

Supplementary note 1: Bliss multiplicativity and Bliss additivity. Growth rate is used as measure of bacterial fitness, hence Bliss model is used in its additive form: $E_{1+2} = E_1 + E_2$, where $E_i = (g_0 - g_i)/g_0$. It is easy to see that this additive form is mathematically identical to the multiplicative form $Y_{1+2} = Y_1 \cdot Y_2$, when normalized yield Y rather than normalized growth is used for fitness. Given the time t_{final} when yield is evaluated, the relative yields can be written as $Y_i = 2^{g_0(1-E_i)t_{final}} / 2^{g_0 t_{final}}$ and $Y_{1+2} = 2^{g_0(1-E_{1+2})t_{final}} / 2^{g_0 t_{final}}$. Substituting these relative yields into the Bliss multiplicative form $Y_{1+2} = Y_1 \cdot Y_2$, yields the Bliss additive form: $E_{1+2} = E_1 + E_2$.

Supplementary note 2: Taylor expansion around an optimal point yields circular isoboles.

We consider a general function describing fitness in the multi-drug concentration space, $f(d_1, d_2, \dots, d_N)$. Assuming fitness is optimal (maximal) at the no-drug point, the first derivatives around the origin should be zero, $\partial f / \partial x_i = 0$. Further assuming that the drugs act independently, the effect of any one drug should not depend on any other, $\partial^2 f / \partial x_i \partial x_j = 0$. Thereby, the second

order Taylor expansion around the origin is simply: $f(d_1, d_2, \dots, d_N) \simeq 1 + \frac{1}{2} \sum_{i=1}^N \frac{d_i^2}{\delta_i^2}$, where

$\delta_i^2 = 1 / \left[\frac{\partial^2 f}{\partial d_i^2} \right]_{d_1, d_2, \dots, d_N=0}$ are the inverse second derivatives with respect to each of the drugs. In

the limit of small drug effects, fixed-fitness surfaces are therefore high dimensional spheres

obeying $\sum_{i=1}^N (d_i / \delta_i)^2 = const$ (rather than linear surfaces as expected by Loewe). We note that this

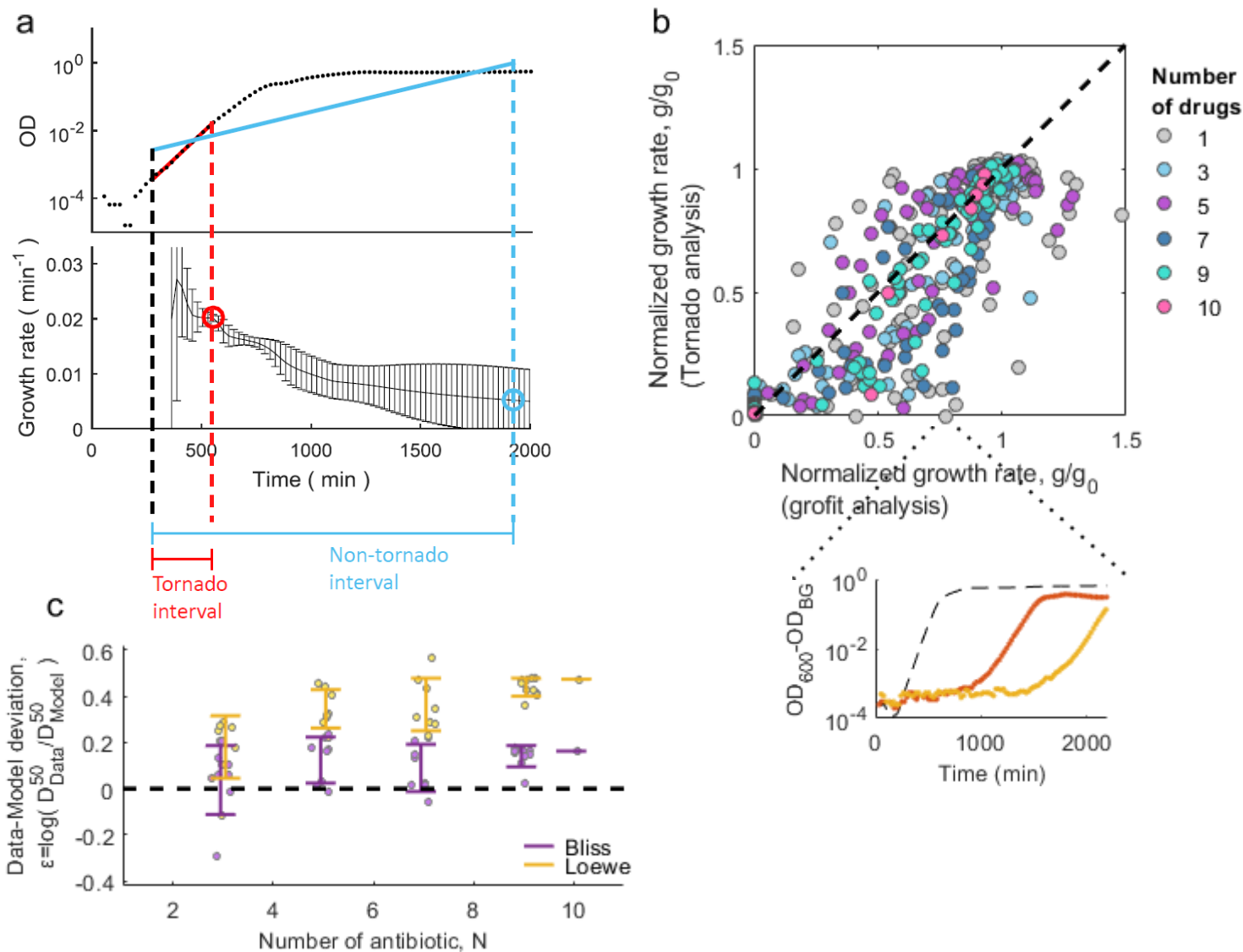
derivation assumes that f at the origin has a finite second derivative and a zero first derivative.

More complex fixed-fitness surfaces can appear for functions such as Hill where $\partial^2 f / \partial x_i^2 \neq 0$

at the origin. Furthermore, when $\partial f / \partial x_i < 0$ (as for Hill with $h = 1$), the Bliss prediction

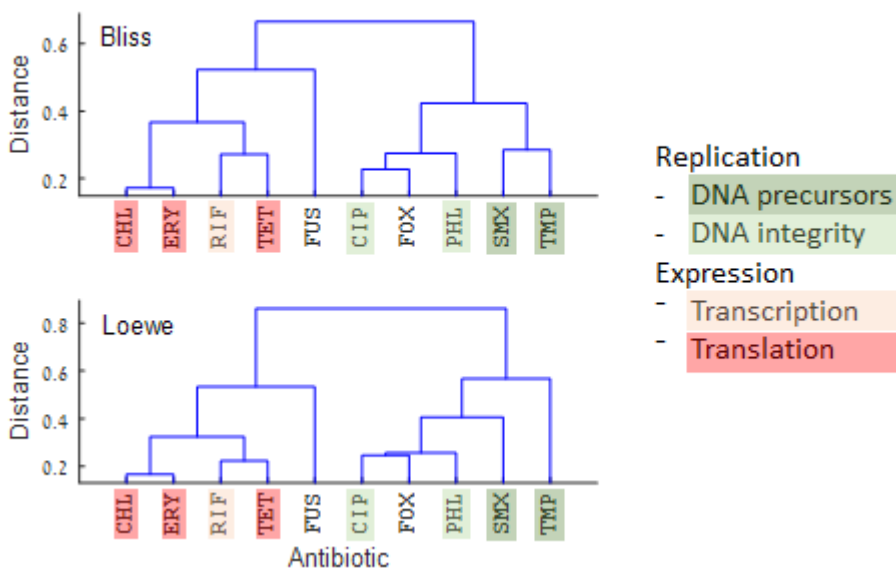
converges to Loewe and thereby drug dosages add linearly not orthogonally (the Bliss-Loewe

convergence mostly appeared in *E. faecalis* where many of the chosen drugs had low h ; see for example CHL-LZD-RIF-TMP and CIP-LZD-RIF-TMP, Supplementary Fig. 3b, and even more so when RIF in these combination was replaced with the synergistic RIF-TET mixture ¹, Supplementary Fig. 11).

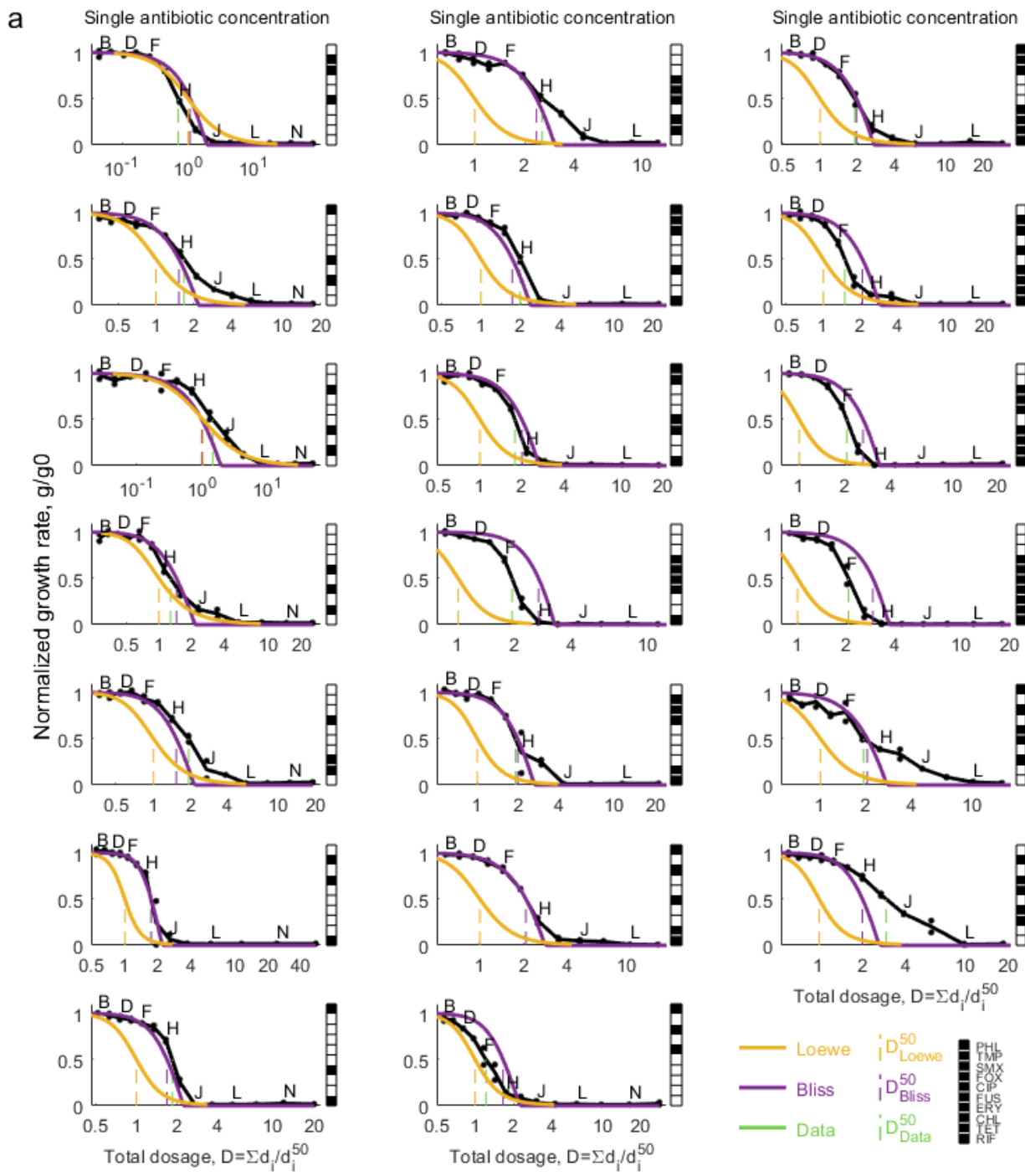


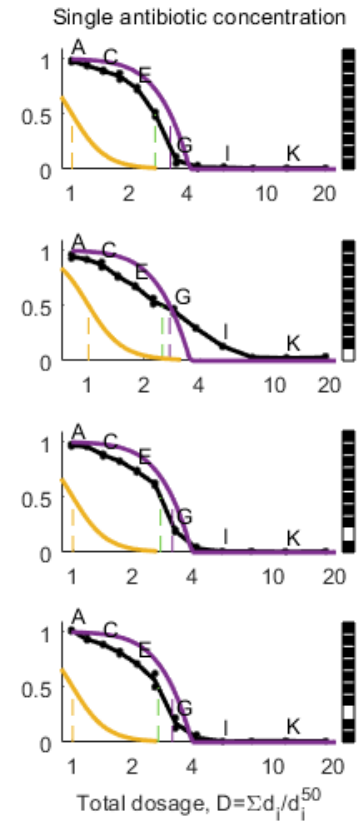
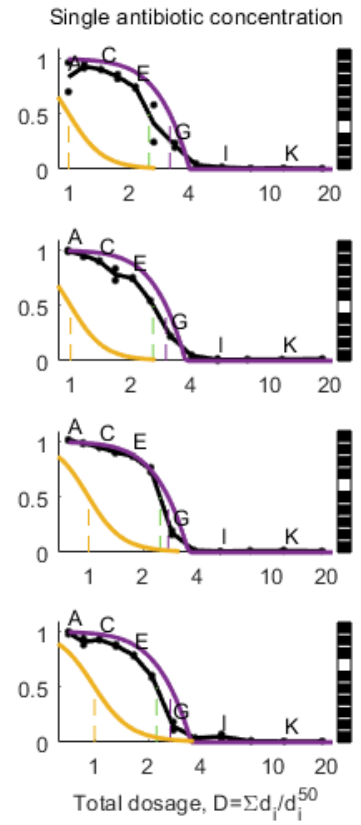
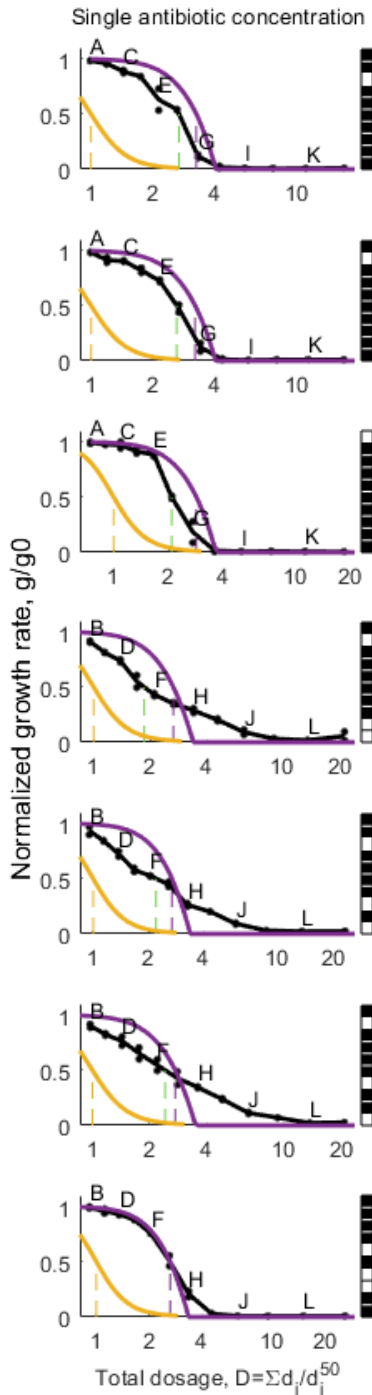
Supplementary Figure 1. The time interval used to fit OD data to exponential growth model was determined using a Tornado analysis. Calculation of growth rate by fit of OD measurement over time to the exponential equation, $OD = OD_0 \cdot 2^{g \cdot t} + OD_{BG}$, is very sensitive to bias of the growth curve slope at later time points. Late in the growth both negative bias (as a result of transition to stationary phase) and positive bias (since we often work close to the minimal inhibitory concentration, the system is prone to the effect of either drug degradation or a resistant mutant) will change the calculated growth rate and increase its error estimation. **a**, To

determine the optimal time interval for the fit we used an algorithm based on the sensitivity analysis method "Tornado analysis". We calculated the growth rate and error estimation (95% confidence interval) for each time interval (80 time intervals in the above example). Optimal time interval is one that have the smallest error while its growth estimation falls within the error estimation of all of the previous intervals. **b**, Scatter plot of bacterial fitness of 1136 *E. coli* populations calculated using "tornado analysis" compared to the fitness under the same conditions calculated by the R-package "grofit". While the two methods yields similar fitness (pearson's $r=0.92$) our method decreases miss-identification of outliers as mutants. In the example - two duplicate measurements (red and yellow) compared to growth without antibiotics. While the grofit identified the fast growth of a probable mutant that start after ~ 1000 min our method identified the slow to non grow at the beginning. **c**, The few disagreements between our method and the grofit package do not change our finding that the Bliss prediction is superior to that of Loewe. Further analysing the grofit-analysed fitness measurements we plot the data-model deviation as function of number of drug and found that it resembles our finding that Bliss remains accurate regardless of number of drugs while Loewe loses its predictive power when the number of drug is increased (35 different drug combinations, for every combination size error bar represent one standard deviation, dashed line show fully accurate prediction).

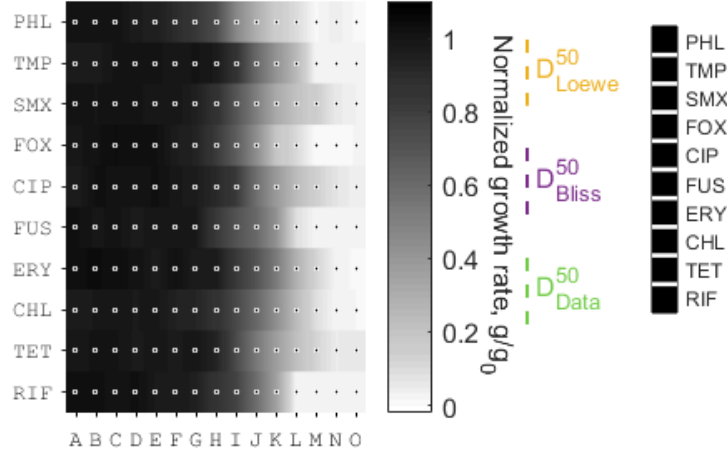


Supplementary Figure 2. Drugs are clustered by their function in respect to either Bliss or Loewe. Similarity between interactions patterns of the drugs based on Pearson correlation was used to create hierarchical clustering of the drugs. In respect to both models the dendrogram has two main branches, one branch encompasses the whole replication effectors (drugs that harm DNA integrity or target enzymes involved in its maintenance and enzymes involved in biosynthesis of DNA precursors), while the other branch encompasses all expression modules (drugs that target transcription and translation machineries). Clustering done based on interactions in respect to Bliss has slight advantage in clustering together fine tuned functionalities.

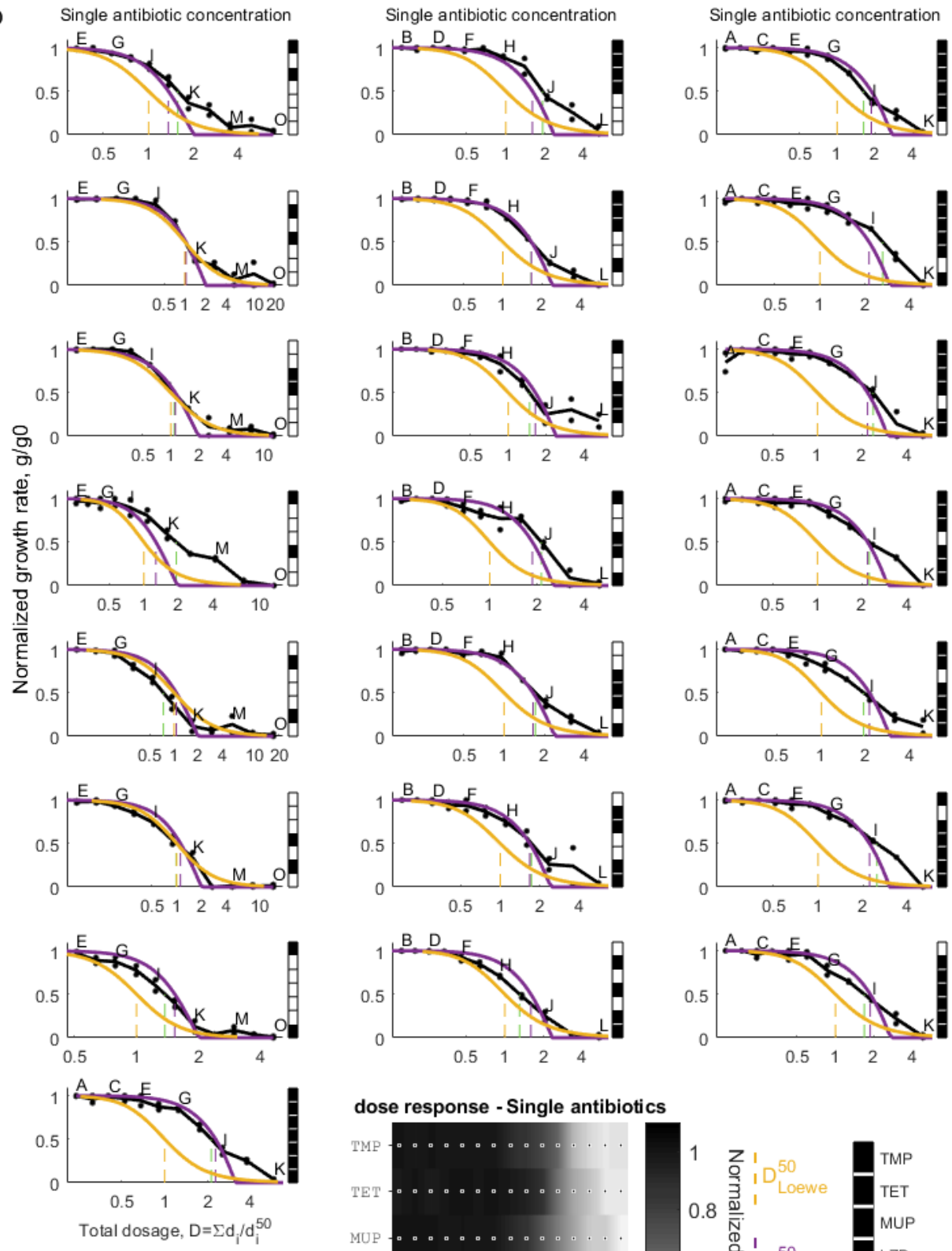




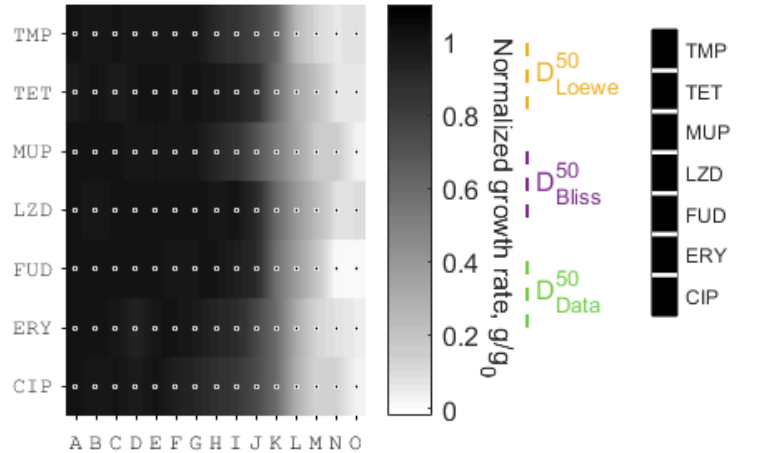
dose response - Single antibiotics



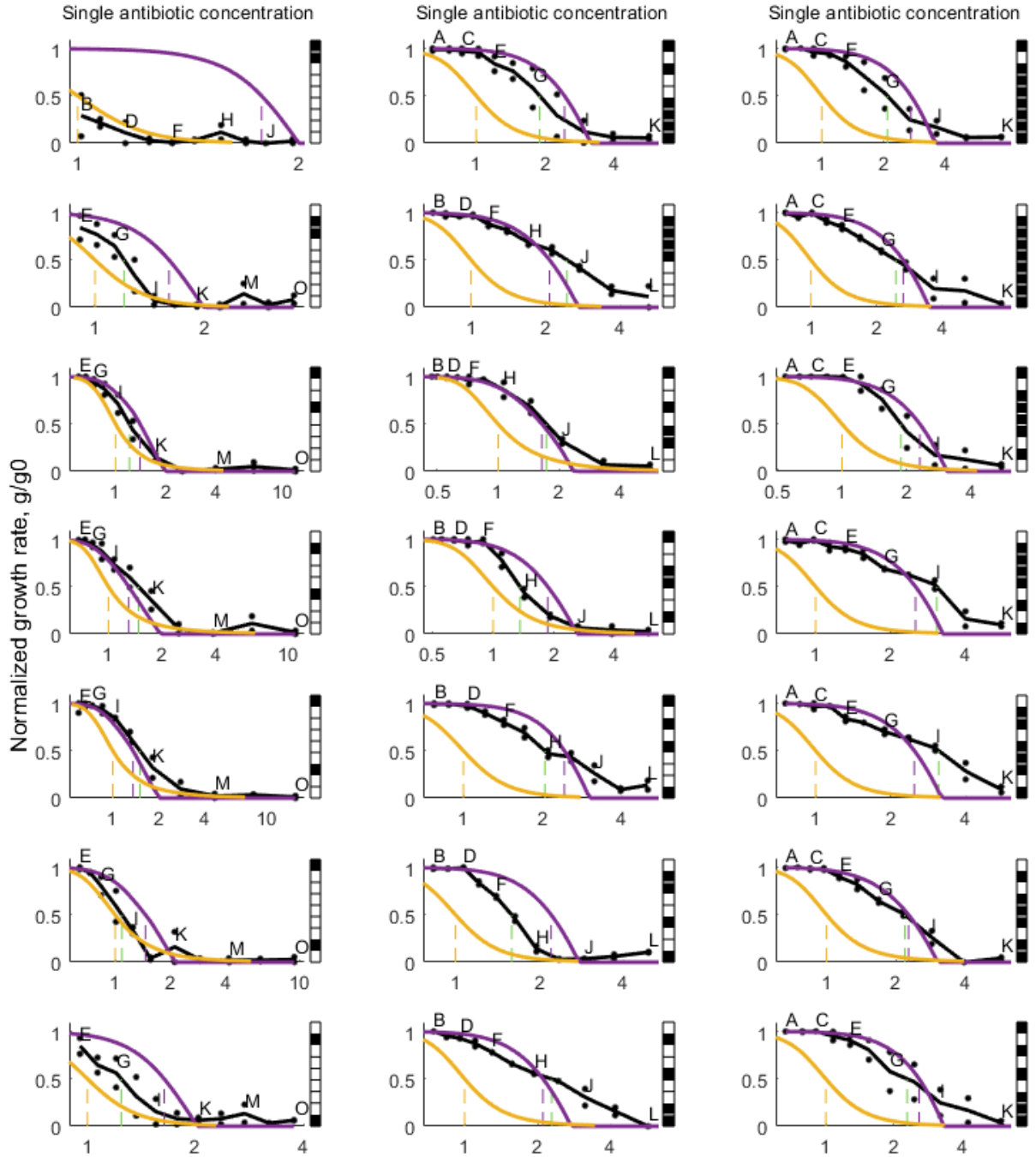
b



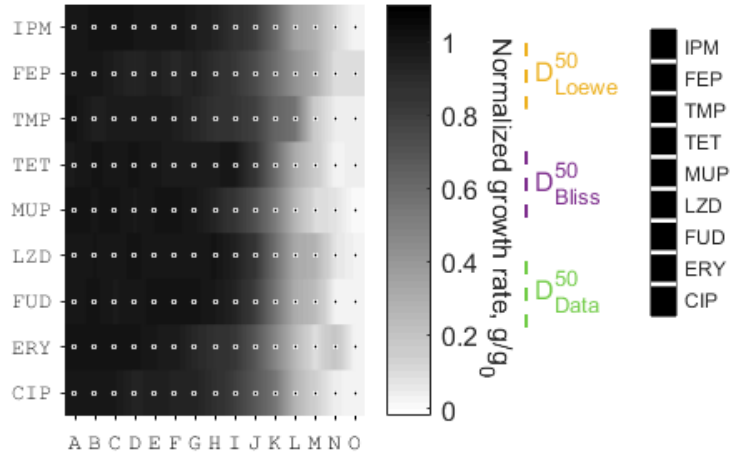
dose response - Single antibiotics



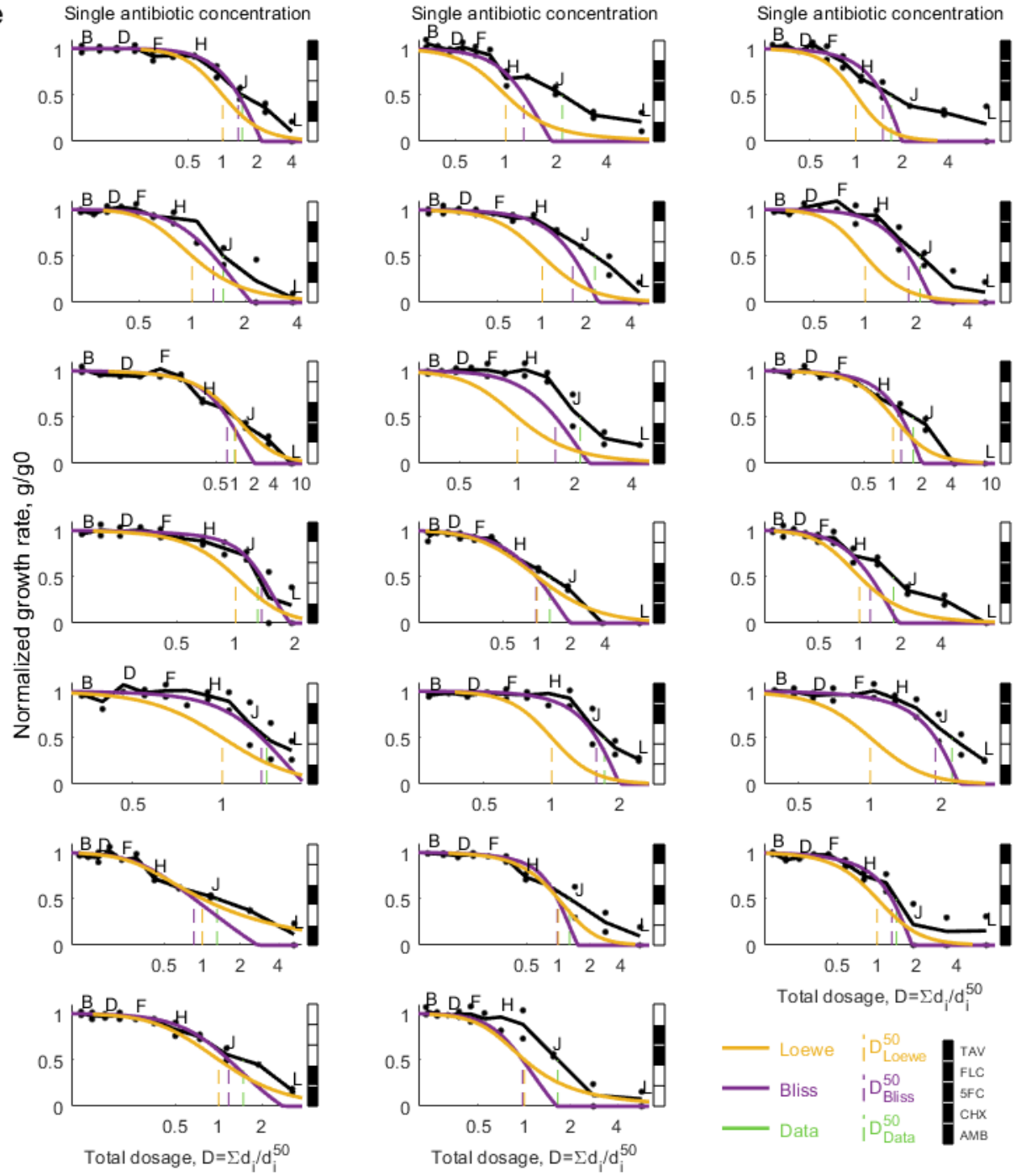
C

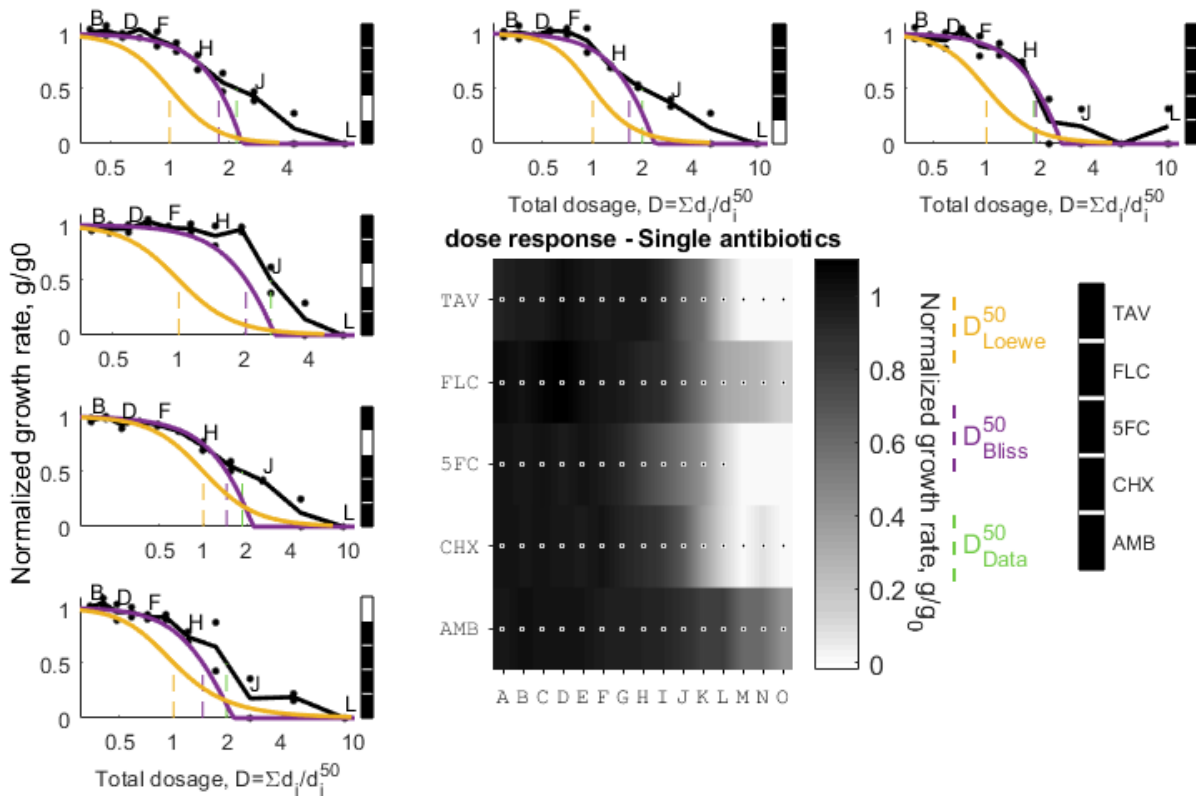


dose response - Single antibiotics

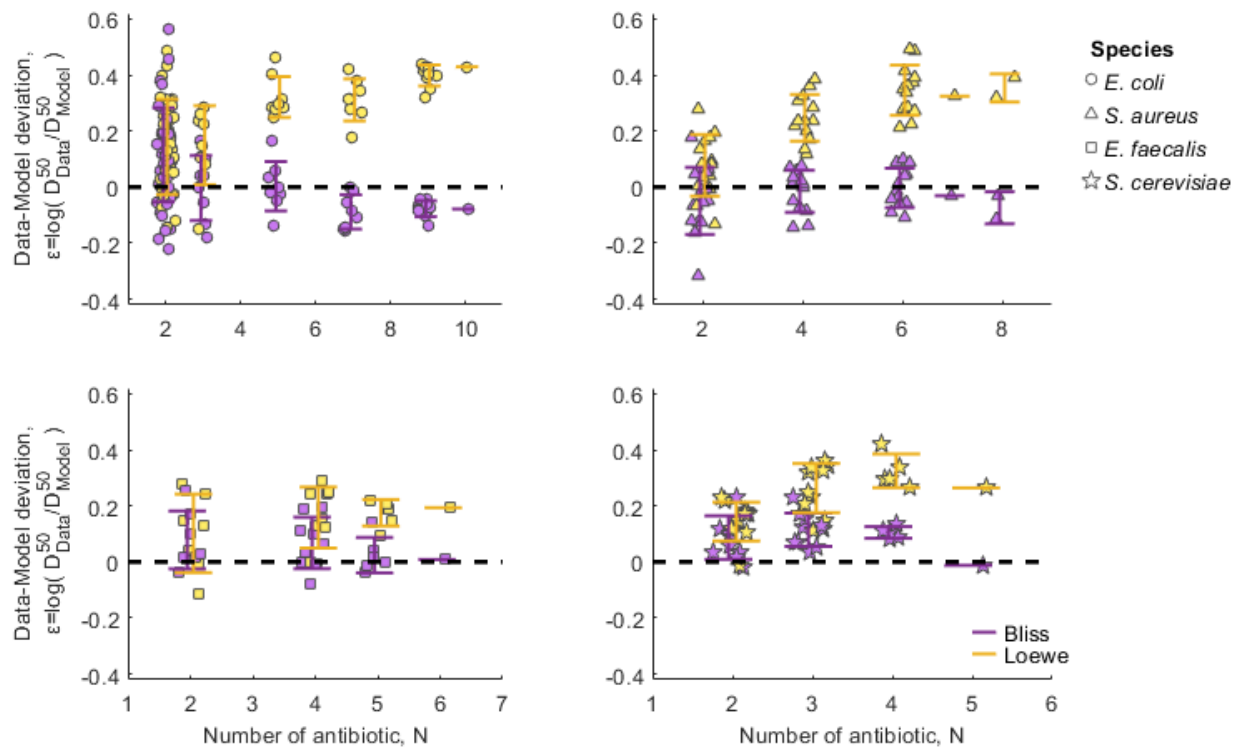


e

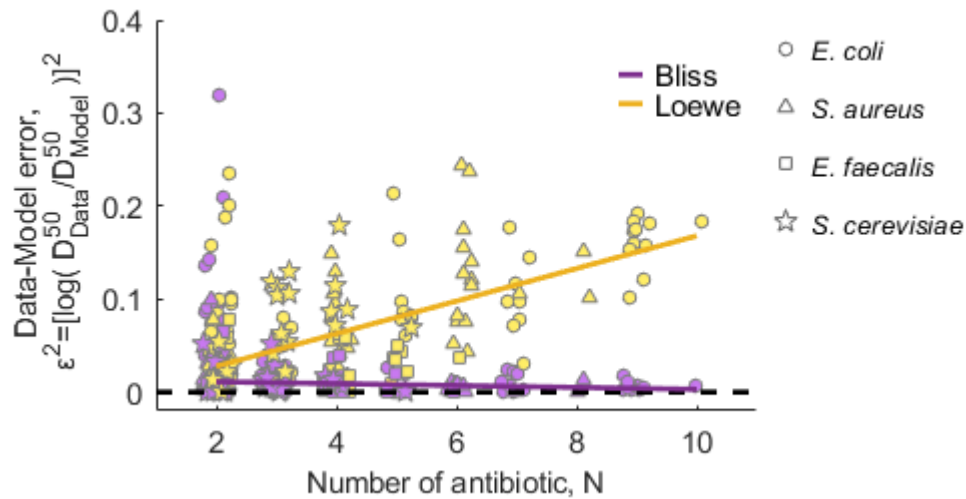




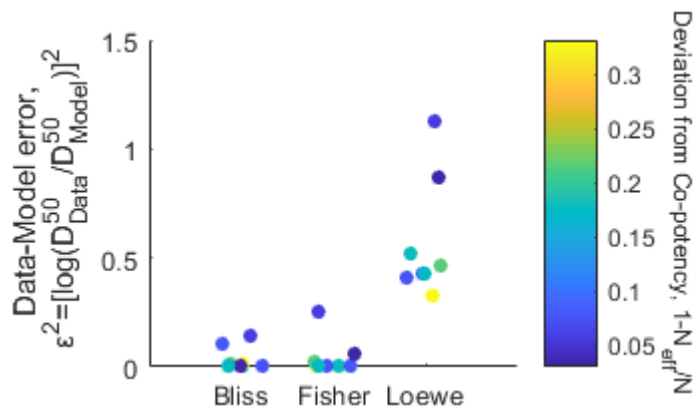
Supplementary Figure 3. Bacterial growth rate under stress of various antibiotics combinations compared to predictions of Bliss and Loewe. Measured normalized growth rate and combined potency D_{Data}^{50} are contrasted with Bliss and Loewe predictions calculated based the single drug measurements (bottom middle) for all drug combinations of: *E. coli* (**a**); *S. aureus* (combinations without **(b)** and with **(c)** beta-lactam antibiotic; *E. faecalis* (**f**) and *S. cerevisiae* (**e**). The drugs used in each combination are indicated by a barcode, and the drug concentrations at the measured well (dots) are indicated With capital letters (Supplementary Tables 3-8).



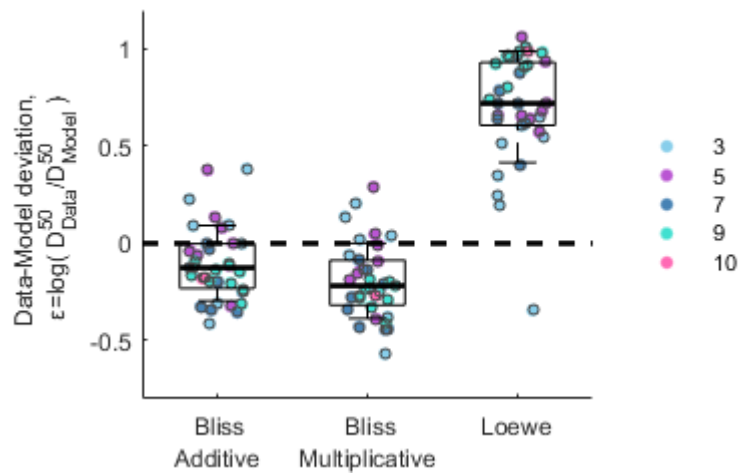
Supplementary Figure 4. Bliss's prediction remain accurate regardless of number of drugs, while Loewe's prediction diverges when number of drugs increases for all tested species. Deviation of each of the models from the data $\epsilon = \log(D_{Data}^{50}/D_{Model}^{50})$ is plotted as a function of number of drugs, showing that, for each of the tested species, the Loewe predictions deviate from the data with increased number of drugs, while Bliss predictions remain accurate (80, 43, 23 and 26 different drug combinations for *E. coli*, *S. aureus*, *E. faecalis* and *S. cerevisiae* respectively. For every combination size error bar represent one standard deviation, dashed line show perfectly accurate prediction).



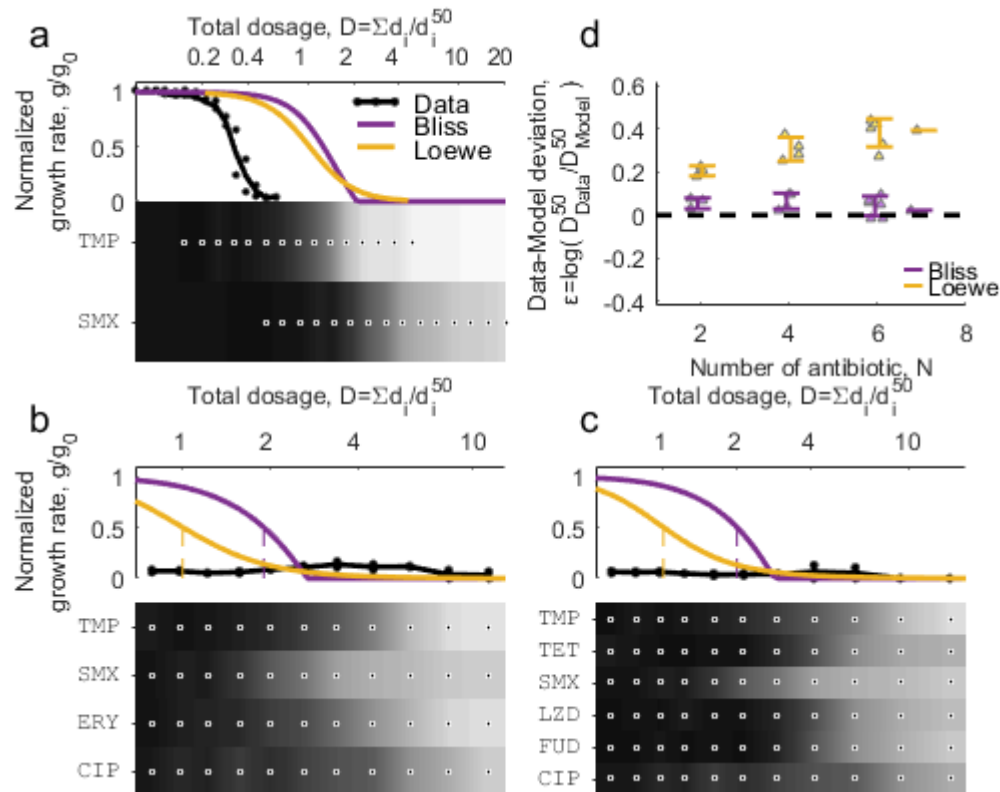
Supplementary Figure 5. The accuracy of Loewe’s prediction declines while that of Bliss improves when number of drugs in combination increases. The error of each model ($\epsilon^2 = [\log(D_{Data}^{50}) - \log(D_{Model}^{50})]^2$) for all measured species (172 different drug combinations in total) is plotted as function of number of drugs in combination, N . The error of Bliss prediction remains constant or even slightly decreases (purple line, robust linear fit $y = ax + b$, $a = -0.001 \pm 0.001$) while that of Loewe increases (Yellow line, robust linear fit $y = ax + b$, $a = 0.018 \pm 0.016$).



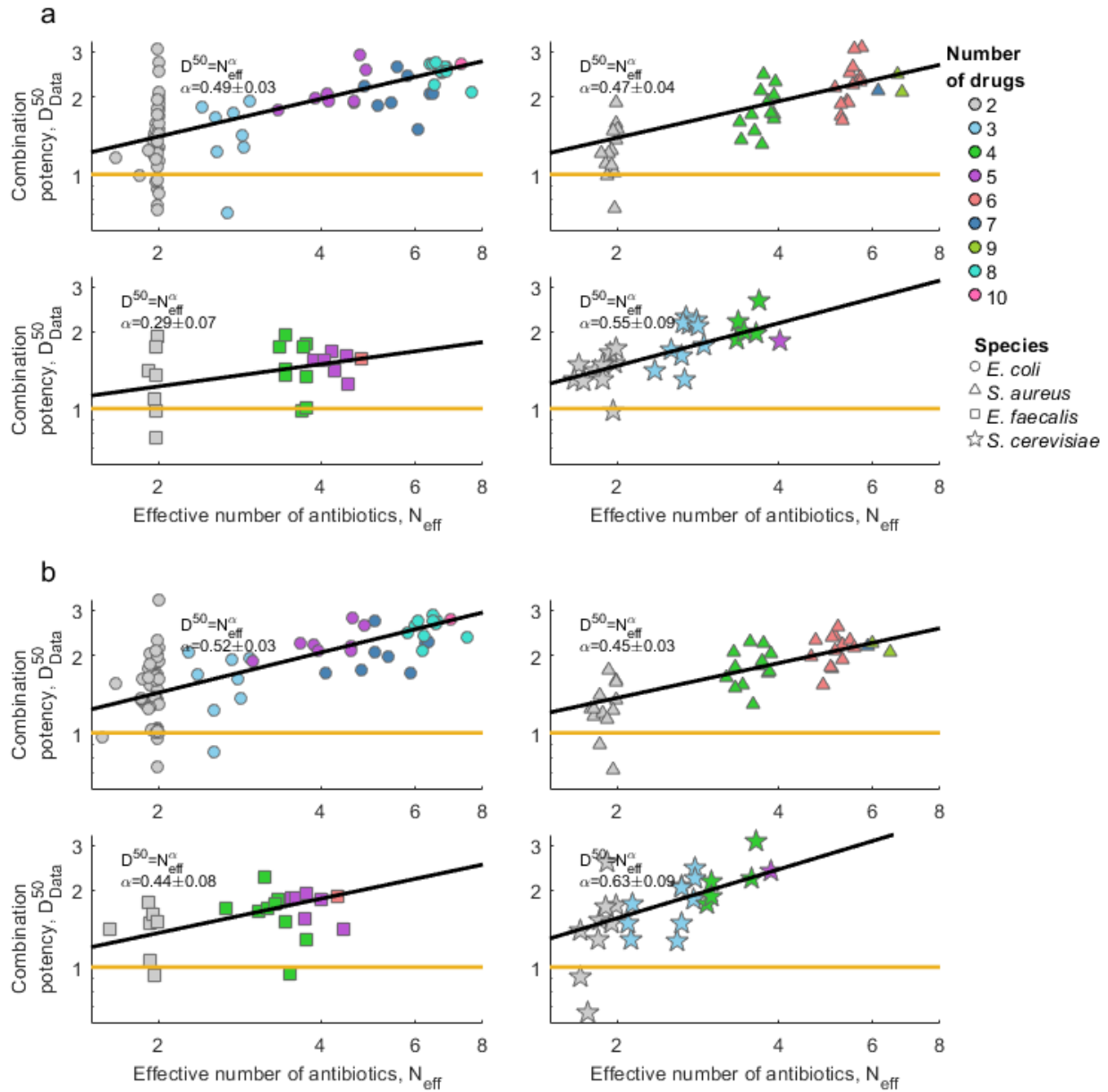
Supplementary Figure 6. Predictions of both Bliss and Dosage orthogonality models are superior to that of Loewe both on and away from the co-potent line. To validate that our findings are correct throughout the dosage space and not limited only to the co-potent line we examined all drug combinations of five drugs applied to *E. coli*. The error, $\epsilon^2 = [\log(D_{Data}^{50}) - \log(D_{Model}^{50})]^2$, of each model for each of the combination is colored by the deviation of the drug combination from co-potency, $1 - N_{Eff}/N$. The accuracy of the predictions of both Bliss and Dosage orthogonality models is higher than Loewe whether the mixture is near or far from the co-potent line.



Supplementary Figure 7. Bliss model of additivity predicts the combination potencies of many-drugs combinations better in its additive form than in its multiplicative form. A box-plot diagram comparing the accuracy of the additive and multiplicative forms of Bliss and the accuracy of Loewe (35 different combinations colored by the number of drugs in each combination). We find that the multiplicative form of bliss is less predictive than the additive form, yet still much better compared to Loewe (box at median and 1st and 3rd quartiles, whiskers at mean \pm two standard deviations, black dashed line perfectly accurate prediction).

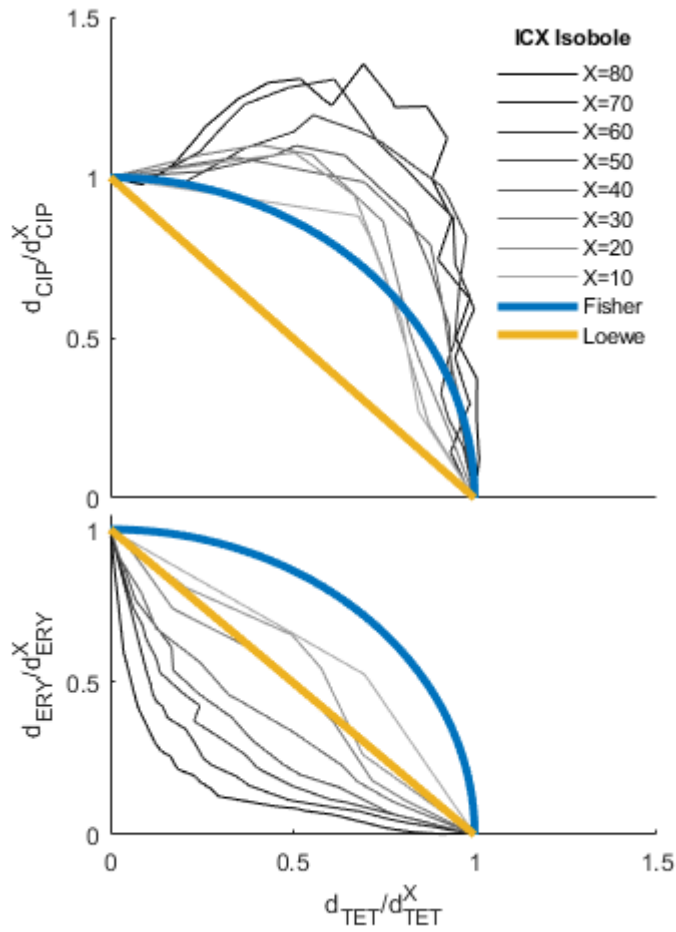


Supplementary Figure 8. Measuring the potency of combinations involves strongly synergistic pairs of drugs is done by considering them as one drug. Measured normalized growth rate and combined potency D_{Data}^{50} are contrasted with Bliss and Loewe predictions calculated based the single drug measurements for combinations involved TMP and SMX together in *S. aureus*. When applied together TMP and SMX show strong synergy (a) therefore the effect of multi-drug combination that contain both drugs is dominated by them (b-c as examples). To avoid that we combined TMP and SMX in a 1:5 ratio respectively (imitating the commercial combination drug Cotrimoxazole) and treated that mixture as a single drug. Combining that Cotrimoxazole-like drug with other antibiotics on a co-potent line (d) yield's same findings of rejection of dose additivity in favor of response additivity (14 different combinations, For every combination size error bar represent one standard deviation).



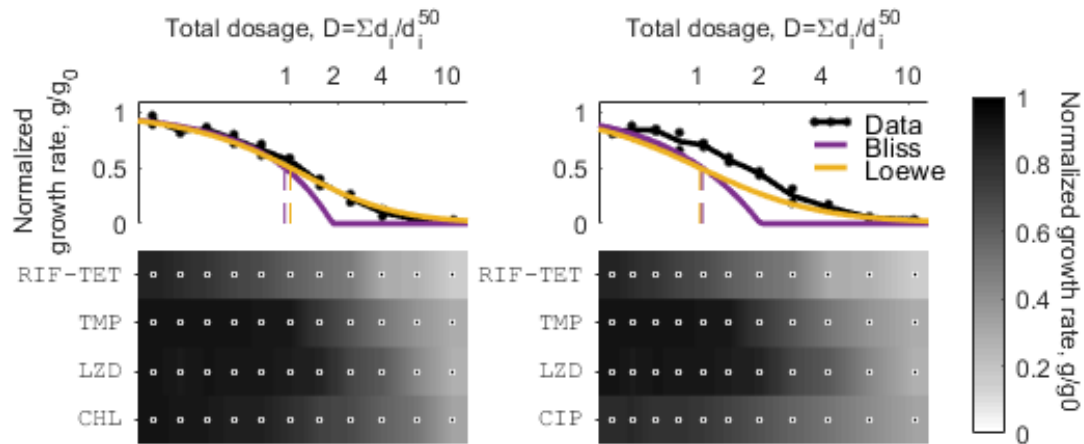
Supplementary Figure 9. Combination potency scales remotely as square-root of number of drugs for each of the measured species. a, Combination potency, D_{Data}^{50} of all different drug combinations is plotted as a function of effective number of drugs (80, 43, 23 and 26 different drug combinations for *E. coli*, *S. aureus*, *E. faecalis* and *S. cerevisiae* respectively). In contrast to Loewe, which assumes that the total dosage required for inhibition is fixed (yellow line), the total dosage required to inhibit growth by 50% increases as square root of the effective

number of drugs for three of the four individual species (black line, fit of $D^{50} = (N_{eff})^\alpha$ representing $\alpha \pm 0.95$ confidence interval). **b**, The accuracy of the square-root scaling can be improved for lower level of inhibition (in this case, considering the total dosage required to inhibit growth by 30%) In alignment with the dose-orthogonality assumptions (Supplementary note 2)

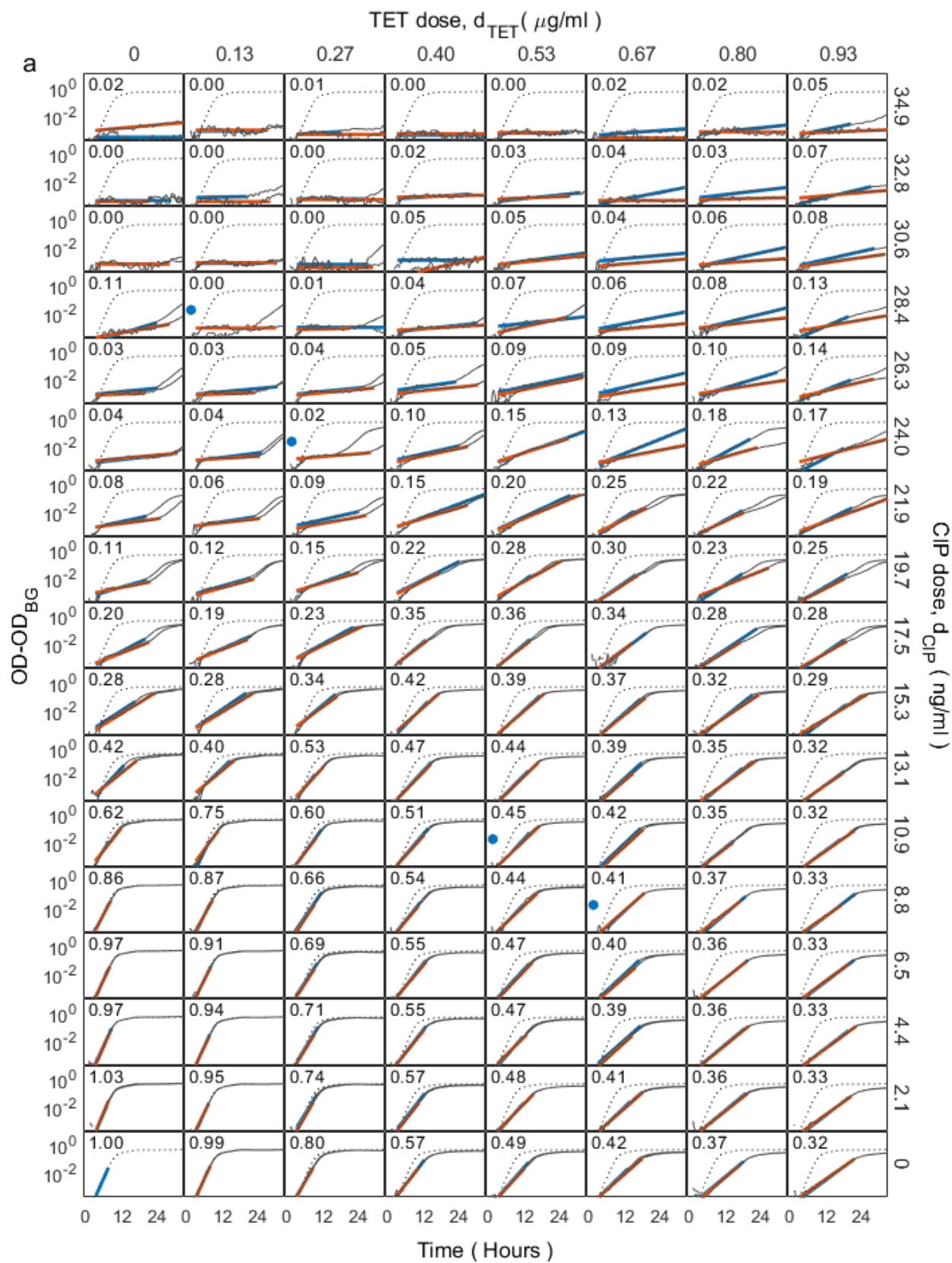


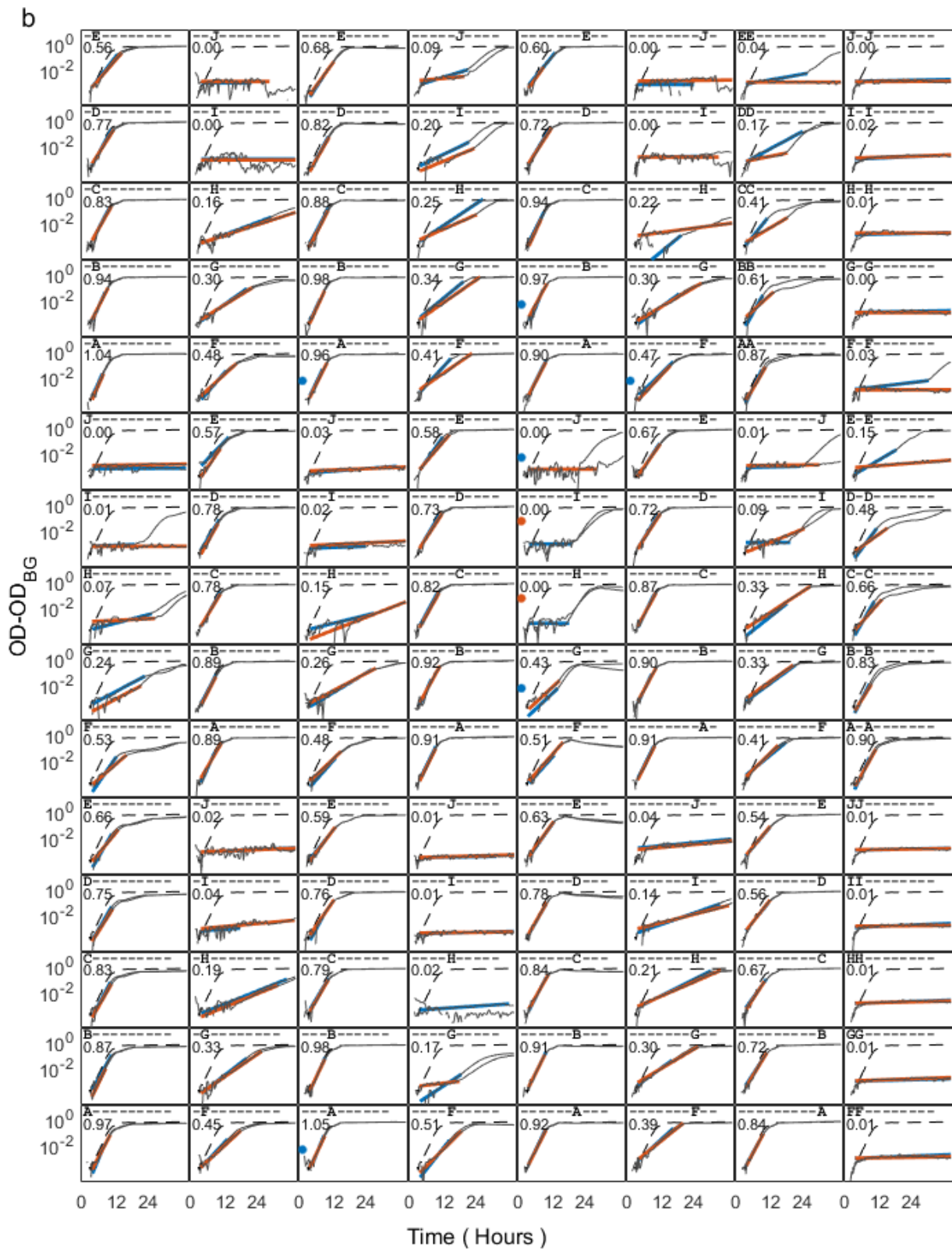
Supplementary Figure 10. At the limit of small dosages, isoboles converge to circles.

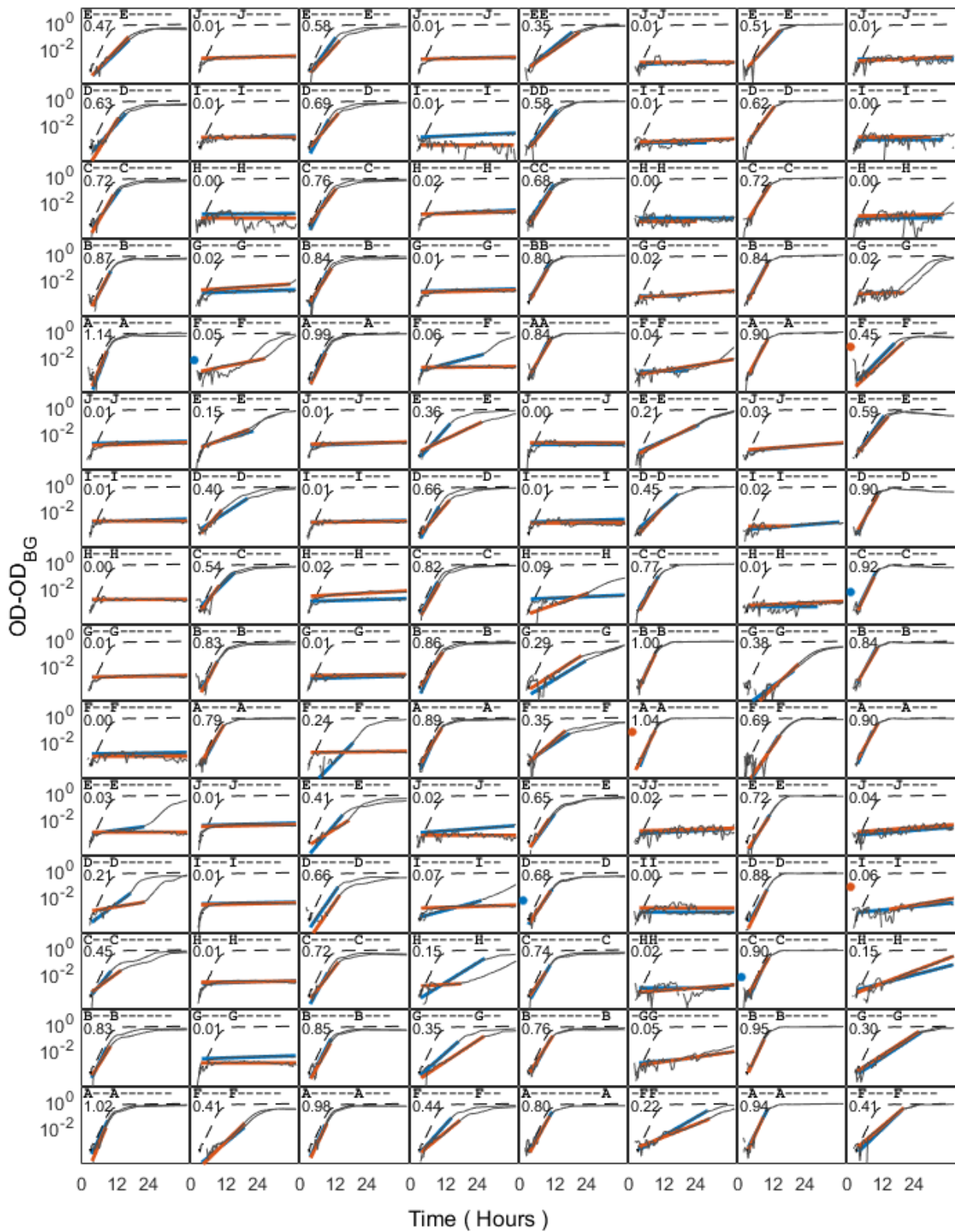
Even for strongly interacting drug pairs CIP-TET (top) and ERY-TET (bottom), isoboles (grey lines) become more circular (Fisher prediction, blue) rather than linear (Loewe prediction, yellow) as the inhibitory effect X approaches zero.

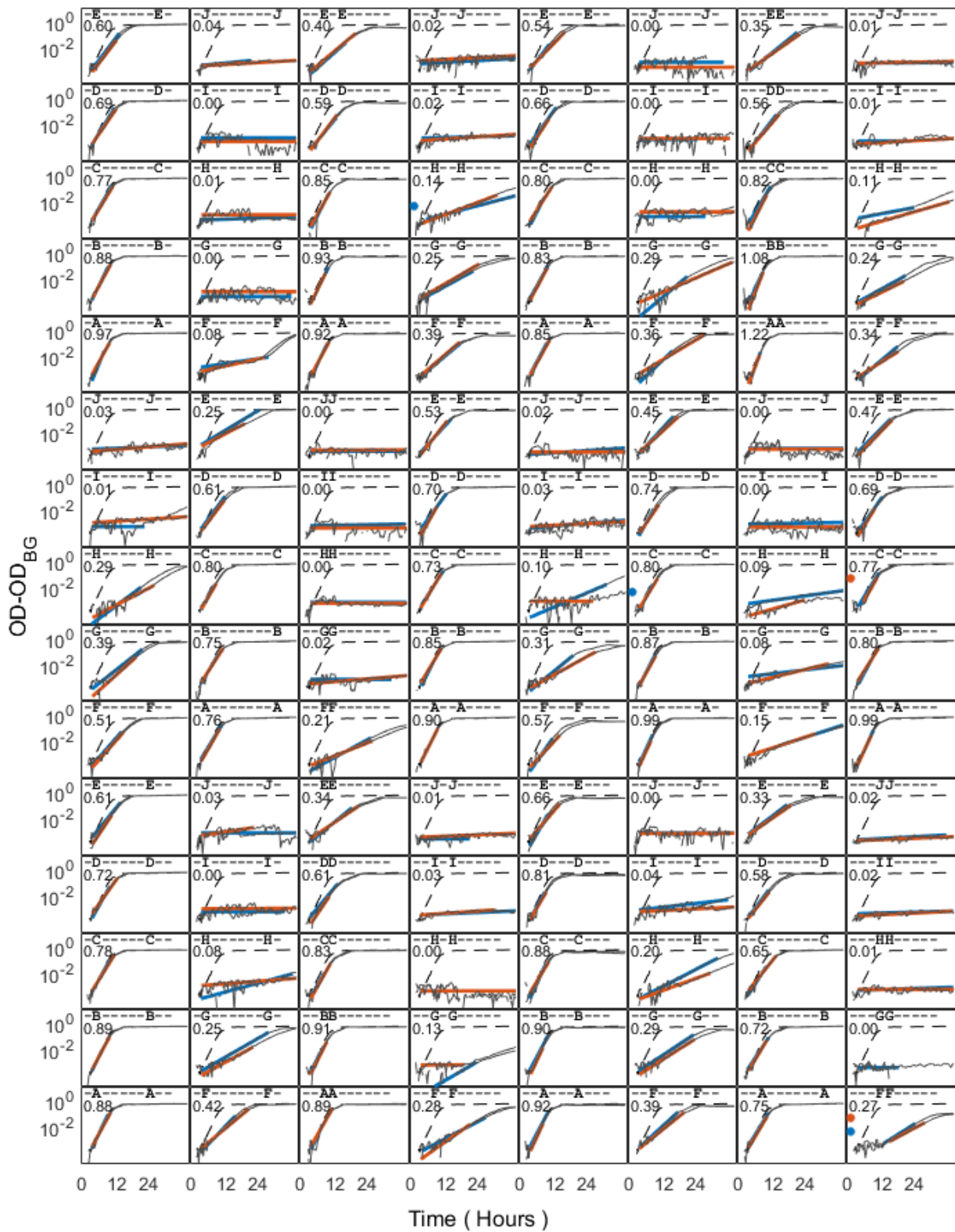


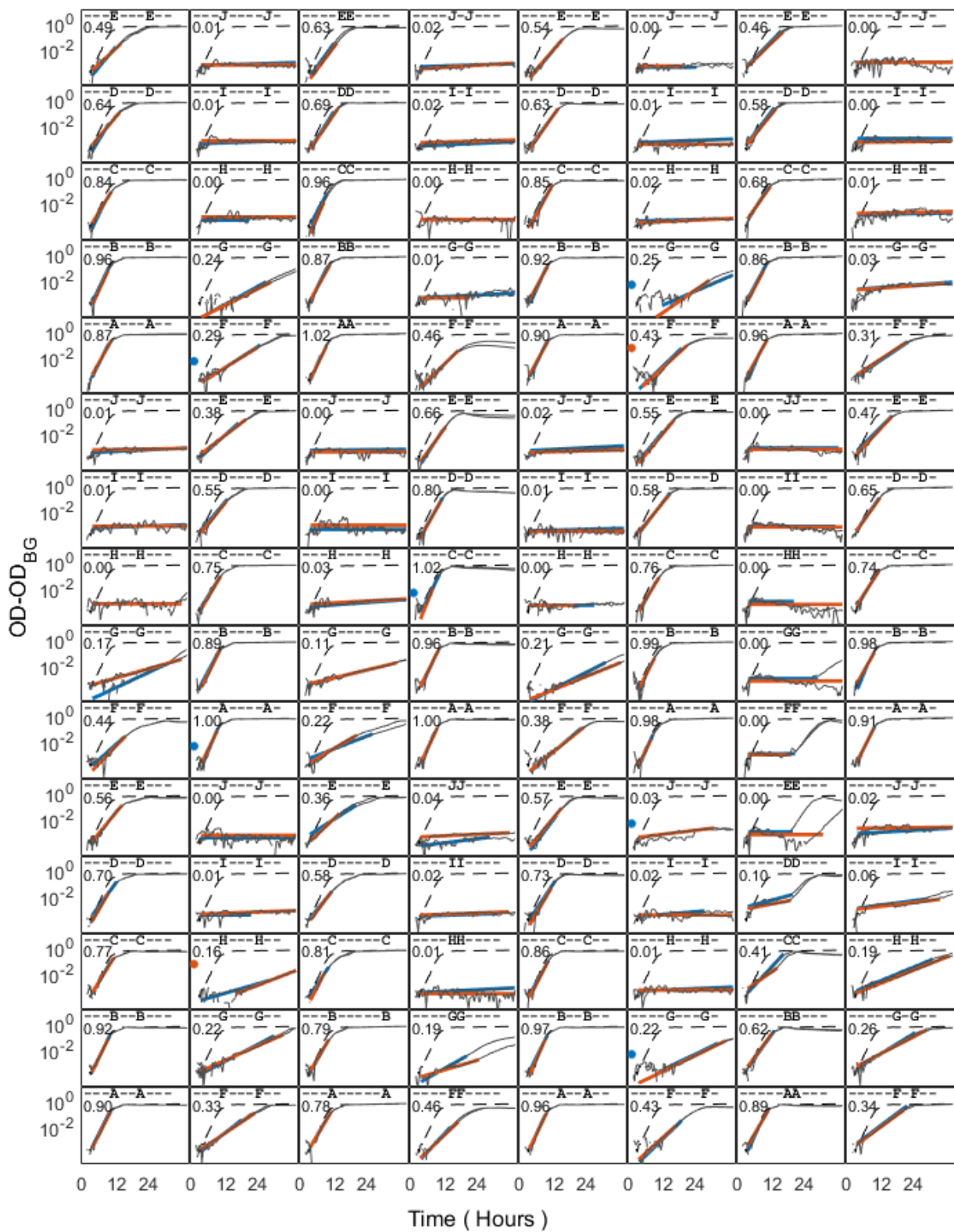
Supplementary Figure 11. Bliss prediction converges to Loewe is seen for combinations that include the synergistic drug-pair RIF-TET. Measured normalized growth rate contrasted with Bliss and Loewe predictions calculated based the single drug measurements for combinations involved RIF and TET together in *E. faecalis*. In combinations where most drugs has low hill coefficient, h , we expect the Loewe's prediction to resemble that of Bliss (seen as the distance on x-axis between D_{Bliss}^{50} and D_{Loewe}^{50}). When applying the synergistic pair of drugs RIF-TET as a mixture along the co-potent line, the combined h is even lower (1.04 in comparison to 1.3 and 1.14 in the single drugs), hence further enhance the Loewe-Bliss resemblance.

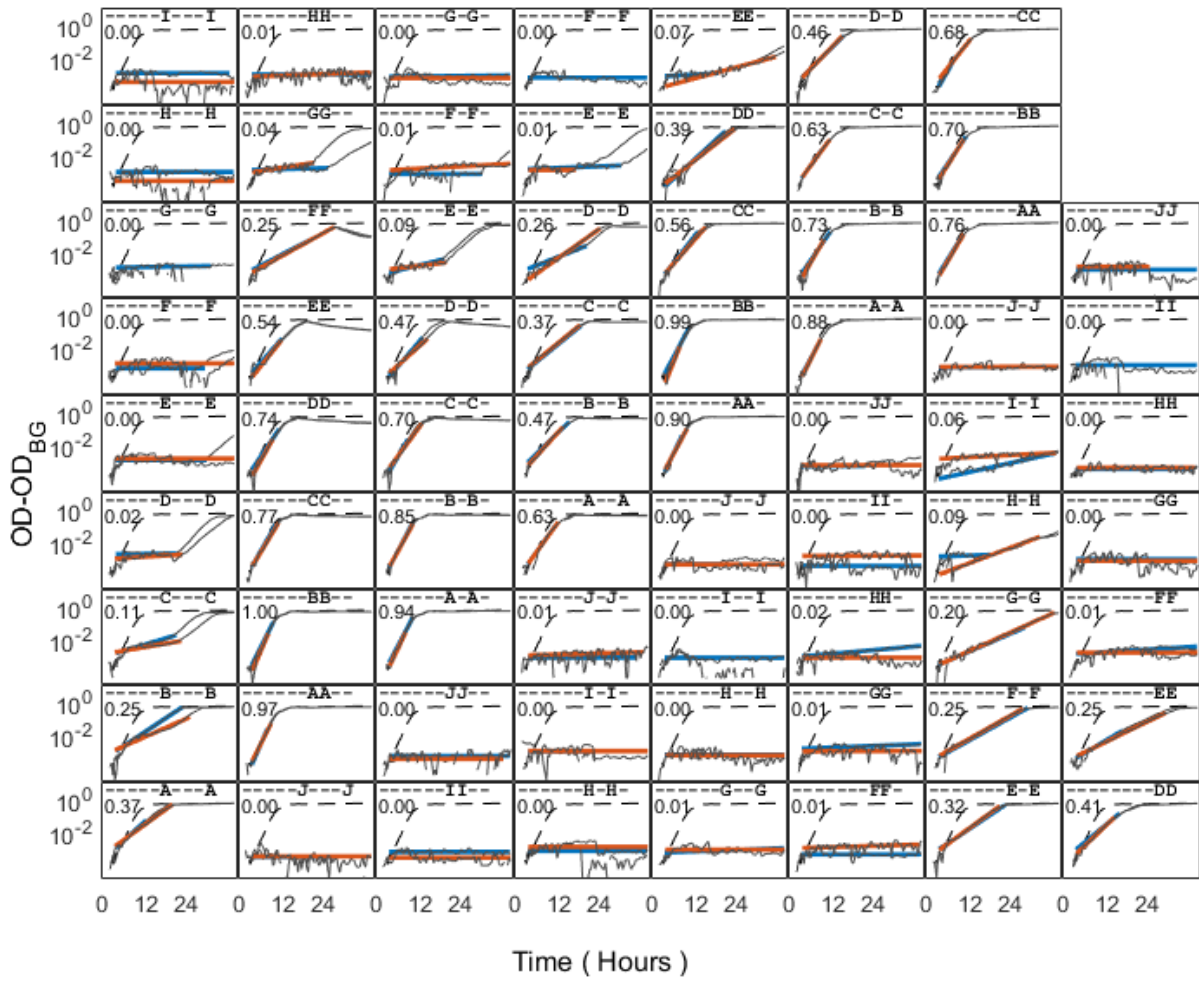


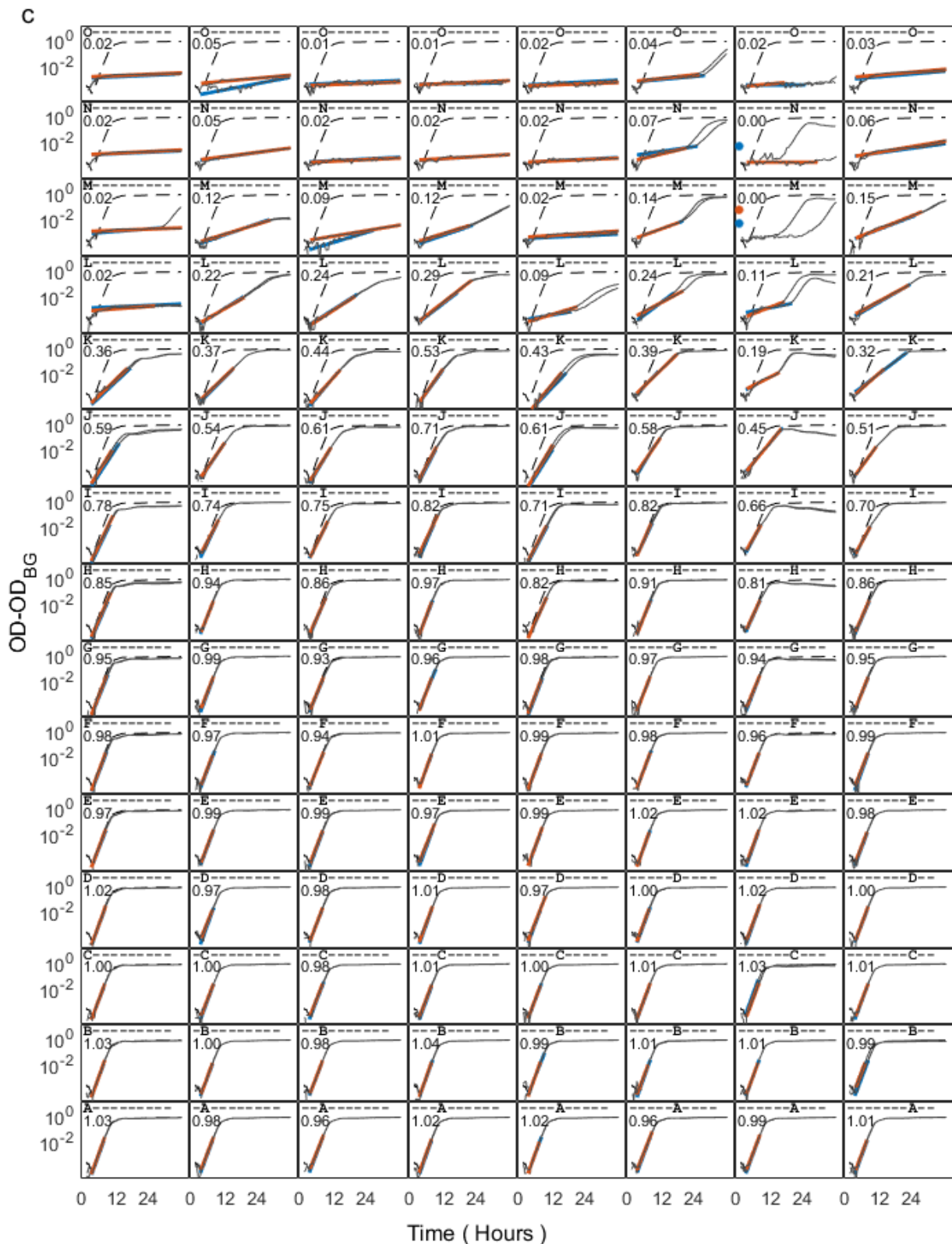


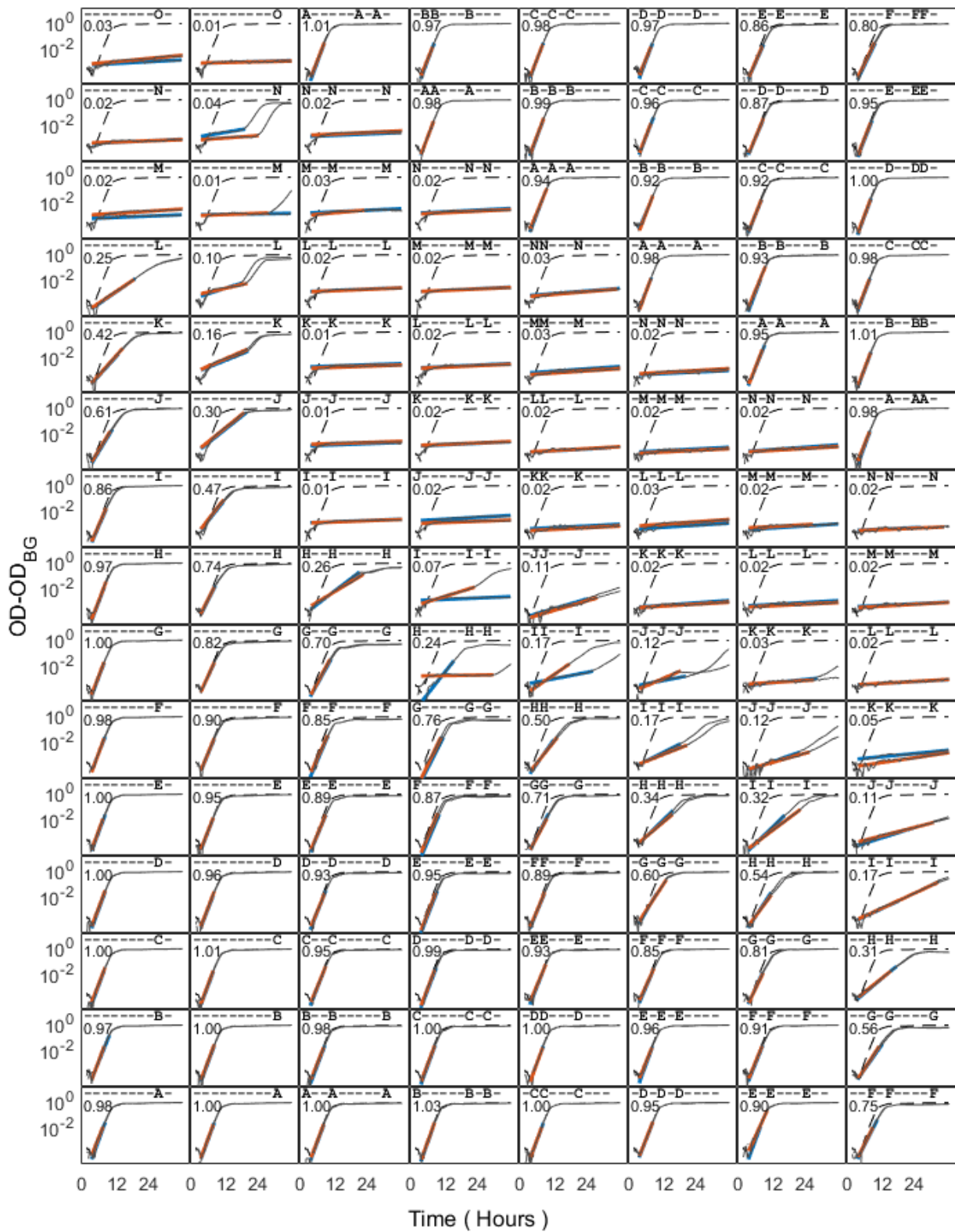


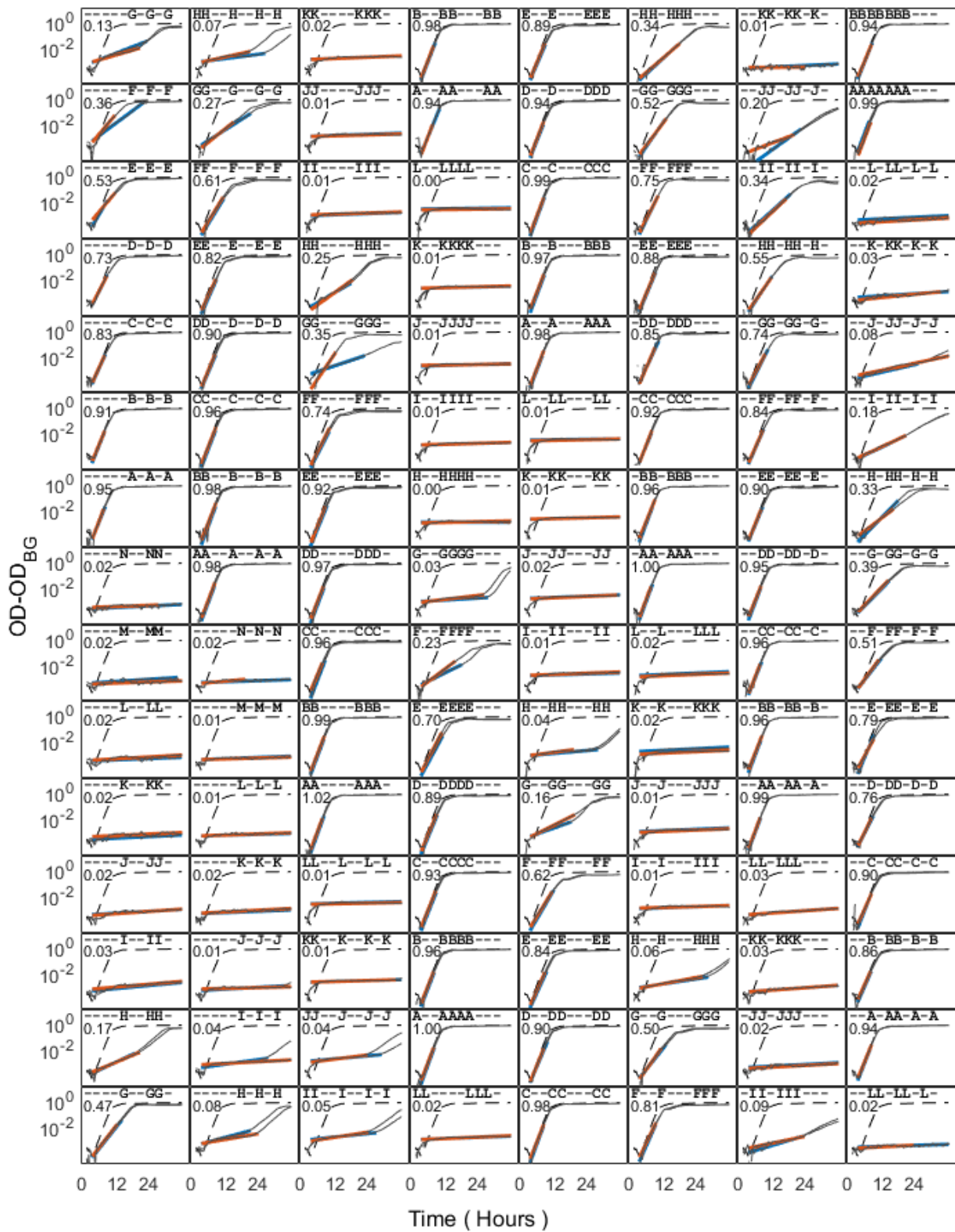


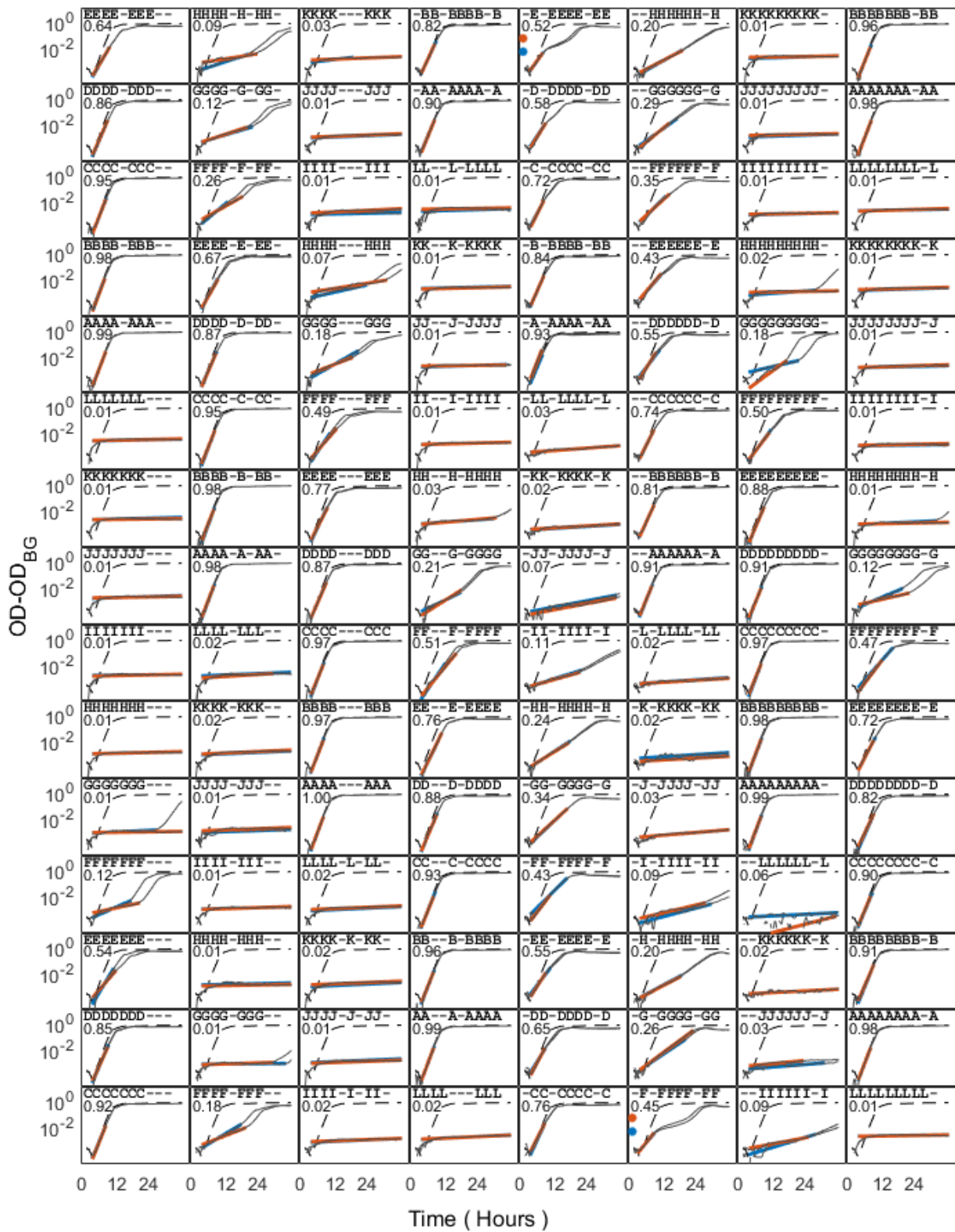


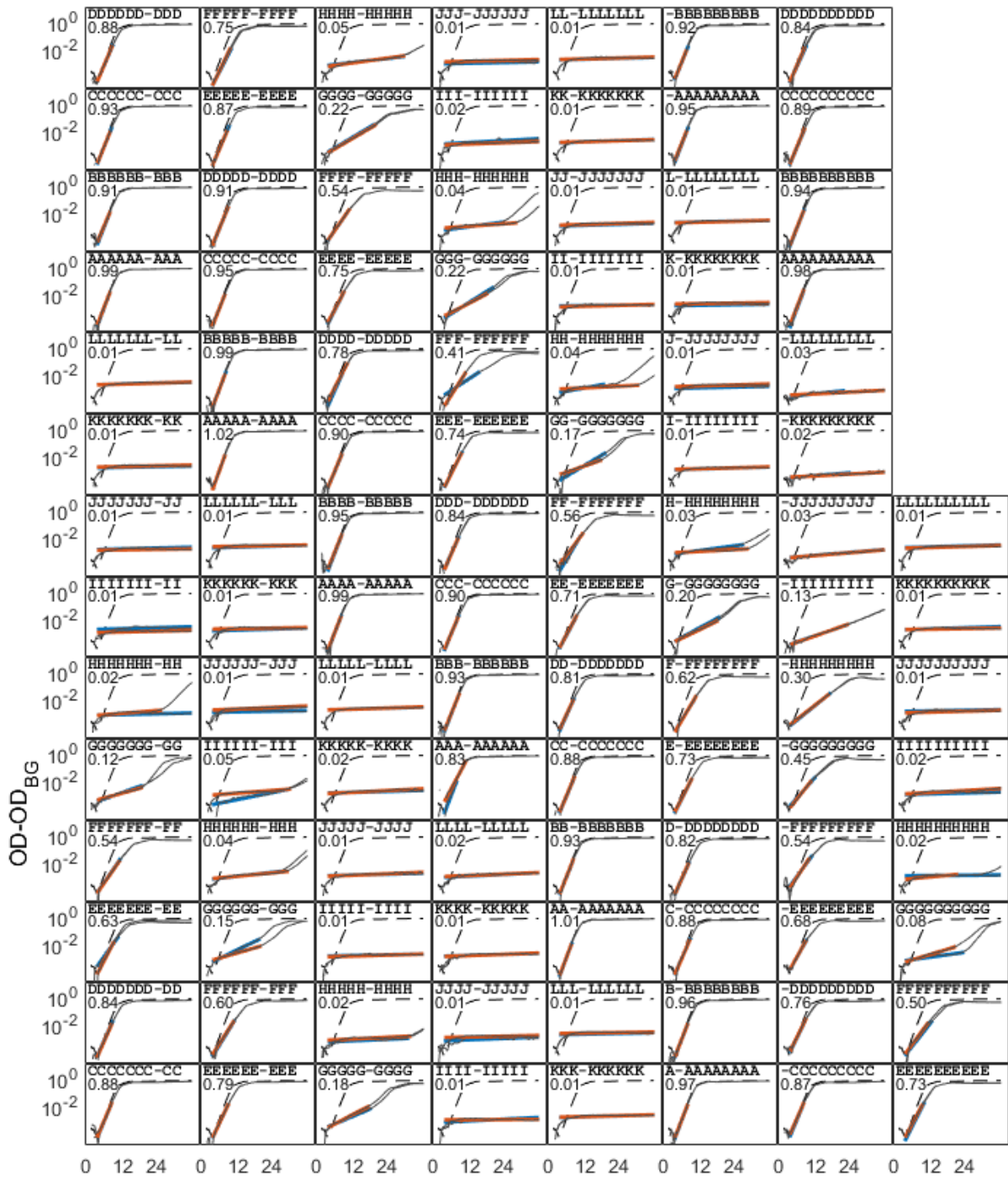


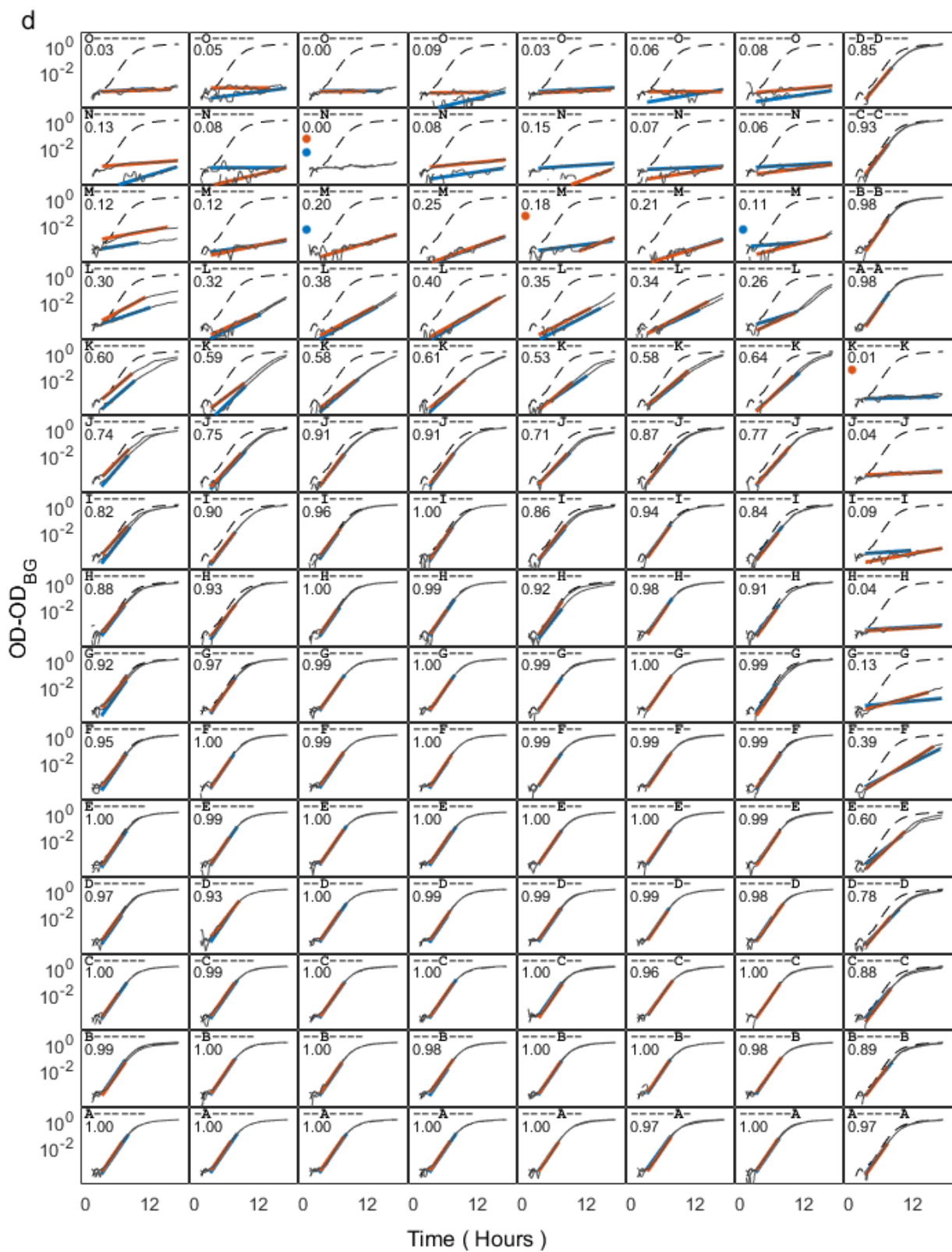


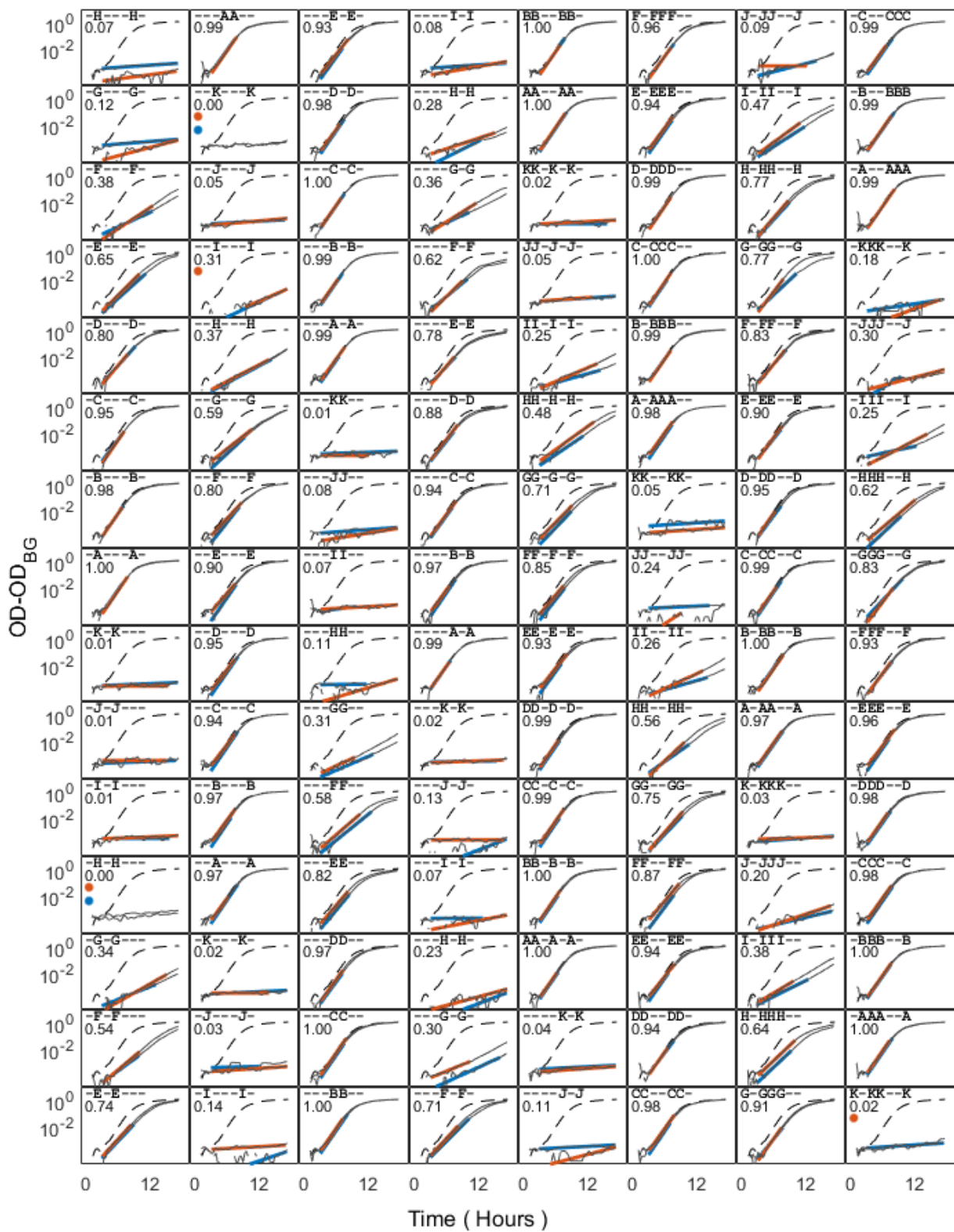


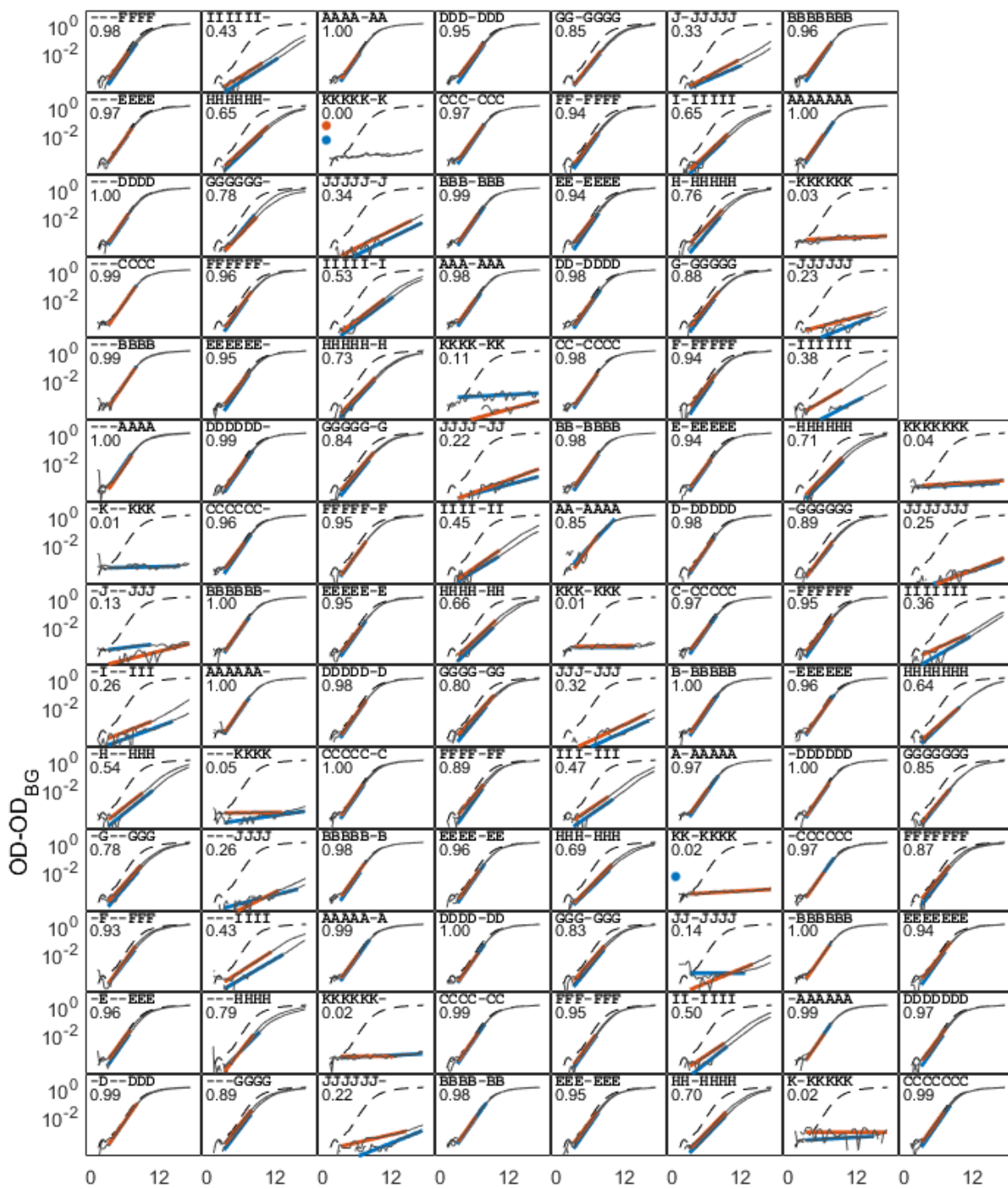


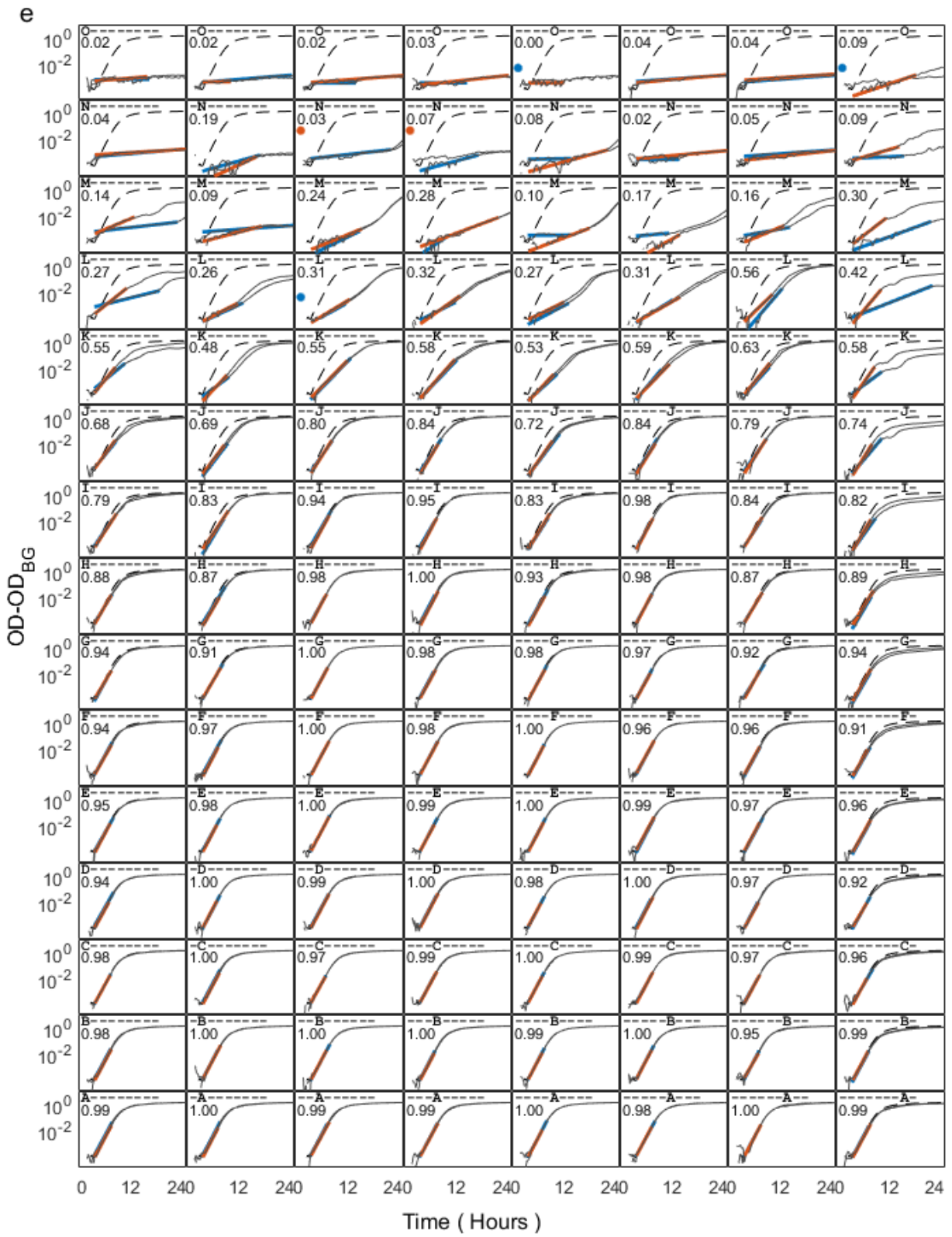


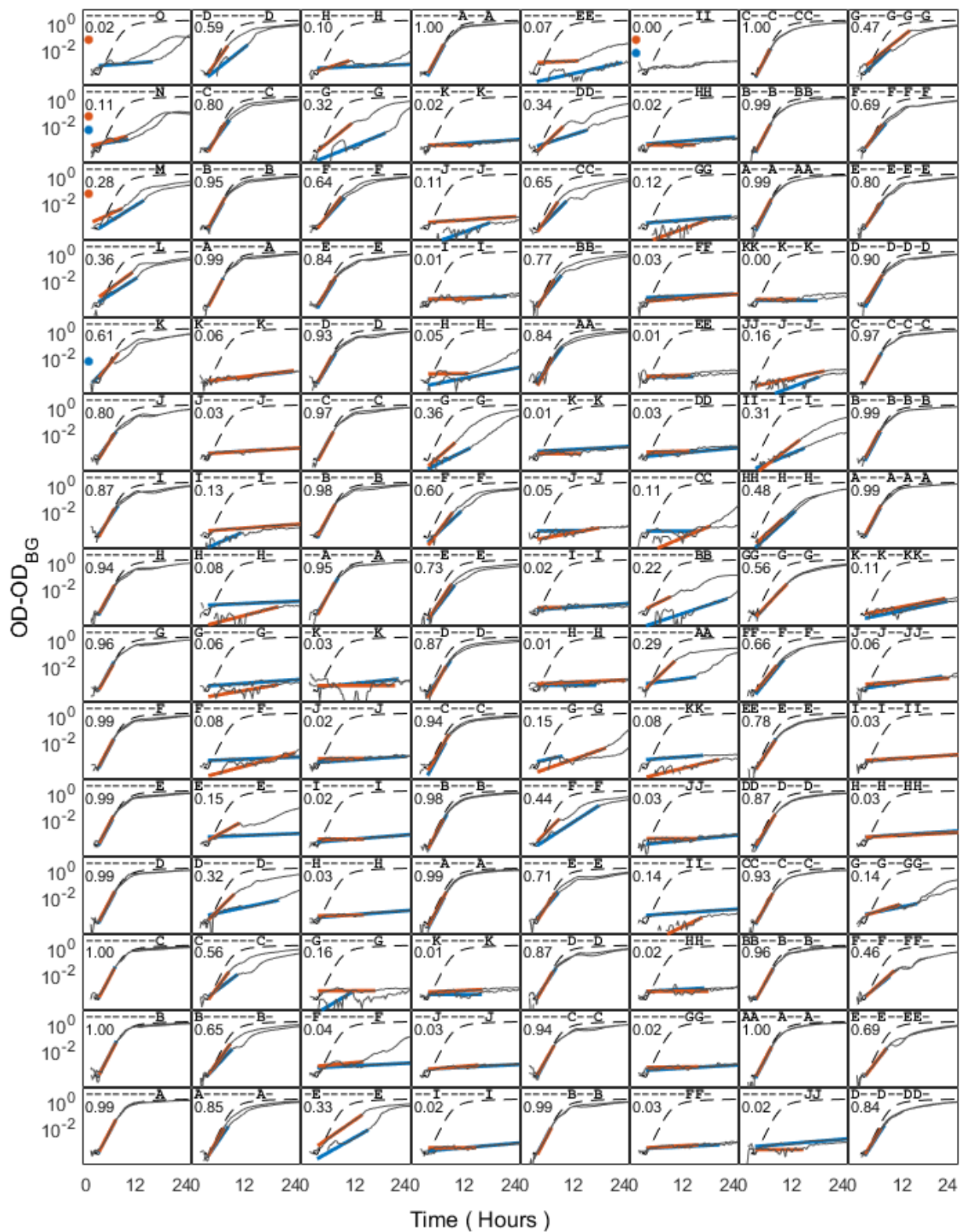


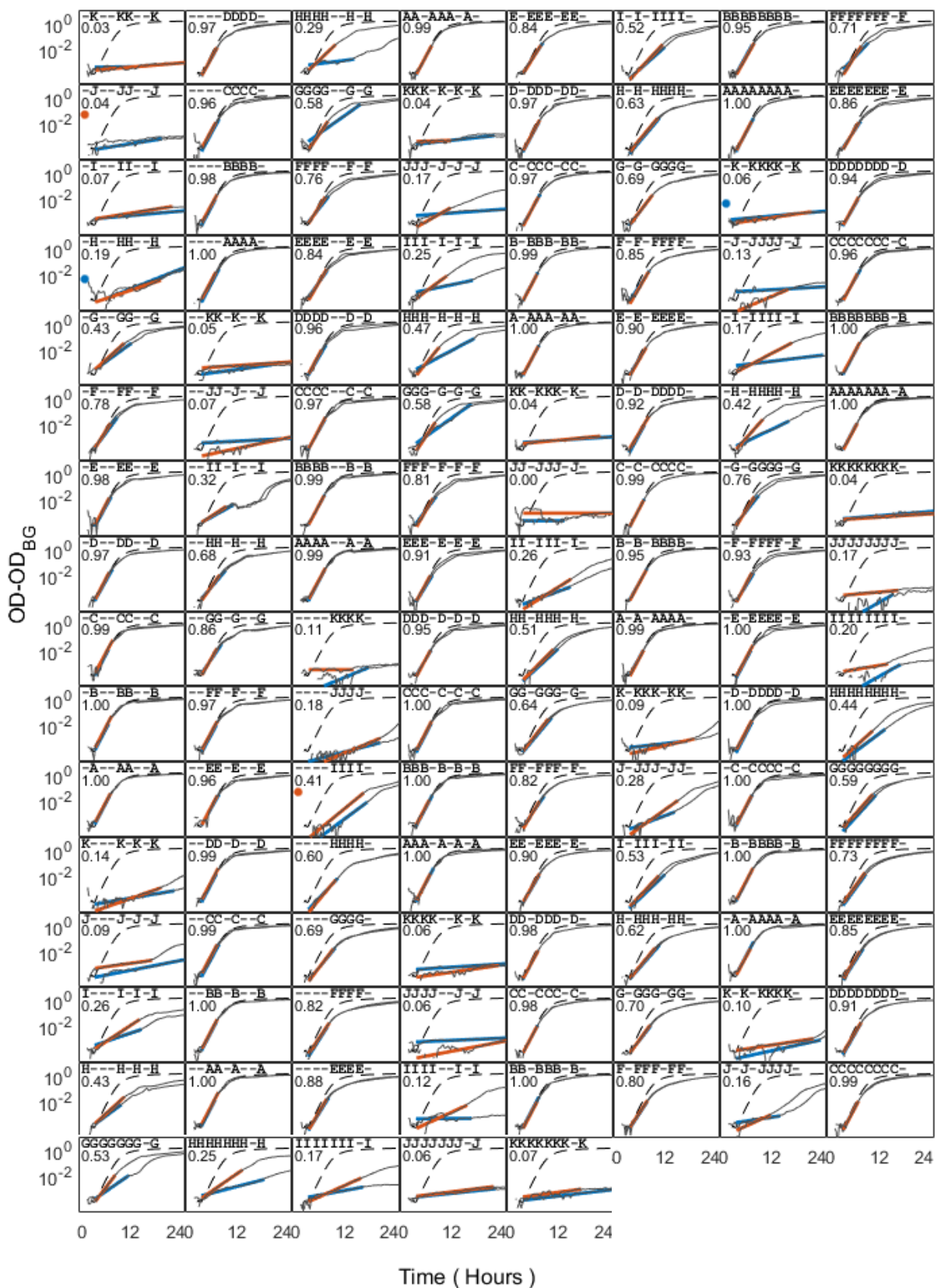




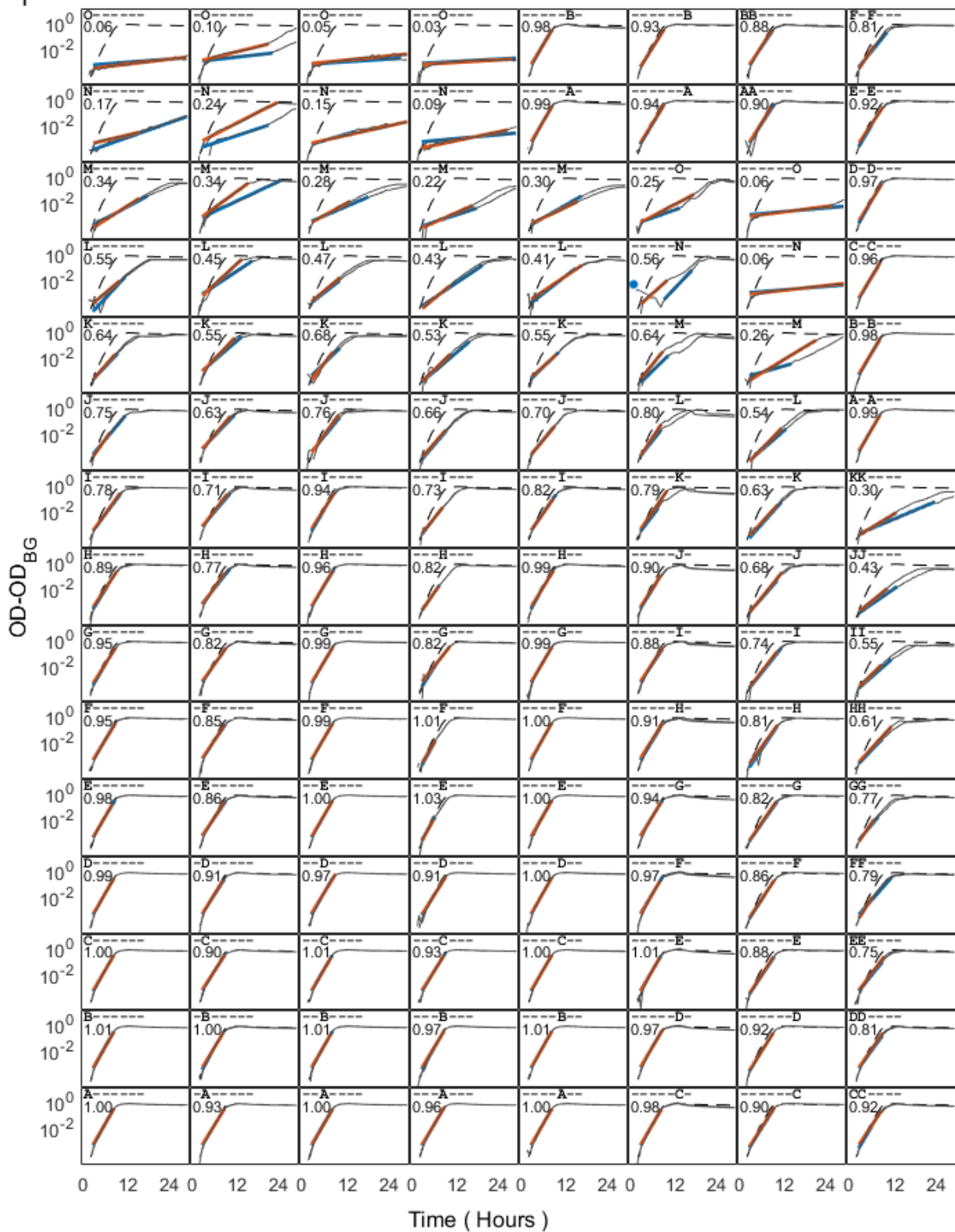


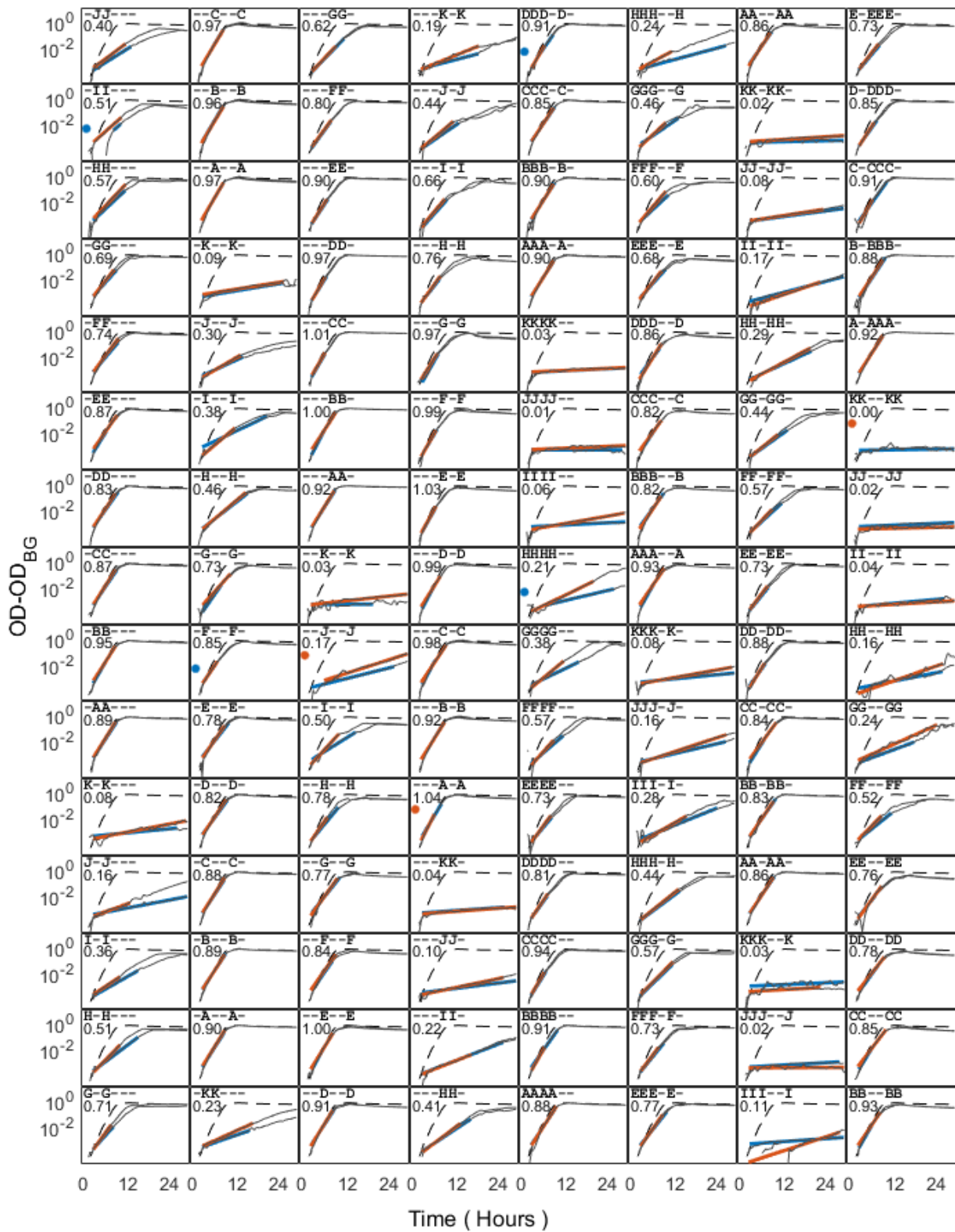


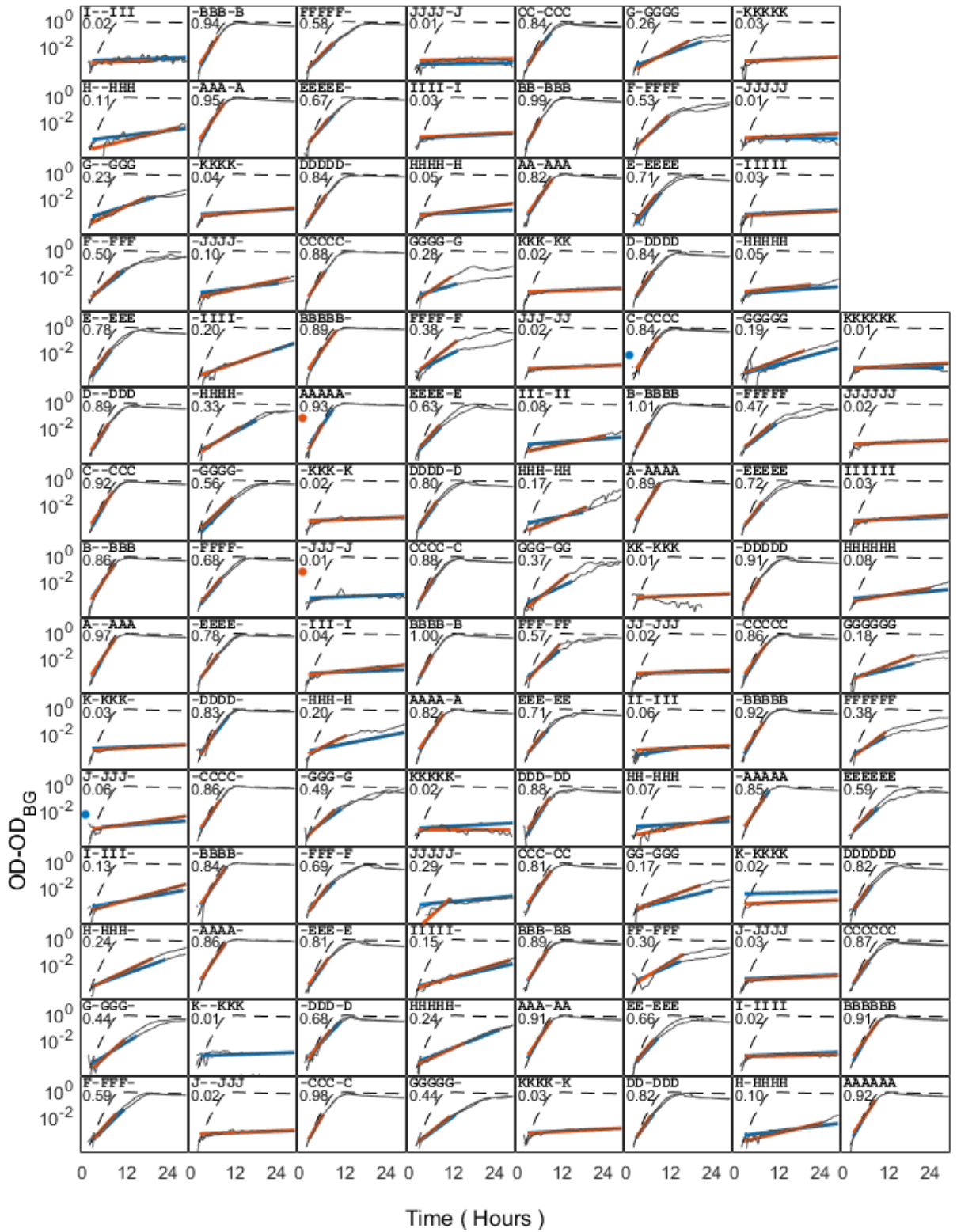


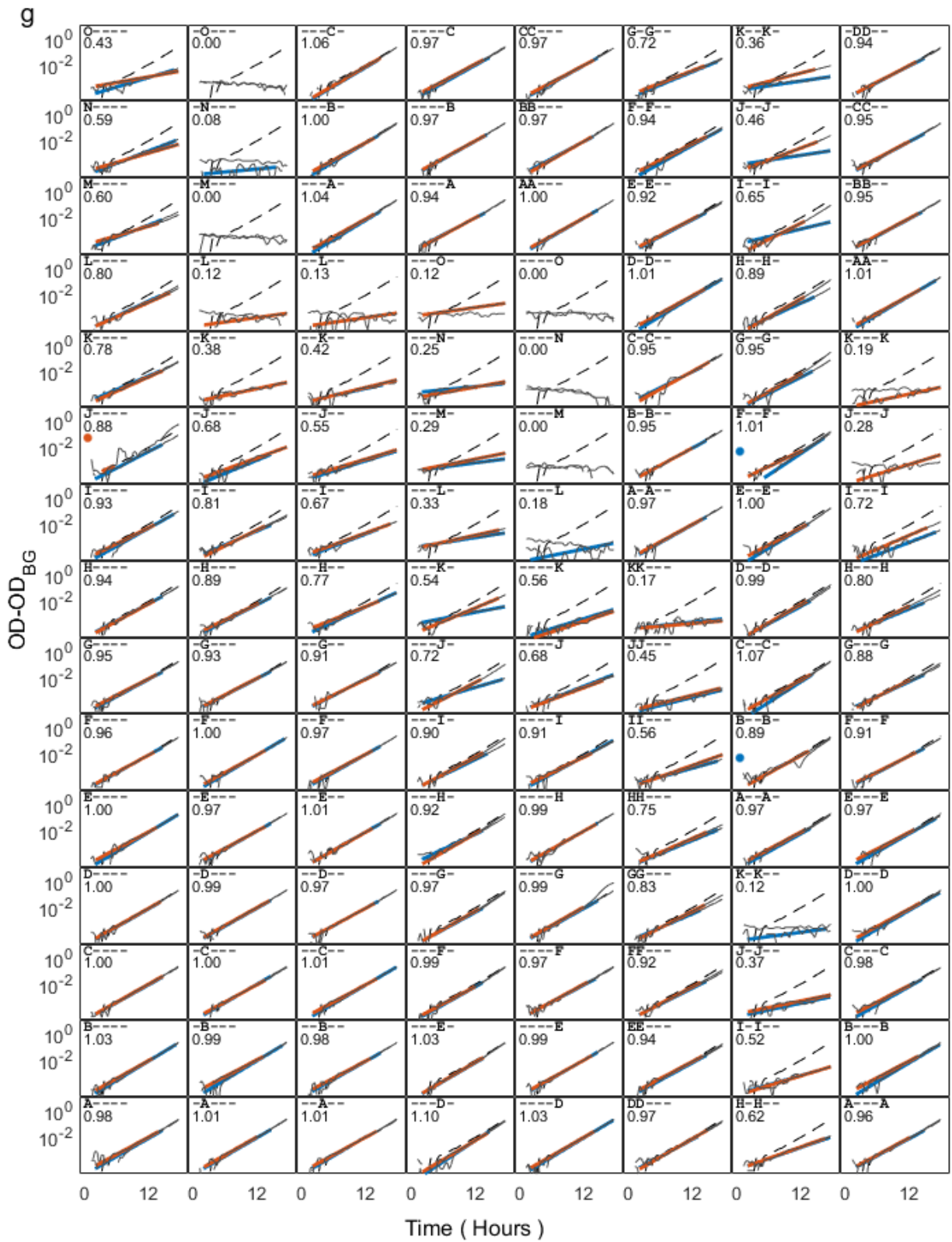


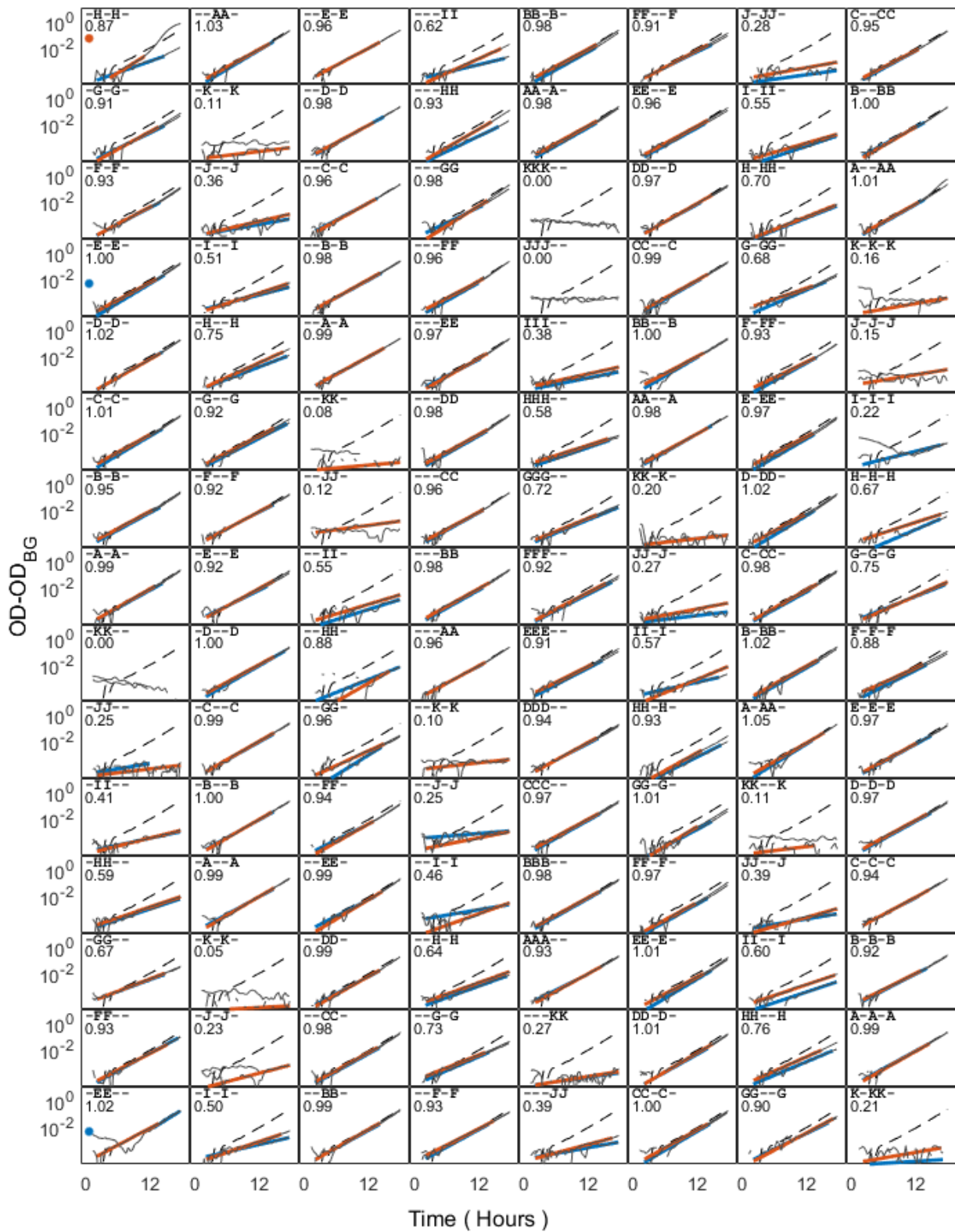
f

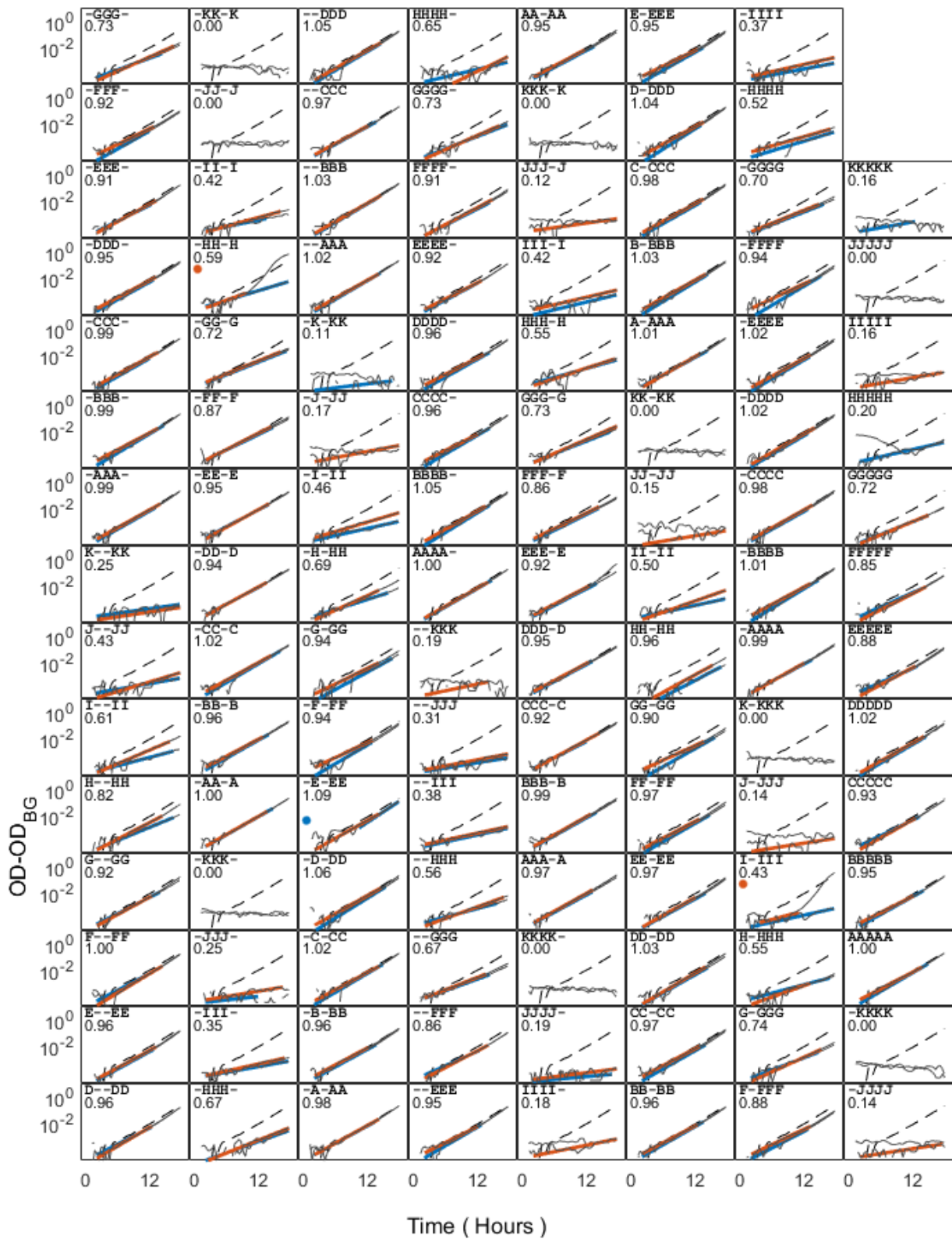




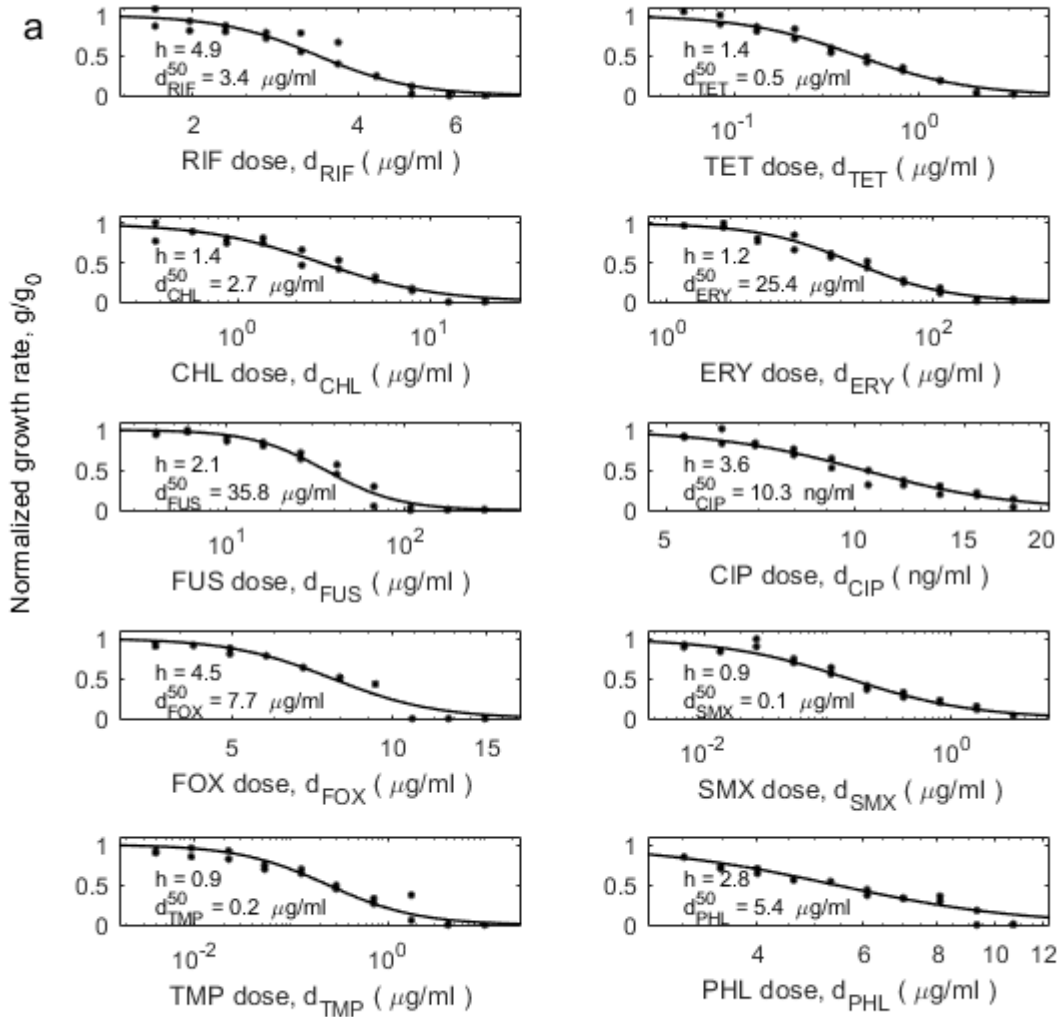


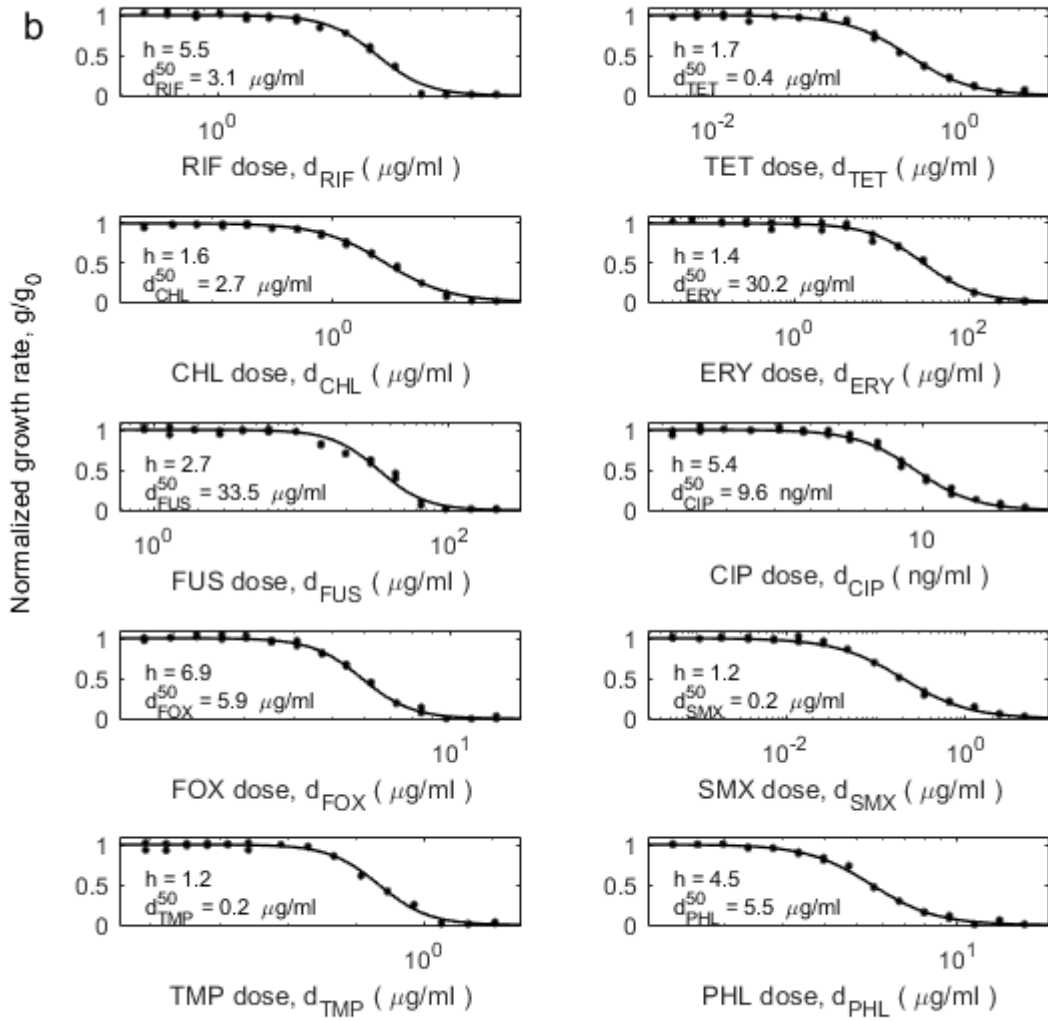


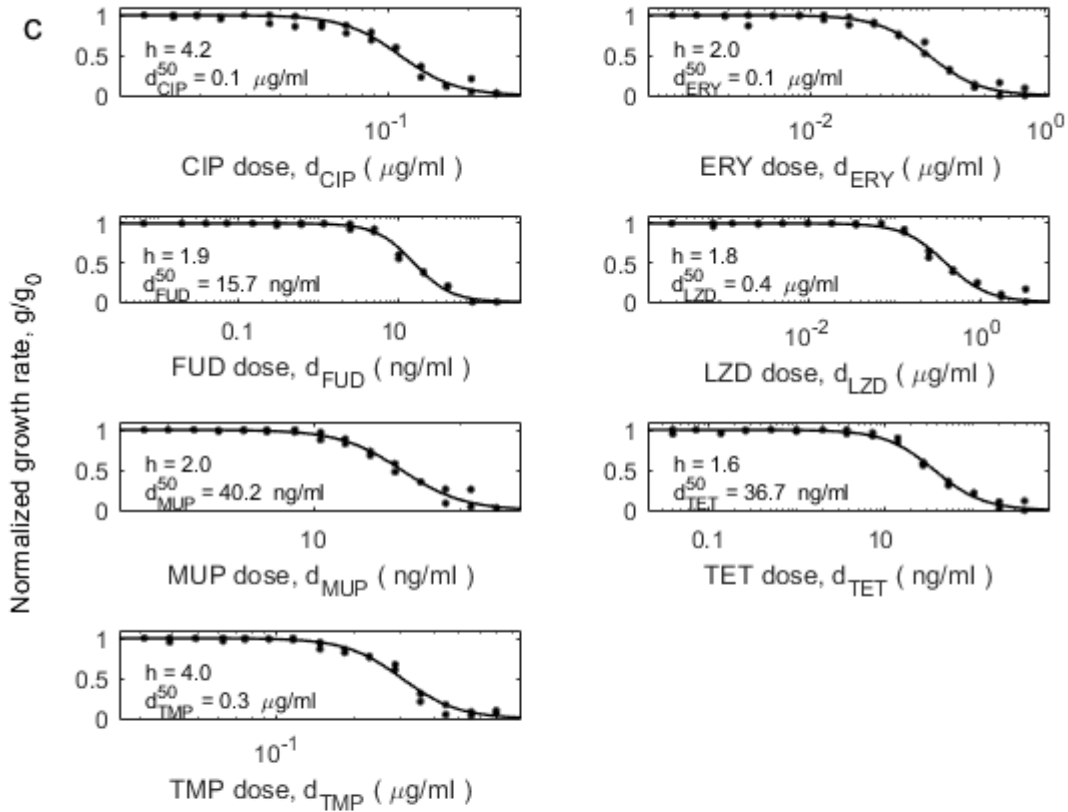


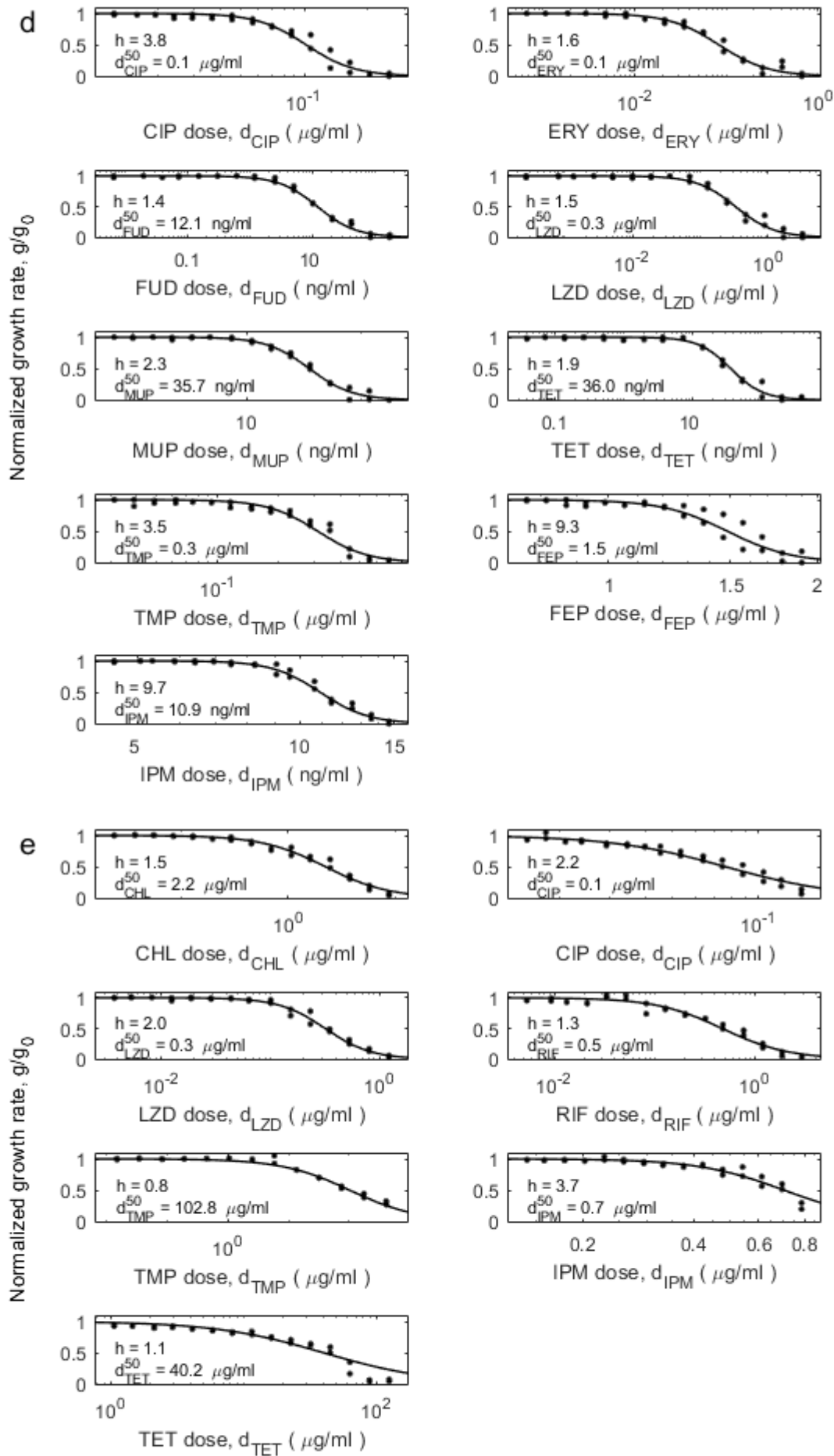


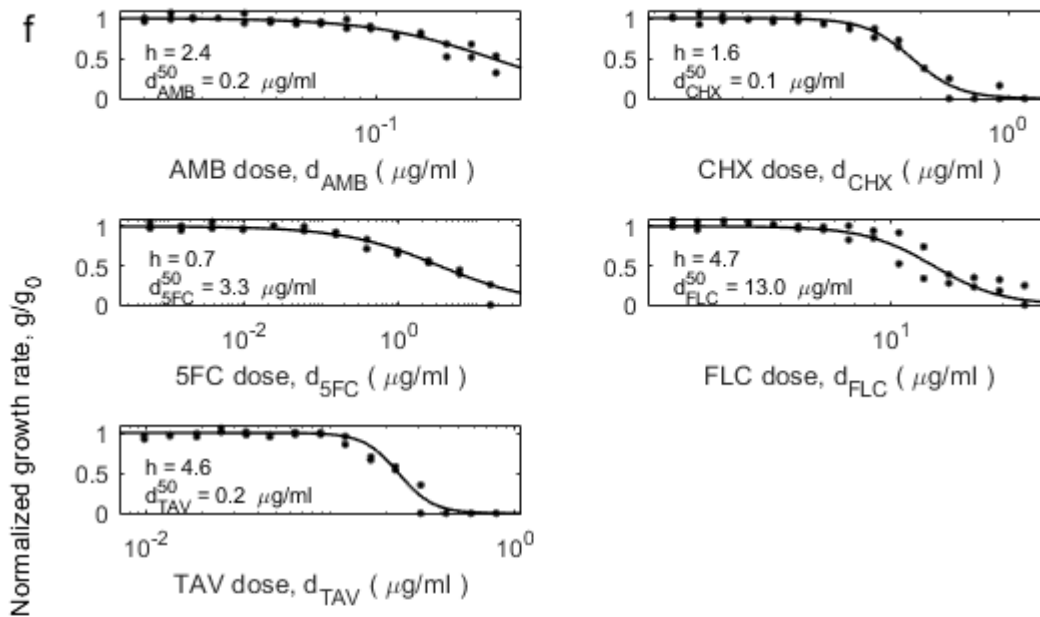
Supplementary Figure 12. Raw growth curve. Measurements of bacterial density over time in duplicate wells (black lines) is used to calculate bacterial growth rate, g , by fit to the exponential equation $OD = OD_0 \cdot 2^{g \cdot t} + OD_{BG}$ (blue and red lines; blue and red dots indicate manual interference in the determining the exponential interval). The calculated growth rate is normalized by the growth rate in the no-drug wells (dashed line), and the normalized growth rate g/g_0 (indicated) is the average of the two replicate wells. Data presented for all the experimental settings: **a**, CIP-TET and ERY-TET 2-D gradient applied to *E. coli*, **b**, drug-pair combinations applied to *E. coli*, **c**, combinations of more than two drugs applied to *E. coli*, **d**, drug combination not involving beta-lactam antibiotics applied to *S. aureus*, **e**, drug combination involving beta-lactam antibiotics applied to *S. aureus*, **f**, drug combinations applied to *E. faecalis* and **g**, drug combinations applied to *S. cerevisiae*. The drug mixture represented by the the capital letters in Supplementary Tables 2 - 8 respectively. (for example, in the drug pairs (b) the curve of -B--B----- is the second concentration ($8.47 \cdot 10^{-2}$ and $6 \mu\text{g/ml}$) of TET and FUS, respectively).











Supplementary Figure 13. Single drug dose response curves fit the Hill equation. Bacterial response to gradient of single (black dots represent the duplicate measurements) fit to Hill equation, $g/g_0 = \frac{1}{1+(d_i/d_i^{50})^h}$ (black line). Data present the single drugs from all the co-potent line experiments: **a**, drug-pair combinations applied to *E. coli*, **b**, combinations of more than two drugs applied to *E. coli*, **c**, drug combination not involving beta-lactam antibiotics applied to *S. aureus*, **d**, drug combination involving beta-lactam antibiotics applied to *S. aureus*, **e**, drug combinations applied to *E. faecalis* and **f**, drug combinations applied to *S. cerevisiae*. Duplicate measurements on the same day show very similar results (two points in each drug concentration). Replicate of the experiment in different days show slight differences, with hill coefficients varying by 20% on average (with maximal observed variation of 38% observed for PHL).

Supplementary Table 1. List of antibiotic used in the study

Antibiotic	Abr.	Cellular Process	Target	Organizms
Rifampicin	RIF	RNA synthesis	RNA polymerase	EC, EF
Tetracycline	TET	Translation	30S subunit of rRNA	EC, SA, EF
Chloramphenicol	CHL	Translation	23S subunit of rRNA	EC, EF
Erythromycin	ERY	Translation	50s subunit of rRNA	EC, SA
Fusaric acid	FUS	Unknown	Dopamine beta-hydroxylase	EC
Ciprofloxacin	CIP	DNA Synthesis	Gyrase	EC, SA, EF
Cefoxitin	FOX	Cell Wall	PBP	EC
Sulfamethoxazole	SMX	DNA Synthesis	DHPS	EC, SA
Trimetoprim	TMP	DNA Synthesis	DHFR	EC, SA, EF
Phleomycin	PHL	DNA ds Breaks	DNA	EC
Fusidic acid	FUD	Translation	Elongation factor G	SA
Linezolid	LZD	Translation	23S subunit of rRNA	SA, EF
Mupirocin	MUP	Translation	Isoleucyl t-RNA synthetase	SA
Cefepime	FEP	Cell Wall	PBP	SA
Imipenem	IPM	Cell Wall	PBP	SA, EF
Amphotericin B	AMB	Cell membrane	Ergosterol	SC
Cycloheximide	CHX	Translation	60S subunit of rRNA	SC
5-Fluorocytosine	5FC	Transcription	RNA	SC
Fluconazole	FLC	Cell membrane	14 α -demethylase	SC
Tavaborole	TAV	Translation	Leucyl-tRNA synthetase	SC

Supplementary Table 2. Comparison of Loewe, Bliss and Fisher model for null additivity

Method	Assumption	Accuracy for multitude of drugs in combination	Language	Requires precise measurements of small effects	Implementation
Loewe - Dosage additivity	A drug does not interact with itself	Low	Dosage	No	$d_1/d_1^{50} + d_2/d_2^{50} = 1$
Bliss - Response additivity	Effect independence	High	Response	Yes	$E_{1+2} = E_1 + E_2$
“Fisher” - Dosage orthogonality	Effect independence, small perturbation	High	Dosage	No	$(d_1/d_1^{50})^2 + (d_2/d_2^{50})^2 = 1$

Supplementary Table 3. The concentrations of antibiotics applied to *E. coli* in drug-pairs experiments

	RIF ($\mu\text{g/ml}$)	TET ($\mu\text{g/ml}$)	CHL ($\mu\text{g/ml}$)	ERY ($\mu\text{g/ml}$)	FUS ($\mu\text{g/ml}$)	CIP ($\mu\text{g/ml}$)	FOX ($\mu\text{g/ml}$)	SMX ($\mu\text{g/ml}$)	TMP ($\mu\text{g/ml}$)	PHL ($\mu\text{g/ml}$)
A	1.71E+00	5.40E-02	3.76E-01	1.35E+00	4.00E+00	5.33E-03	3.60E+00	6.93E-03	4.00E-03	3.02E+00
B	1.97E+00	8.47E-02	5.84E-01	2.67E+00	6.00E+00	6.13E-03	4.24E+00	1.36E-02	9.33E-03	3.48E+00
C	2.29E+00	1.33E-01	8.80E-01	4.80E+00	1.00E+01	6.93E-03	4.96E+00	2.67E-02	2.27E-02	4.00E+00
D	2.72E+00	2.13E-01	1.36E+00	9.07E+00	1.60E+01	8.00E-03	5.80E+00	5.33E-02	5.33E-02	4.60E+00
E	3.15E+00	3.33E-01	2.16E+00	1.71E+01	2.60E+01	9.20E-03	6.80E+00	1.07E-01	1.28E-01	5.30E+00
F	3.68E+00	5.20E-01	3.36E+00	3.20E+01	4.16E+01	1.05E-02	7.96E+00	2.08E-01	2.93E-01	6.10E+00
G	4.32E+00	8.13E-01	5.20E+00	6.00E+01	6.72E+01	1.20E-02	9.27E+00	4.11E-01	7.20E-01	7.02E+00
H	5.01E+00	1.29E+00	8.08E+00	1.13E+02	1.08E+02	1.37E-02	1.09E+01	8.10E-01	1.76E+00	8.07E+00
I	5.86E+00	2.03E+00	1.25E+01	2.13E+02	1.74E+02	1.57E-02	1.27E+01	1.60E+00	4.21E+00	9.30E+00
J	6.82E+00	3.20E+00	1.93E+01	4.00E+02	2.81E+02	1.80E-02	1.49E+01	3.17E+00	1.01E+01	1.07E+01

Supplementary Table 4 . The concentrations of antibiotics applied to *E. coli* in multi-drug experiments.

	RIF ($\mu\text{g/ml}$)	TET ($\mu\text{g/ml}$)	CHL ($\mu\text{g/ml}$)	ERY ($\mu\text{g/ml}$)	FUS ($\mu\text{g/ml}$)	CIP ($\mu\text{g/ml}$)	FOX ($\mu\text{g/ml}$)	SMX ($\mu\text{g/ml}$)	TMP ($\mu\text{g/ml}$)	PHL ($\mu\text{g/ml}$)
A	5.87E-01	4.67E-03	2.80E-02	4.00E-02	8.60E-01	2.13E-03	1.68E+00	5.33E-04	8.31E-05	1.40E+00
B	6.93E-01	7.33E-03	4.80E-02	6.67E-02	1.28E+00	2.53E-03	1.96E+00	1.07E-03	1.66E-04	1.66E+00
C	8.53E-01	1.20E-02	7.60E-02	1.47E-01	1.88E+00	2.93E-03	2.28E+00	1.87E-03	3.33E-04	1.98E+00
D	1.01E+00	1.93E-02	1.24E-01	2.80E-01	2.80E+00	3.47E-03	2.64E+00	3.73E-03	6.66E-04	2.36E+00
E	1.23E+00	3.13E-02	1.96E-01	5.47E-01	4.00E+00	4.13E-03	3.04E+00	7.20E-03	1.33E-03	2.81E+00
F	1.44E+00	4.93E-02	3.16E-01	1.07E+00	6.00E+00	4.80E-03	3.52E+00	1.36E-02	2.67E-03	3.34E+00
G	1.76E+00	7.87E-02	5.08E-01	2.08E+00	9.20E+00	5.60E-03	4.08E+00	2.59E-02	8.00E-03	3.98E+00
H	2.08E+00	1.20E-01	8.00E-01	4.00E+00	1.36E+01	6.40E-03	4.72E+00	4.80E-02	2.00E-02	4.74E+00
I	2.51E+00	2.00E-01	1.28E+00	8.00E+00	2.00E+01	7.60E-03	5.44E+00	9.60E-02	4.80E-02	5.63E+00
J	2.99E+00	3.20E-01	2.08E+00	1.57E+01	2.96E+01	8.80E-03	6.28E+00	1.81E-01	1.20E-01	6.71E+00
K	3.57E+00	5.07E-01	3.36E+00	3.07E+01	4.36E+01	1.03E-02	7.28E+00	3.47E-01	2.93E-01	7.98E+00
L	4.32E+00	8.13E-01	5.36E+00	6.00E+01	6.48E+01	1.20E-02	8.40E+00	6.61E-01	7.20E-01	9.49E+00
M	5.17E+00	1.29E+00	8.56E+00	1.17E+02	9.55E+01	1.40E-02	9.71E+00	1.26E+00	1.81E+00	1.13E+01
N	6.18E+00	2.07E+00	1.38E+01	2.30E+02	1.41E+02	1.63E-02	1.12E+01	2.41E+00	4.45E+00	1.34E+01
O	7.41E+00	3.30E+00	2.20E+01	4.50E+02	2.10E+02	1.89E-02	1.30E+01	4.60E+00	1.10E+01	1.60E+01

Supplementary Table 5 . The concentrations of antibiotics applied to *S. aureus* in experiments not involved beta-lactam antibiotics

	CIP ($\mu\text{g/ml}$)	ERY ($\mu\text{g/ml}$)	FUD ($\mu\text{g/ml}$)	LZD ($\mu\text{g/ml}$)	MUP ($\mu\text{g/ml}$)	TET ($\mu\text{g/ml}$)	TMP ($\mu\text{g/ml}$)
A	1.24E-02	6.67E-04	6.67E-06	2.67E-04	6.93E-04	4.00E-05	3.11E-02
B	1.60E-02	1.07E-03	2.00E-05	8.00E-04	1.01E-03	7.33E-05	3.89E-02
C	1.96E-02	1.87E-03	4.00E-05	1.33E-03	1.52E-03	1.40E-04	4.89E-02
D	2.40E-02	2.93E-03	7.33E-05	2.67E-03	2.24E-03	2.67E-04	6.22E-02
E	2.93E-02	4.80E-03	1.53E-04	5.07E-03	3.33E-03	5.20E-04	7.56E-02
F	3.64E-02	8.00E-03	3.07E-04	9.87E-03	4.80E-03	1.01E-03	9.33E-02
G	4.53E-02	1.29E-02	6.20E-04	1.87E-02	7.47E-03	2.00E-03	1.16E-01
H	5.69E-02	2.12E-02	1.20E-03	3.55E-02	1.12E-02	3.73E-03	1.47E-01
I	7.02E-02	3.47E-02	2.53E-03	6.93E-02	1.65E-02	7.33E-03	1.82E-01
J	8.71E-02	5.60E-02	5.07E-03	1.28E-01	2.45E-02	1.41E-02	2.27E-01
K	1.08E-01	9.33E-02	1.03E-02	2.45E-01	3.63E-02	2.75E-02	2.84E-01
L	1.33E-01	1.52E-01	2.09E-02	4.64E-01	5.44E-02	5.31E-02	3.55E-01
M	1.65E-01	2.48E-01	4.22E-02	8.85E-01	8.05E-02	1.03E-01	4.44E-01
N	2.05E-01	4.05E-01	8.55E-02	1.68E+00	1.20E-01	1.99E-01	5.55E-01
O	2.54E-01	6.64E-01	1.73E-01	3.20E+00	1.79E-01	3.86E-01	6.93E-01

Supplementary Table 6 . The concentrations of antibiotics applied to *S. aureus* in experiments involved beta-lactam antibiotics

	CIP ($\mu\text{g/ml}$)	ERY ($\mu\text{g/ml}$)	FUD ($\mu\text{g/ml}$)	LZD ($\mu\text{g/ml}$)	MUP ($\mu\text{g/ml}$)	TET ($\mu\text{g/ml}$)	TMP ($\mu\text{g/ml}$)	FEP ($\mu\text{g/ml}$)	IPM ($\mu\text{g/ml}$)
A	1.24E-02	6.67E-04	6.67E-06	2.67E-04	6.93E-04	4.00E-05	3.11E-02	7.62E-01	4.53E-03
B	1.60E-02	1.07E-03	2.00E-05	8.00E-04	1.01E-03	7.33E-05	3.89E-02	8.13E-01	5.07E-03
C	1.96E-02	1.87E-03	4.00E-05	1.33E-03	1.52E-03	1.40E-04	4.89E-02	8.69E-01	5.33E-03
D	2.40E-02	2.93E-03	7.33E-05	2.67E-03	2.24E-03	2.67E-04	6.22E-02	9.27E-01	5.87E-03
E	2.93E-02	4.80E-03	1.53E-04	5.07E-03	3.33E-03	5.20E-04	7.56E-02	9.88E-01	6.40E-03
F	3.64E-02	8.00E-03	3.07E-04	9.87E-03	4.80E-03	1.01E-03	9.33E-02	1.05E+00	6.93E-03
G	4.53E-02	1.29E-02	6.20E-04	1.87E-02	7.47E-03	2.00E-03	1.16E-01	1.13E+00	7.47E-03
H	5.69E-02	2.12E-02	1.20E-03	3.55E-02	1.12E-02	3.73E-03	1.47E-01	1.20E+00	8.27E-03
I	7.02E-02	3.47E-02	2.53E-03	6.93E-02	1.65E-02	7.33E-03	1.82E-01	1.28E+00	9.07E-03
J	8.71E-02	5.60E-02	5.07E-03	1.28E-01	2.45E-02	1.41E-02	2.27E-01	1.37E+00	9.60E-03
K	1.08E-01	9.33E-02	1.03E-02	2.45E-01	3.63E-02	2.75E-02	2.84E-01	1.46E+00	1.07E-02
L	1.33E-01	1.52E-01	2.09E-02	4.64E-01	5.44E-02	5.31E-02	3.55E-01	1.56E+00	1.15E-02
M	1.65E-01	2.48E-01	4.22E-02	8.85E-01	8.05E-02	1.03E-01	4.44E-01	1.67E+00	1.25E-02
N	2.05E-01	4.05E-01	8.55E-02	1.68E+00	1.20E-01	1.99E-01	5.55E-01	1.78E+00	1.36E-02
O	2.54E-01	6.64E-01	1.73E-01	3.20E+00	1.79E-01	3.86E-01	6.93E-01	1.90E+00	1.47E-02

Supplementary Table 7 . The concentrations of antibiotics applied to *E. faecalis*

	CHL ($\mu\text{g/ml}$)	CIP ($\mu\text{g/ml}$)	LZD ($\mu\text{g/ml}$)	RIF ($\mu\text{g/ml}$)	TMP ($\mu\text{g/ml}$)	IPM ($\mu\text{g/ml}$)
A	2.40E-02	1.55E-02	3.73E-03	5.33E-03	1.49E-02	1.41E-01
B	3.73E-02	1.80E-02	5.33E-03	9.33E-03	3.47E-02	1.57E-01
C	5.60E-02	2.11E-02	8.27E-03	1.33E-02	8.27E-02	1.79E-01
D	8.53E-02	2.40E-02	1.25E-02	2.13E-02	1.92E-01	2.03E-01
E	1.29E-01	2.93E-02	1.89E-02	3.33E-02	4.50E-01	2.29E-01
F	1.97E-01	3.47E-02	2.88E-02	5.20E-02	1.06E+00	2.59E-01
G	2.93E-01	4.00E-02	4.37E-02	8.27E-02	2.53E+00	2.93E-01
H	4.53E-01	4.53E-02	6.40E-02	1.28E-01	5.87E+00	3.31E-01
I	6.93E-01	5.33E-02	1.01E-01	2.01E-01	1.36E+01	3.76E-01
J	1.07E+00	6.40E-02	1.55E-01	3.20E-01	3.18E+01	4.24E-01
K	1.60E+00	7.47E-02	2.35E-01	4.80E-01	7.47E+01	4.80E-01
L	2.45E+00	8.80E-02	3.52E-01	7.73E-01	1.75E+02	5.44E-01
M	3.73E+00	1.04E-01	5.33E-01	1.20E+00	4.10E+02	6.13E-01
N	5.68E+00	1.20E-01	8.10E-01	1.87E+00		6.96E-01
O	8.66E+00	1.41E-01	1.23E+00	2.93E+00		7.86E-01

Supplementary Table 8 . The concentrations of antifungal drugs applied to *S. cerevisiae*

	AMB ($\mu\text{g/ml}$)	CHX ($\mu\text{g/ml}$)	5FC ($\mu\text{g/ml}$)	FCL ($\mu\text{g/ml}$)	TAV ($\mu\text{g/ml}$)
A	2.00E-02	1.60E-04	5.87E-04	2.56E+00	9.67E-03
B	2.40E-02	3.20E-04	1.49E-03	2.99E+00	1.33E-02
C	2.80E-02	5.87E-04	3.74E-03	3.52E+00	1.87E-02
D	3.33E-02	1.15E-03	9.45E-03	4.11E+00	2.53E-02
E	4.00E-02	2.19E-03	2.38E-02	4.80E+00	3.47E-02
F	4.80E-02	4.21E-03	5.87E-02	5.60E+00	4.67E-02
G	5.73E-02	8.13E-03	1.52E-01	6.56E+00	6.40E-02
H	6.80E-02	1.60E-02	3.81E-01	7.68E+00	8.80E-02
I	8.13E-02	3.07E-02	9.59E-01	8.96E+00	1.20E-01
J	9.60E-02	5.73E-02	2.42E+00	1.05E+01	1.65E-01
K	1.15E-01	1.12E-01	6.10E+00	1.23E+01	2.25E-01
L	1.36E-01	2.15E-01	1.54E+01	1.43E+01	3.09E-01
M	1.63E-01	4.13E-01		1.68E+01	4.24E-01
N	1.93E-01	7.95E-01		1.97E+01	5.81E-01
O	2.29E-01	1.53E+00		2.30E+01	7.96E-01

Supplementary Table 9. Dose response of all drug combinations.

Available as an external file. Contains drug concentrations and calculated normalised growth rates of duplicate measurements for all drug combinations in the experiments (xlsx sheet name in parenthesis): pairs of drugs applied to *E. coli* (EC_Pairs); Drug combinations of over two drugs applied to *E. coli* (EC_Multi); Drug combinations not containing Beta-lactam antibiotics applied to *S. aureus* (SA_Multi); Drug combinations containing Beta-lactam antibiotics applied to *S. aureus* (SA_BL); Drug combinations applied to *E. faecalis* (EF); Drug combinations applied to *S. cerevisiae* (SC).

Supplementary Table 10. Measured and predicted potencies of drug combinations.

Available as an external file. Contains the measured combination potency as well as the potency predicted by each of the models in the experiments (xlsx sheet name in parenthesis): pairs of drugs applied to *E. coli* (EC_Pairs); Drug combinations of over two drugs applied to *E. coli* (EC_Multi); Drug combinations not containing Beta-lactam antibiotics applied to *S. aureus* (SA_Multi); Drug combinations containing Beta-lactam antibiotics applied to *S. aureus* (SA_BL); Drug combinations applied to *E. faecalis* (EF); Drug combinations applied to *S. cerevisiae* (SC).

Reference

1. Kilic, S., Dizbay, M., Hizel, K. & Arman, D. In vitro synergistic activity of antibiotic combinations against *Brucella melitensis* using E-test methodology. *Braz. J. Microbiol.* **39**, 233–237 (2008).