

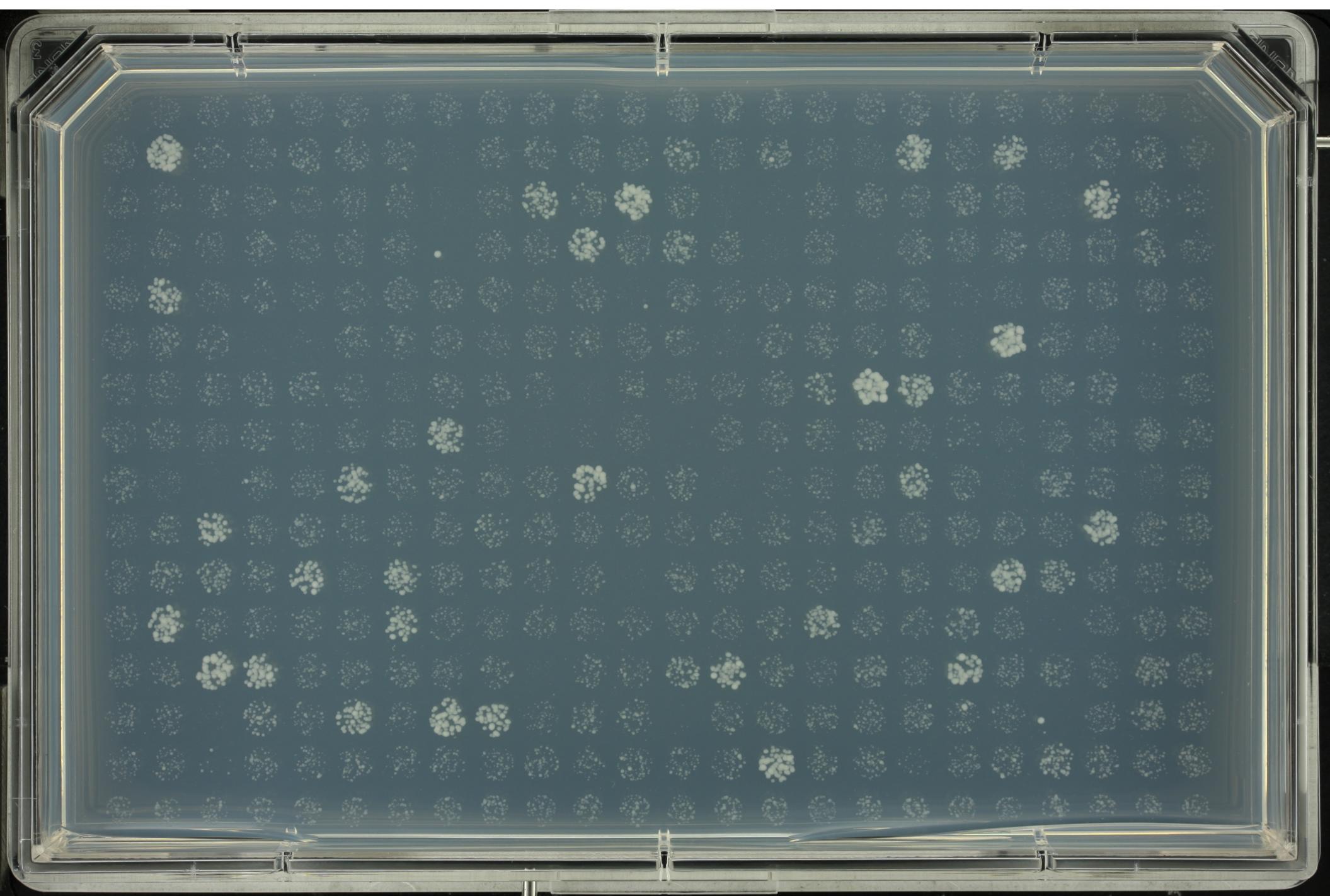
Modelling competition for nutrients between QFA spots

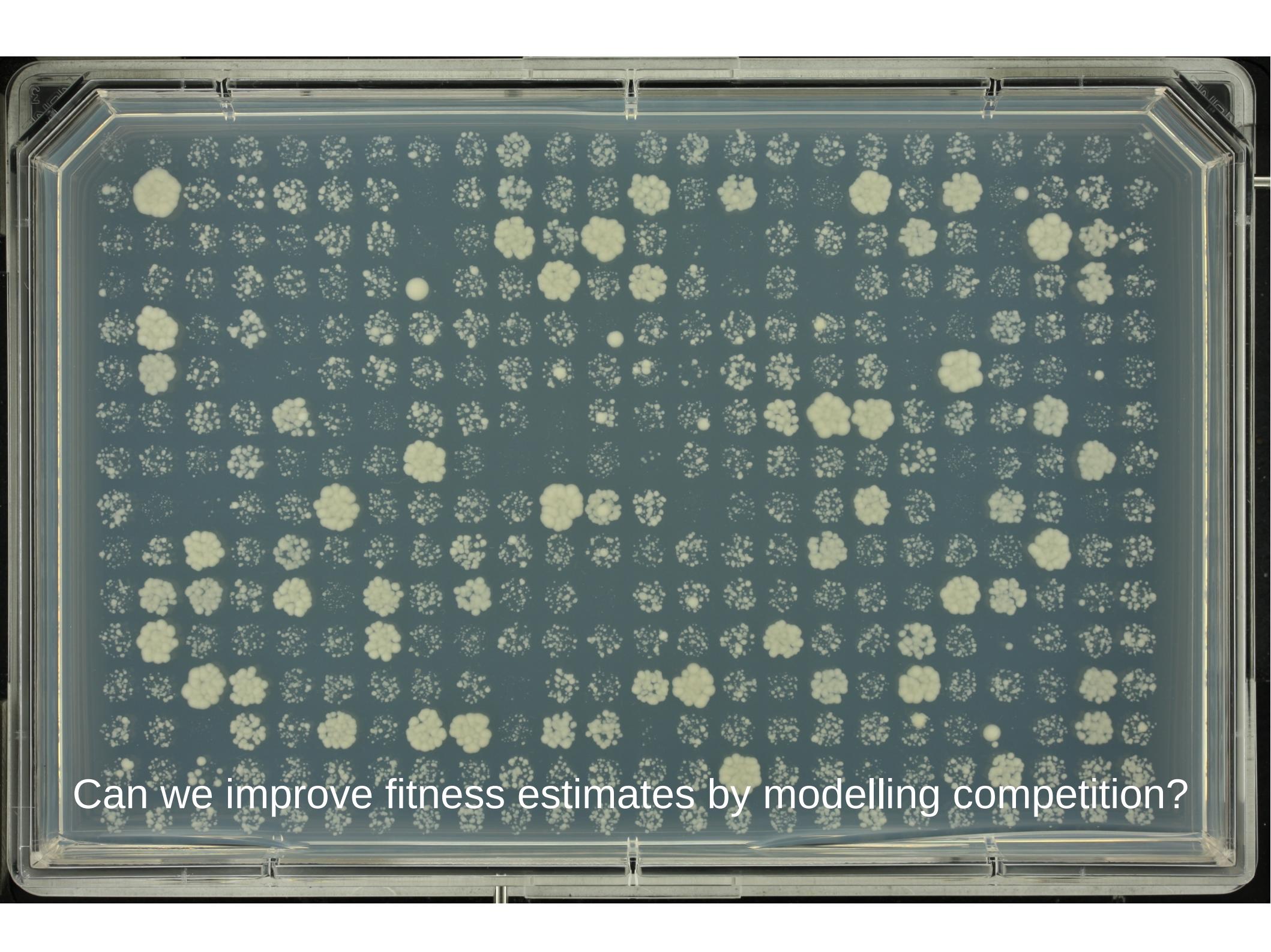
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25/07/2016**

Quantitative Fitness Analysis (QFA)

- Microbial cultures are inoculated in a grid on a solid agar surface
- Repeatedly photographed
- Analysed to get cell density estimates
- Growth curves are fit with the logistic model
- Fits are used to derive fitness estimates







Can we improve fitness estimates by modelling competition?

QFA fits the logistic model to summarise data

$$\dot{C} = rC \left(1 - \frac{C}{K}\right)$$

Plate level: C_0
Culture level: r, K

- From r and K we can define fitness measures
- MDP: no. of doublings undergone from the inoculum density (C_0) to carrying capacity (K)
- MDR: inverse of the doubling time at the beginning of the experiment
- One fitness measure is MDR*MDP
- We can obtain the same shape curve using a more mechanistic model

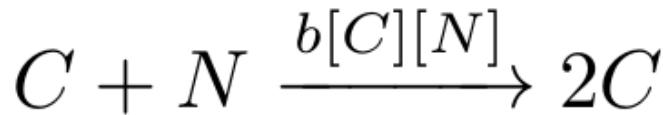
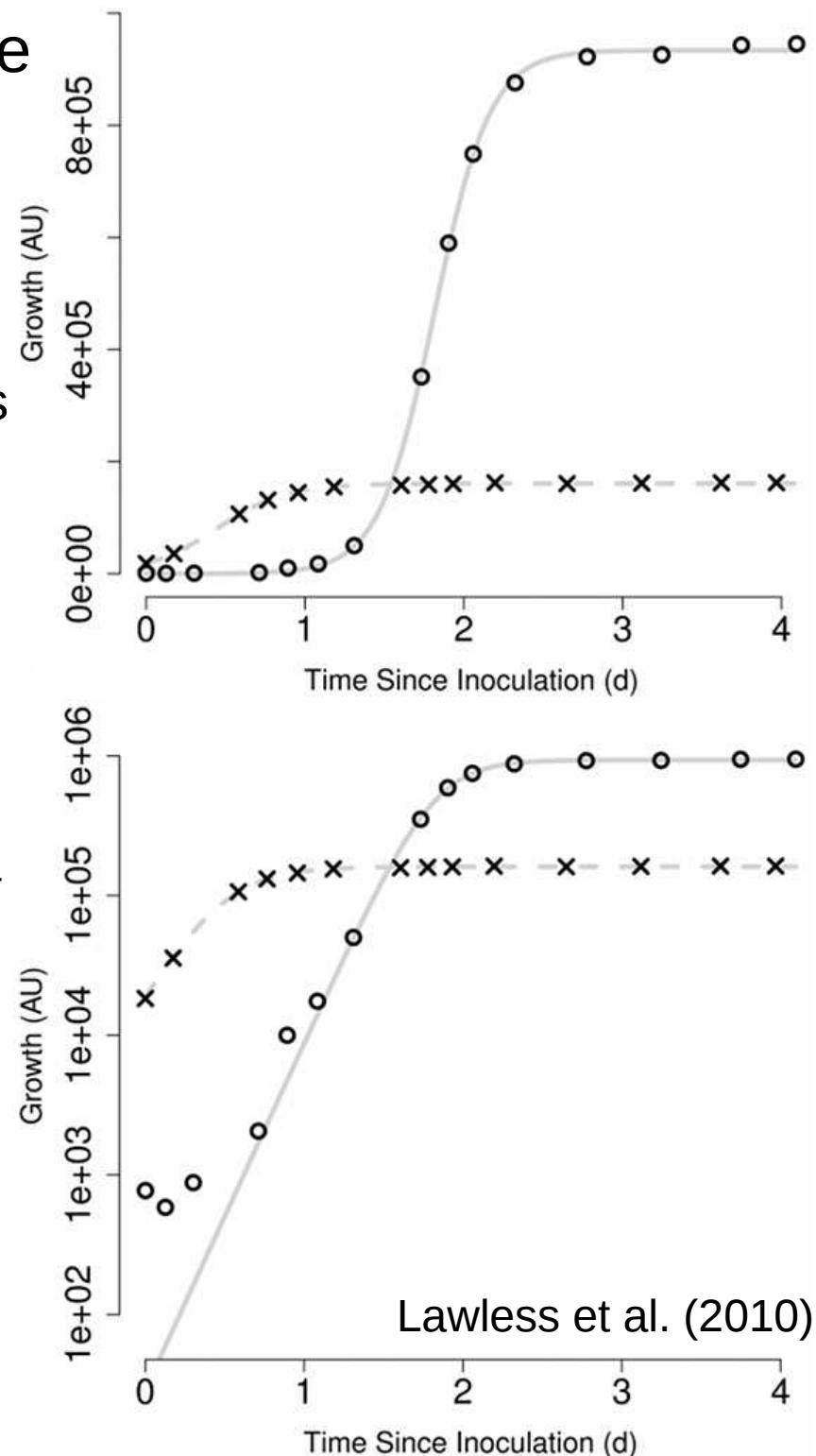


Plate level: C_0
Culture level: b, N_0

- Conversion:
$$r = b(N_0 + C_0)$$

$$K = (N_0 + C_0)$$



Can we improve fitness estimates by modelling competition?

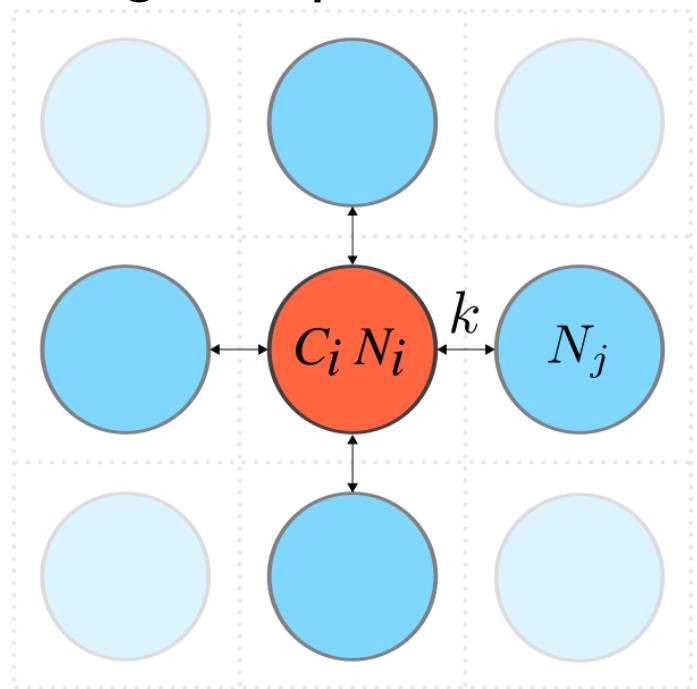
- We use a network diffusion model and mass action kinetics

$$\frac{dC_i}{dt} = b_i N_i C_i,$$

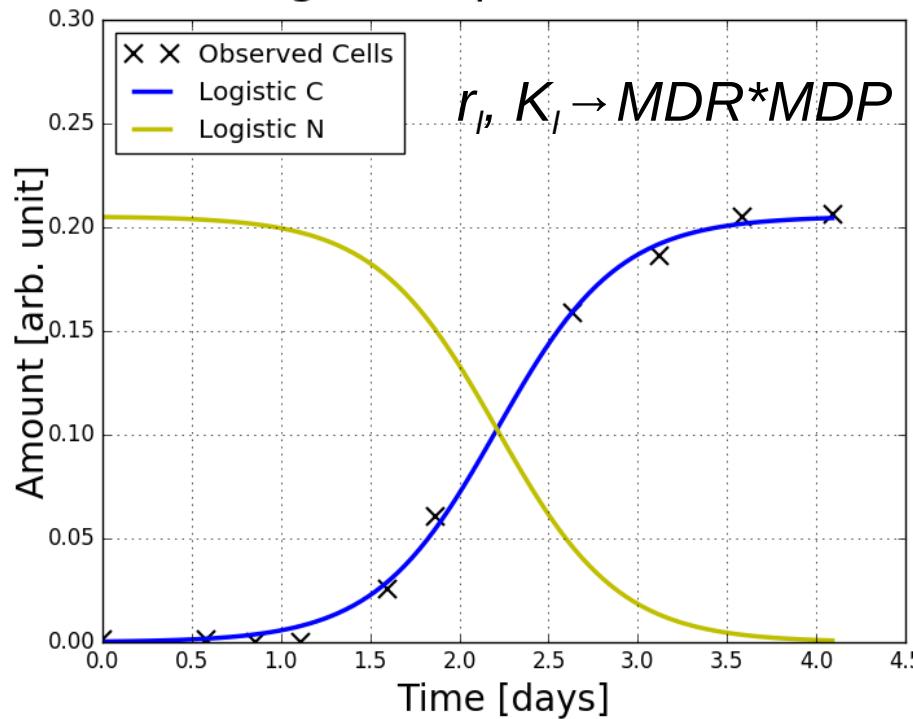
Plate level: C_0, N_0, k
 Culture level: b_i (384)

$$\frac{dN_i}{dt} = - b_i N_i C_i - k \sum_{j \in \delta_i} (N_i - N_j)$$

- If we set $k = 0$ we return to the logistic equivalent model.
- Can be thought of as a correction
- Cell arrest, metabolism, or signalling could also be modelled

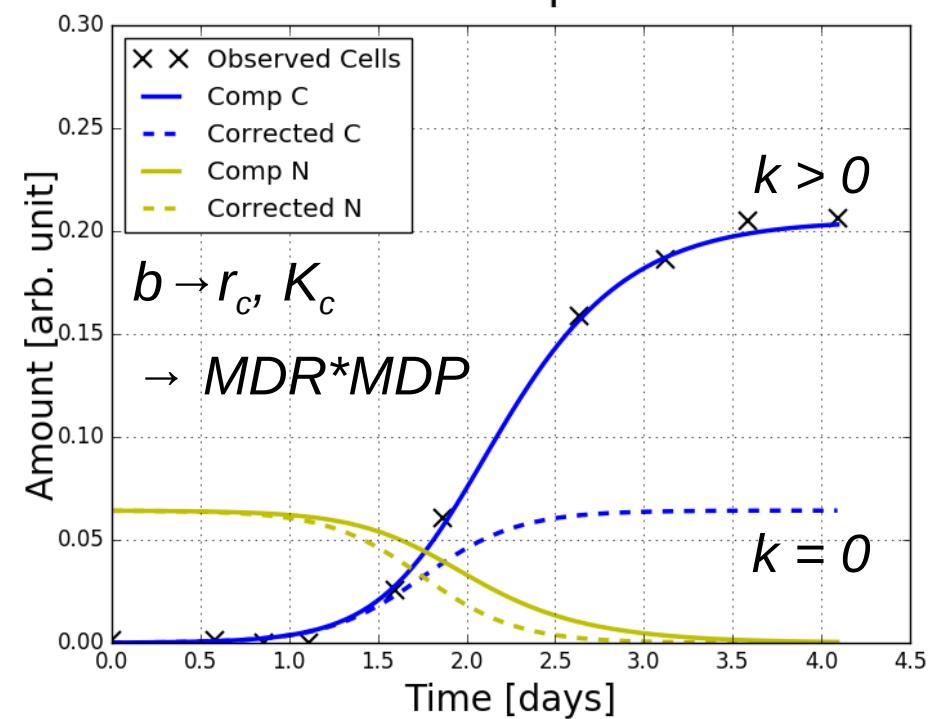


Logistic Equivalent Fit



$r_c, K_c \rightarrow MDR^*MDP$

Corrected Competition Fit



$b \rightarrow r_c, K_c$

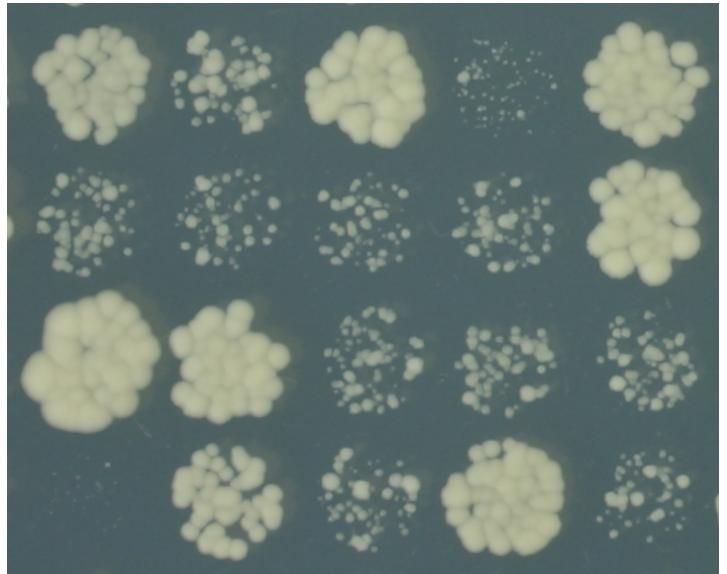
$\rightarrow MDR^*MDP$

$k > 0$

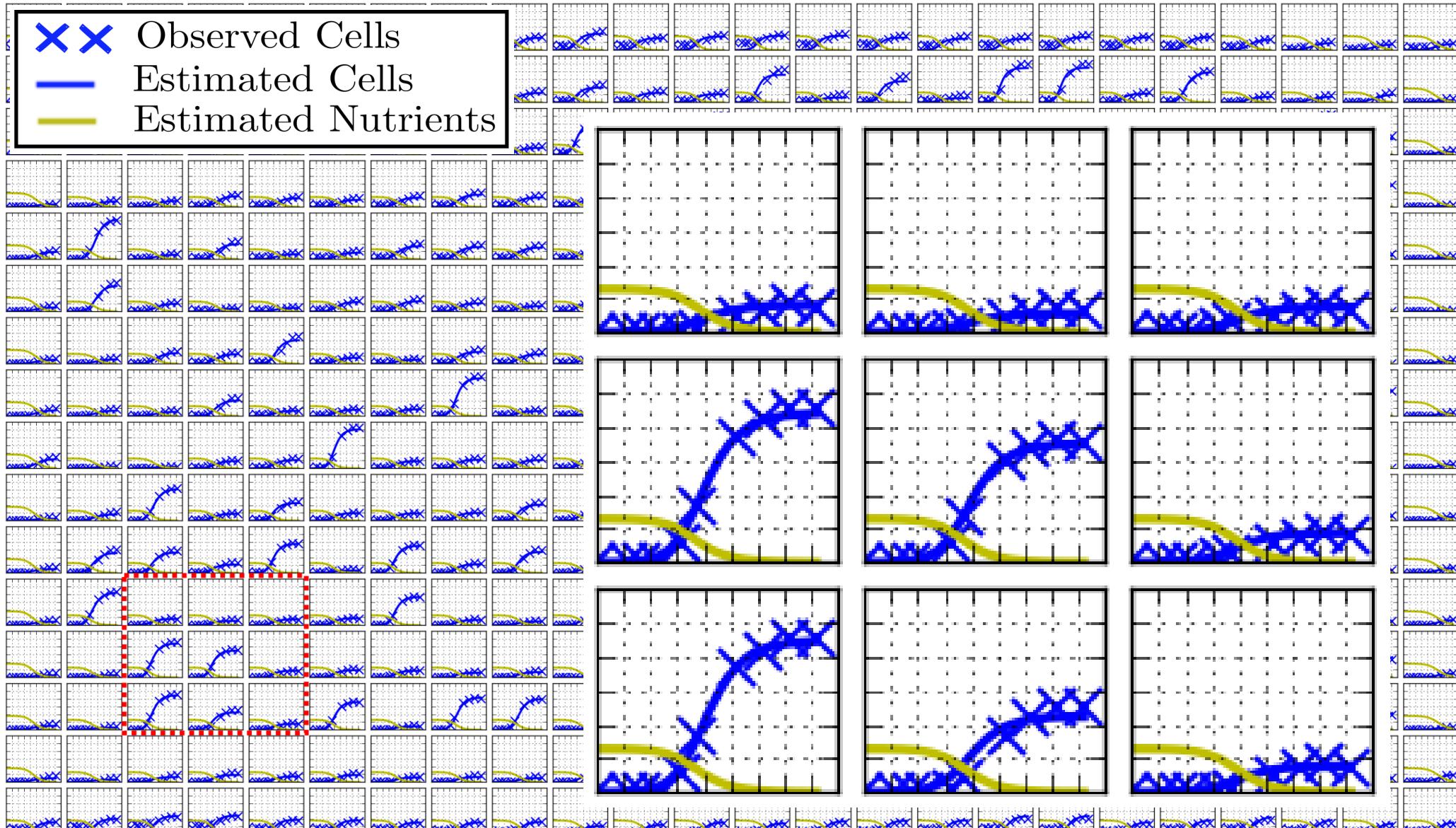
$k = 0$

We study plate 15 from a *cdc13-1* screen at 27C

- Yeast cells
- 15th plate in a standard deletion library
- *cdc13-1* is background mutation
- *CDC13* is a gene important for telomere stability
- ~50 deletions chosen for relevance to telomere biology
- Why did we choose this data set?
 - Biology of many strains on this plate is well understood
 - Lots of replicates (6 per deletion)
 - Large variation in fitness of strains (suppress or enhance defect associated with *cdc13-1*)
 - We would like to test for effects of competition for nutrients between fast-growing and slow-growing



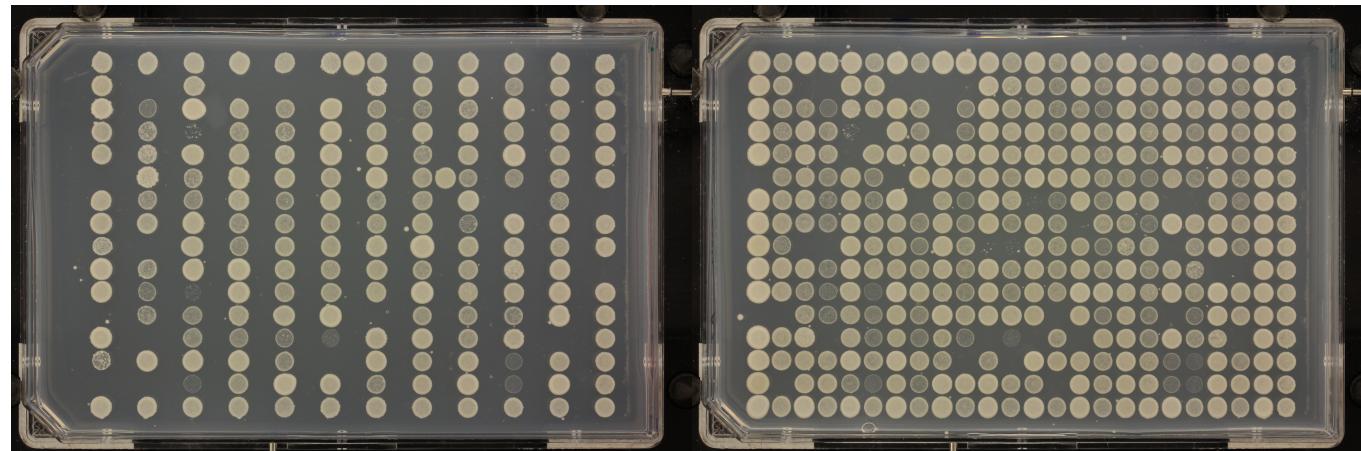
Competition Model Fit to *cdc13-1* P15 Data



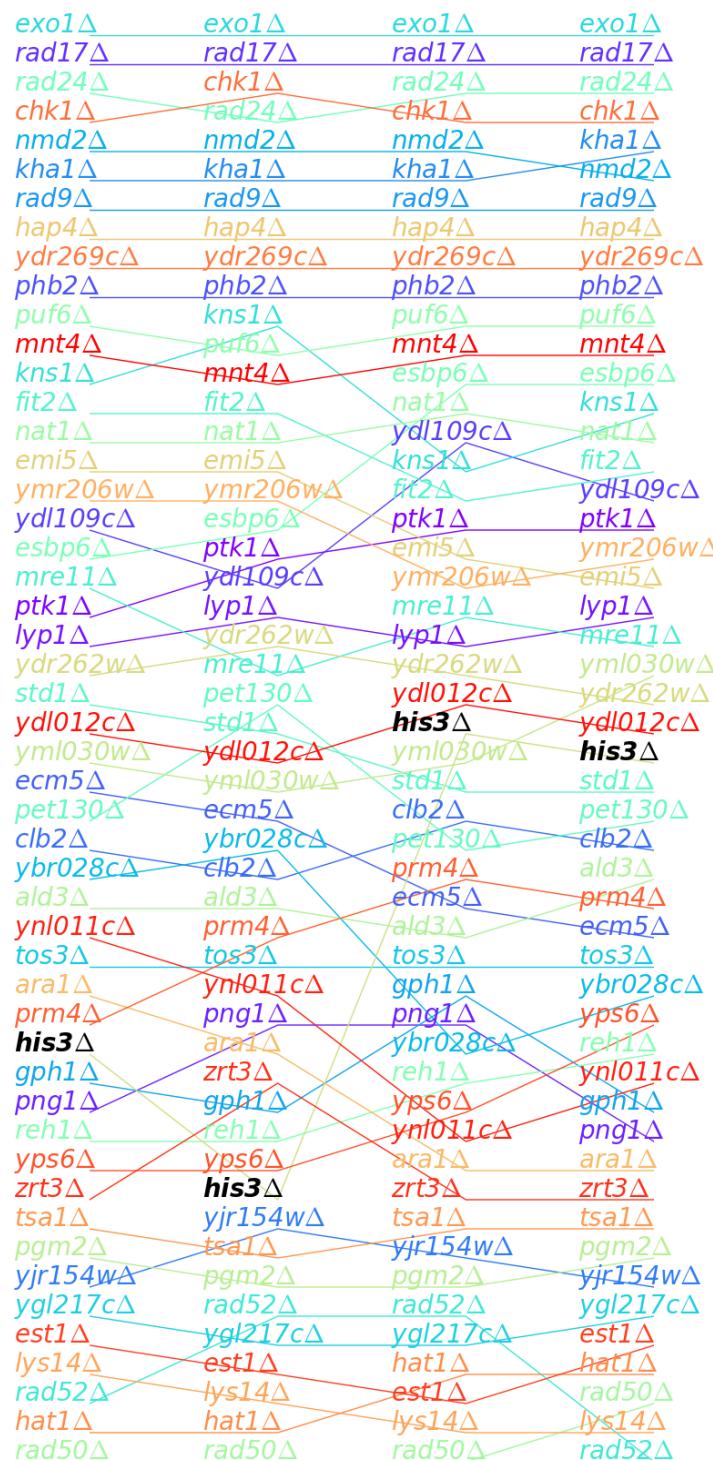
- It takes ~ 3 hours for estimates to converge for a 384 format plate
- We cannot yet find global minima. Confounding effect between b and C_0 . Can we directly measure C_0 ?
- However, the rank order of genotypes is fairly consistent among the best estimates

How can we asses the Competition Model?

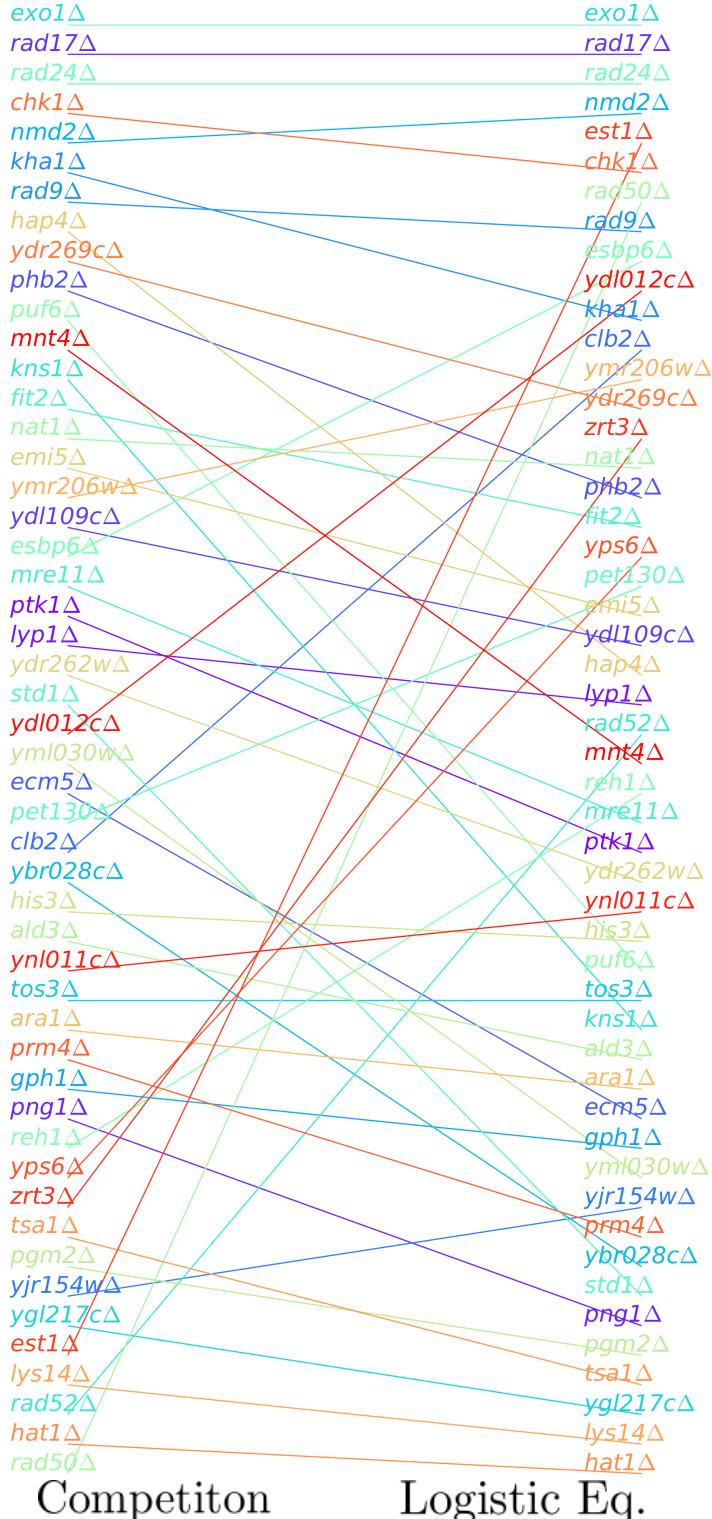
- Competition model b is proportional to MDR*MDP
 - Do the rankings on the left agree with known biology?
 - How do they compare to logistic model fits?
 - We will compare variances
 - Are fitness estimates more reliable?
 - We also plan to compare between plates using miniQFA.



b rankings for top four competition model fits



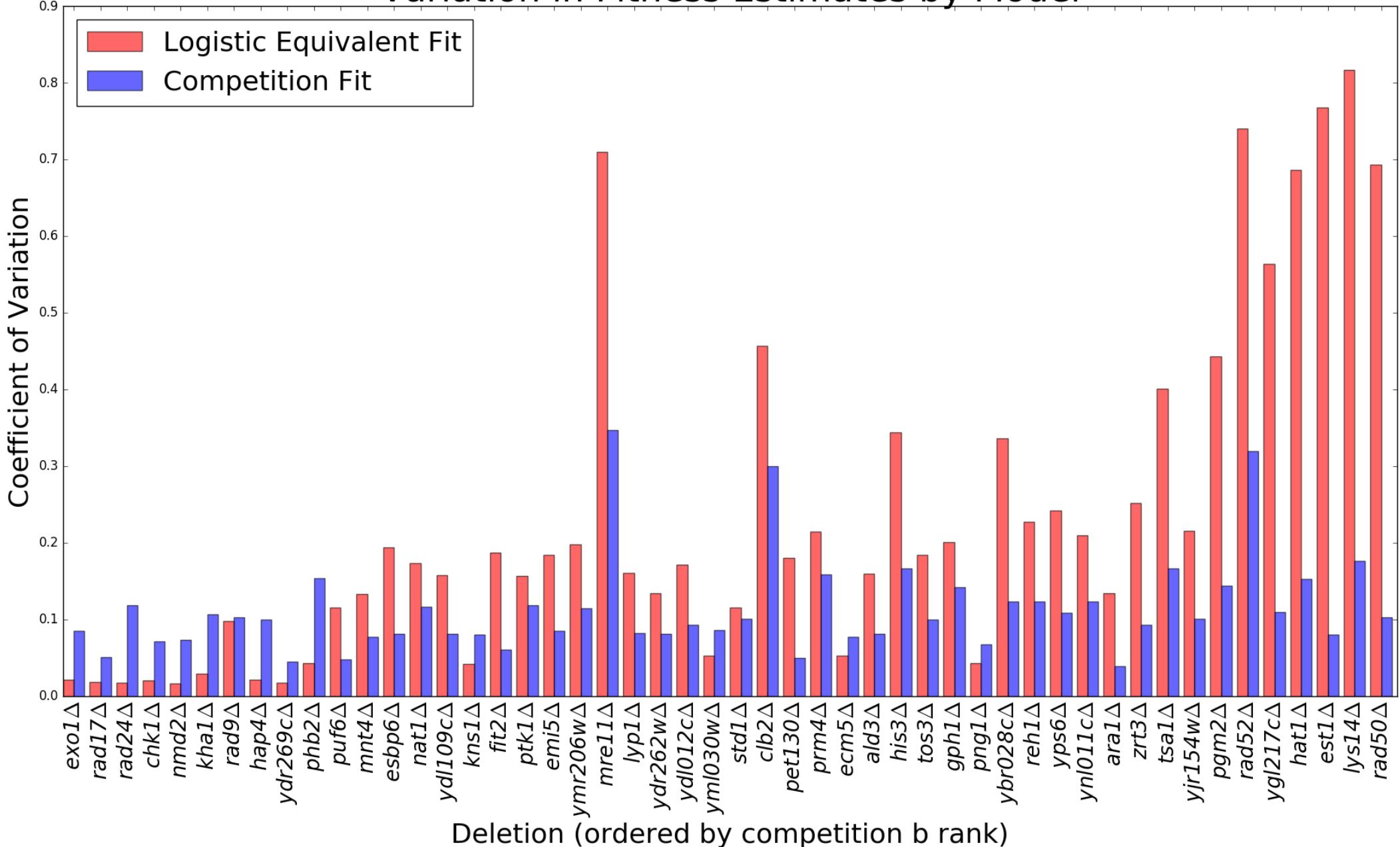
MDR*MDP Rank



Comparison of Competition and Logistic model MDR*MDP rankings

- There is some agreement but many ranks are very different
- Fitting very slow growing cultures such as *rad50Δ* difficult due to noise
- Logistic eq. estimates $C_0 = 2.2 \times 10^{-7}$. Too low?
- Plate level C_0 valid?
- May be better off fitting the standard logistic model with Colonyzer

Variation in Fitness Estimates by Model



- Variation in MDR*MDP is less for the logistic equivalent model for top ranked
- Logistic equivalent fits for slow growing strains not yet accurate

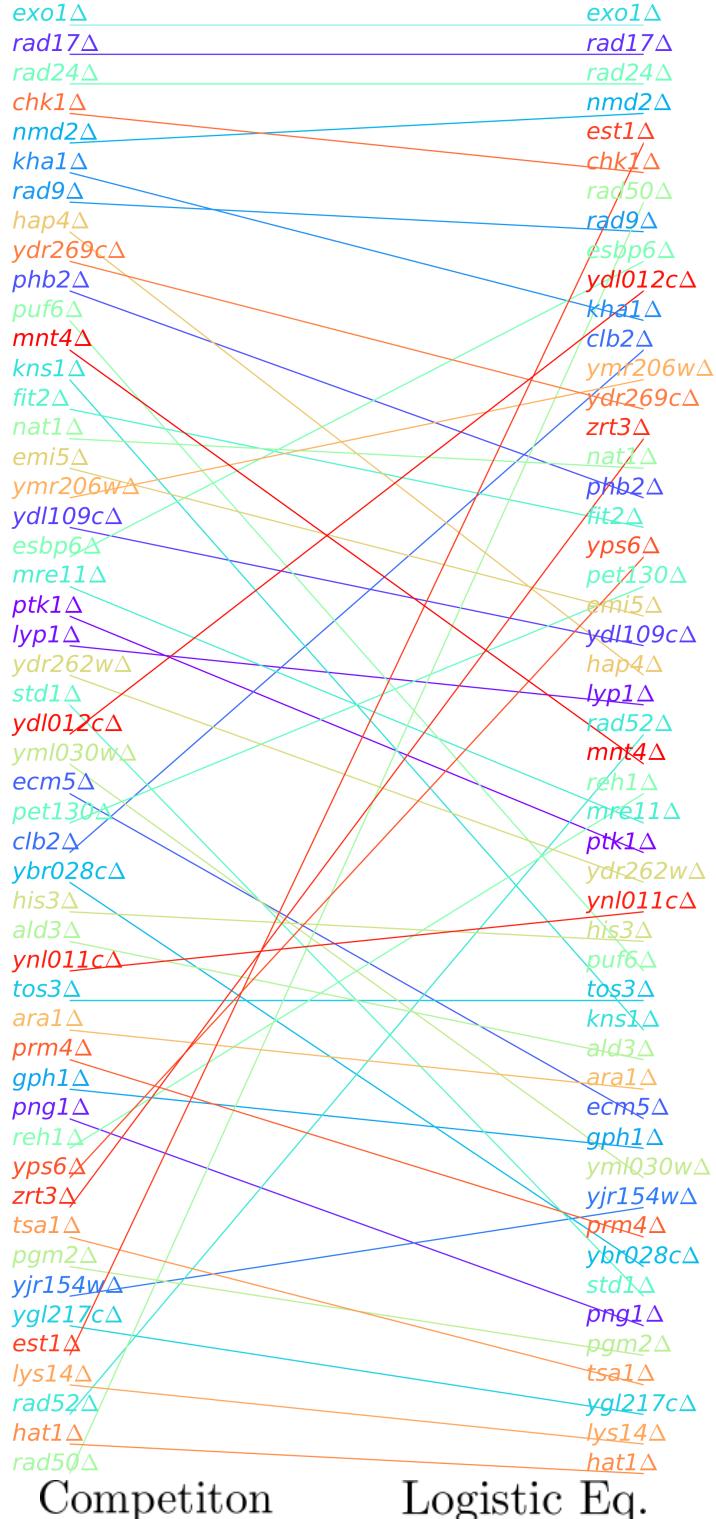
Further Work

- We still need to work on finding global minima
- Can we decide whether it is worth doing so now?
 - Agreement with biological knowledge
 - Compare variance in fitness estimates with the logistic model
 - Cross-plate comparison of b
- Could experiments start to measure C_o ?
 - Make fitting easier
 - Reduce computation time
- Could we validate the independent limit?
 - Do all cultures really reach the same final cell level?
 - Should we model metabolism?
- Fitness estimates should be judged based on their predictions
- Where can I find references for validation based on existing knowledge?

Best Logistic Equivalent Fit (Plate Level C0)



MDR*MDP Rank



Comparison of Competition and Logistic model MDR*MDP rankings

- There is some agreement but many ranks are very different
- Logistic eq. fitted $C_0 = 2.2 \times 10^{-7}$. Too low?
- Not sure we are finding the global minimum for the logistic equivalent model either
- Could heterogeneity require culture level C_0 ?
Need to think about this
- Or has C_0 lost its meaning?
- May be better off fitting the standard logistic model with Colonyzer
- Fitting very slow growing cultures such as *rad50Δ* difficult due to noise
- Below plot best logistic model fit

- Think about bias when using biological knowledge.