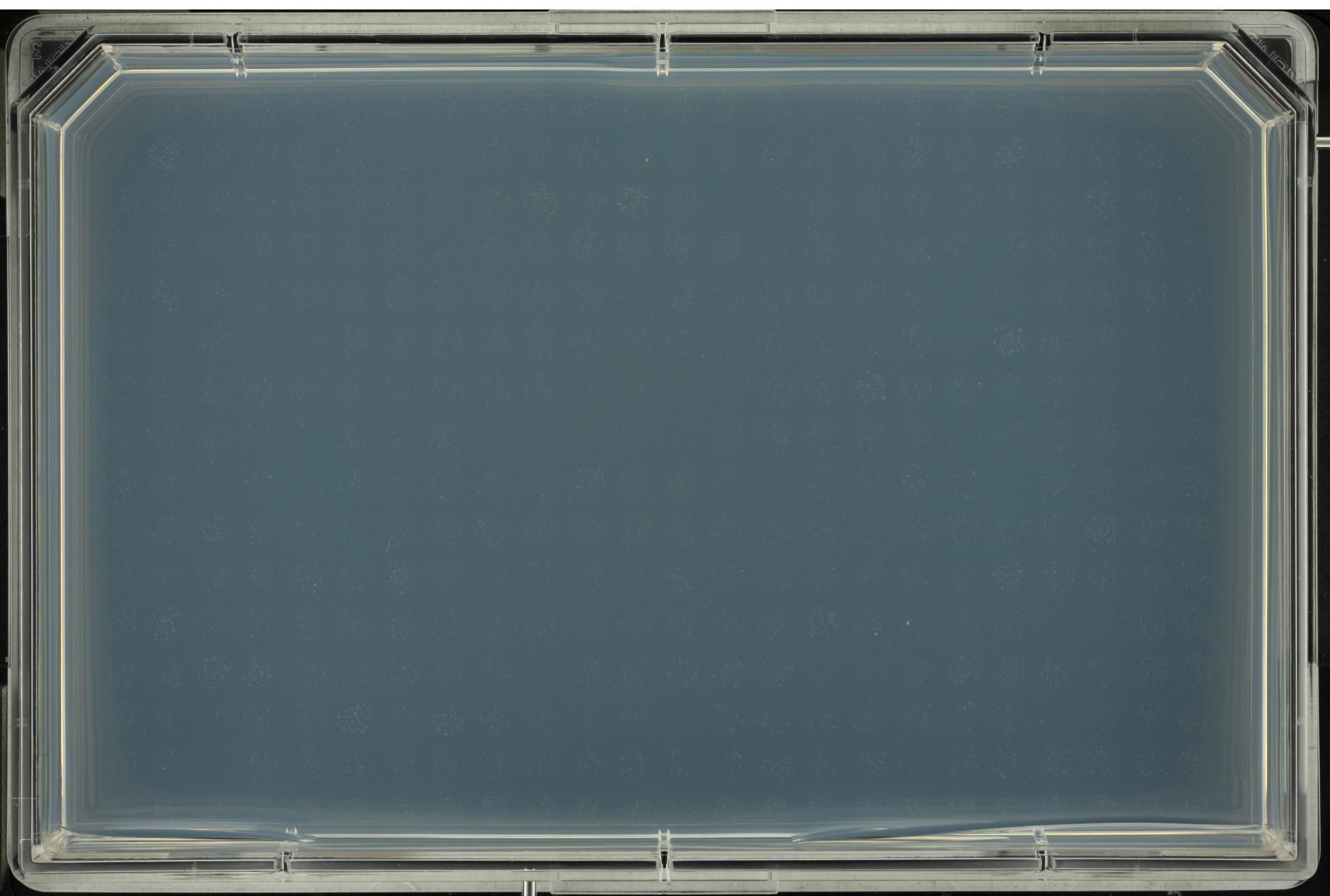


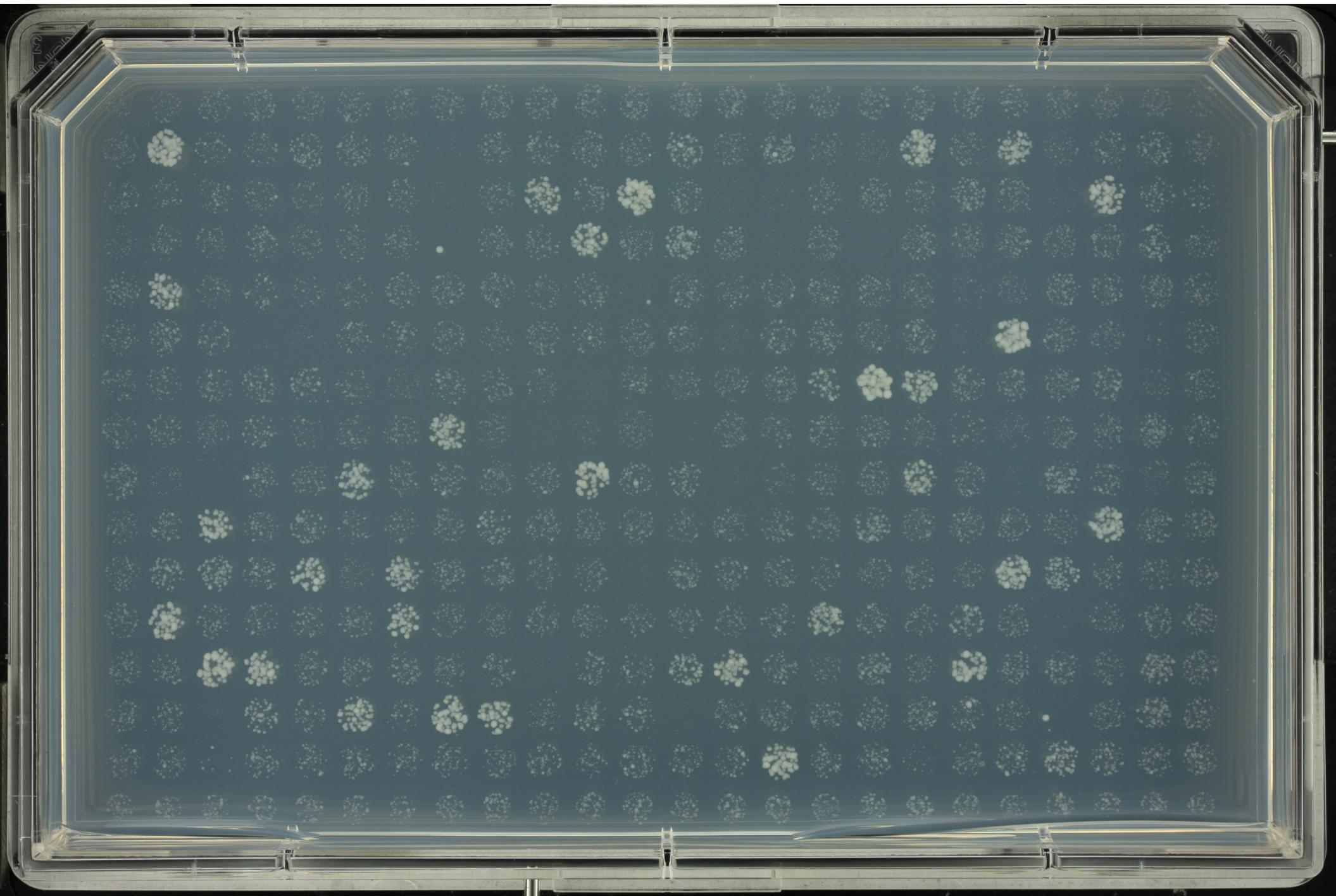
# Modelling competition for nutrients between QFA spots

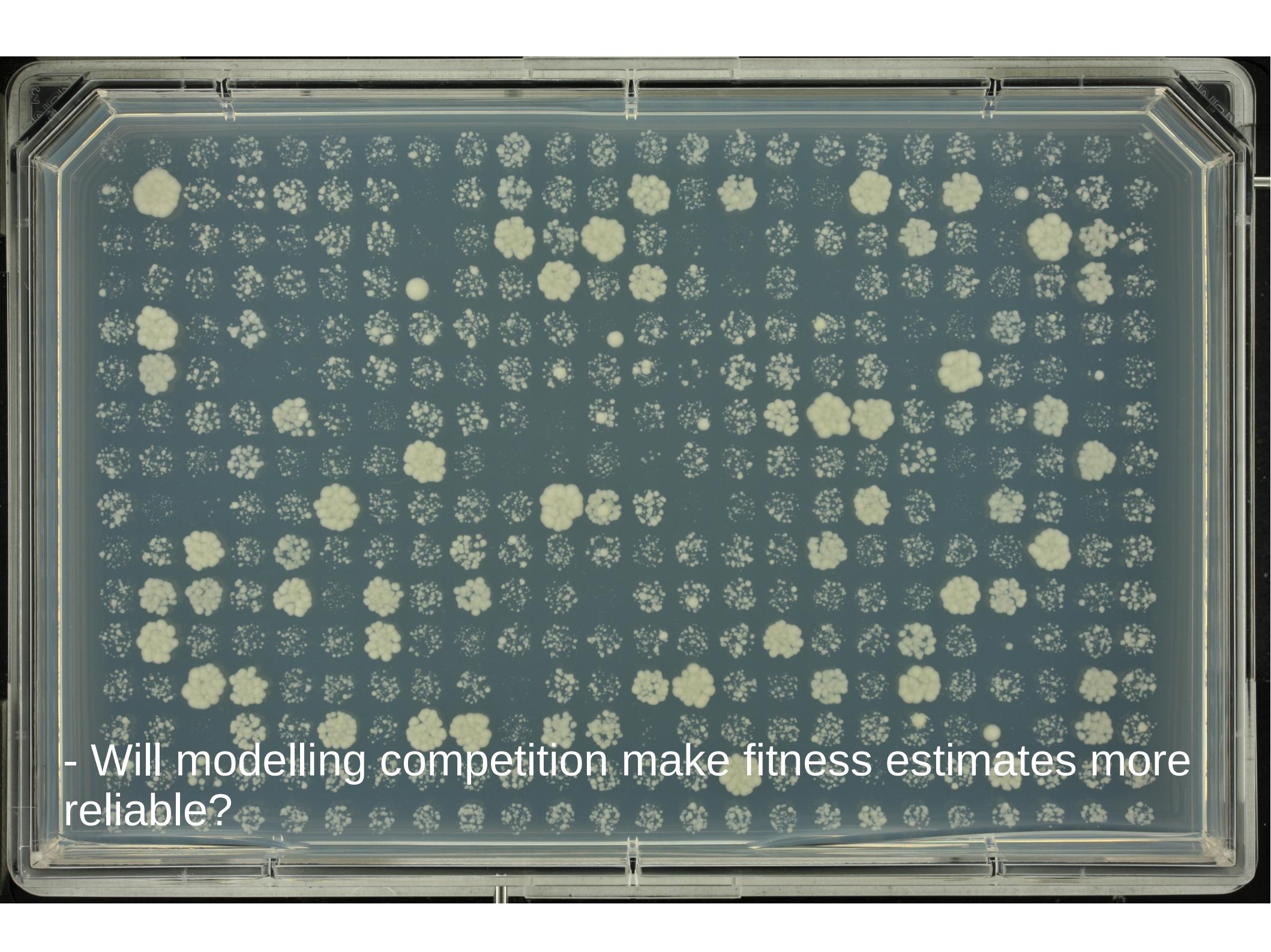
Daniel Boocock  
25/07/2016

# 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
- Infer genetic interactions



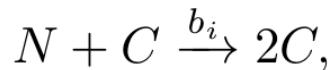




- Will modelling competition make fitness estimates more reliable?

# QFA uses fits of the logistic model

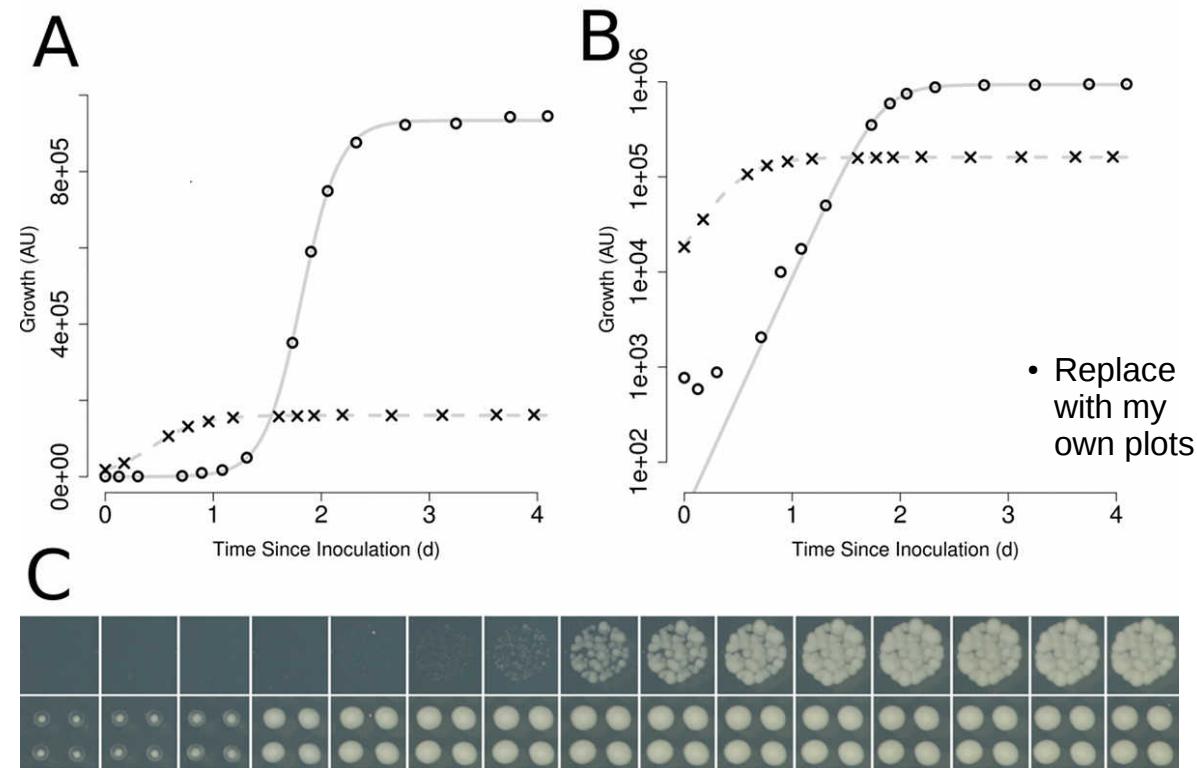
- From this fitness estimates are derived.
- MDP is the number of doublings undergone from the inoculum density to carrying capacity (K).
- MDR is the inverse of the doubling time at the beginning of the experiment.
- We can obtain the same shape curve using a mechanistic model.



$$\text{rate} = b_i[N][C]$$

- Mass action kinetic logistic equivalent model.
- Assumes all cultures would reach the same final cell density if starting with the same nutrient density.

$$\dot{x} = rx \left(1 - \frac{x}{K}\right) \quad x(t) = \frac{KPe^{rt}}{K + P(e^{rt} - 1)}$$

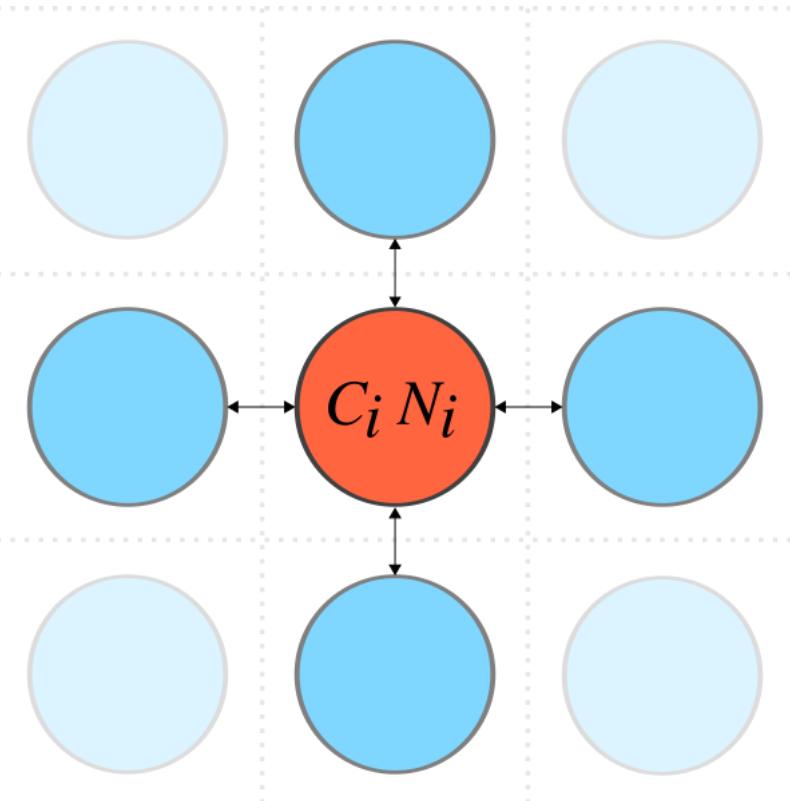


$$r = b_i(N_0 + C_0)$$

- What is a nutrient?
- Can convert between models

$$K = (N_0 + C_0)$$

# Can we improve the reliability of fitness estimates by modelling competition?



$C_i$  – Cells

$N_i$  – Nutrients

- ← Put correction plot here.

- We use a network diffusion model and mass action kinetics.

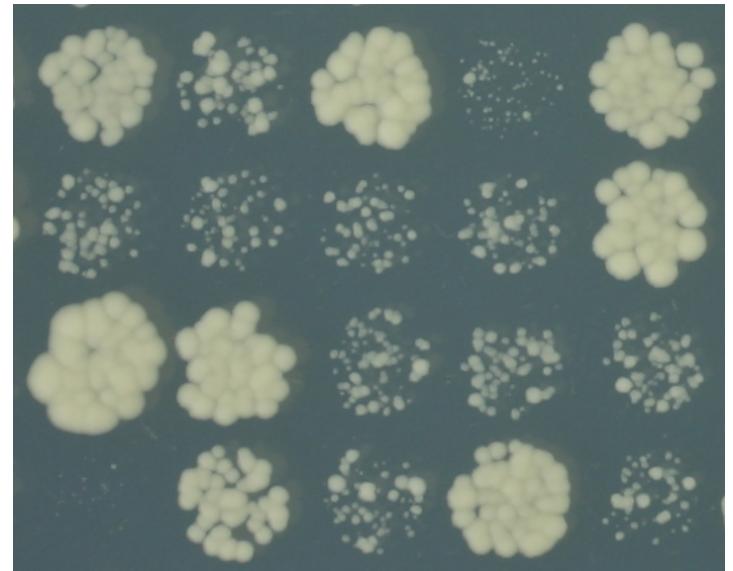
$$\frac{dC_i}{dt} = b_i N_i C_i,$$

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

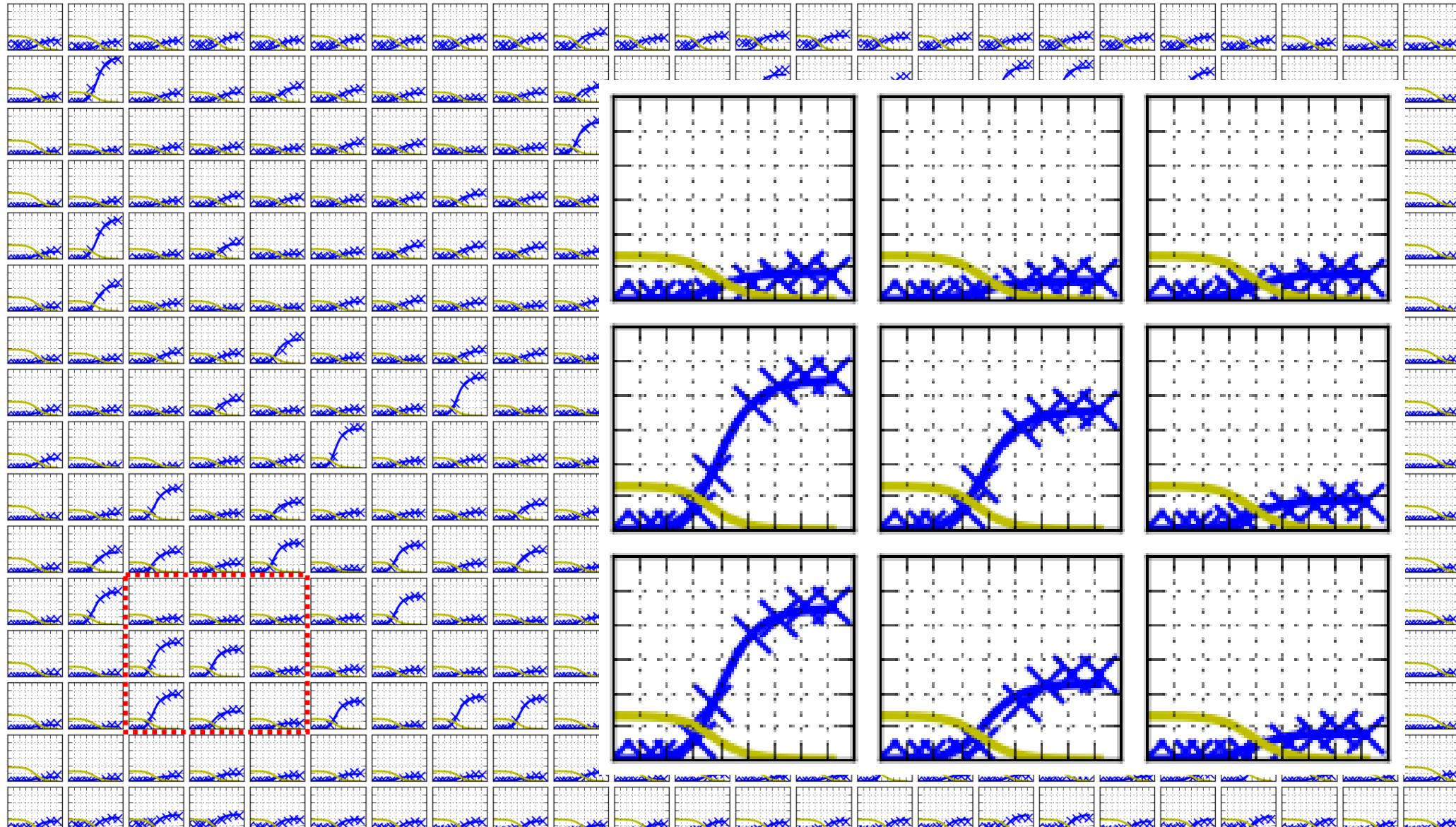
- $C_0$ ,  $N_0$ , and  $k_n$  are fit at the plate level.
- $b$  is fit on a culture level.
- If we set  $k_n = 0$  we return to the logistic equivalent model.
- In order to fit the logistic equivalent model we have to allow  $N_0$  to vary at the culture level.
- Cell arrest, metabolism, or signalling could also be modelled.

# We study the dataset p15

- *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?
  - We are interested in detecting competition.
  - Large variation in fitness of strains (suppress or enhance defect associated with *cdc13-1*).
  - Lots of replicates.
  - Hopefully our results will be interpretable by this audience.

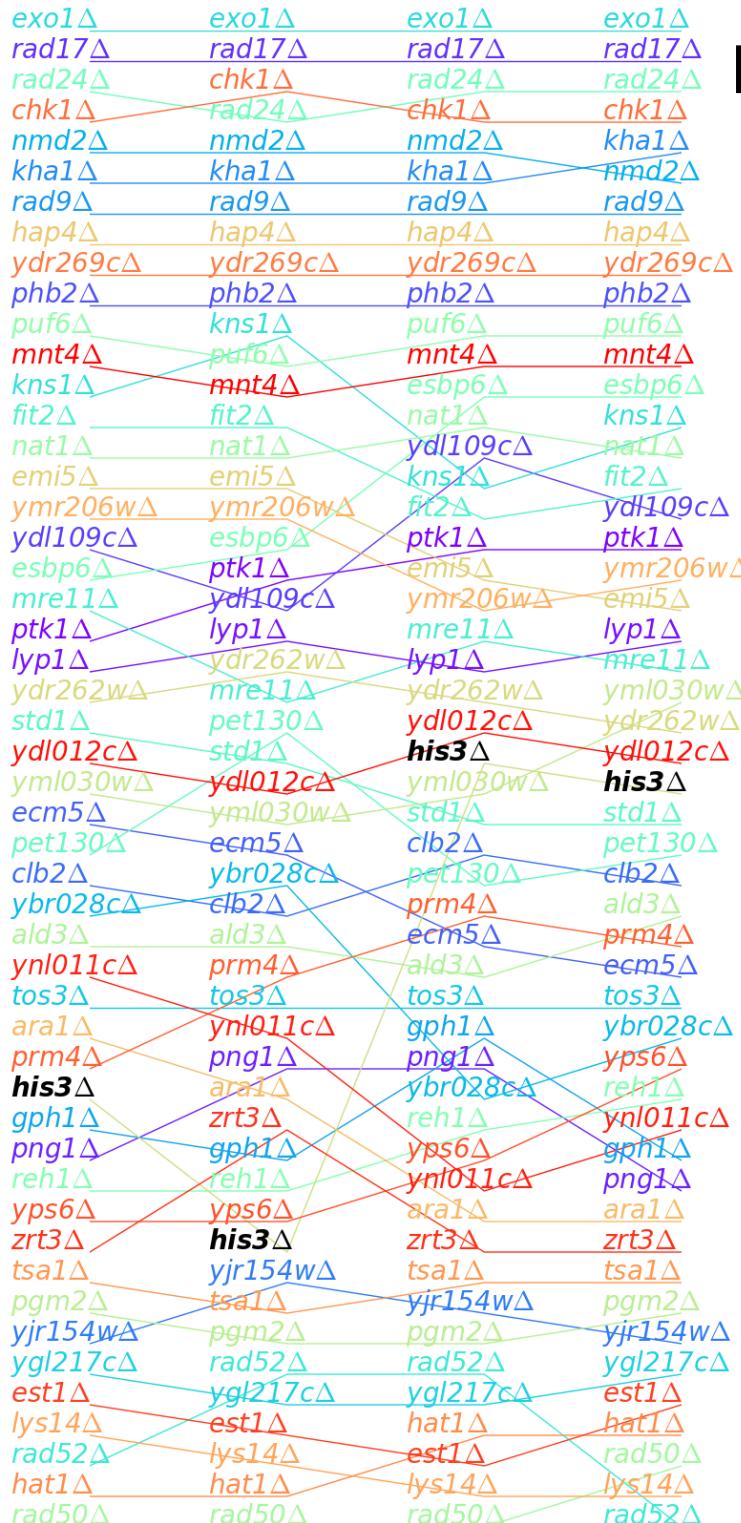


# Best Competition Model BC Fit to p15

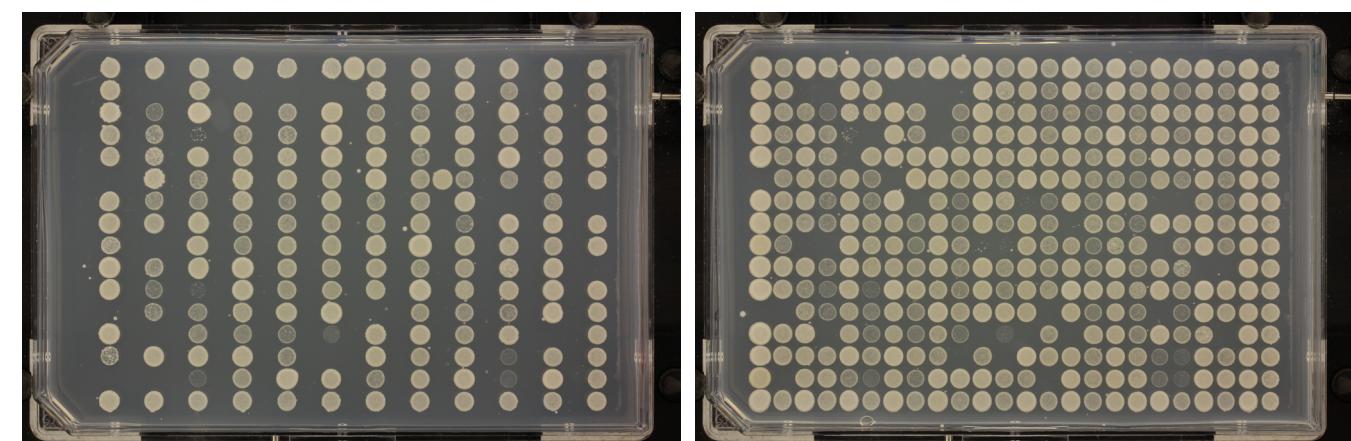


- Each fit takes  $\sim 3$  hours.
- We are assuming fairly large diffusion effects.
- We cannot yet find global minima. Confounding effect between  $b$  and  $C_0$ . Can we directly measure  $C_0$ ?
- However, ranks of  $b$  are correlated for the best fits.

# How can we asses the Competition Model?

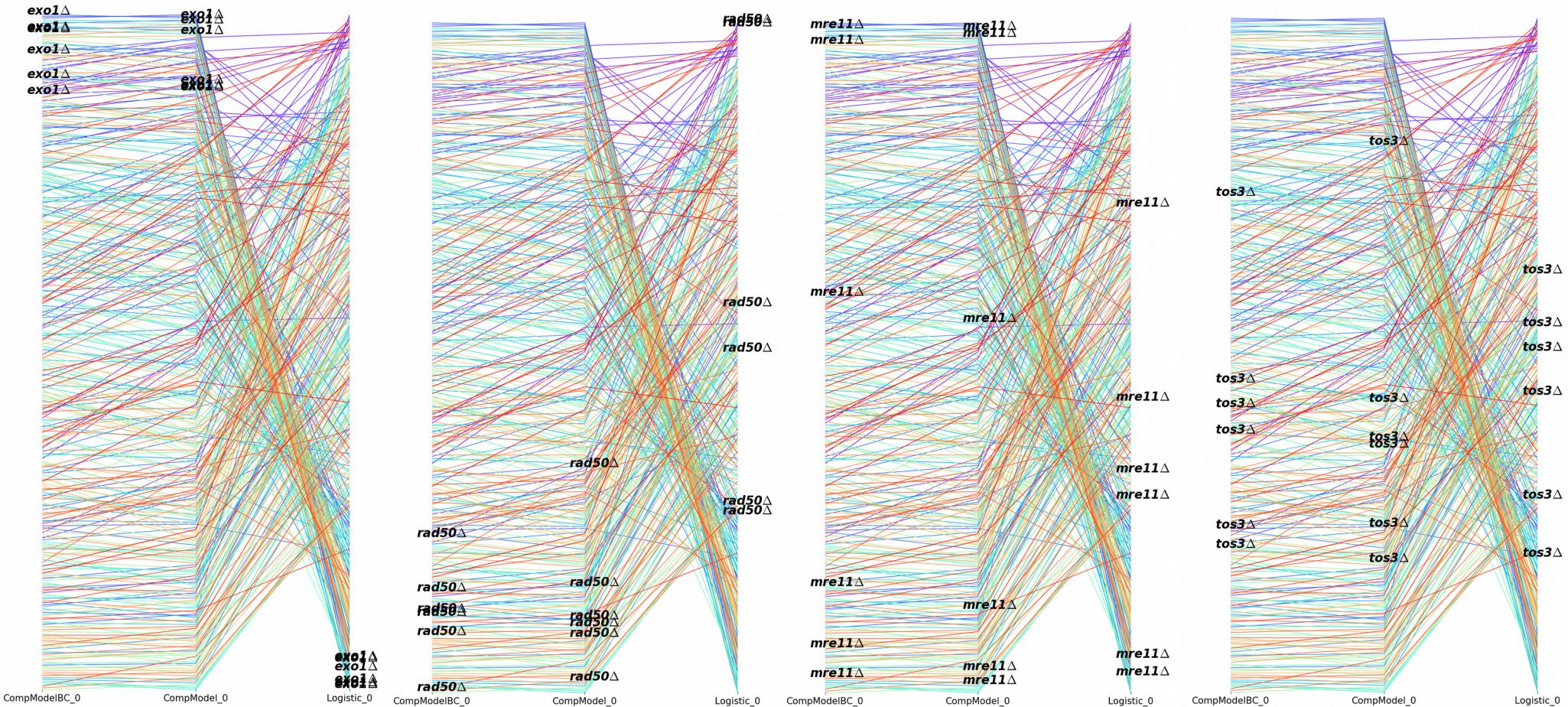


- For the competition mode, b rank is equal to MDR\*MDP rank.
  - Do the rankings on the left match your expectations?
- Compare variances
  - Are fitness estimates more reliable? (Yet to do this. Will by Monday.)
- Compare between plates using miniQFA. (Might be able to do by Monday)



# A quick preview of parameter variance.

All rankings are for b.



## Further Work

- We still need to work on finding global minima.
- We can decide whether it is worth doing so now.
- Could experiments start to measure  $C_0$ ?
- Could we validate the independent limit?
  - Currently we assume fairly fast diffusion.
  - Do all cultures really reach the same final level?
  - Incorporate Metabolism?
- Fitness estimates should be tested based on their predictions.
- Where can I find references for validation based on existing knowledge?