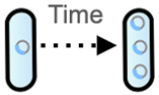
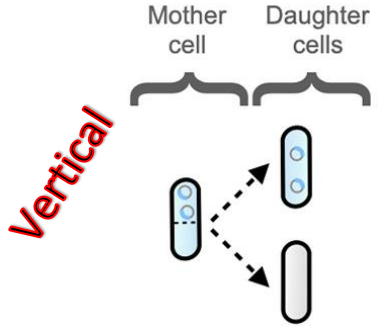
Plasmid review – Hernández-Beltrán 2021

Plasmid transfer mechanisms:

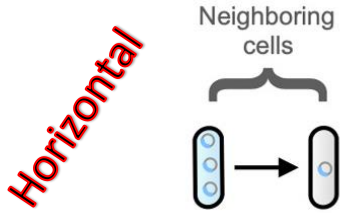
(1) **Replicating** until reaching a critical copy-number inside the host cell (highly regulated, assume constant).



(2) **Segregation** between daughter cells upon division. Probability of segregation loss scales like $2^{1 - \text{copy number}}$ (unlikely for large copy-number).



(3) **Conjugation** by cell-cell contact.



(4) **Transformation** uptake of naked DNA from environment.

(5) **Transduction** via bacteriophages.

Who benefits from the transfer: donor, recipient, or plasmid?

Benefit to Host

- decontaminate heavy-metal polluted environments
- symbiosis between bacteria and plants
- virulence factors
- antibiotic resistance

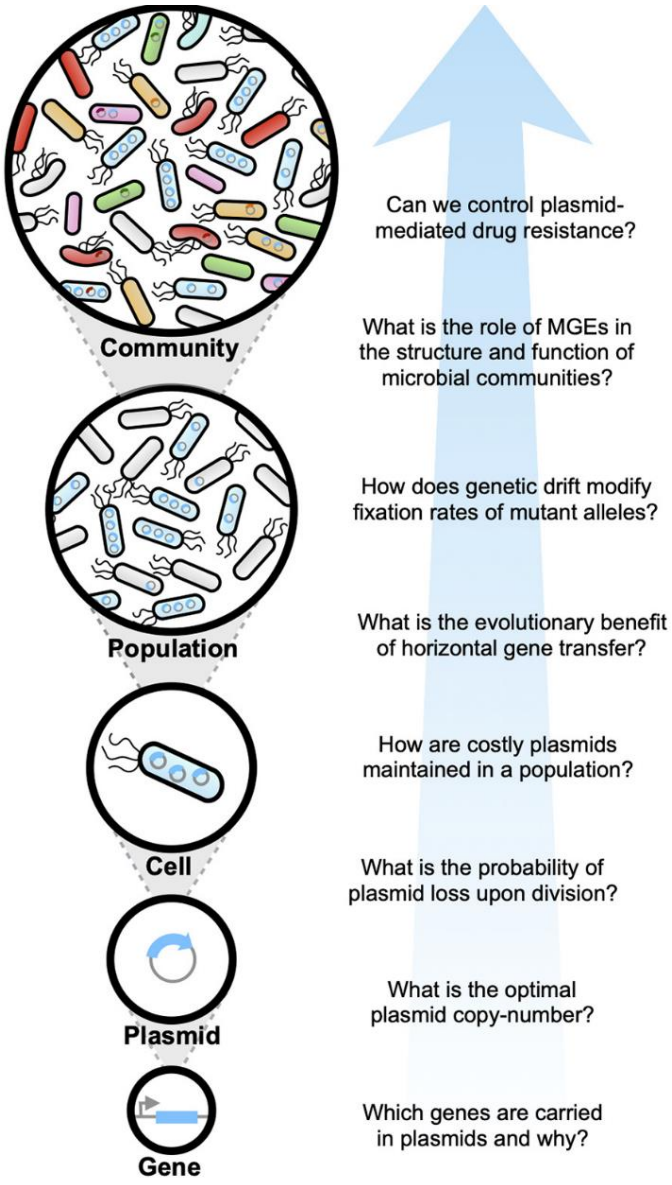
Cost to Host

- Replication of additional DNA
- Protein synthesis
- Plasmid products that harm the host
- Inhibition of cell division

Cost can be introduced by a coefficient (between zero and one) multiplying the growth rate, or a Monod parameter.

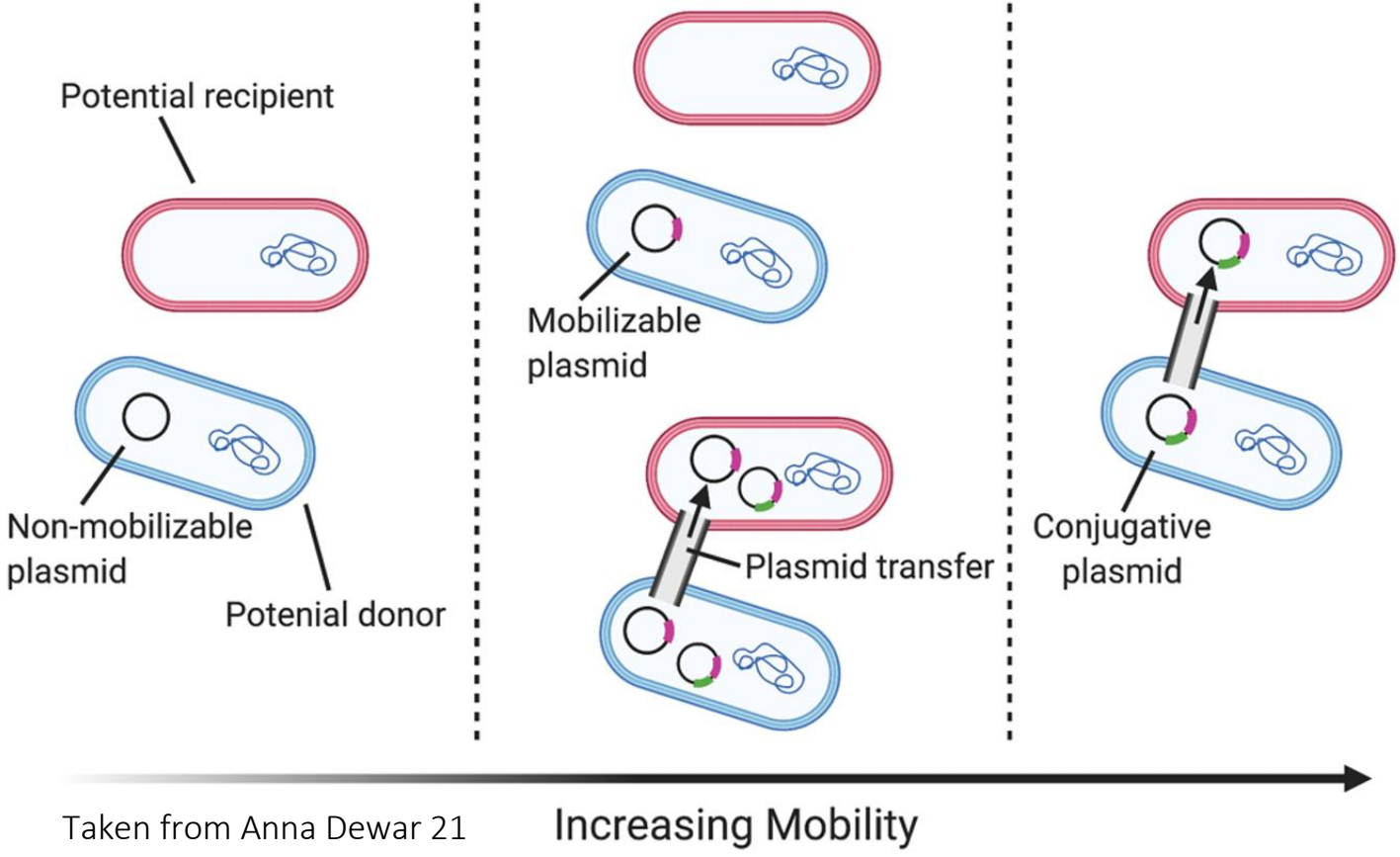
Conjugation counter-balances segregation loss and purifying selection, maintaining plasmid populations.

Show HGT can influence the competition outcomes of bacterial warfare.

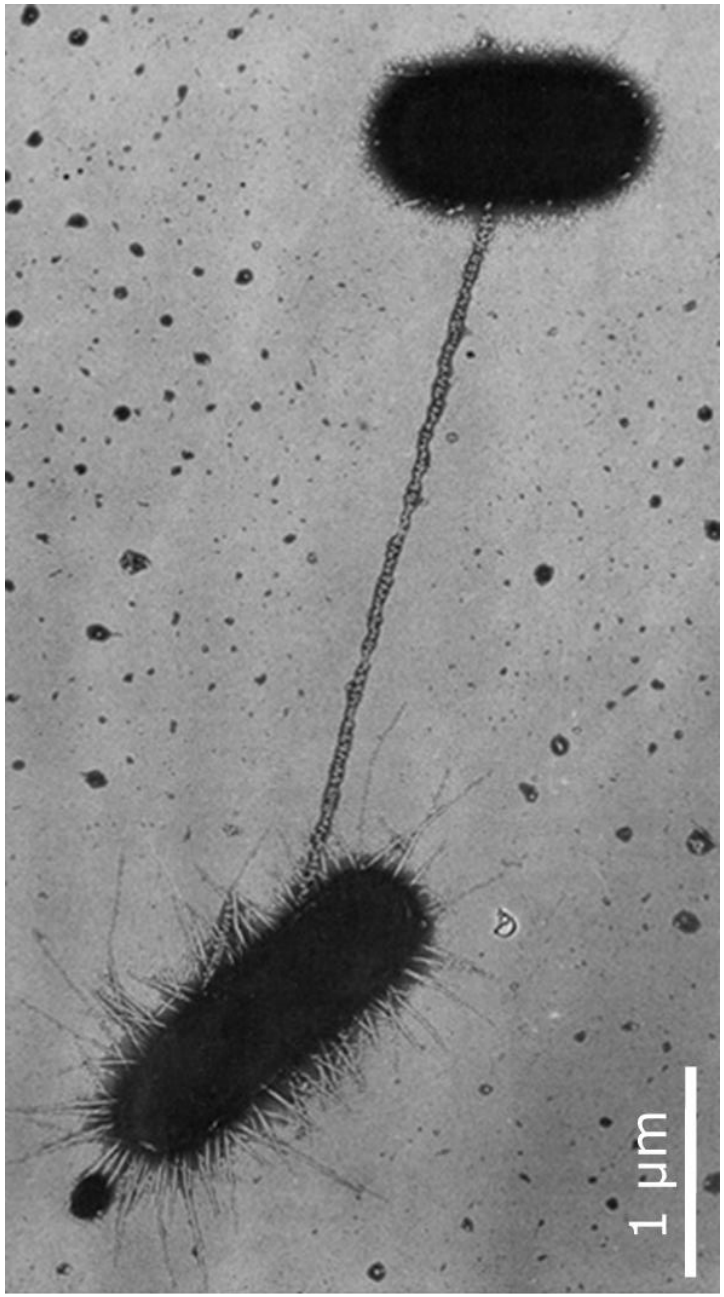


1/2 + **1/4** + **1/4** = **All Plasmids**

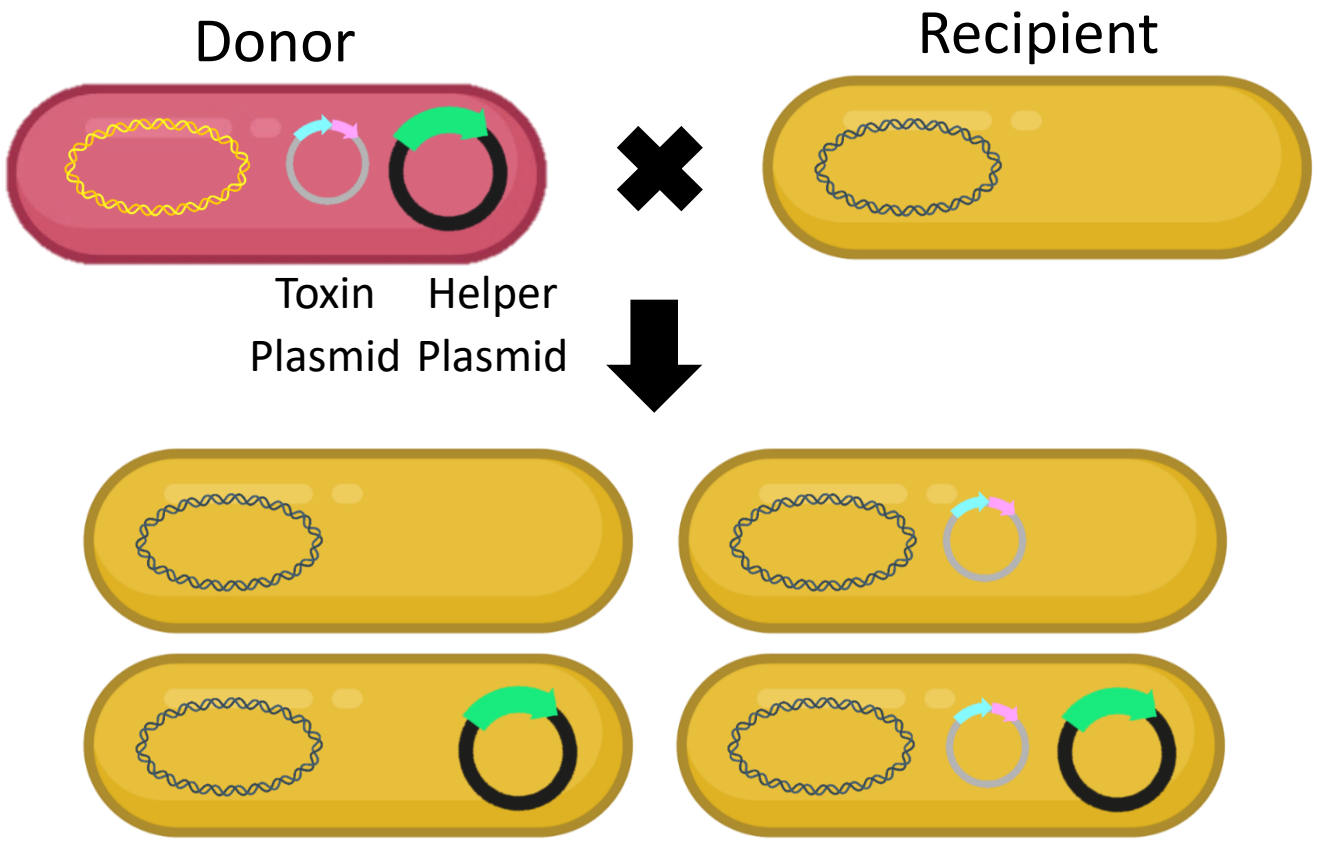
Smillie10



Taken from Anna Dewar 21



Elisa's Experiments - Why aren't immunity genes immobilised/chromosomal?



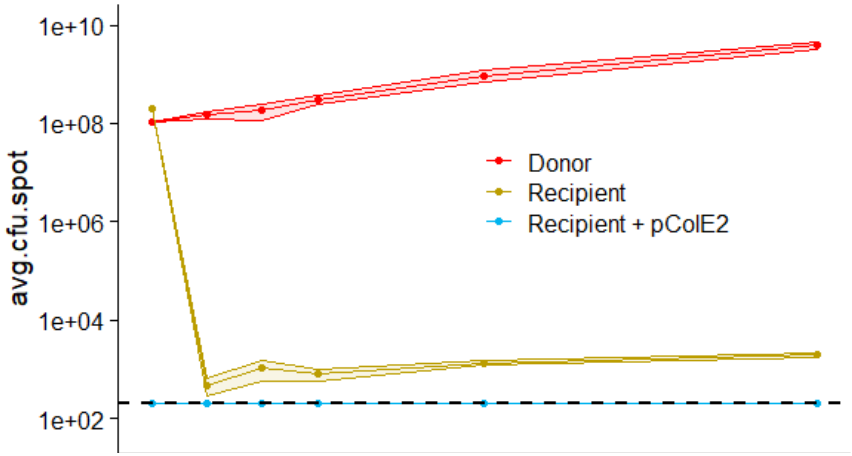
Toxin is released via lysis, should this be encoded as a lower growth rate of donors and transconjugates?

Distinction between **immunity** and **resistance**:

Immunity is provided by plasmids, whereas resistance is evolved.

Superinfection is blocked by the helper plasmids.

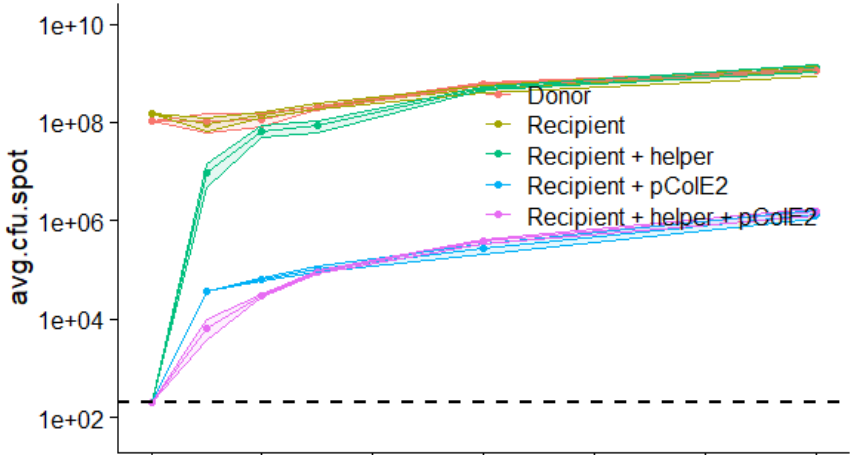
High-density 1:1 competitions



Toxin only

b = 0 is equivalent to toxin traits being chromosomal.

2-fold reduction in susceptible recipients.

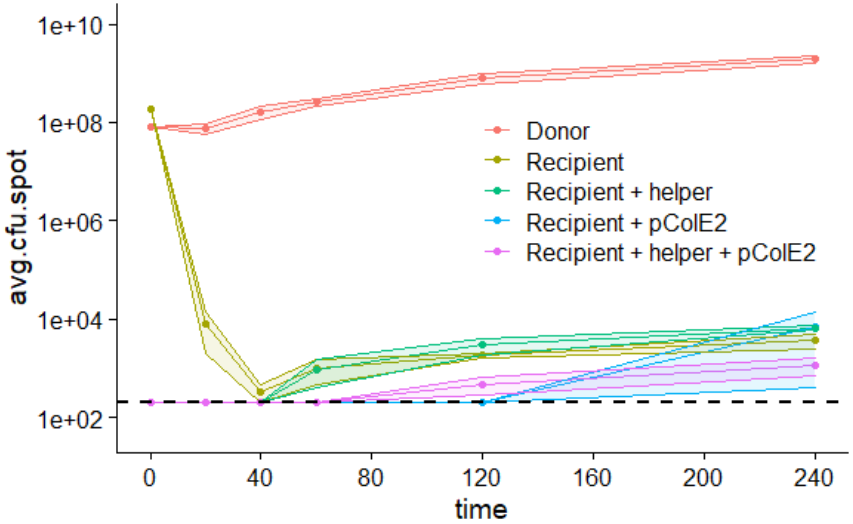


HGT only (toxin-resistant recipient)

As soon as the green and orange curves meet, there are no more recipients (recipients are saturated with helpers, which prevent super-infection).

Number of donors not depleted by HGT. Growth balances the low HGT rate.

The toxin was rarely able to hitchhike with the helper.



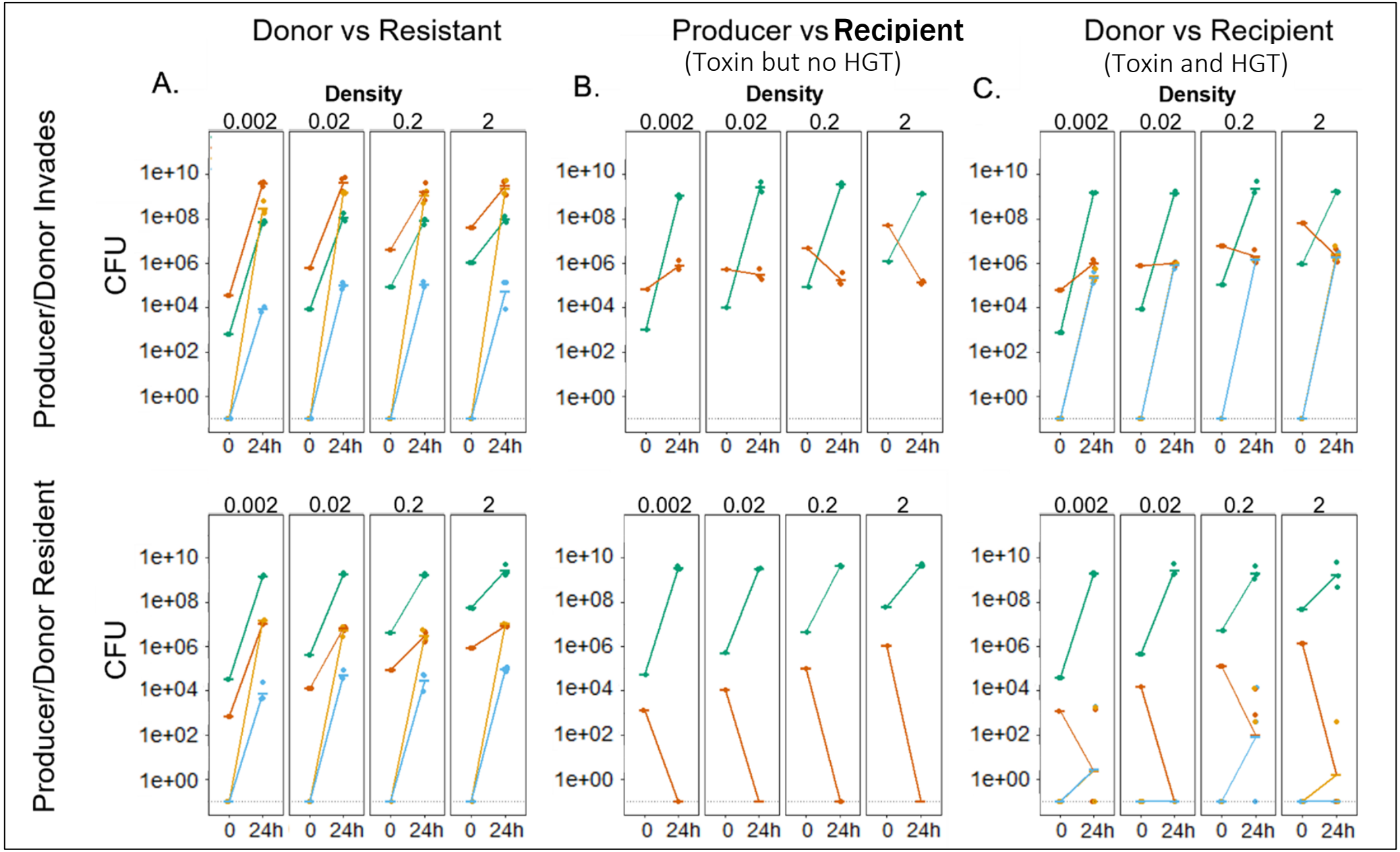
Toxin and HGT

Comparing top and bottom, sensitive strain performs equally (poorly) with and without HGT.

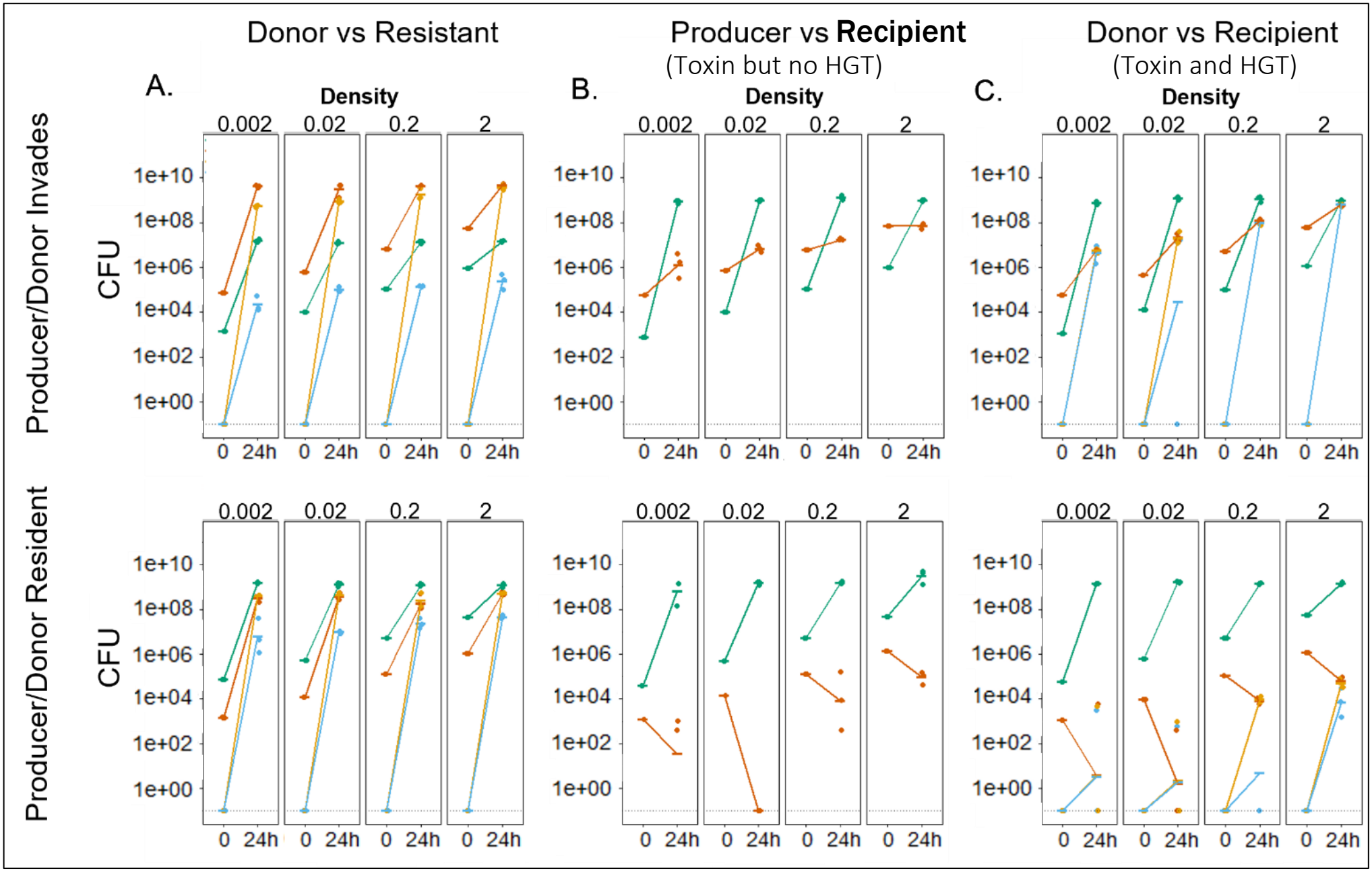
Invasion single nutrient

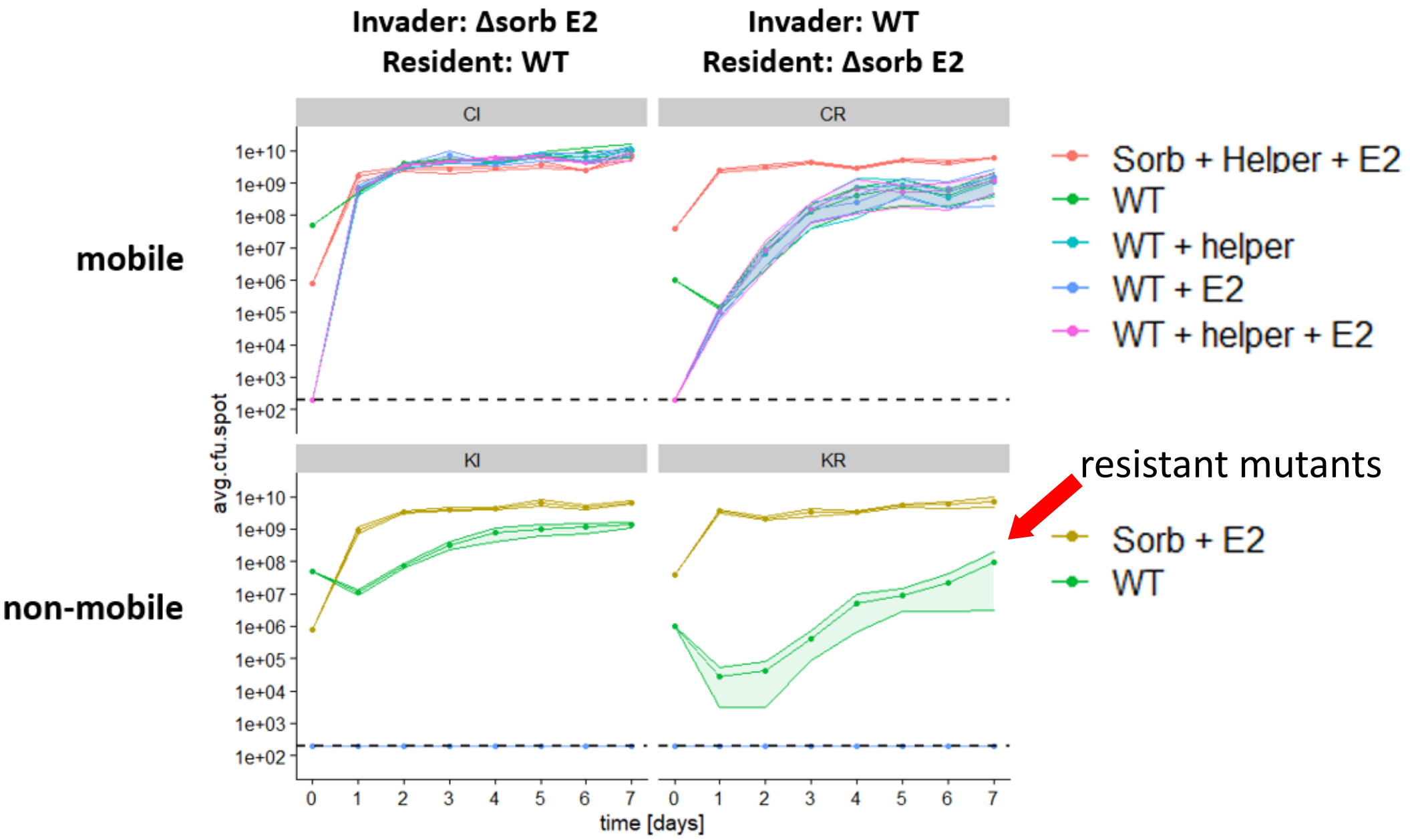
Producer: Toxin but no HGT
Donor: Toxin and HGT
Target = Recipient

Producer/Donor
Target/Resistant/Recipient
With Helper Plasmid
With Both Plasmids



Invasion second nutrient




Invader: Δsorb E2
Resident: WT
Invader: WT
Resident: Δsorb E2
mobile
non-mobile
CI
CR
KI
KR
avg.cfu.spot
1e+10
1e+09
1e+08
1e+07
1e+06
1e+05
1e+04
1e+03
1e+02
0
1
2
3
4
5
6
7
time [days]
Sorb + Helper + E2
WT
WT + helper
WT + E2
WT + helper + E2
resistant mutants
Sorb + E2
WT

Stewart and Levin criterion: Plasmid persistence requires horizontal transmission compensate for the plasmid upkeep costs.

Local adaptation hypothesis: Genes which are useful sporadically tend to be plasmidic rather than chromosomal.

Rodriguez-Beltran18 used stochastic simulations to show that a high rate of environmental fluctuations was correlated with an increase of genetic diversity in the population, resulting in an enhanced plasmid stability.

Modelling: Consider noise/variability of parameters either by sampling parameters from a distribution or by a sensitivity analysis.

Coevolution

Plasmids can control their own replication (autonomously or via host manipulation). Their fitness interests may not always align with their hosts. And addiction mechanisms exist. **Selfish plasmids**.

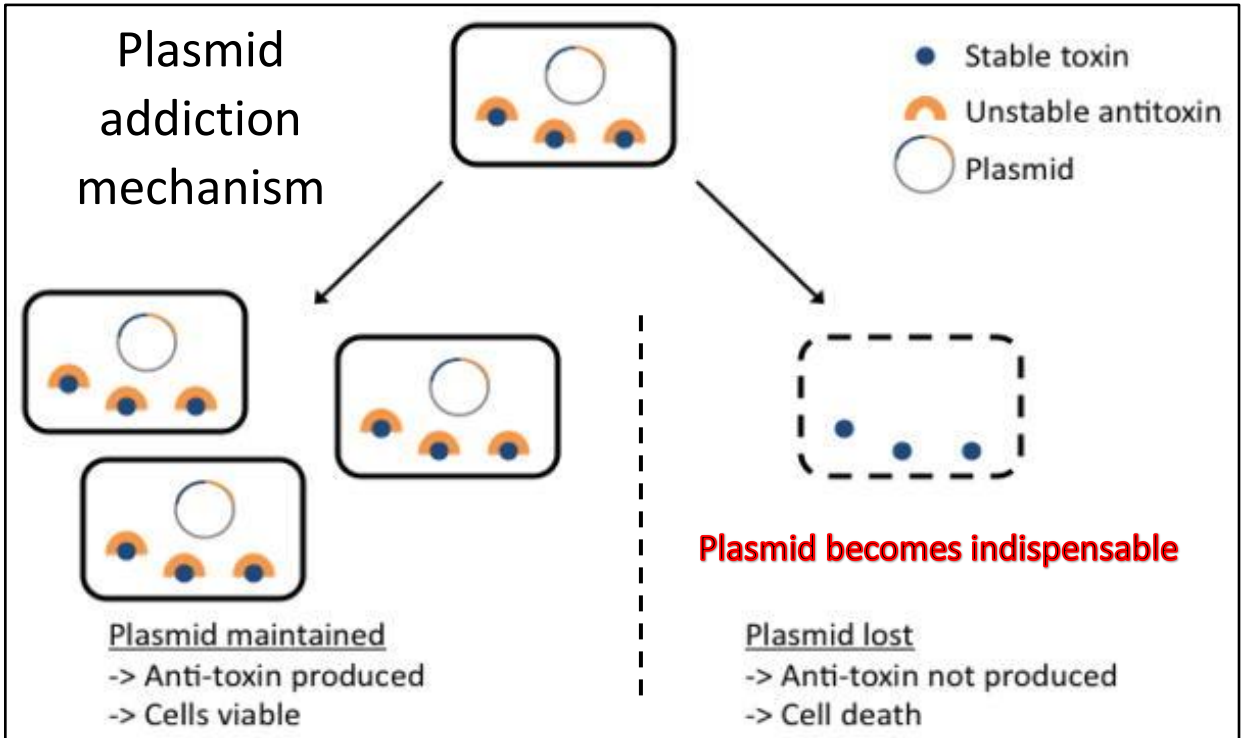
Why do bacteria allow valuable weapons to be transferred to their competitors?

What advantage does the recipient receive?

The recipient cannot use the toxin against the donor (although it could be used against some third party). However, the recipient does gain toxin immunity after HGT.

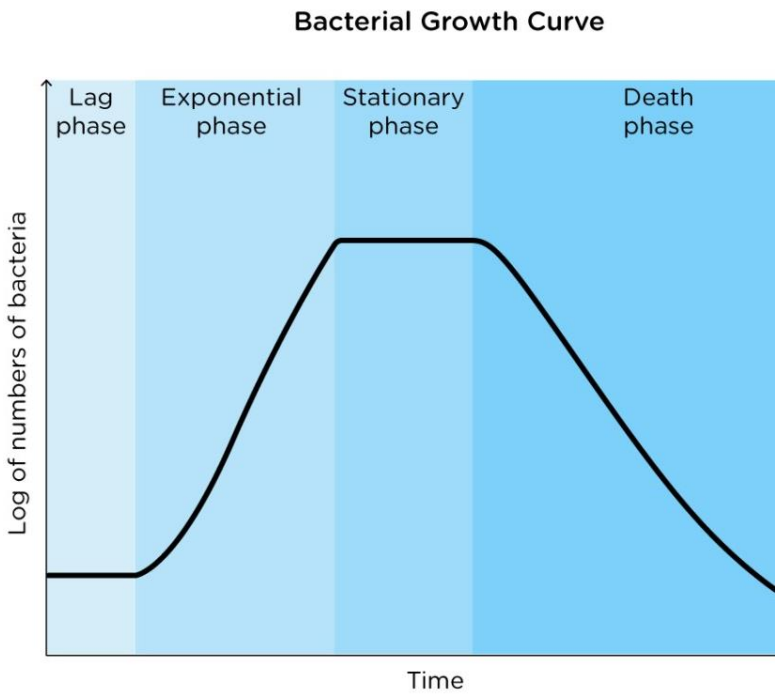
Do recipients pay plasmid associated costs?

The helper plasmid is costly.



HGT is almost exclusively modelled using mass action (Leclerc19 42/43 papers reviewed).

Conjugation rate has been shown to depend on environmental factors such as nutrient availability.



Modelling: Uncertainty and Sensitivity analysis

How much uncertainty is there?

How much does an input contribute to the output uncertainty?

Unlike something like field ecology, I am modelling a well-controlled, precise experiment.

Modelling: Effect of initial conditions, invasion vs 50:50.

Modelling: parameter reduction via non-dimensionalisation.

Equilibrium: How to avoid trivial one?

Do ICs change equilibrium?

What are good **phenotypes** for each actor?

Donor:

Recipient: p (in the diversion sense)

Would selection push for niche partitioning?

Plasmid: HGT rate b?

Toxin plasmids encode for three functions:

1. Toxin production
2. Toxin secretion
3. Toxin immunity

These functions rarely occur independently (a.k.a. orphan).

Niche Overlap - is a proportion, but needn't be of the total resource distribution.

It may describe the size of the intersection independently of the complement part, in which case p describes **diversification**, or if instead investment in one nutrient necessarily diminishes investment in the other, p would describe **diversion**. The total effort expended by the competitor strain on predation a constant?

We have discrete prey categories.

Pluralistic Approach: working with different models/hypothesis to identify robust predictions, keeping things abstract/general.

Toxin-mediated competition – Jake Palmer 2022

ODEs

$$A' = \left(r_A(1-f_A)m(N_1) - k\, m(T_B, kBA)\right) A$$

$$T_A' = f_A m(N_1) A - d T_A$$

Equivalently for B' and T_B'

$$C' = \left(r_C\left(m(N_2) + p\, m(N_1)\right) - k\left(m(T_A, kAC) + m(T_B, kBC)\right)\right) C$$

$$N_1' = -\, m(N_1)(A + B + pC)$$

$$N_2' = -\, m(N_2) A$$

$$\frac{dA}{dt} = A(t) * \left(\frac{N_1(t)}{(N_1(t)+K_{N1})} * r_A * (1-\gamma_A) - E * \left(\frac{T_B^h(t)}{T_B^h(t)+K_{BA}^h}\right)\right) \quad [1]$$

$$\frac{dB}{dt} = B(t) * \left(\frac{N_1(t)}{(N_1(t)+K_{N1})} * r_B * (1-\gamma_B) - E * \left(\frac{T_A^h(t)}{T_A^h(t)+K_{AB}^h}\right)\right) \quad [2]$$

$$\frac{dC}{dt} = C(t) * \left(\frac{N_2(t)}{(N_2(t)+K_{N2})} * r_C + \frac{N_1(t)}{(N_1(t)+K_{N1})} * \Omega_1 * r_C - E * \left(\frac{T_A^h(t)}{T_A^h(t)+K_{AC}^h}\right) - E * \left(\frac{T_B^h(t)}{T_B^h(t)+K_{BC}^h}\right)\right) \quad [3]$$

$$\frac{dT_A}{dt} = \gamma_A * A(t) * \left(\frac{N_1(t)}{N_1(t)+K_{N1}}\right) - L_T * T_A(t) \quad [4]$$

$$\frac{dT_B}{dt} = \gamma_B * B(t) * \left(\frac{N_1(t)}{N_1(t)+K_{N1}}\right) - L_T * T_B(t) \quad [5]$$

$$\frac{dN_1}{dt} = -\left(\frac{N_1(t)}{N_1(t)+K_{N1}}\right) * (A(t) + B(t) + \Omega_1 * C(t)) \quad [6]$$

$$\frac{dN_2}{dt} = -\left(\frac{N_2(t)}{N_2(t)+K_{N2}}\right) * C(t), \quad [7]$$

Parameters

Monod equation

$$m(X) = \frac{X}{X + k_X}$$

$$m(X, Y) = \frac{X}{X + k_{XY}}$$

rate at which X is converted to product,

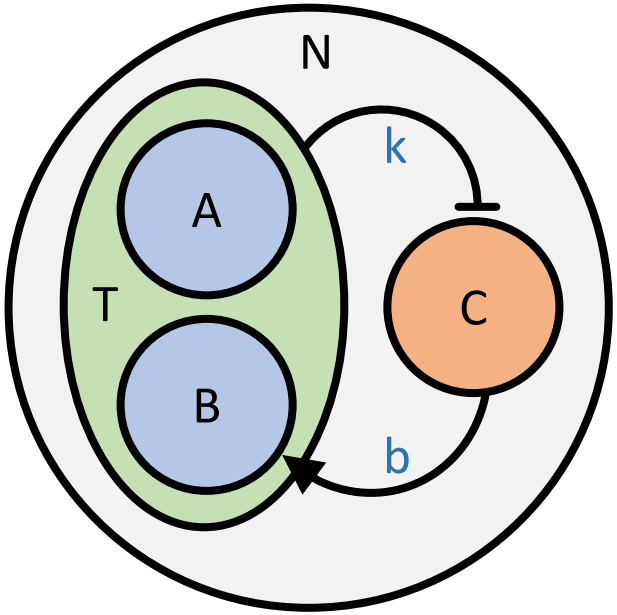
scales like X/k for small concentration and saturates to 1

k is the half max density. Production decelerates with K.

X	biomass of cell strain [kg]
T_X	biomass of Toxin produced by strain X
N_X	biomass of Nutrient X
r_X	growth rate of strain X
$k \leftarrow E$	killing efficiency of toxin (same for all)
$d \leftarrow L_T$	toxin degradation rate (same for all)
$f_X \leftarrow \gamma_X$	proportion of nutrient for toxin
$0 \leq p \leq 1 \leftarrow \Omega_1$	niche overlap proportion

Toxin and HGT (single nutrient)

ODEs	Parameters	
$A' = r_A(1-f_A)m(N)A - bAC$	A	Concentration of plasmid donor strain
$B' = r_B(1-f_B)m(N)B + b(A+B)C$	B	Concentration of transconjugates
$C' = r_C m(N)C - k\left(m(T,A)+m(T,B)\right)C - bBC$	C	Concentration of sensitive strain
$T' = f\,m(N)(A+B) - dT$	T	biomass of Toxin produced by strain X
$N' = -m(N)(A+B+C)$	N	biomass of Nutrient X
	r_X	growth rate of strain X
	k	killing efficiency of toxin (same for all)
	d	toxin degradation rate (same for all)
	f	proportion of nutrient for toxin
	b	horizontal transmission rate



Equivalent to diversification model with N1=N2=N and p=0
Or diversion model with just N1=N2=N

Toxin and HGT, nutrient diversification

ODEs

$$A' = (1 - f_A)\, r \frac{N_1}{N_1 + K_1} A$$

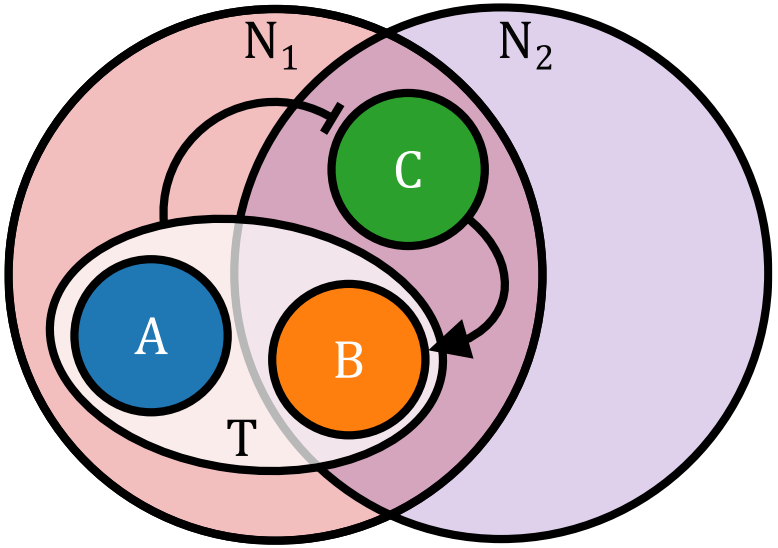
$$B' = (1 - f_B)\, r \left(p \frac{N_1}{N_1 + K_1} + \frac{N_2}{N_2 + K_2} \right) B + b(A + B)C$$

$$C' = r \left(p \frac{N_1}{N_1 + K_1} + \frac{N_2}{N_2 + K_2} \right) C - k \frac{T}{T + K_T} C - b(A + B)C$$

$$N_1' = - \frac{N_1}{N_1 + K_1} \left(A + p(B + C) \right)$$

$$N_2' = - \frac{N_2}{N_2 + K_2} (B + C)$$

$$T' = f_A \mu \frac{N_1}{N_1 + K_1} A + f_B \mu \left(p \frac{N_1}{N_1 + K_1} + \frac{N_2}{N_2 + K_2} \right) B - \frac{T}{T + K_T} C$$



Parameters

Conversion rate of both nutrient and toxin into energy is governed by a Monod form, $r \frac{X}{X+K}$. Mass action for small concentration and saturates when large, as if cells are satiated by nutrient or toxins. Lowering the half-saturation concentration K means production saturates more so.
Conjugation is presumed to be rare, hence mass action.

b horizontal transmission rate

$0 \leq f_A, f_B \leq 1$ energy allocation to toxin

k killing efficiency of toxin

K_T half-saturation concentration

K_1, K_2 half-saturation concentration

$0 \leq p \leq 1$ niche overlap proportion

r max intrinsic growth rate of cell X

μ toxin secretion rate

Toxin and HGT, nutrient diversion

$$A' = r_A(1 - f_A)m(N_1, k_{N_1})A - bAC$$

$$B' = r_B(1 - f_B)\left(p\, m(N_1, k_{N_1}) + (1 - p)m(N_2, k_{N_2})\right)B + b(A + B)C$$

$$C' = r_C\left(p\, m(N_1, k_{N_1}) + (1 - p)m(N_2, k_{N_2})\right)C - k\left(m(T, k_{AC}) + m(T, k_{BC})\right)C - bBC$$

$$T' = f_A m(N_1, k_{N_1})A + f_B\left(p\, m(N_1, k_{N_1}) + (1 - p)m(N_2, k_{N_2})\right)B - dT$$

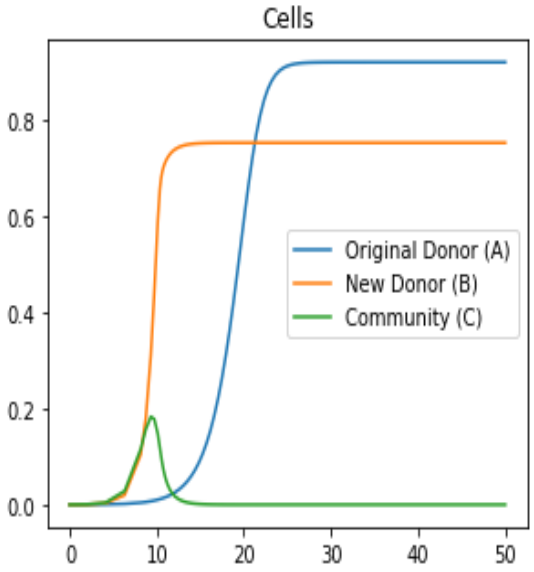
$$N_1' = -m(N_1, k_{N_1})\left(A + p\,(B + C)\right)$$

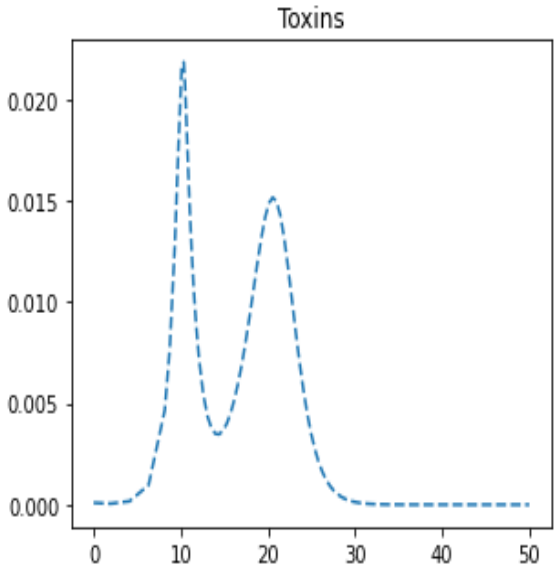
$$N_2' = -m(N_2, k_{N_2})(1 - p)(B + C)$$

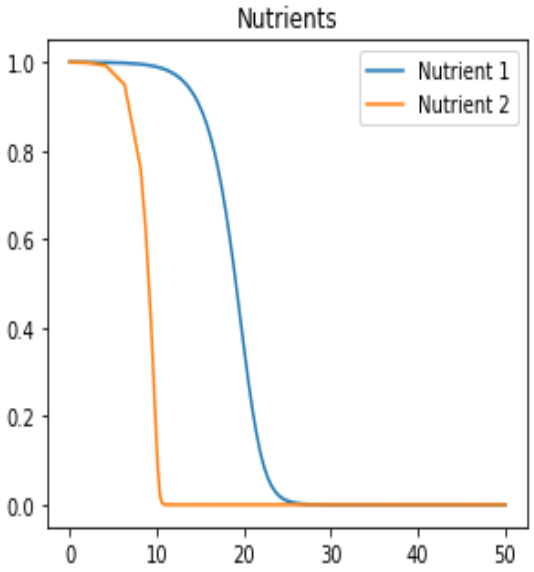
Altering yield should have the same effect as changing the initial nutrient abundance. Therefore, we may remove it as a parameter.

Niche overlap alters competition outcomes in nutrient diversification model.

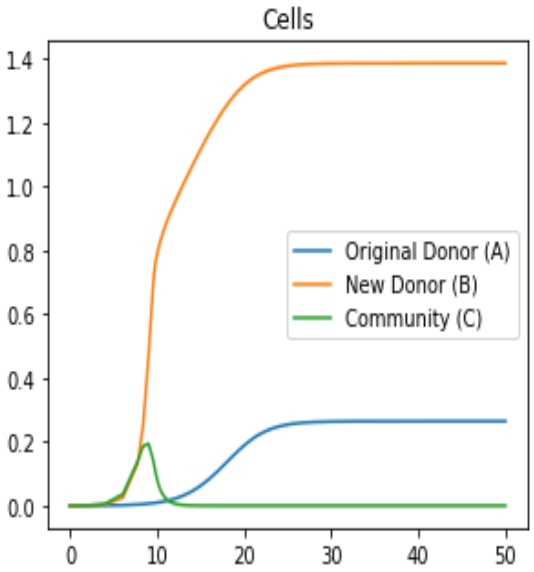
Niche overlap = 0

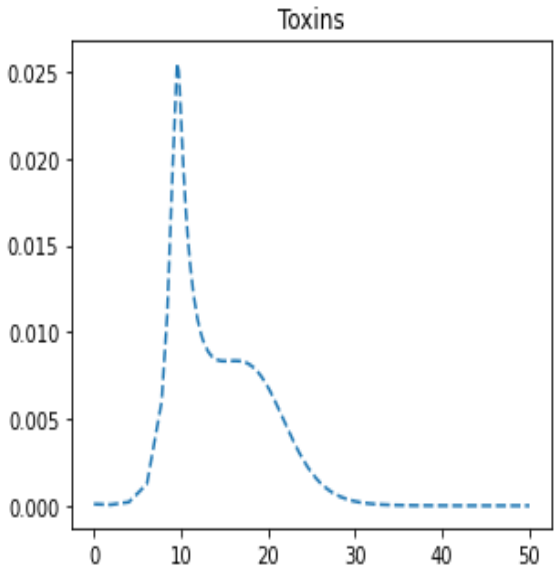


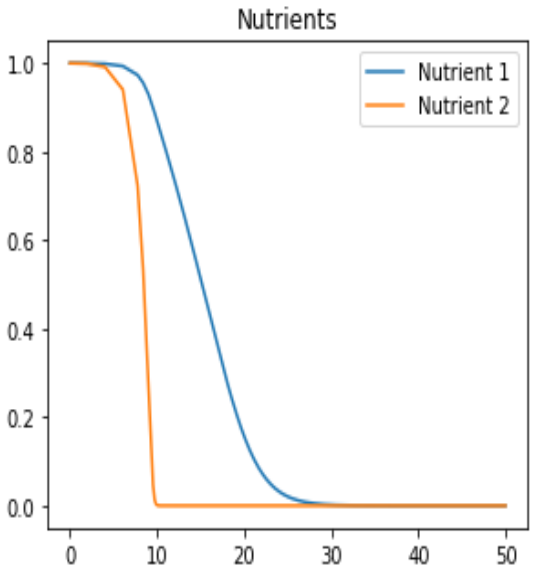




Niche overlap = 0.15








```
{'A' : 10**-4,
 'B' : 10**-4,
 'C' : 10**-4,
 'T' : 10**-4,
 'N1': 1,
 'N2': 1}


{'rA'  : 1,
 'rB'  : 1,
 'rC'  : 1,
 'k'   : 1,
 'd'   : .75,
 'f'   : .08,
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 'kAC' : .05,
 'kBC' : .05}
```
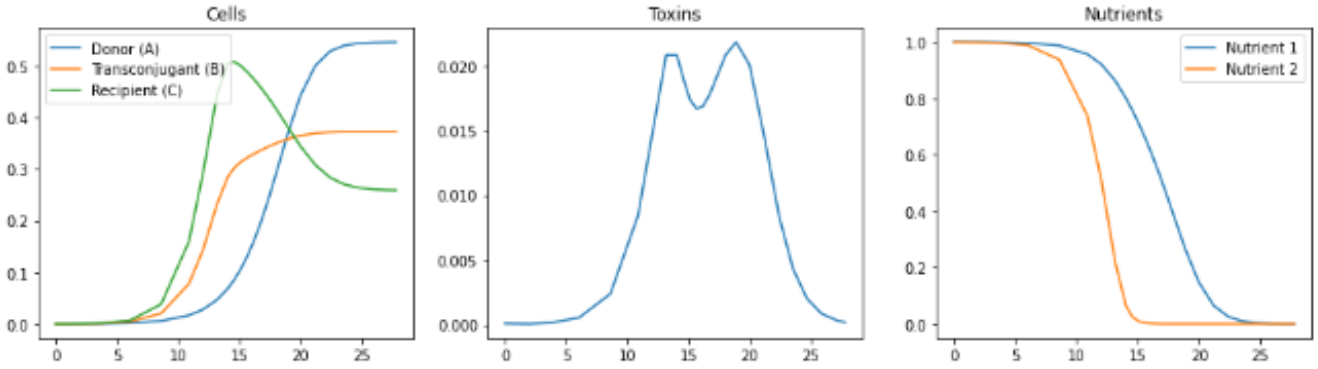
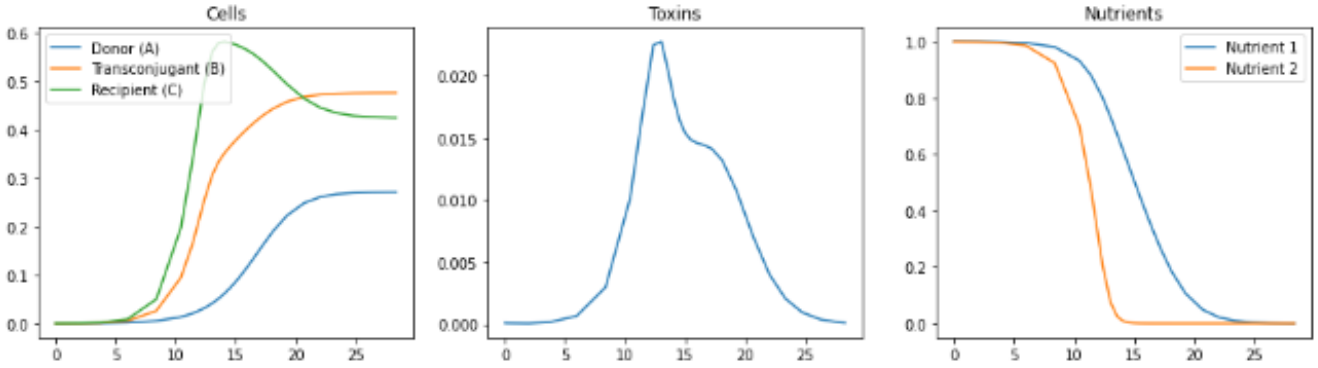
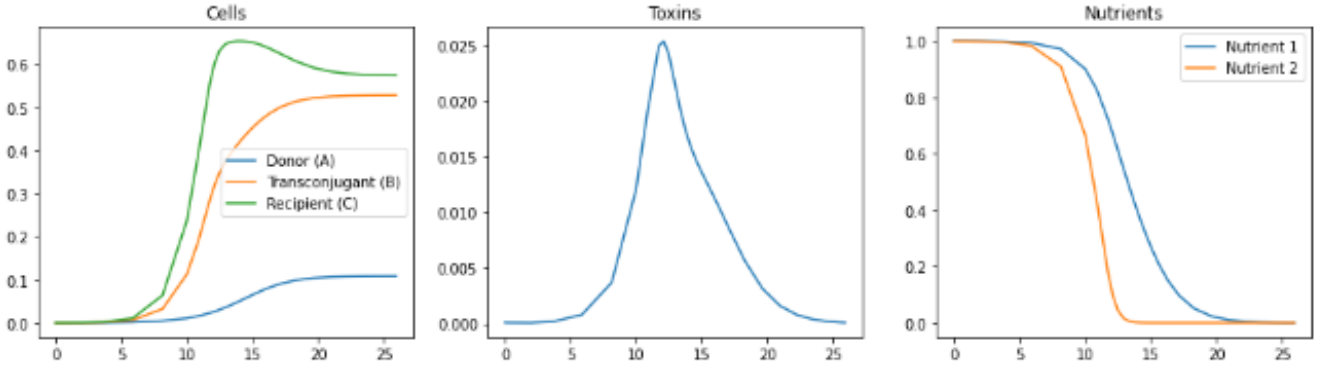




```
rC = 0.9, k = 0.2, b = 0.0, p = 0.1
Donor (A) Wins
```



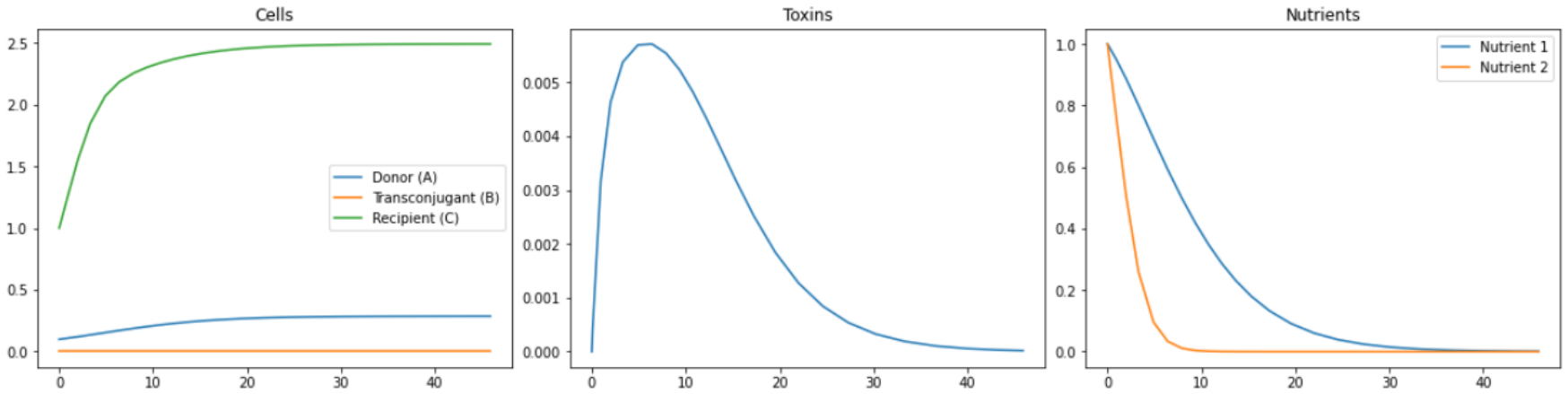

```
rC = 0.9, k = 0.2, b = 0.0, p = 0.2
Transconjugant (B) Wins
```



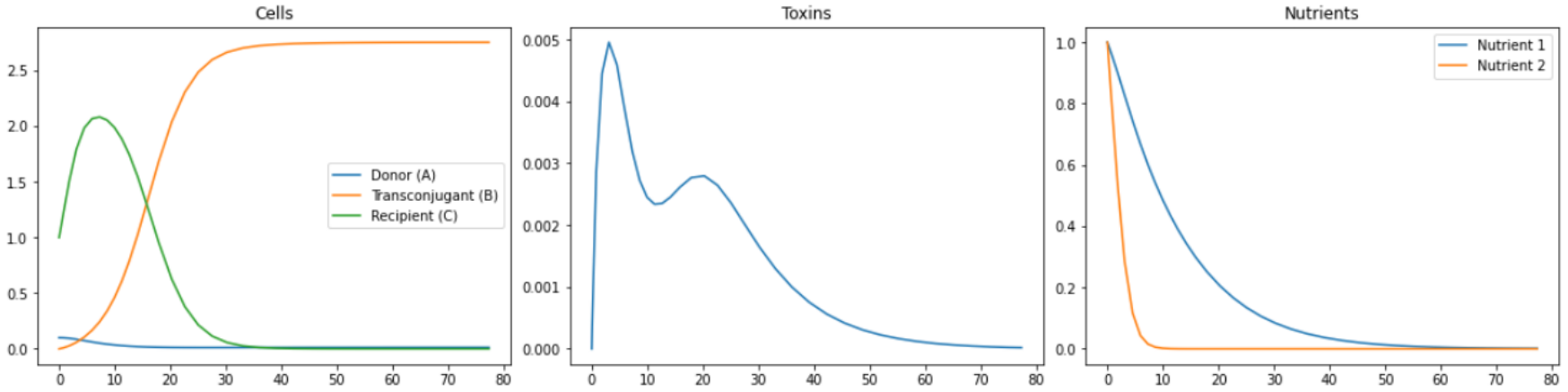

```
rC = 0.9, k = 0.2, b = 0.0, p = 0.3
Recipient (C) Wins
```

All three winners as niche overlap increases. No HGT but initially small amount of transconjugates.

no HGT

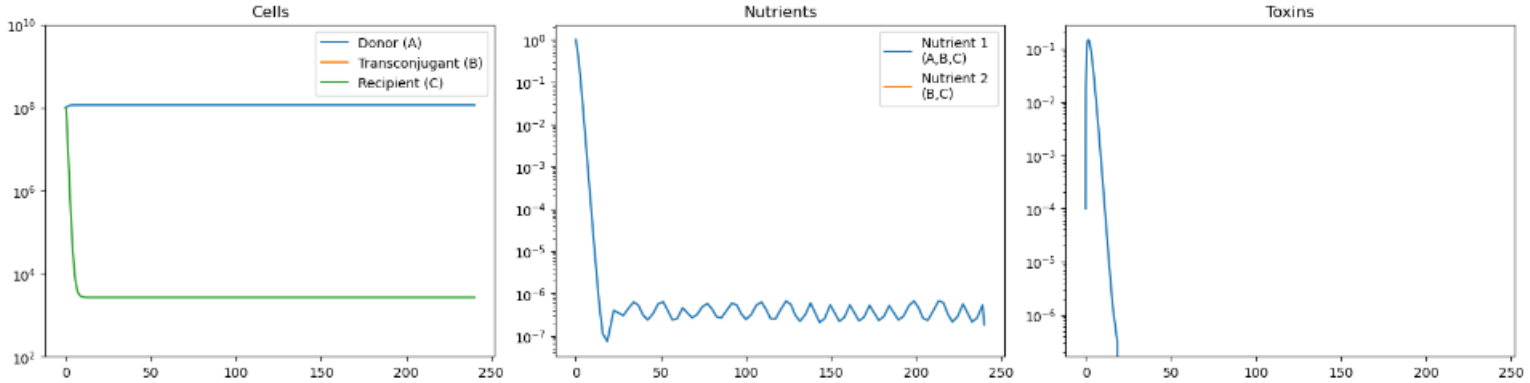


some HGT

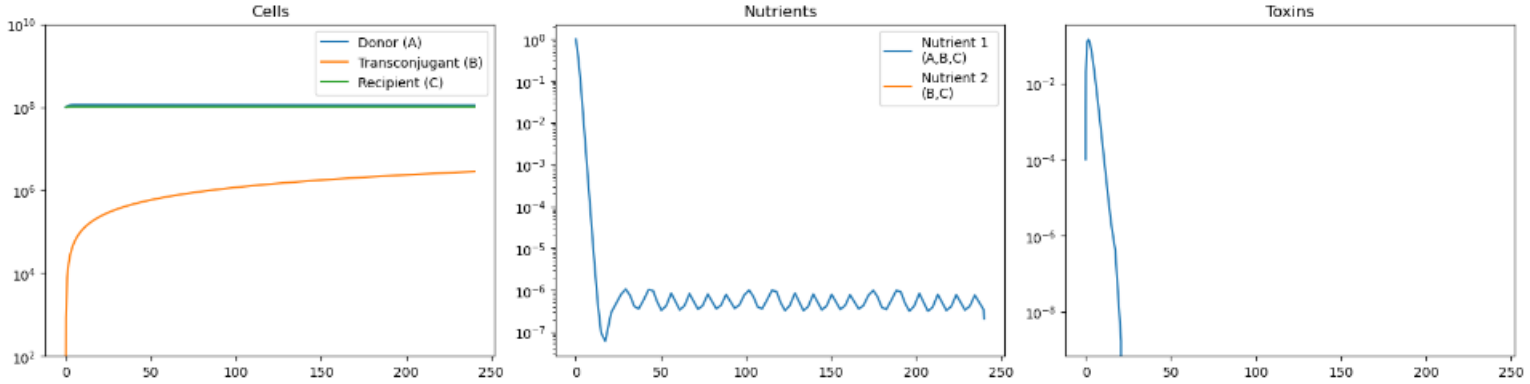



```
{'A' : 0.1,
 'B' : 0,
 'C' : 1,
 'T' : 0,
 'N1': 1,
 'N2': 1,
}


{'b'   : 0.1,
 'd'   : 1,
 'fA'  : .2,
 'fB'  : .2,
 'k'   : .1,
 'kN1' : 3,
 'kN2' : 3,
 'kAC' : 1,
 'kBC' : 1,
 'p'   : .1,
 'rA'  : .5,
 'rB'  : .5,
 'rC'  : 1
}
```

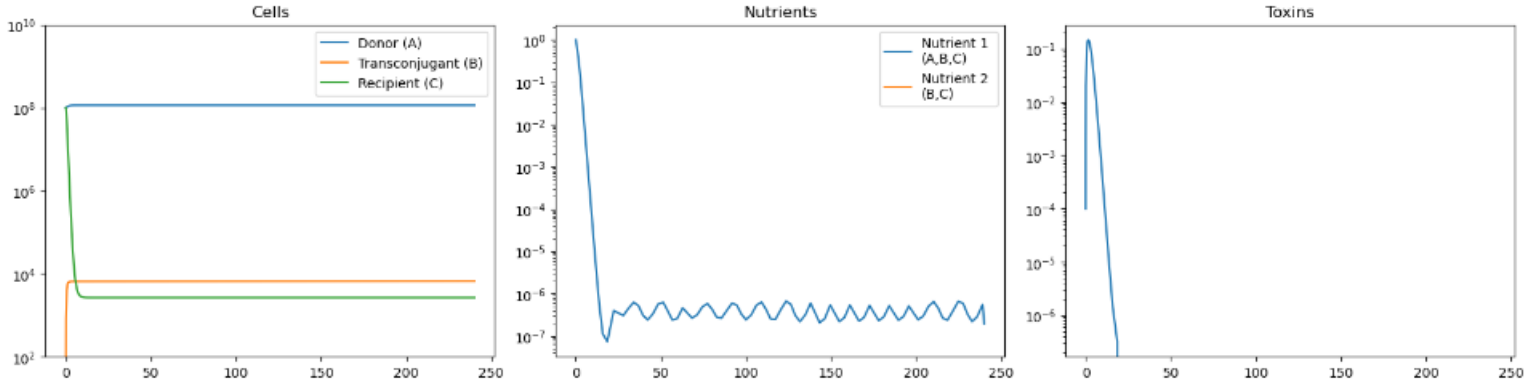
No Additional Nutrient
Toxin only (b = 0.0001 and k = 0)



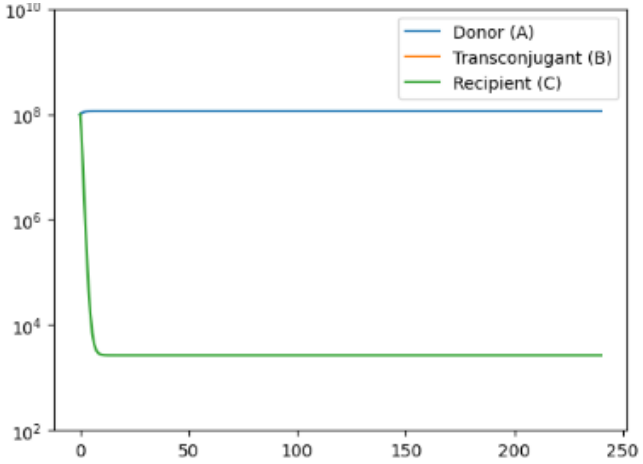
HGT only (b = 0 and k = 1.5)

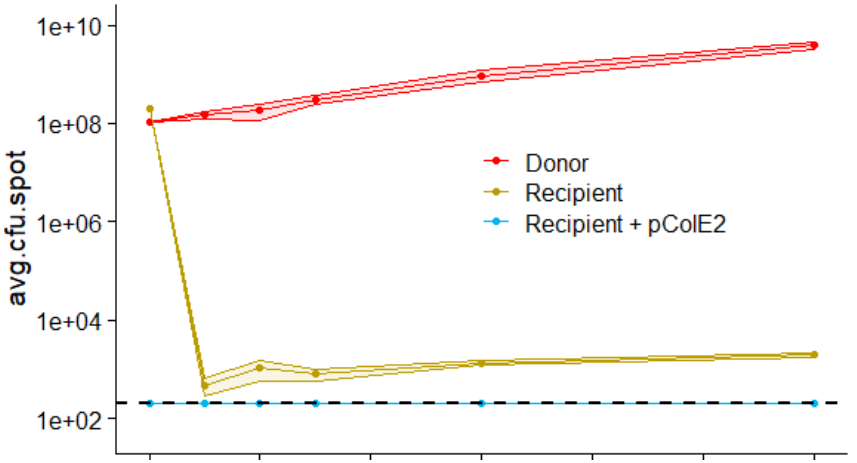


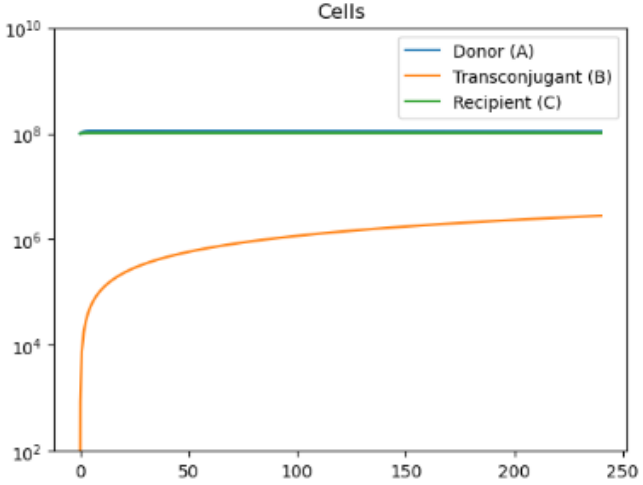
Toxin and HGT (b = 0.0001 and k = 1.5)

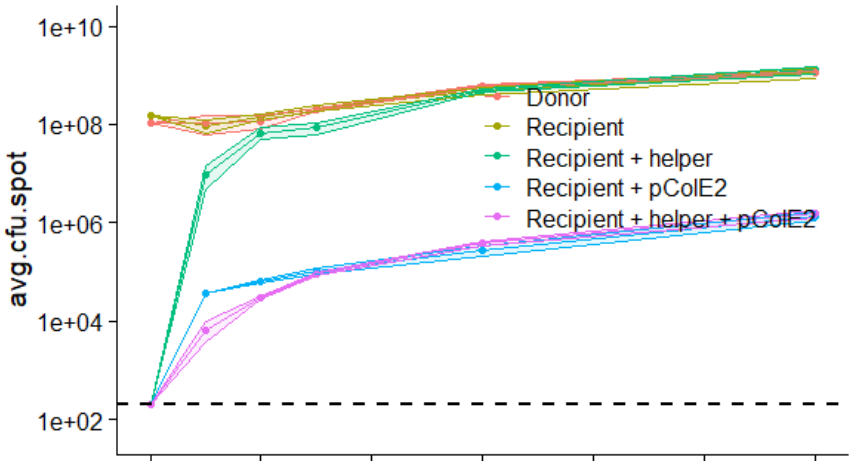


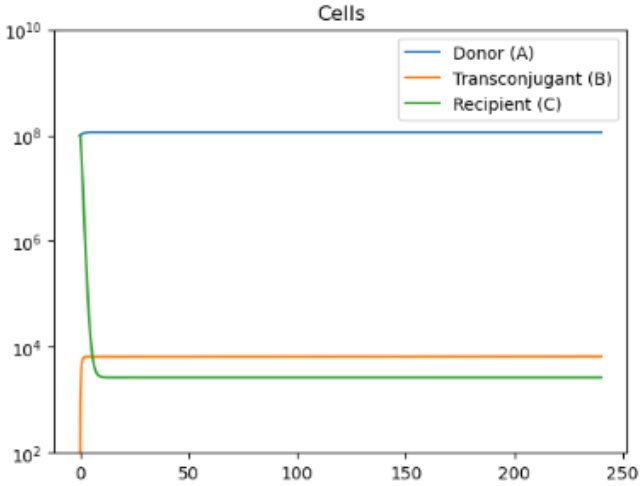

```
{'A' : 1,
 'B' : 0,
 'C' : 1,
 'N1': 1,
 'N2': 0,
 'T' : 10**-4}


{'b'   : 0.1,
 'd'   : 1,
 'fA'  : .5,
 'fB'  : .5,
 'k'   : 1.5,
 'kAC' : .05,
 'kBC' : .05,
 'kN1' : 1,
 'kN2' : 2,
 'p'   : 0.1,
 'rA'  : .3,
 'rB'  : .3,
 'rC'  : .3}
```

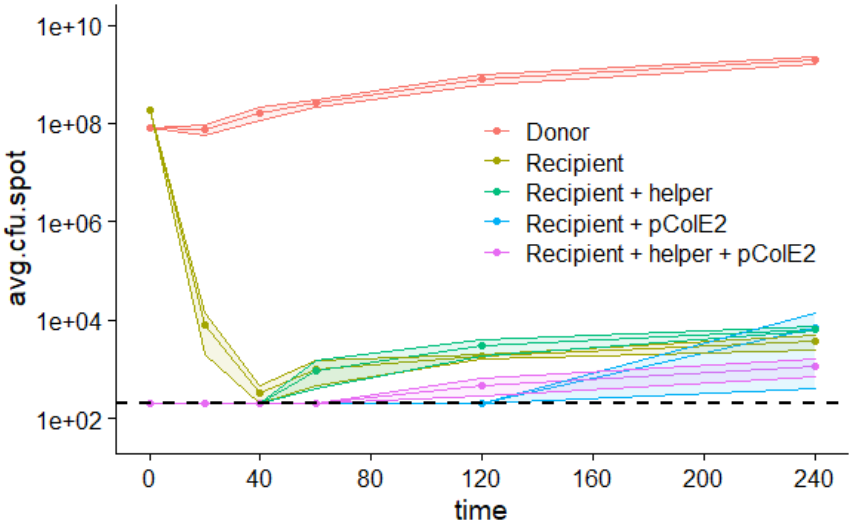

Donor (A)
Transconjugant (B)
Recipient (C)


avg.cfu.spot
Donor
Recipient
Recipient + pColE2


Cells
Donor (A)
Transconjugant (B)
Recipient (C)


avg.cfu.spot
Donor
Recipient
Recipient + helper
Recipient + pColE2
Recipient + helper + pColE2


Cells
Donor (A)
Transconjugant (B)
Recipient (C)


avg.cfu.spot
Donor
Recipient
Recipient + helper
Recipient + pColE2
Recipient + helper + pColE2
time

Only communal nutrient and 1:1

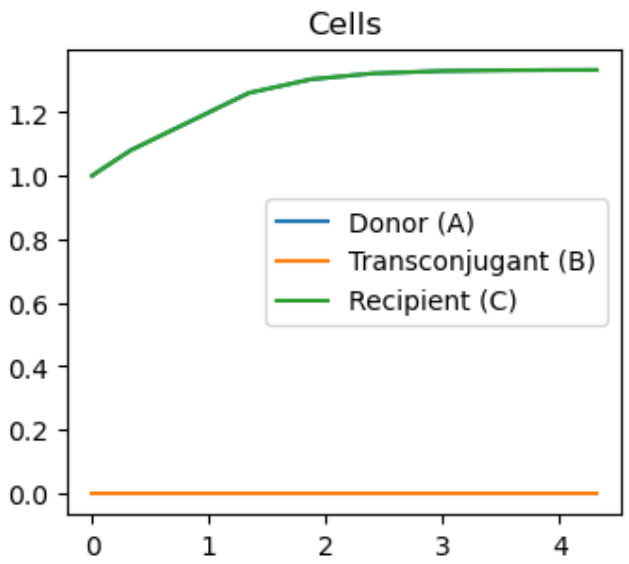
Toxin

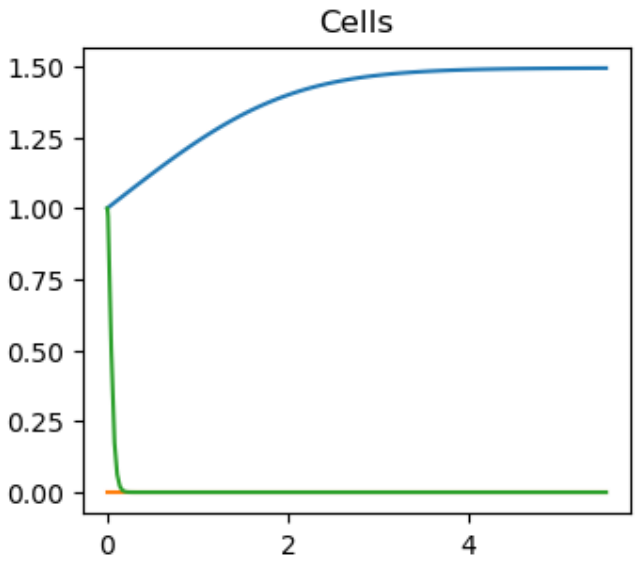
no

yes

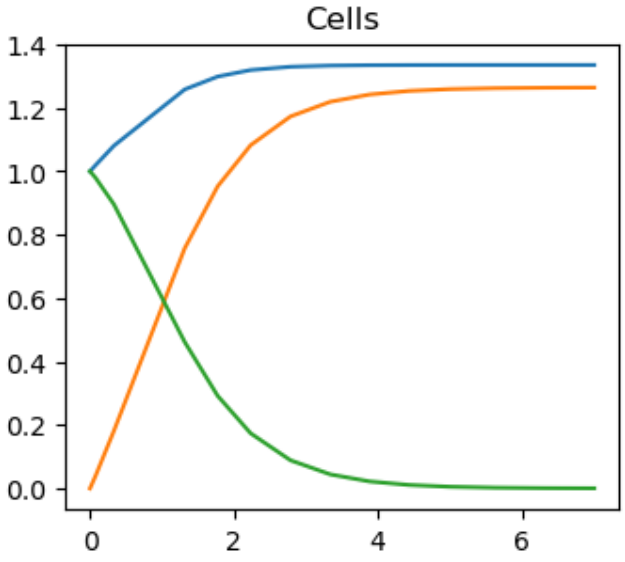
Conjugation

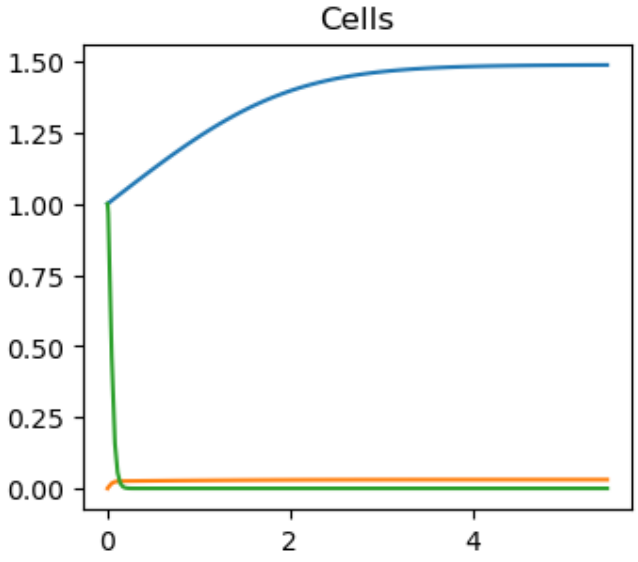
no





yes





Invasion and nutrient for B and C

Toxin

no

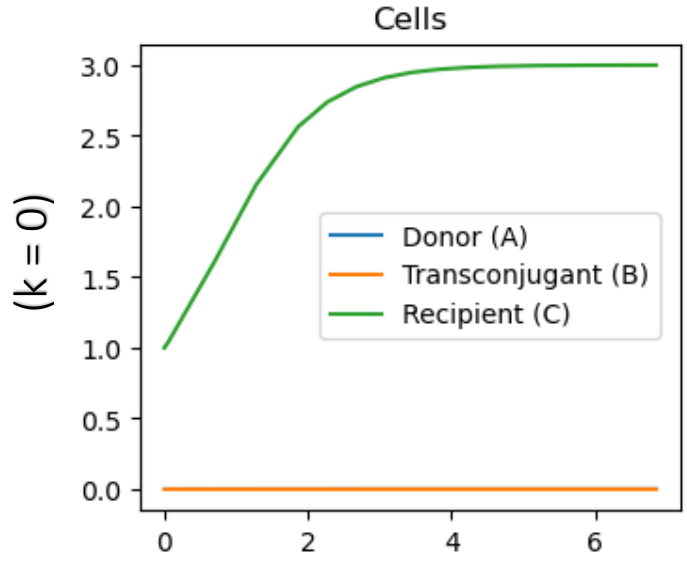
yes

Conjugation

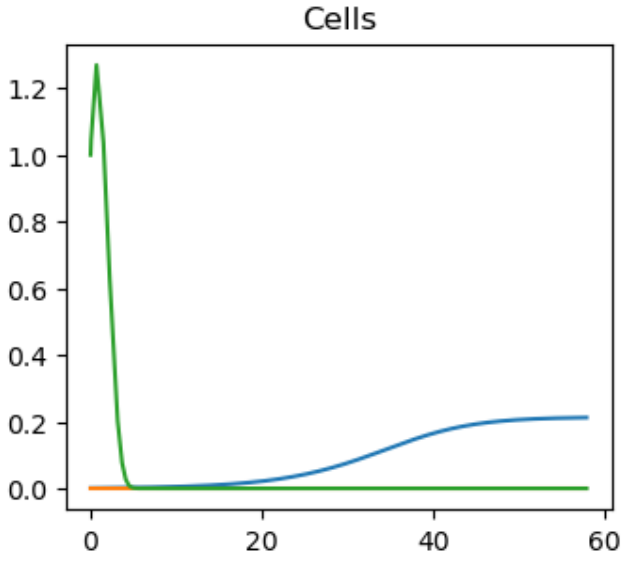
no

(k = 0)

(b = 0)

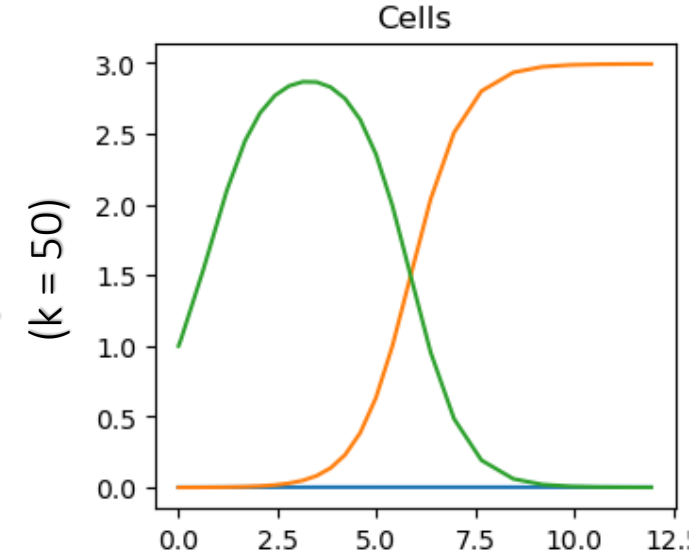


(b = .5)



yes

(k = 50)



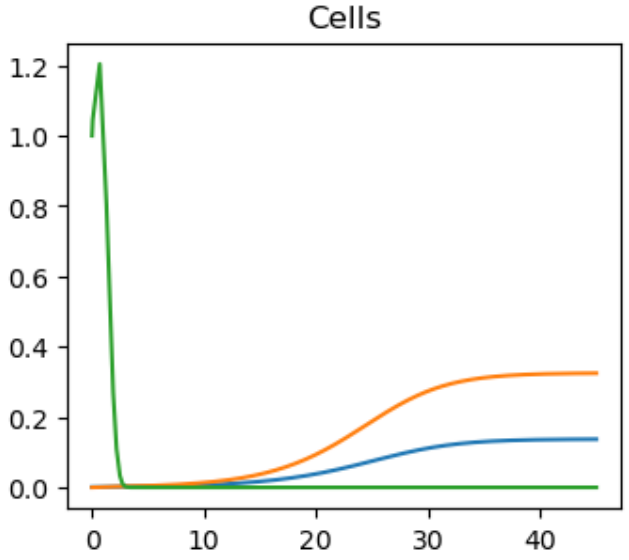


Table 1. References to the same model in ecology and microbiology. s is prey density or substrate concentration, x is predator density or density of organism that grows on substrate s, a is predator attack rate, h is handling time, μ_{max} is the maximum growth rate, K_s the Michaelis-Menten or half saturation constant, α total searching efficiency and c, m, s_m, s_b are empirical positive constants.

functional response or growth rate	reference in ecology	reference in microbiology
$\begin{cases} as & s \le s_b \\ as_m & s \ge s_b \end{cases}$	Holling (1959) type I with added upper limit	Blackman (1905)
$\frac{as}{1+ahs} = \mu_{max}\frac{s}{K_s+s}$	Holling (1959) type II	Monod (1942)
$a(1-e^{-cs})$	Ivlev (1961)	Teissier (1936)
$\frac{as^m}{1+ahs^m}$	Real (1977)	Moser (1958)
$\frac{\alpha s/x}{1+\alpha hs/x} = \frac{\alpha s}{x+\alpha hs}$	Arditi and Ginzburg (1989), Arditi and Akçakaya (1990)	Contois (1959)
$\mu_{max}\frac{s}{K_s+s}\frac{1}{x}$	Hassell and Rogers (1972) (special case)	Ashby (1976)
$\mu_{max}\frac{s}{K_s+s+cx}$	Beddington (1975), DeAngelis et al. (1975)	Roques et al. (1982) (special case)

$H_a =$

Derivation of Beddington-DeAngelis (For Holling II, $T_{interference} = 0$)

$$T = T_{search} + T_{handeling} + T_{interference}$$

$$= \frac{H_a}{a\,s} + H_a \times h + \frac{bH_a x}{s}$$

For number of consumptions, H_a.

Monod: for micro-organisms growth and enzymatic reactions.

$$m(x) = \frac{r_{max}\, x}{x + k}$$ units $1/T$

r_{max} : maximum growth rate units $1/T$

k : half-saturation constant units X

measure of substrate affinity to enzyme.

Are we assuming a quasi-steady state or equilibrium approximation? This will affect what *k* means.

Conversion efficiency

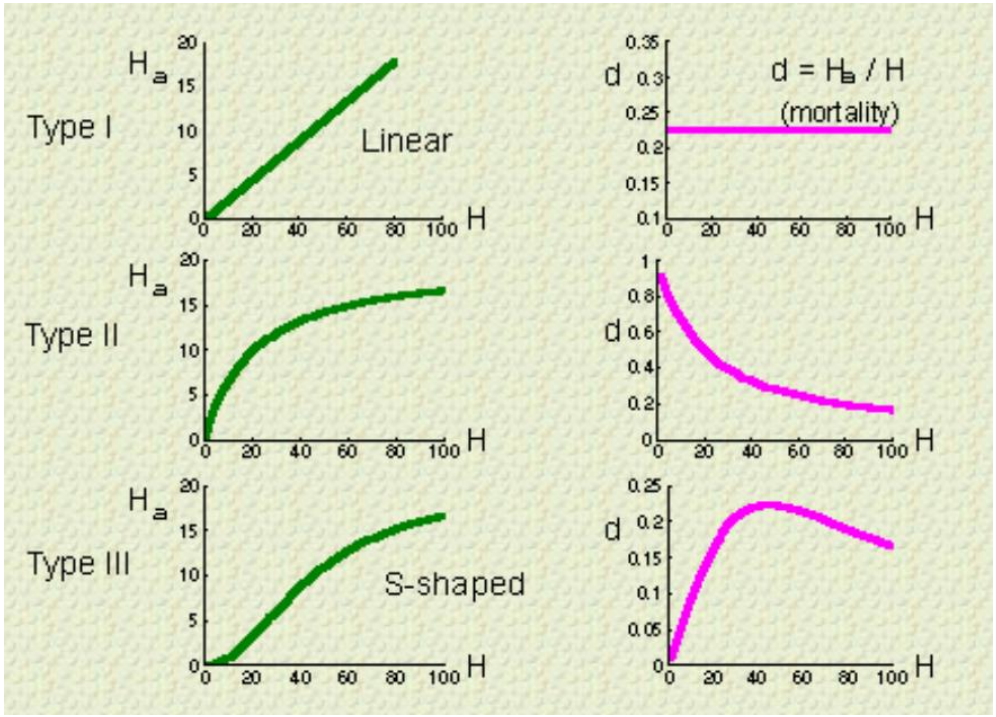
Holling Type II: ecological predation rate dependent on prey density, x.

$$H_2(x) = \frac{a\, x}{ahx + 1}$$ units

h : handling 'time' units

a : attack rate units

$1/h$ is like r_{max}
and
$1/a$ is like k



Contois's Function: ratio of prey to predator

$$m(s/x)$$

Negative dependence of the growth rate on organism concentration, unlike Monod which assumes independence.

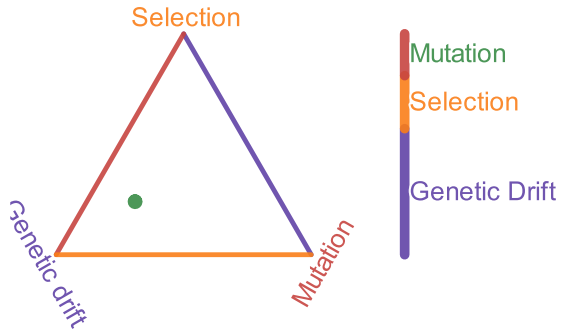
Catabolite repression = prey switching, think Holling type III.

Toxin Depletion

Toxins are used up when they kill. Look back at Jake's paper. Previous lab work showed interface cells absorb toxin and die. If surface cells are resistant, then the next layer die.

Plasmids may produce toxins *constitutively* (without regulation) or in response to various stimuli including nutrient levels, quorum sensing, or damage from a competitor's toxin. **In our model toxins are produced depending on nutrient availability (r.e. Niehus21).**

Consider a trilinear coordinate output (called a de Finetti diagram) like:



Model Amendments

Can transconjugants go on to transmit plasmids? i.e. Can plasmids be transmitted more than once? YES. Recall that in Elisa's experiment, the toxin plasmid and helper plasmid can both be transmitted. Amended HGT ODE term to include this.

k_{AC} and k_{BC} are redundant as both A and B produce the same toxin. Amended toxin term.

Conjugation removes recipients and not donors (presuming all plasmids are not conjugated from one cell to another). $-bAC$ moved from A' to C' term.

Consulting with Elisa, and with precedent from Jake's model, we determined $r_A = r_B = r_C$ is a reasonable simplification.

It was reasoned that the toxin is relatively inert compared to the time scale of lysis/secretion and absorption into target cells. Thus, a decay term was removed in place of an absorption term (proportional to the rate of killing).

If there is any HGT, eventually all recipients will become transconjugates.

To Do: Sensitivity analysis of winning strain.

What parameters have an effect on plasmid success?

How do I infer the direction of each parameters effect? Is transconjugant steady-state abundance diminished by increased niche overlap?

Should I try fsolve? Which is more computationally intensive? No, the outcomes are steady-states and not equilibria, so aren't amenable to fsolve or equilibrium analysis.

Which nutrient is easiest to uptake? Thinking about the relative sizes of the half-saturation constants K1 and K2.

How can a model capture the possibility of only one (toxin or helper) conjugating? Include a transconjugate removal term or only import into C a fixed proportion of exports from A and B.

Uncertainty/Sensitivity Analysis Pitfalls – Saltelli19

- Partial derivatives are not a valid measure of sensitivity for **nonlinear** models. The commonly used One-At-a-Time (OAT) approach fails for this reason. The partial change due to an input parameter will itself depend on where in the range of the input one measures i.e. it is a **local** measure. A similar issue arises if there is a correlation between input parameters. **Global** methods should be used instead.

Highly cited papers get this wrong, and then others follow suit. Good practice is also impeded by lack of interdisciplinary research.

- Too many inputs. Screening and sampling can be used to reduce dimensionality. Too many outputs are considered.
- Model run-time is too long. Emulators can reduce run time.
- Input probability distributions are subjectively chosen.
- Unclear purpose of the analysis. Different statistical tests and measures are applied to the problem and different factors rankings are obtained e.g. Monte Carlo filtering is used to find which factors generate high/low output values.

SALib Package: https://salib.readthedocs.io/en/latest/

- Sensitivity Analyis in Python
- Sensitivity Analysis with SALib
- Running Sobol using SALib
- Extensions of SALib for more complex sensitivity analyses

Uncertainty quantification tutorial. Monte Carlo, Epidemic, Latin Hypercube sampling: https://towardsdatascience.com/performing-uncertainty-analysis-in-three-steps-a-hands-on-guide-9110b120987e

Making SA more accessible: https://sesmo.org/article/view/18155/17856

Table 1 Various types of commonly used global sensitivity analysis techniques comparison

Variance Based As is HDMR

	Commonly used global sensitivity analysis methods				
Criteria for comparison	**Weighted average of local sensitivity analysis (WALS)**	**Partial rank correlation coefficient (PRCC)**	**Multi-parametric sensitivity analysis (MPSA)**	**Fourier amplitude sensitivity analysis (FAST)**	**Sobol**
Discrete inputs	Yes	Yes	Yes	Yes	Yes
Model independence	No	No	No	Yes	Yes
Non-linear, input-output relationship	Yes	Yes	Yes	Yes	Yes
Non-monotonic input-output relationship	Yes	No	Yes	Yes	Yes
Robustness	Yes	Yes	Yes	Yes	Yes
Reproducibility	Yes	Yes	Yes	Yes	Yes
Ability to apportion the output variance	No	No	No	Yes	Yes
Higher order interaction of parameters	No	No	No	Yes	Yes
Quantitative measure for ranking	Yes	Yes	Yes	Yes	Yes
Computational efficiency	Yes	Yes	Yes	No	No

Morris method is a good, low-computation first step for large systems with many parameters/ICs. But only for monotonic models.

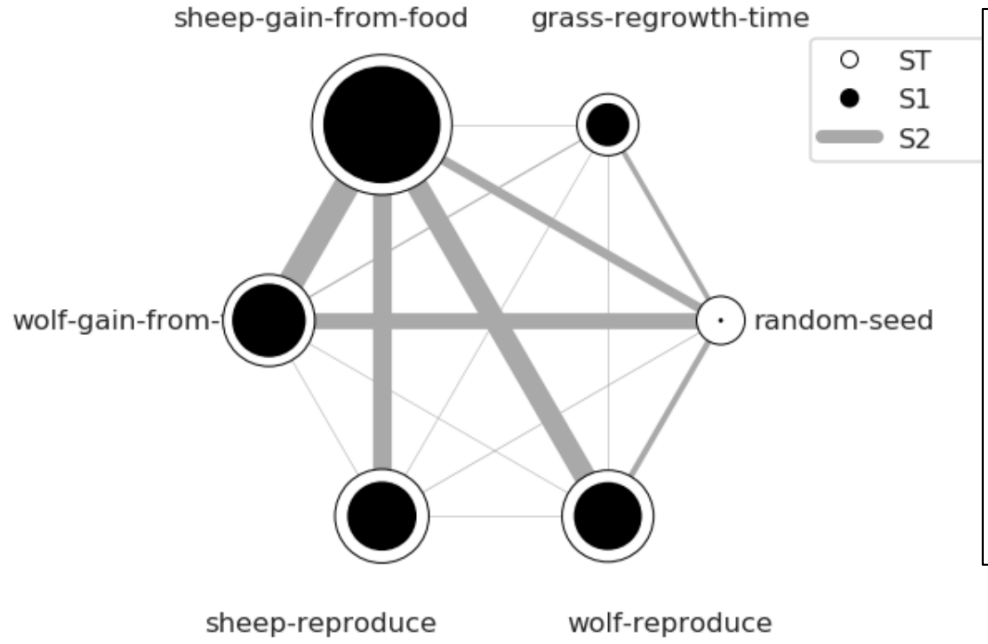
PRCC is only for monotonic models.

I went with Sobol

Tutorial using an agent-based model of predation:

[Example 2: Sensitivity analysis for a NetLogo model with SALib and ipyparallel — pyNetLogo]

Edge width by weight: [Introduction to NetworkX (Python) - Data Science with Harsha (harshaash.com)]



- Triangular, “triang” (assumed lower bound of 0)
  - first “bound” is width of distribution (scale, must be greater than 0)
  - second “bound” is location of peak as a fraction of the scale (must be on [0,1])
- Normal, “norm”
  - first “bound” is the mean (location)
  - second “bound” is the standard deviation (scale, must be greater than 0)
- Lognormal, “lognorm” (natural logarithms, assumed lower bound of 0)
  - first “bound” is the ln-space mean
  - second “bound” is the ln-space standard deviation (must be greater than 0)
- Uniform, “unif”
  - first “bound” is the lower bound
  - second “bound” is the upper bound (must be greater than lower bound)

In this case, the “sheep-gain-from-food” variable has strong interactions with the “wolf-gain-from-food” and “wolf-reproduce” inputs in particular. The size of the ST and S1 circles correspond to the normalized variable importances.

Scaling

Bucci11 derived the critical bacteriocin range (Lbac) which combines physical and biological parameters.

Conjugation rate: 0.15 transconjugants per donor per minute.

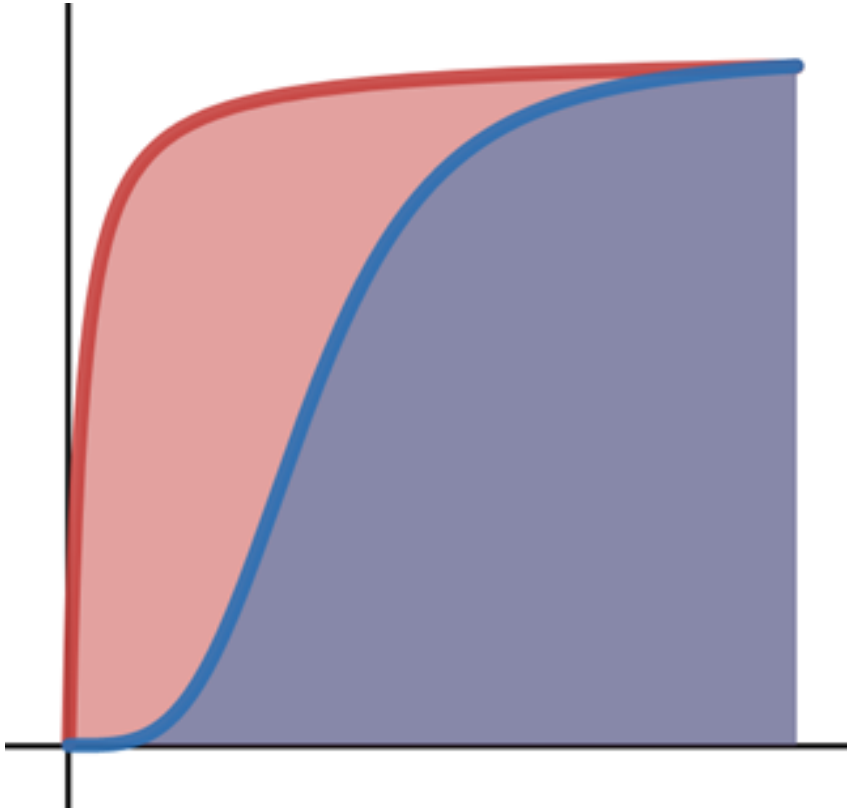
Typical Parameters

From Bucci11

μ_{max}	Maximum growth rate	1.02 h^{-1}
k_d	Decay rate	.001 h^{-1}
K_N	Half-saturation constant	3.5×10^{14} g $O_2/\mu m^3$
Y	Yield	.5 g X/g N
α	Toxin-biomass stoichiometric ratio	$2.7 \times 10^{-16} - 2 \times 10^{2}$ g T/g X
N_{bulk}	Nutrient bulk concentration	$2 \times 10^{-13} - 2 \times 10^{-8}$ g $O_2/\mu m^3$
k_T	Toxin killing efficacy	$0-2 \times 10^{3}$ μm^3 g T^{-1} h^{-1}

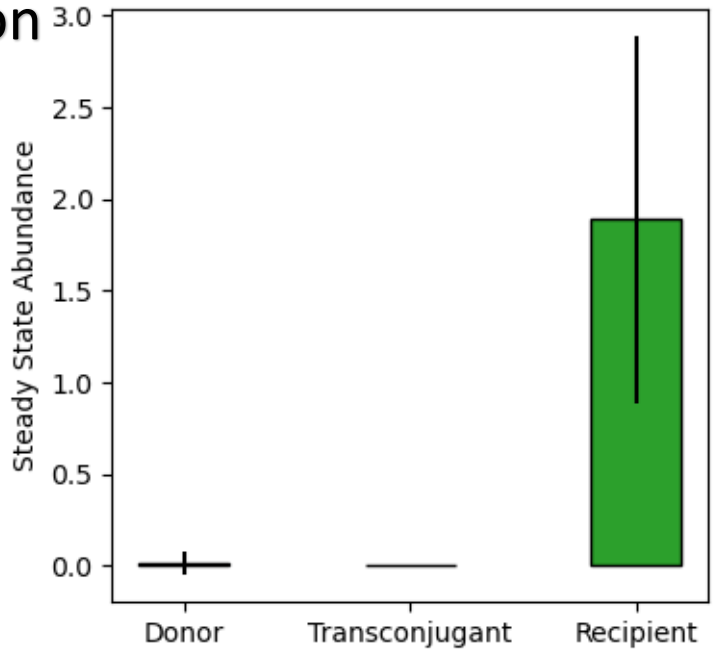
Model Output considered during Sensitivity Analysis

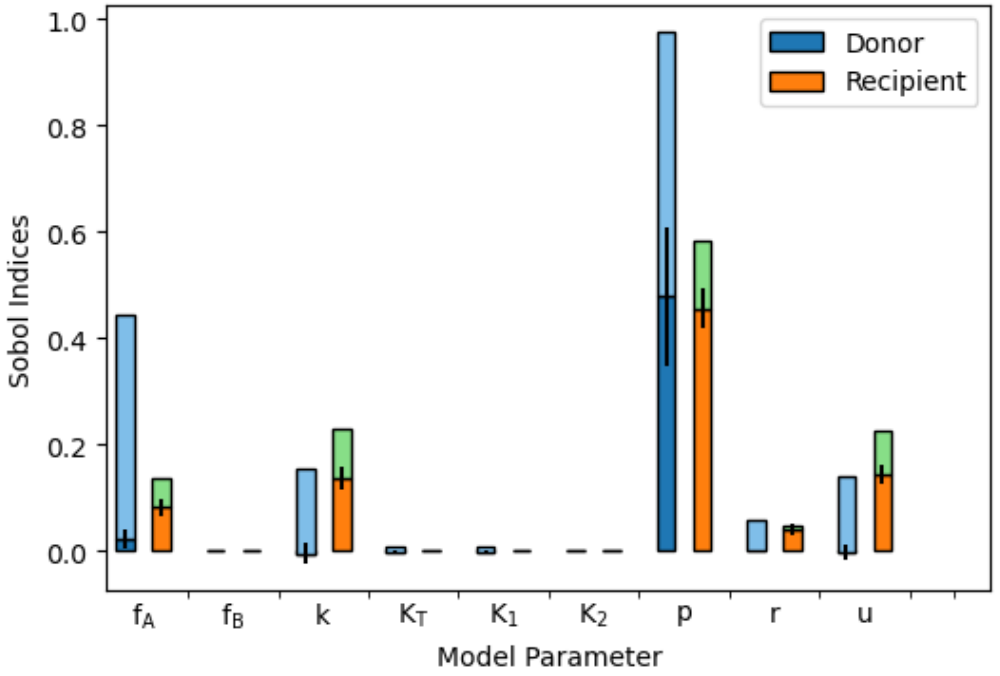
1. **Steady-state strain densities?** This would neglect all the prior dynamics, which might be of interest. The two trajectories on the right arrive at the same place by very different means.
2. **Integral of abundance?** This poses a numerical challenge. The solver does not return a uniform t_eval.
3. **Plasmid Abundance?**
4. **Winner?** This is a vector output generally, but would be binary when conjugation exists.



No Conjugation

b = 0



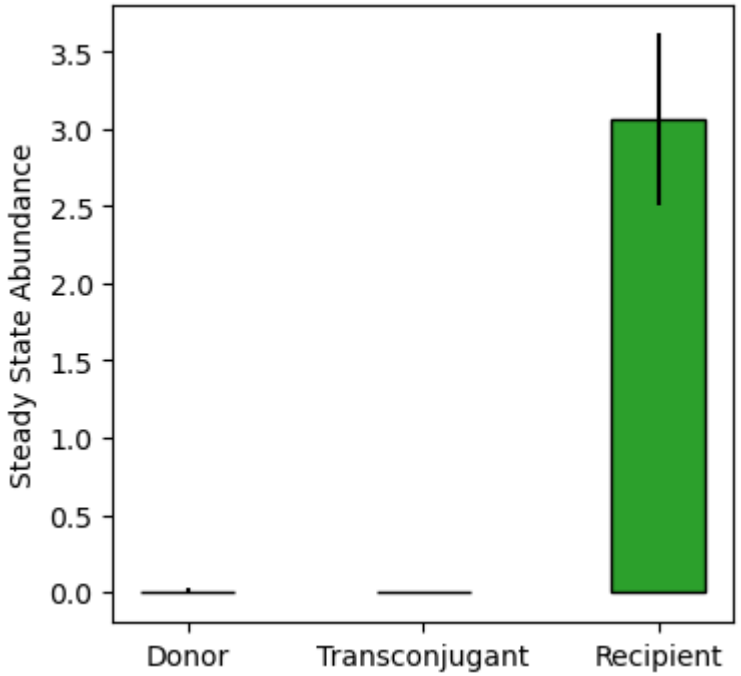


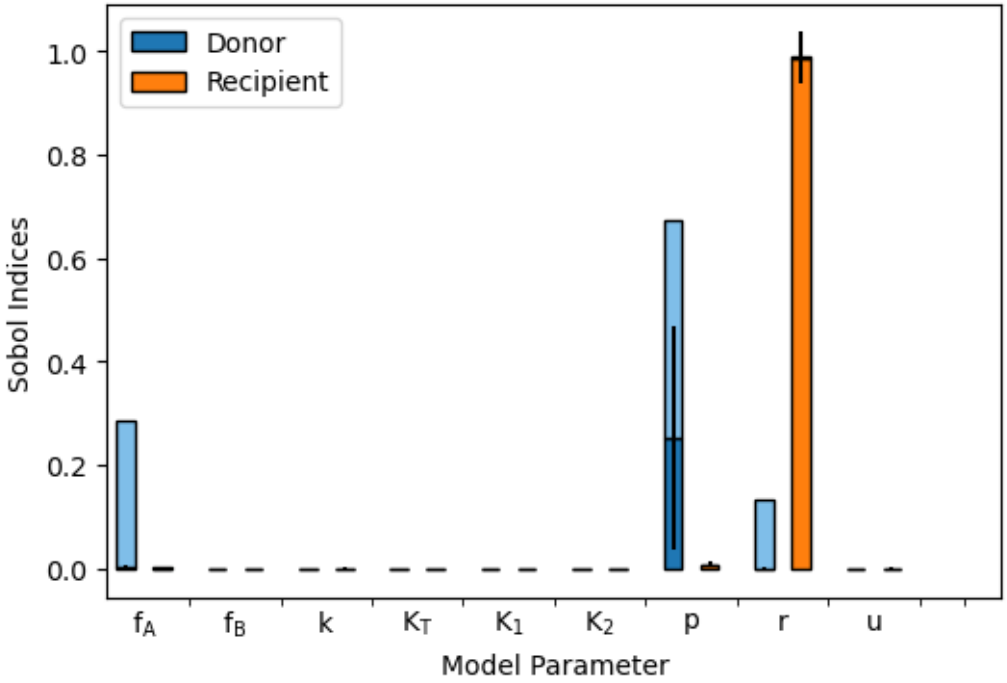
Results are highly sensitive to the numerical method used in scipy.solve_ivp(). More work needs to be done.

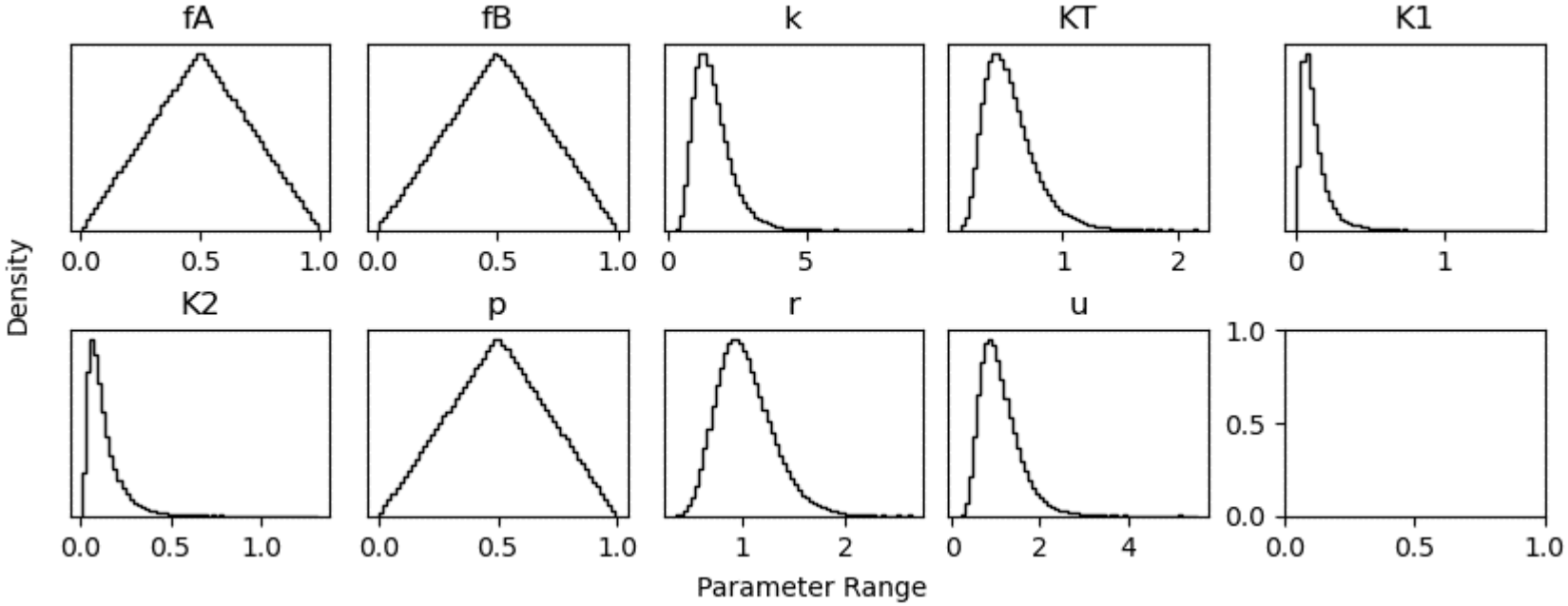
method = 'Radau' vs 'RK45' produce qualitatively different results. Is the system stiff?

No Conjugation

b = 0

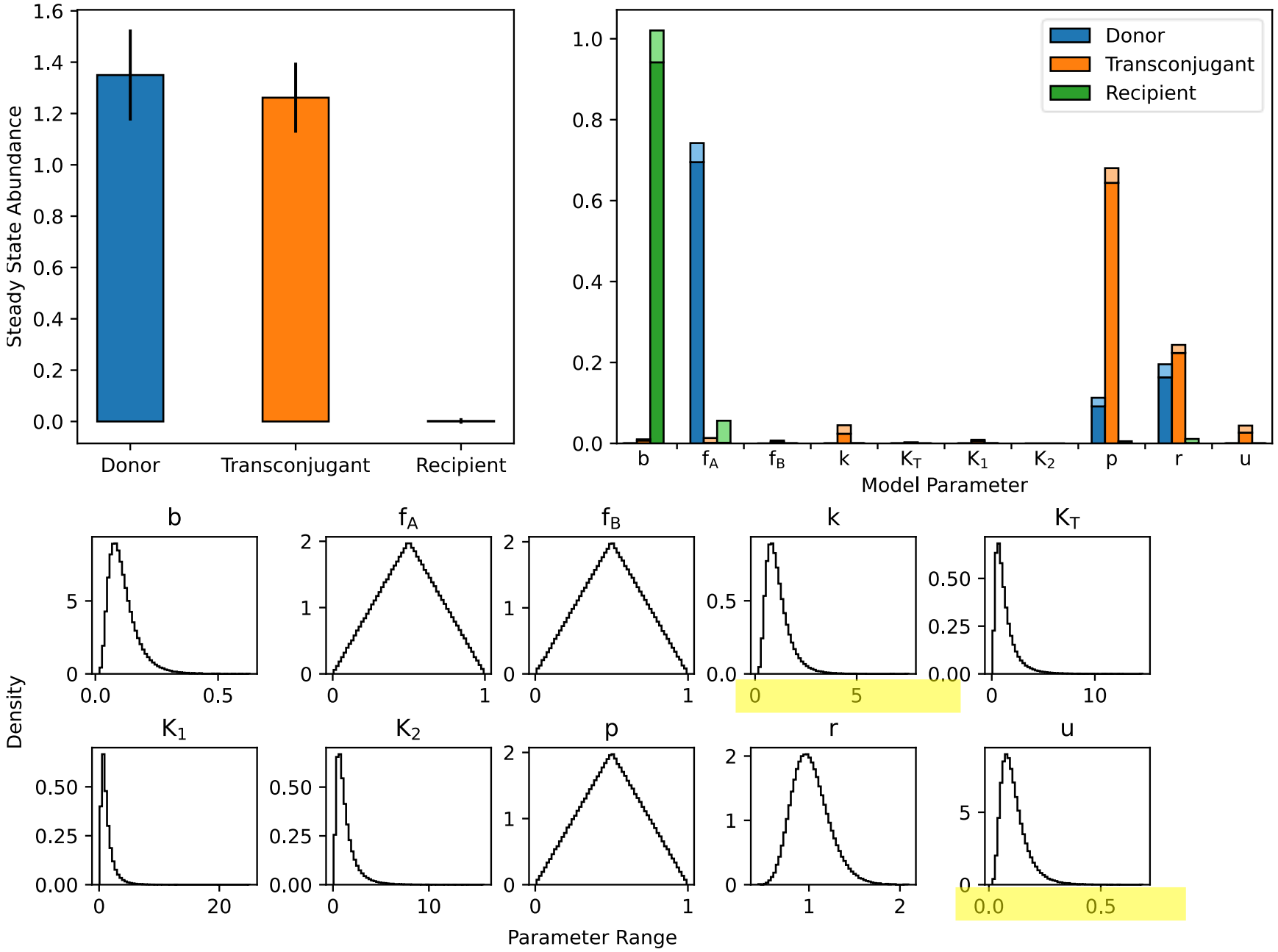






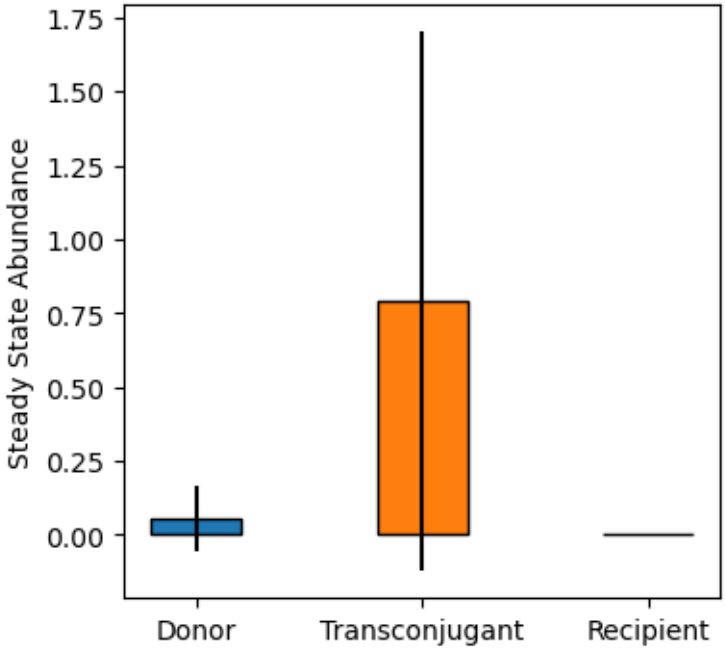
Conjugation

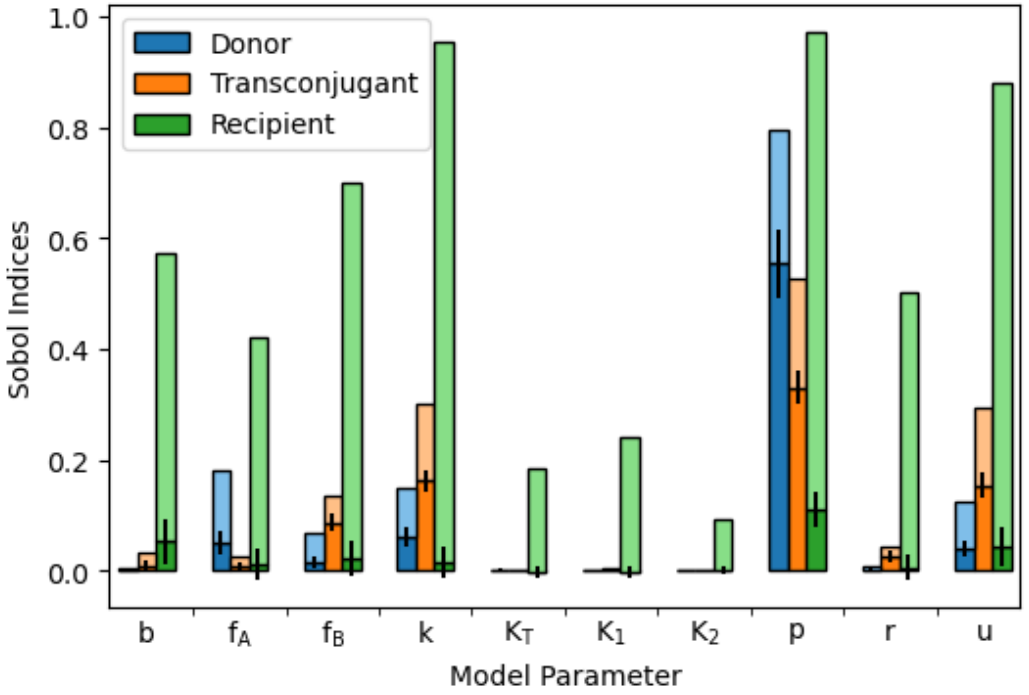
b > 0

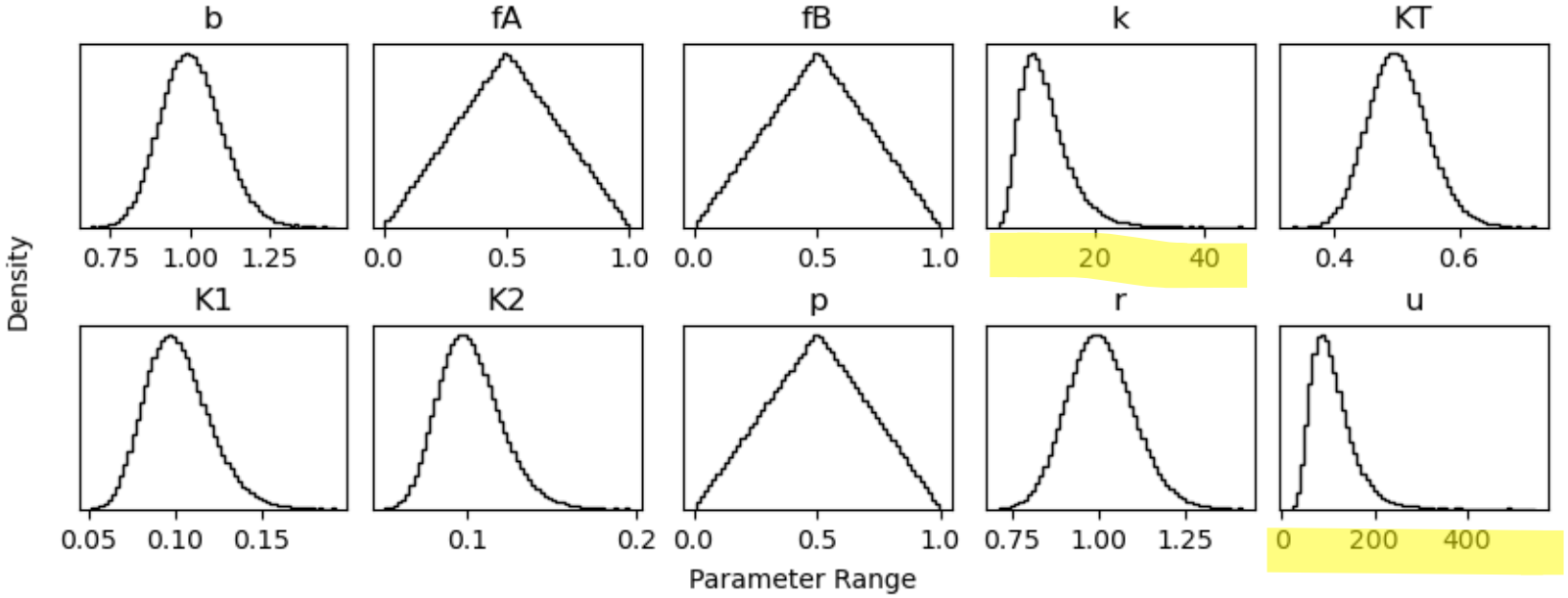


Conjugation

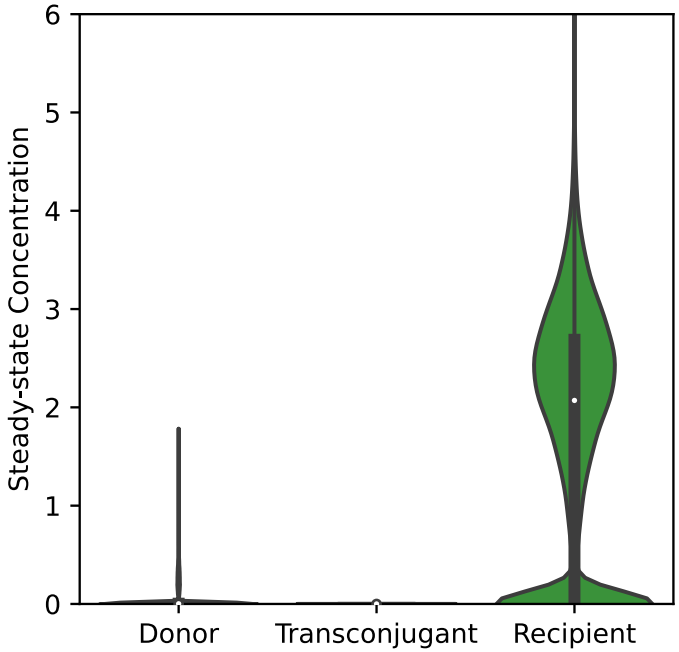
b > 0

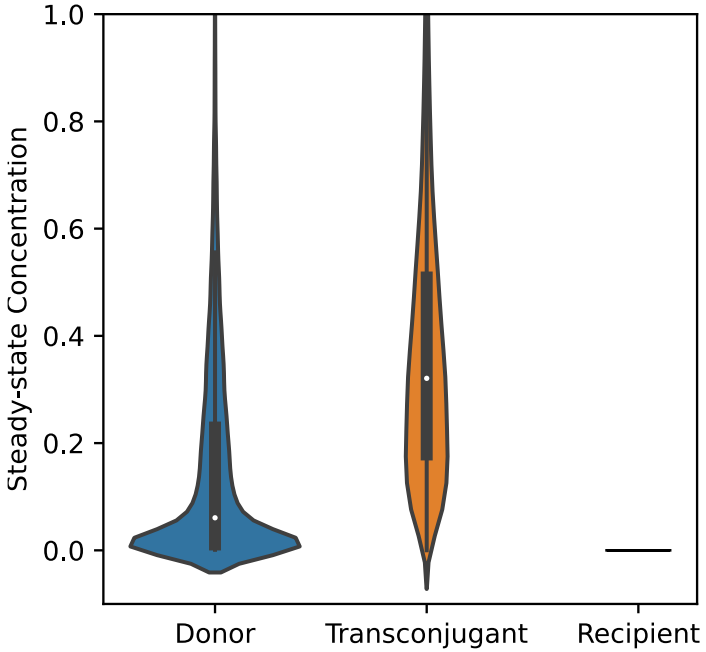


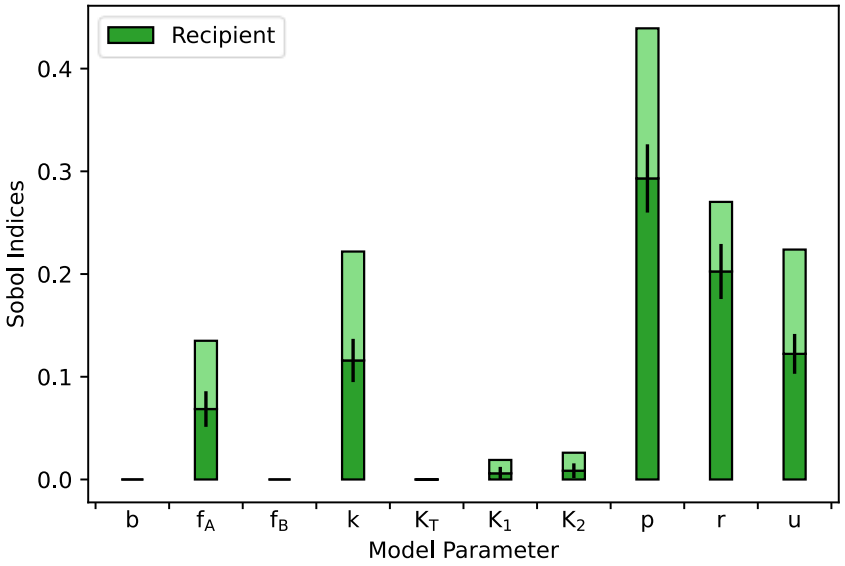


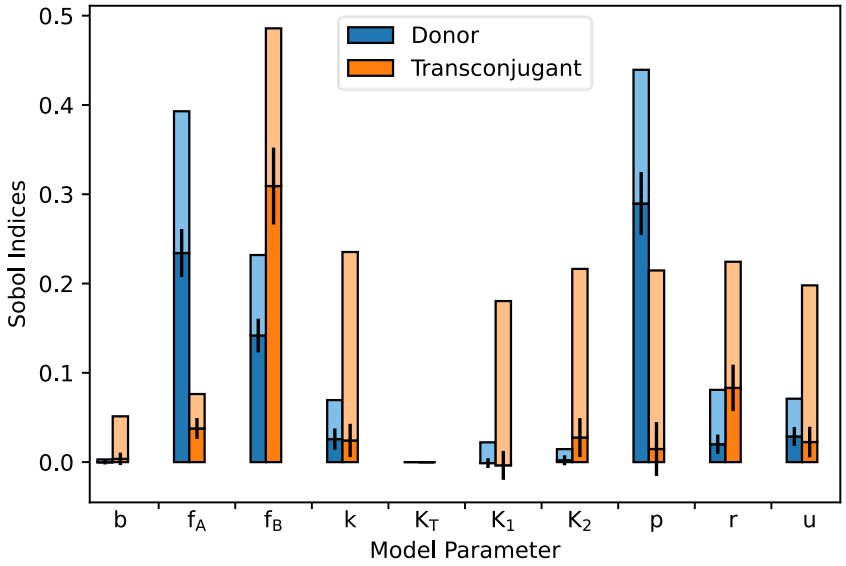


Assumed param distributions affect result


Steady-state Concentration
0
1
2
3
4
5
6
Donor
Transconjugant
Recipient


Steady-state Concentration
0.0
0.2
0.4
0.6
0.8
1.0
Donor
Transconjugant
Recipient


Recipient
Sobol Indices
0.0
0.1
0.2
0.3
0.4
b
f_A
f_B
k
K_T
K_1
K_2
p
r
u
Model Parameter


Donor
Transconjugant
Sobol Indices
0.0
0.1
0.2
0.3
0.4
0.5
b
f_A
f_B
k
K_T
K_1
K_2
p
r
u
Model Parameter