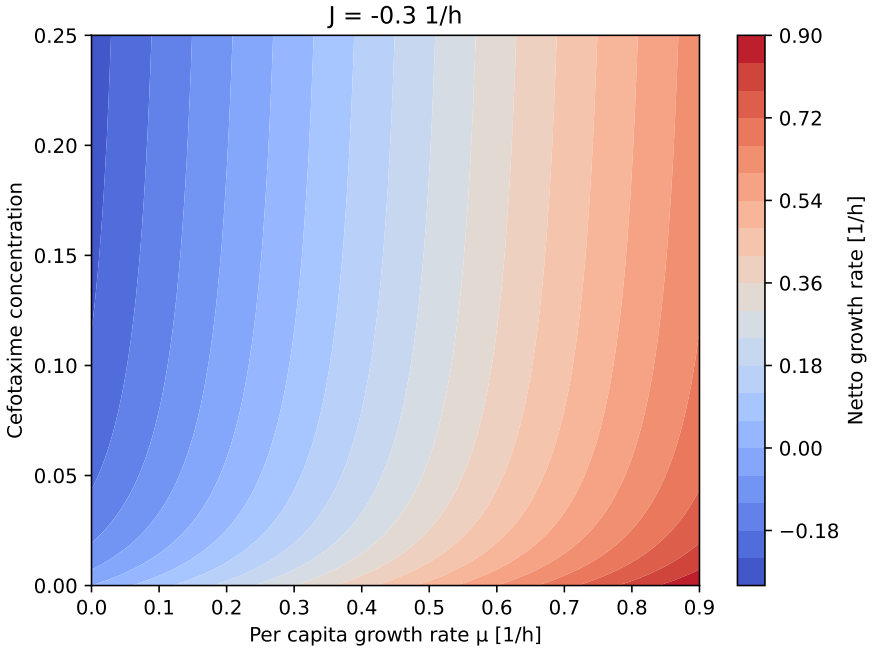
N : *Abundance E . coli*
μ : *Per capita growth rate*
J : *Maximum death rate*
Cf : *Cefotaxime*
$IC50$: *Half − maximal inhibitory concentration*



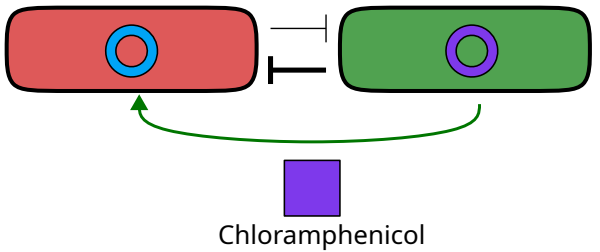

J = -1 1/h
Cefotaxime concentration µg/mL
0.25
0.20
0.15
0.10
0.05
0.00
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
Per capita growth rate µ [1/h]
Netto growth rate [1/h]
0.8
0.6
0.4
0.2
0.0
−0.2
−0.4
−0.6
−0.8

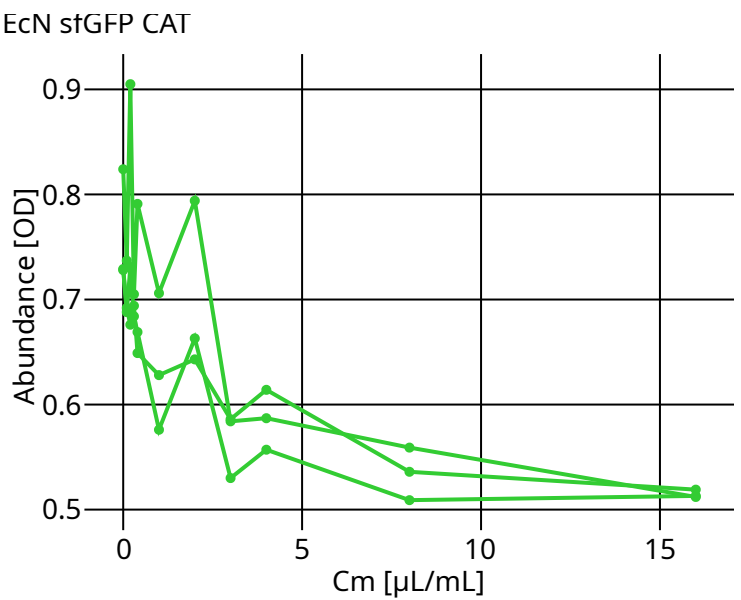
Variation affects netto growth rate

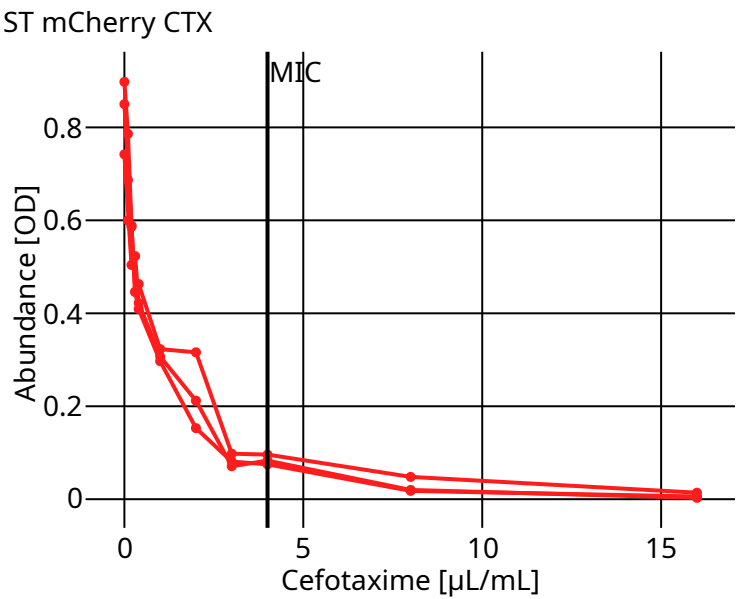
- Variation in maximum death rate
- Already little detoxification will enable *E. coli* to grow close to its maximum growth rate
- Co-existence feasible



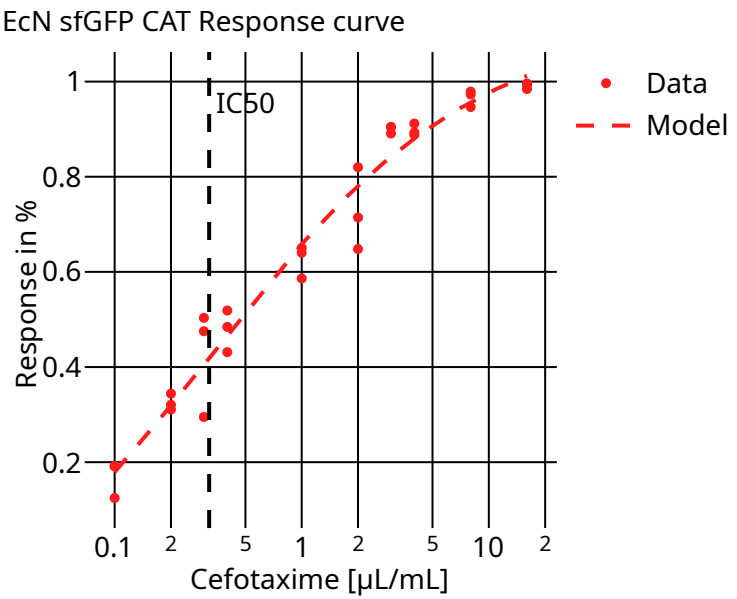
Chloramphenicol







IC50 Chloramphenicol



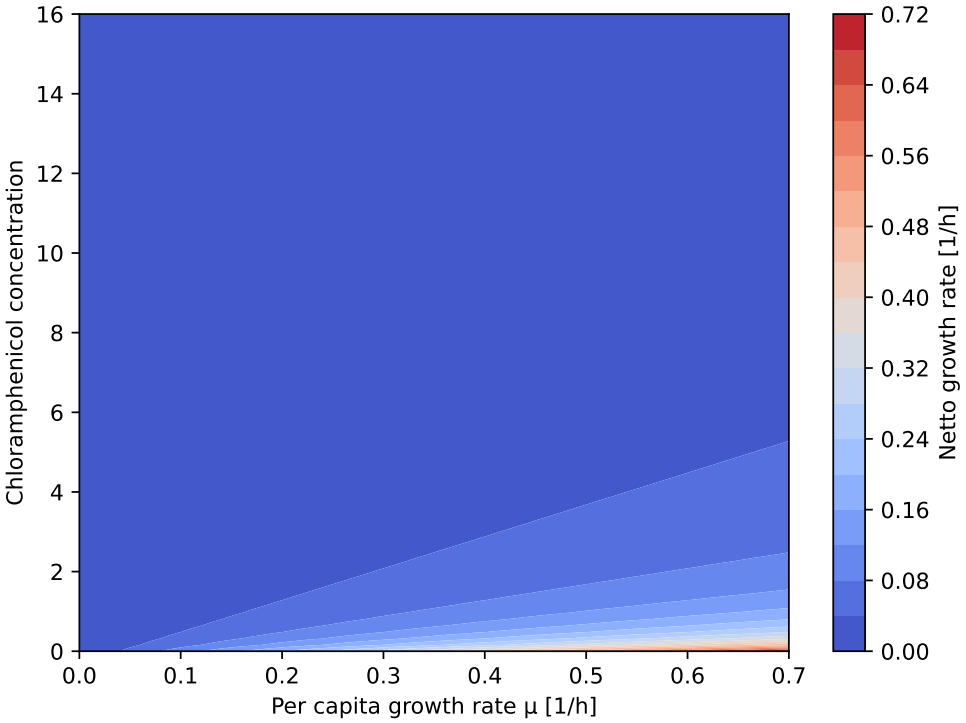
- IC50 for Chloramphenicol: 0.32 µg/mL
- MIC: 4 µg/mL
- Chloramphenicol is still effective at 0.025x MIC

Chloramphenicol is very effective

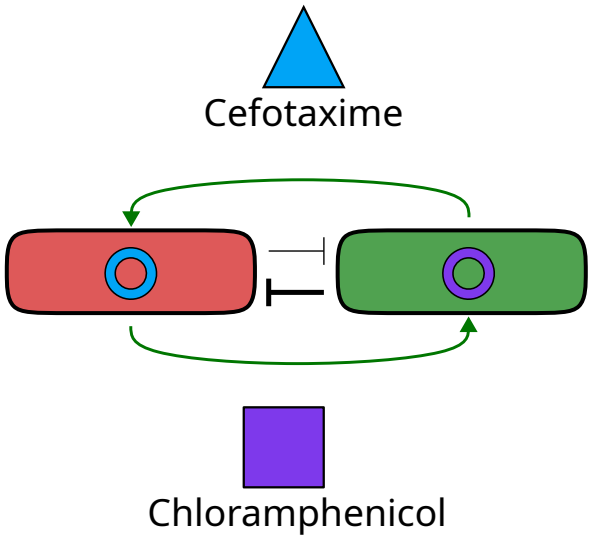
netto growth rate

$$\frac{dN}{dt} = \mu \frac{1}{1 + \frac{Cm}{IC\,50}} N$$

$N : Abundance\ of\ ST$
$\mu : Per\ capita\ growth\ rate$
$Cm : Chloramphenicol\ concentration$



What does that mean for cross-protection



- *ST* is effectively getting killed by Chloramphenicol
- *E. coli* looses its partner species
- *E. coli* goes extinct in absence of the partner
- In every transfer experiment Chloramphenicol susceptible strains go extinct