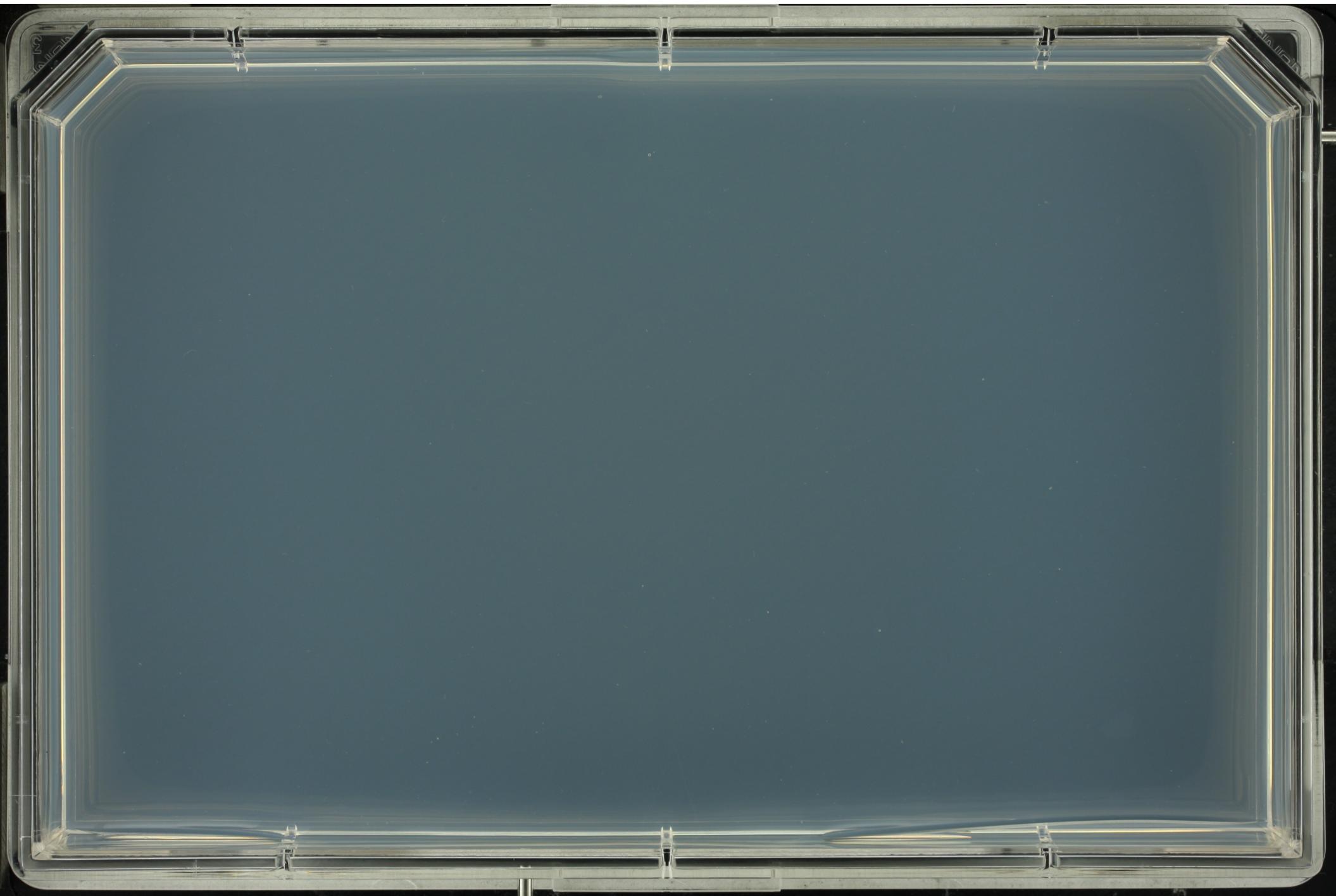
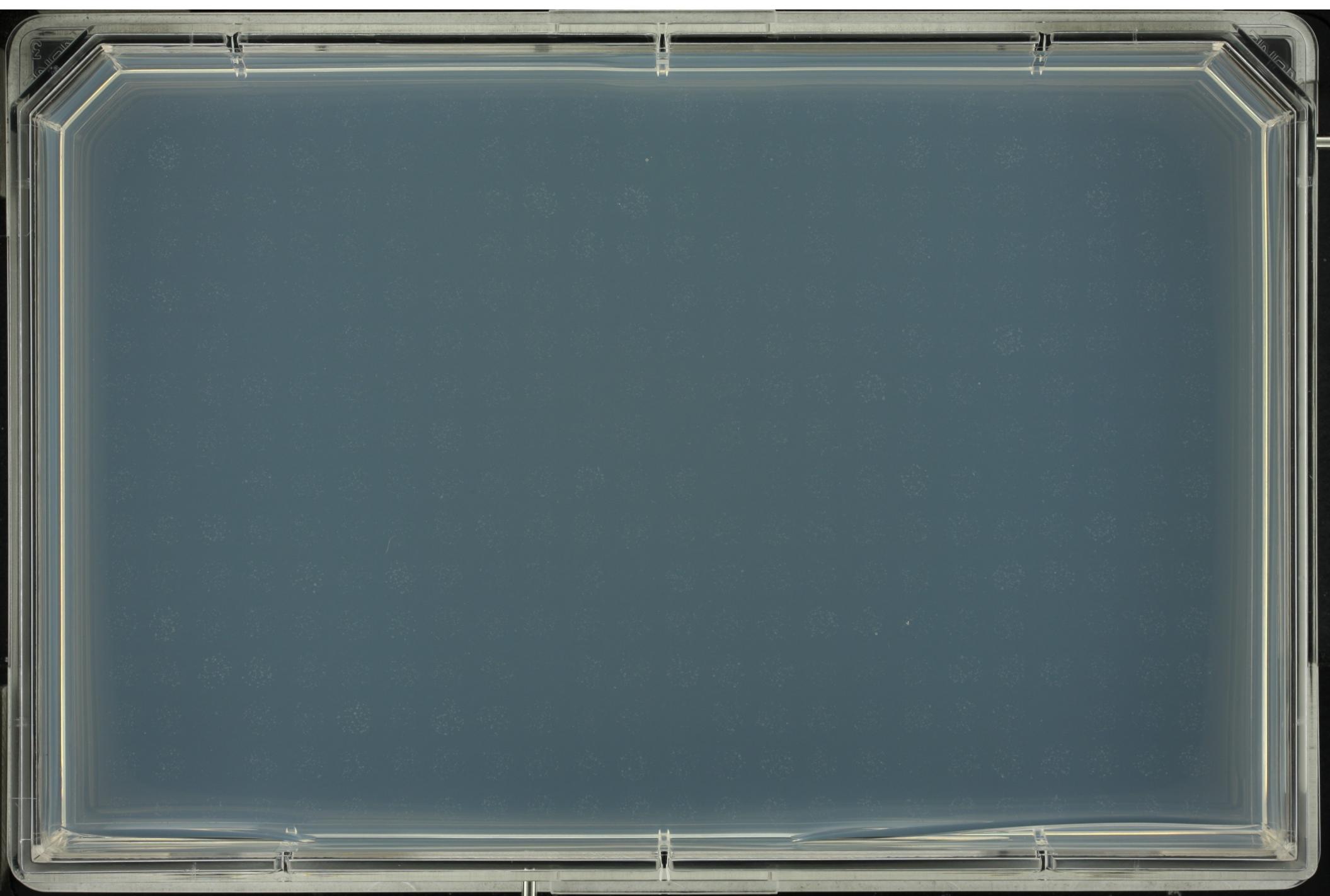
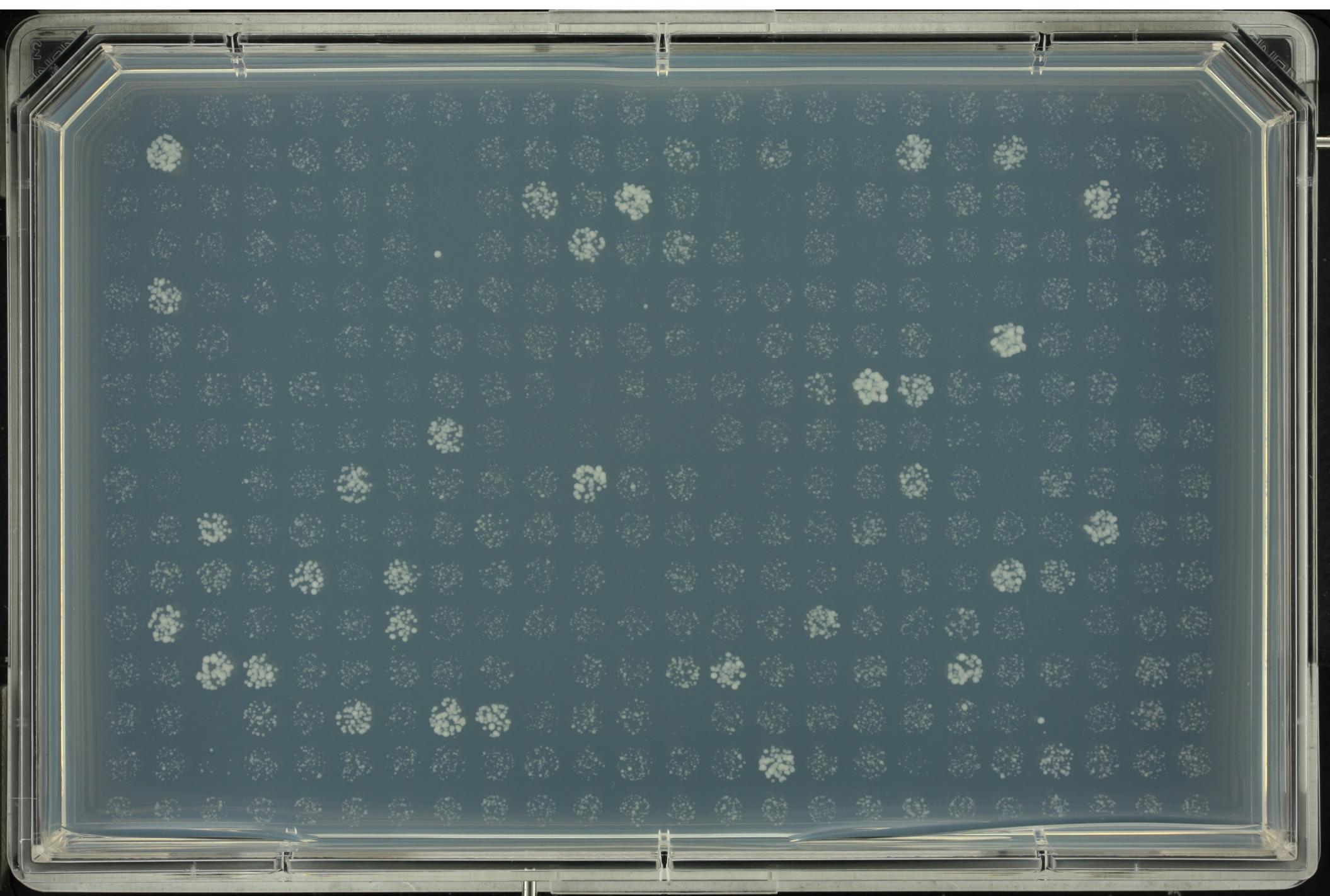


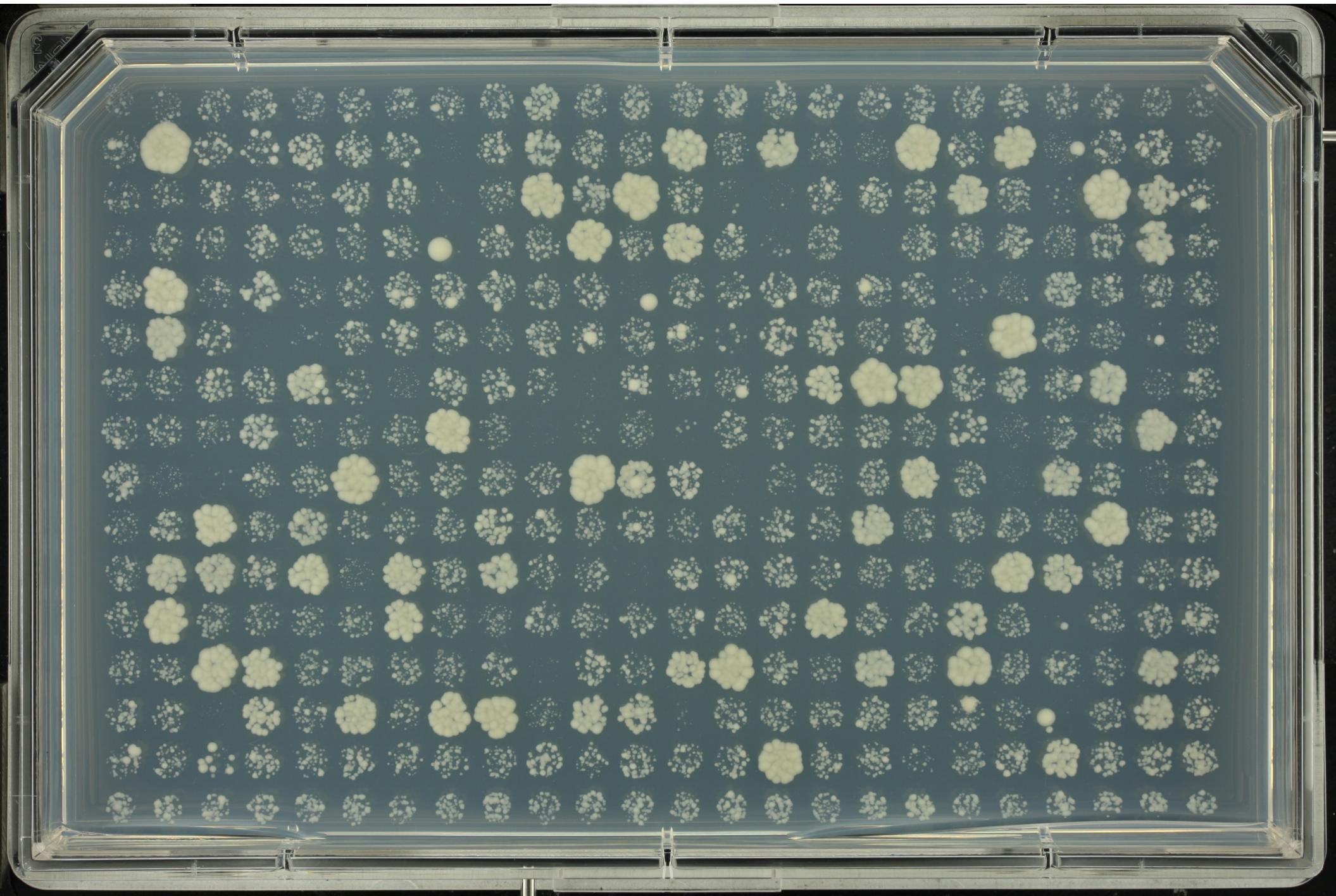
Modelling Competition and Signalling Between Microbial Cultures Growing on Solid Agar Surfaces

Daniel Boocock
15/04/2016



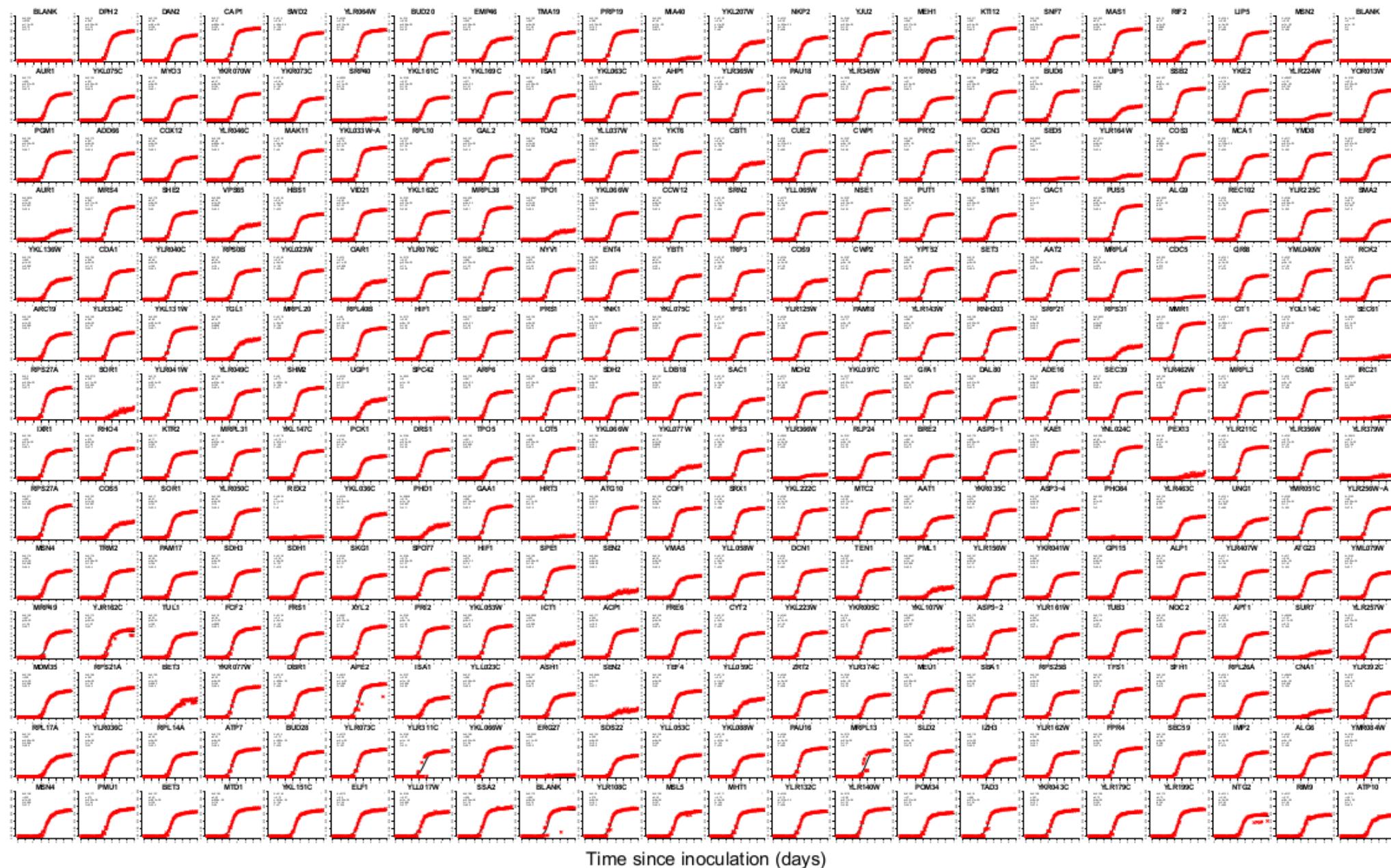






Quantitative Fitness Analysis (QFA) Growth Curves

DLR00030513 Treatment: gal20 Medium: gal Plate: 9



Time since inoculation (days)

Banks et al. (2012)

Fitness Screening is used in Functional Genomics

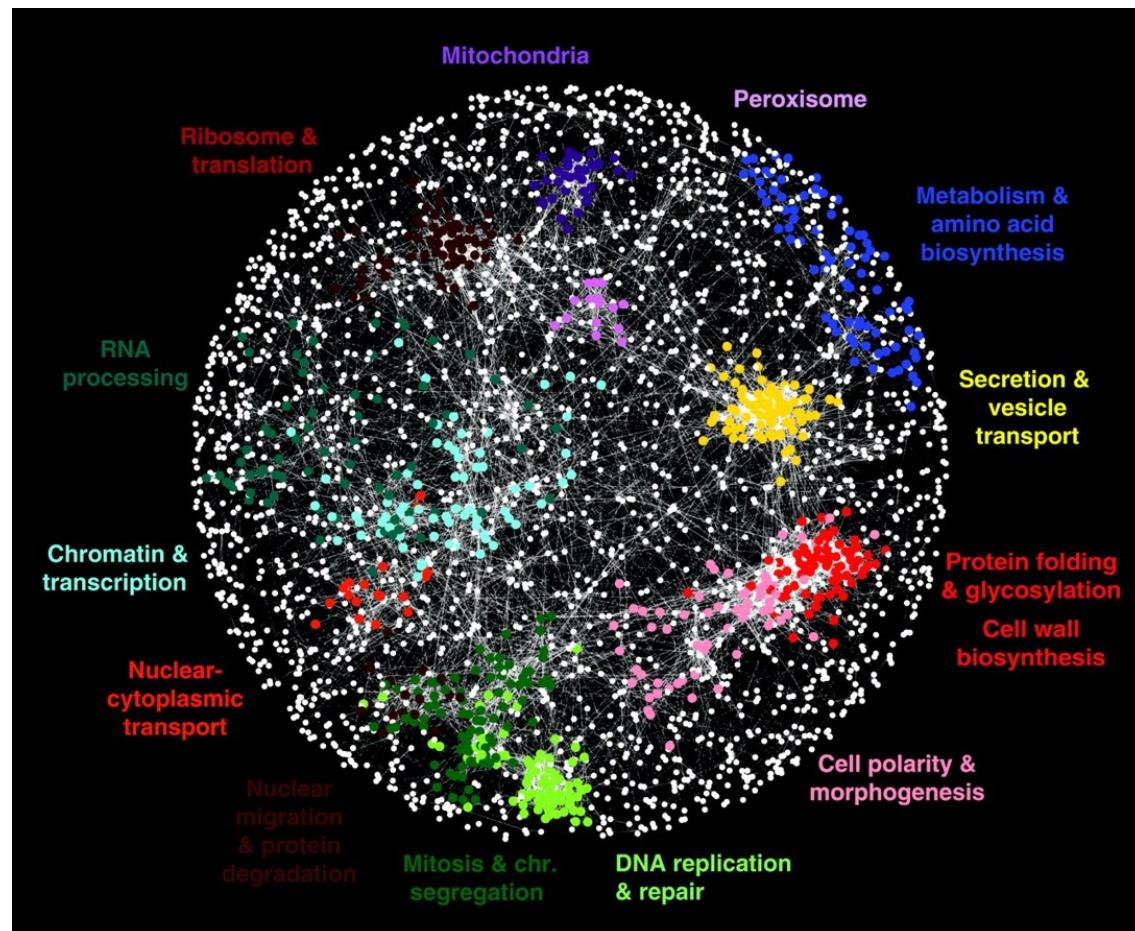
Quantitative Fitness Analysis (QFA) and Synthetic Genetic Array (SGA) are high-throughput fitness screening techniques.

Infer genetic interactions

Costanzo et al. (2010) use SGA data to construct a genetic interaction map for ~75% of the yeast genome.

Can also measure response to a drug or environmental condition.

Can be performed using microbial organisms – we study yeast.



Costanzo et al. (2010)

Does competition for nutrients and/or signalling affect growth?

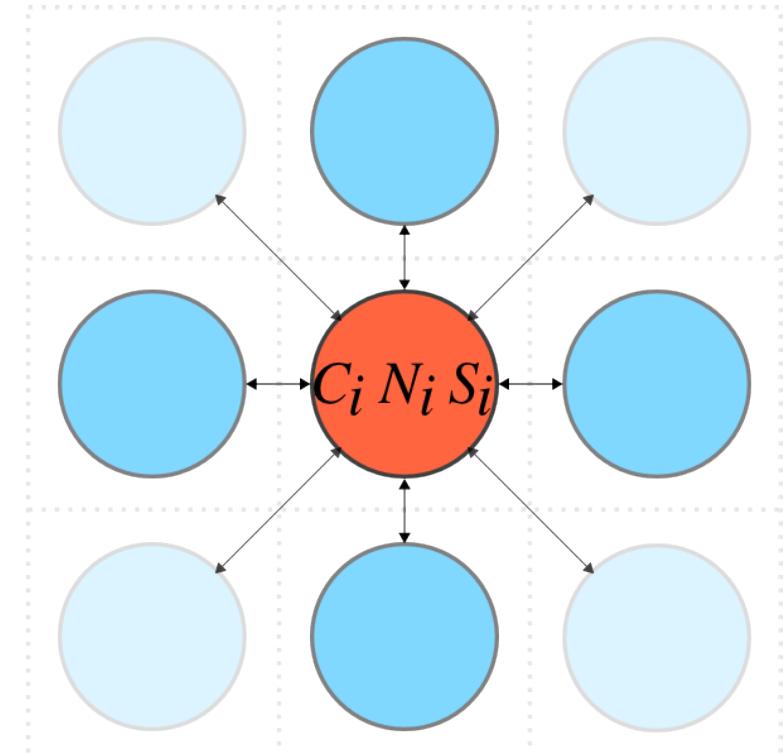


Diffusion Network

C_i – Cells

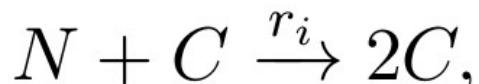
N_i – Nutrients

S_i – Signal



Signal could be ethanol or ammonia.

We will model using mass action kinetics



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

Uses a deterministic approximation

CANS Model:

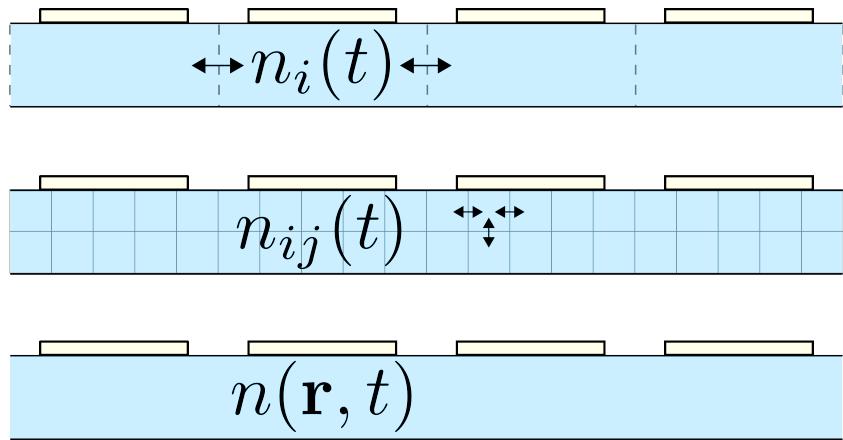
$$\frac{dC_i}{dt} = r_i N_i C_i - \beta S_i,$$

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

$$\frac{dS_i}{dt} = \alpha C_i - k_s \sum_{j \in \delta_i} (S_i - S_j),$$

Assumes mixture is well stirred

Do we need to improve the model?

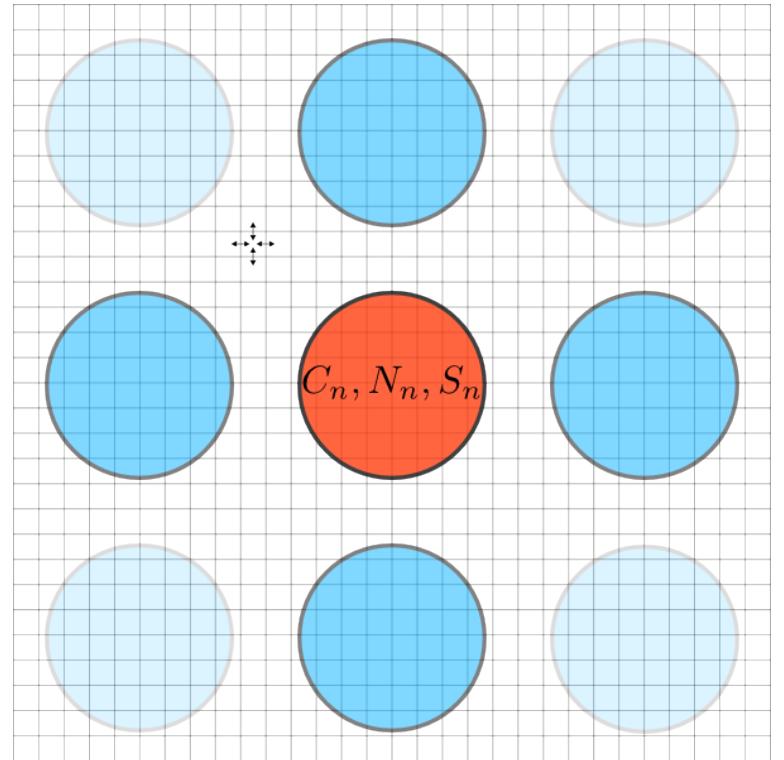


An iterative process:

Fit the model to data → analyse → improve → ...

We may look at different models for signalling or diffusion, e.g.,

$$\frac{dC_i}{dt} = r_i N_i C_i \left(1 - \frac{S_i}{S_{crit}} \right)$$



$$C_n, N_n = \sum_{i,j} N_{i,j}, S_n = \sum_{i,j} S_{i,j}$$

Have to avoid overfitting when we are unsure of the underlying mechanism.

More complicated diffusion models will be slower and more difficult to implement.

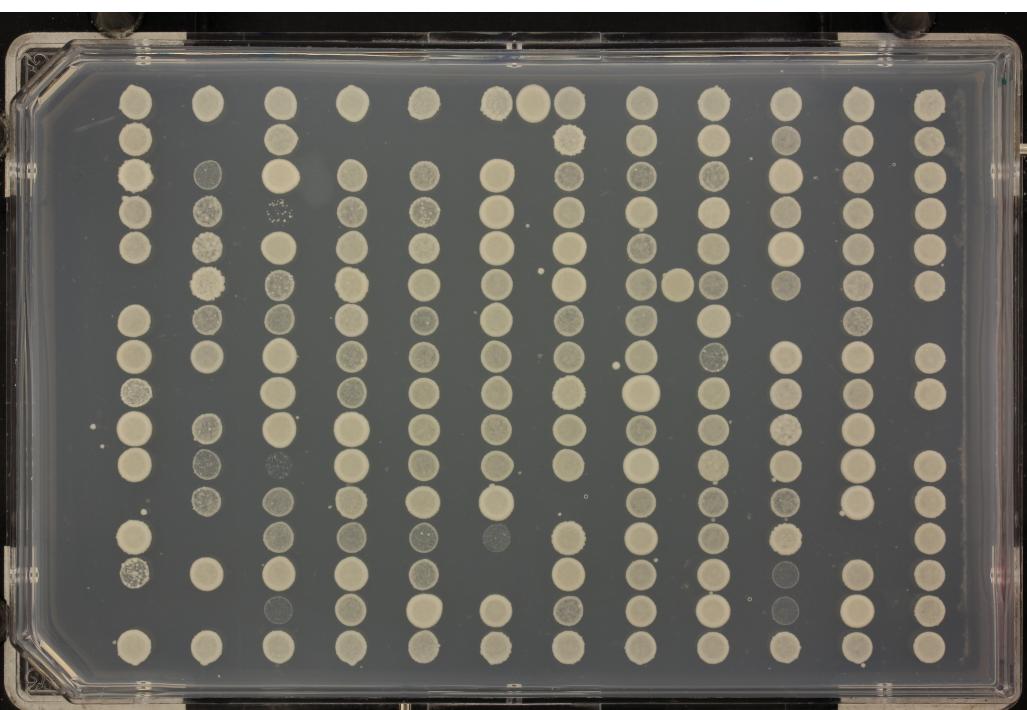
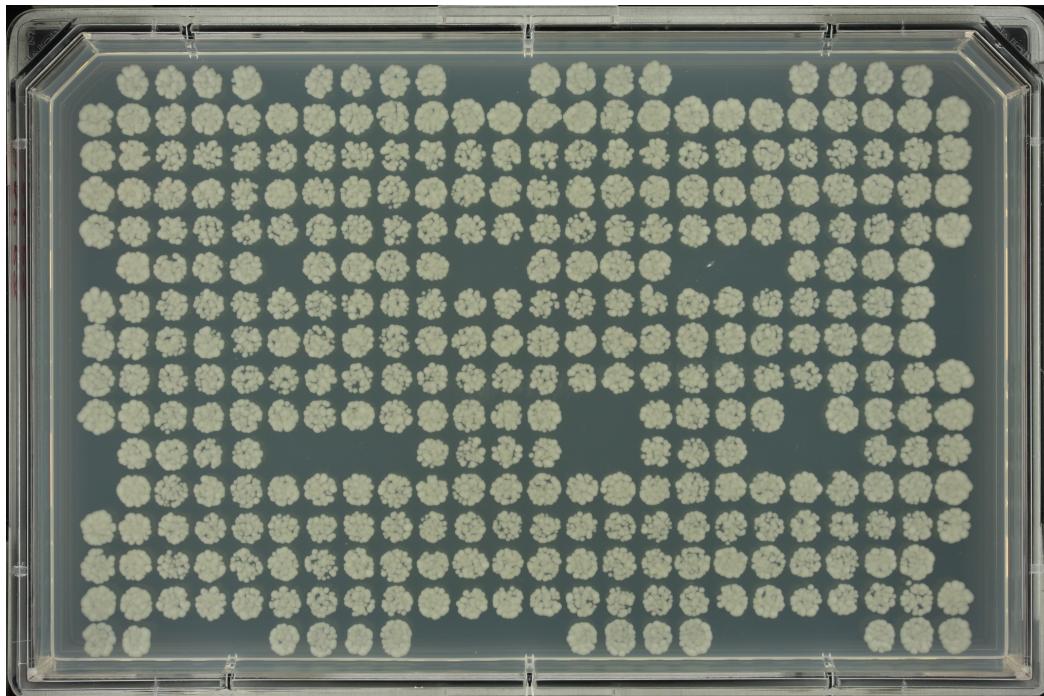
Data to test models

We have lots of data from spotted and pinned QFA – past and unpublished.

We have QFA data specifically designed for studying competition.

We also have miniQFA data to study diffusion across height and length (remaining in 2D).

Separate data for training and validation



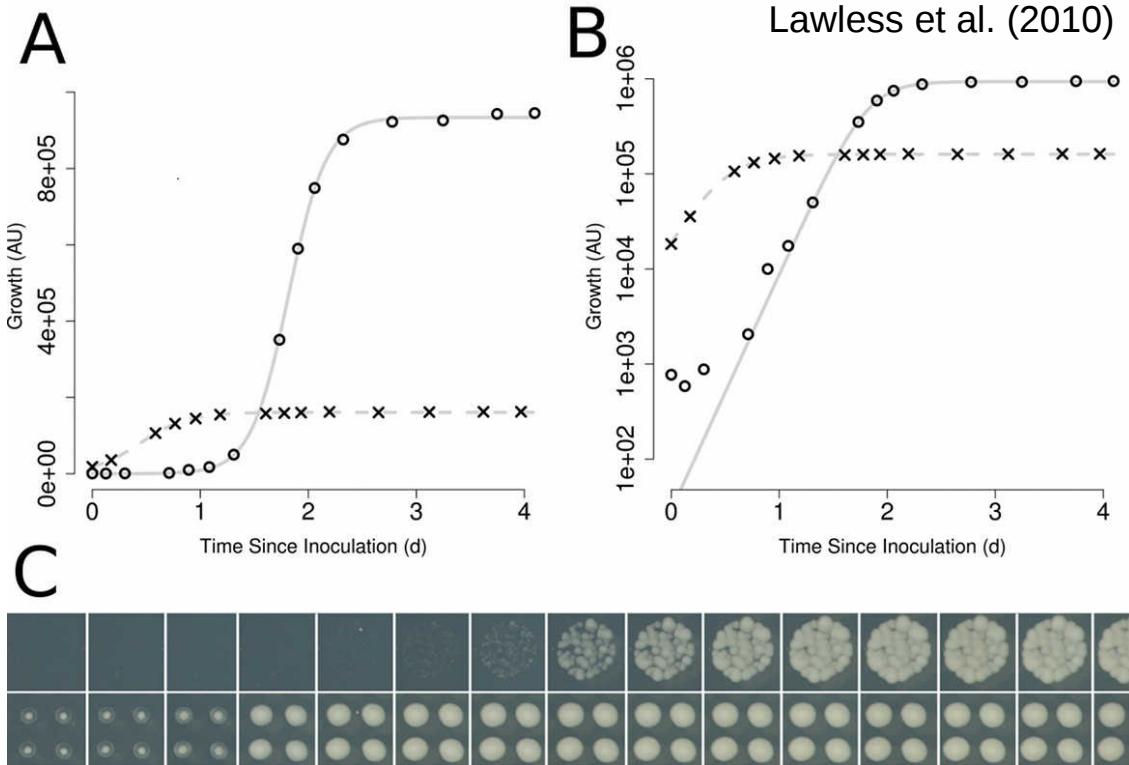
Comparing Experimental Designs

Randomisation

- Analysis with the CANS model could be slow.
- We could improve results, without having to consider competition or signalling effects using randomisation – how much?

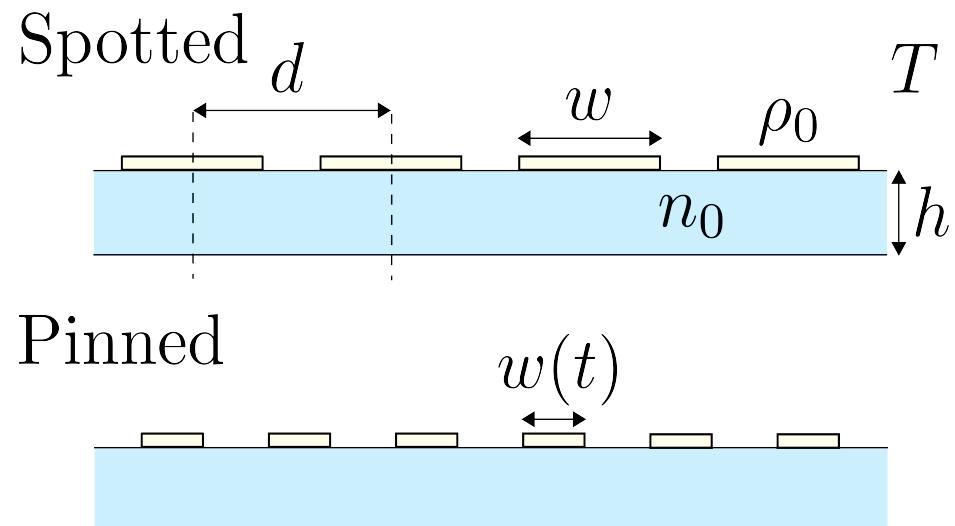
Comparing spotted and pinned QFA

- QFA (pinned or spotted) and SGA (pinned) are fitness screening techniques using solid agar
- Pinned SGA is higher throughput - 1536 vs 384 cultures per plate
- Spotted QFA has lower initial culture density so growth curves are more complete

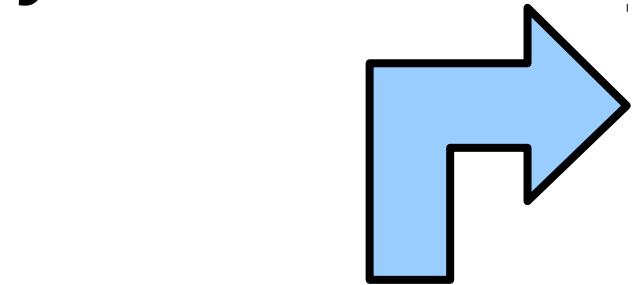


Packaging and Distribution

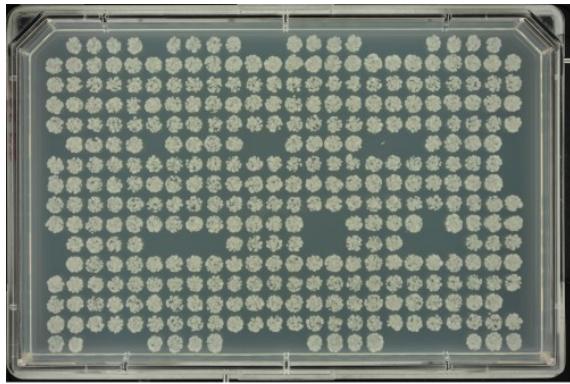
- We will write models in SBML and publish them in the BioModels database.
- Analysis tools will be written in Python, packaged, and made available through GitHub.
- We will publish an article in arXiv.org



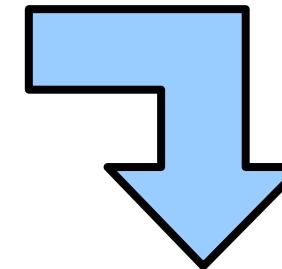
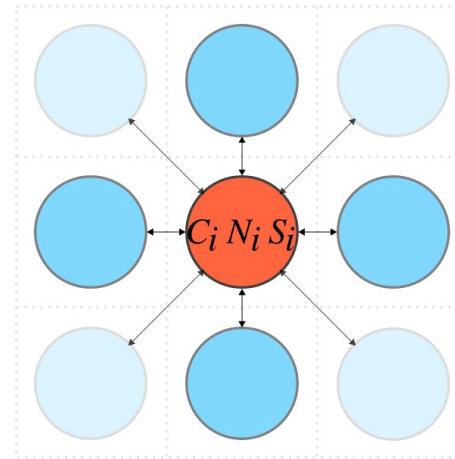
Development Cycle



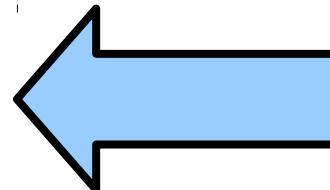
Analyse Data



Model



Package



Distribute



- Is growth affected by competition or signalling?
- How does this affect fitness measures?
- How do different experimental designs compare?



References

QFA

Addinall, S. G., Holstein, E.-M., Lawless, C., Yu, M., Chapman, K., Banks, A. P., Ngo, H.-P., Maringele, L., Taschuk, M., Young, A., Ciesiolka, A., Lister, A. L., Wipat, A., Wilkinson, D. J., and Lydall, D. (2011). Quantitative fitness analysis shows that nmd proteins and many other protein complexes suppress or enhance distinct telomere cap defects. *PLoS Genet*, 7(4), 1–16.

Banks, A., Lawless, C., and Lydall, D. (2012). A quantitative fitness analysis workflow. <http://www.jove.com/video/4018/a-quantitative-fitness-analysis-workflow>.

Heydari, J., Lawless, C., Lydall, D. A., and Wilkinson, D. J. (2016). Bayesian hierarchical modelling for inferring genetic interactions in yeast. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 65(3), 367–393.

SGA

Costanzo, M., Baryshnikova, A., Bellay, J., Kim, Y., Spear, E. D., Sevier, C. S., Ding, H., Koh, J. L., Toufighi, K., Mostafavi, S., et al. (2010). The genetic landscape of a cell. *science*, 327(5964), 425–431.

Colonyzer

Lawless, C., Wilkinson, D. J., Young, A., Addinall, S. G., and Lydall, D. A. (2010). Colonyzer: automated quantification of micro-organism growth characteristics on solid agar. *BMC Bioinformatics*, 11(1), 1–12.

<http://research.ncl.ac.uk/colonyzer/>