Supplementary Information

Evolutionary paths to antibiotic resistance under dynamically sustained drug selection

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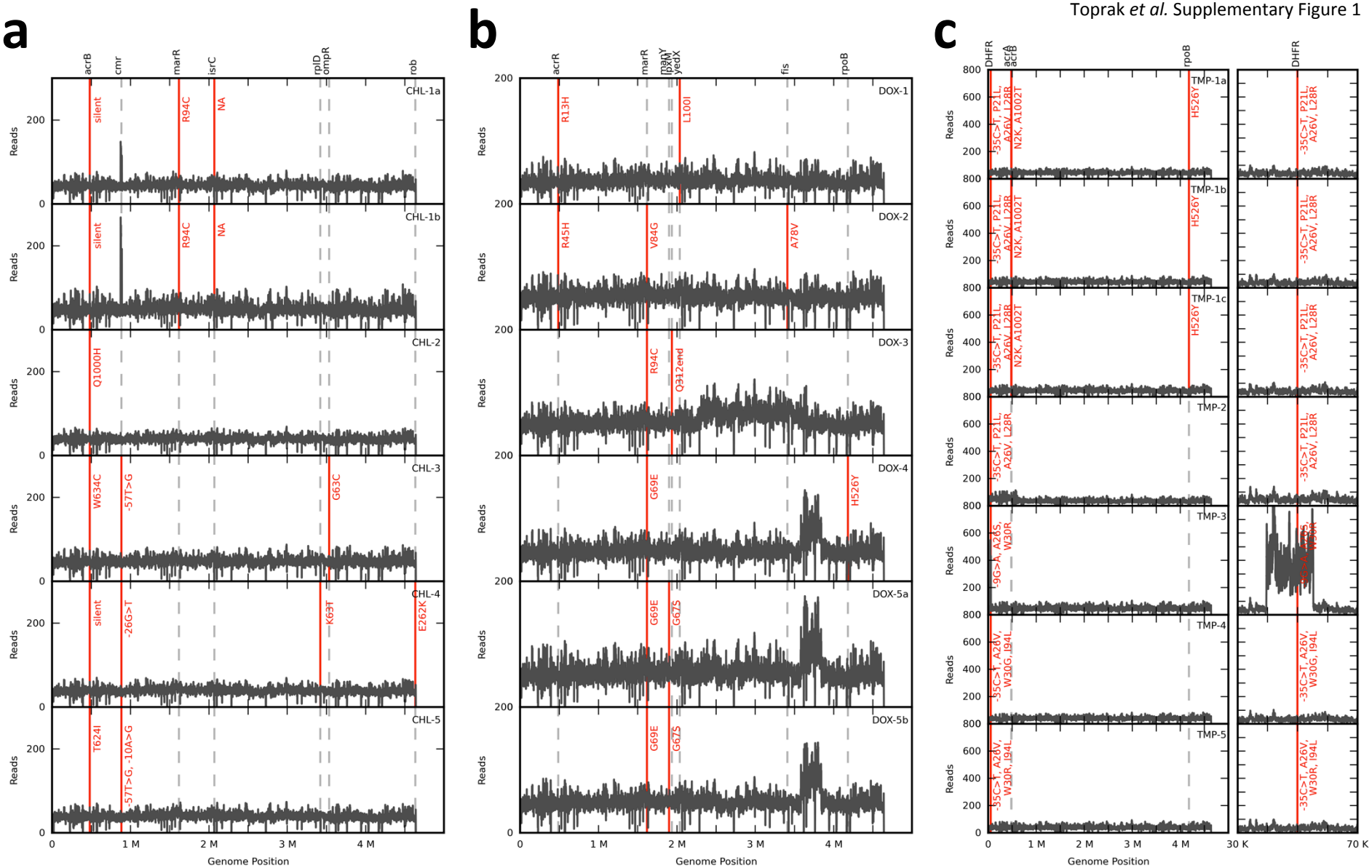

Supplementary Figure 1: Number of reads per genome positions of the drug resistant strains. Vertical lines indicate positions of SNPs in the genome, with the mutated gene names identified at the top of the figure. When mutated, the specific change is identified in the strain's plot. **a**, CHL-1a and CHL-1b are two colonies isolated from CHL-1. Both these colonies display gene amplification in the genome region containing the *cmr* gene. The remaining four strains, CHL-2,5 do not show evidence for gene amplification. **b,** Strains DOX-4, DOX-5a and DOX-5b (a and b are two colonies isolated from DOX-5) show evidence of genomic amplification in the genomic region delimited by positions ~3580000-3840000. Strains DOX-1,3 do not show evidence of genomic amplification. **c,** Strain TMP-3 shows evidence of strong gene amplification in the ~40,000-55,000 region of genome. This region contains the DHFR gene. The left panels show the number of per reads per position of the whole genome. The right panels highlight the amplification of the DHFR locus. Comparison of average number of reads per position indicate amplification as strong as 6-fold compared to the genome average. The remaining strains do not exhibit instances of gene amplification.

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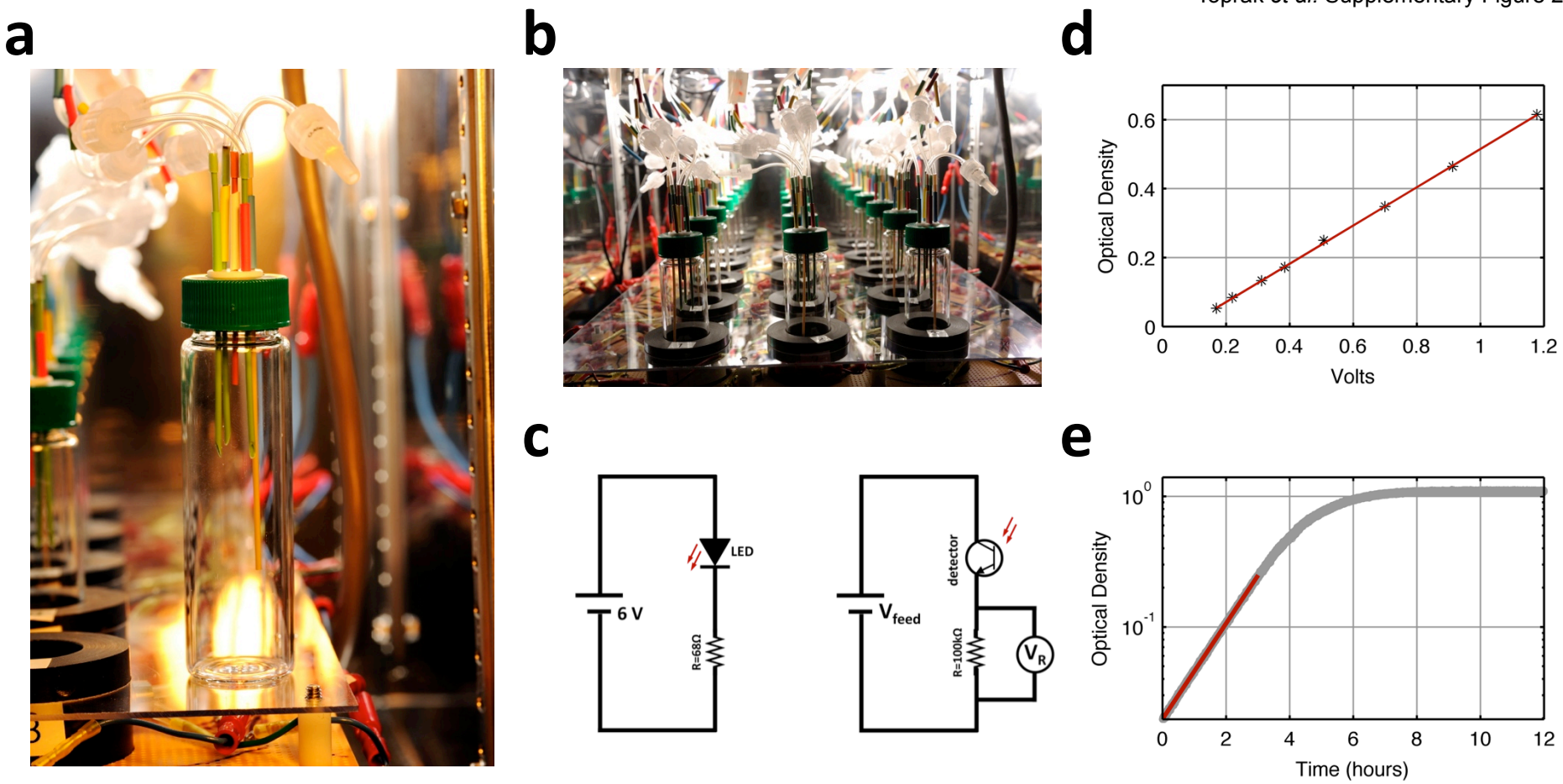

Supplementary Figure 2: Schematics of the morbidostat. a, Morbidostat culture tube. **b,** Assembled morbidostat device. The entire apparatus sits in a commercial incubator for temperature control. **c,** Circuits for the light detection system. Photos (a-b) taken by Len Rubenstein. **d,** A sample calibration curve. 1 OD unit corresponds to 5 x10^8 cells/ml. **e,** A sample growth curve for *E. Coli* cells growing in minimal media at 30 celcius. Cells grow exponentially when OD is less than ~0.3. An exponential function is fitted to calculate the growth rate (red line).

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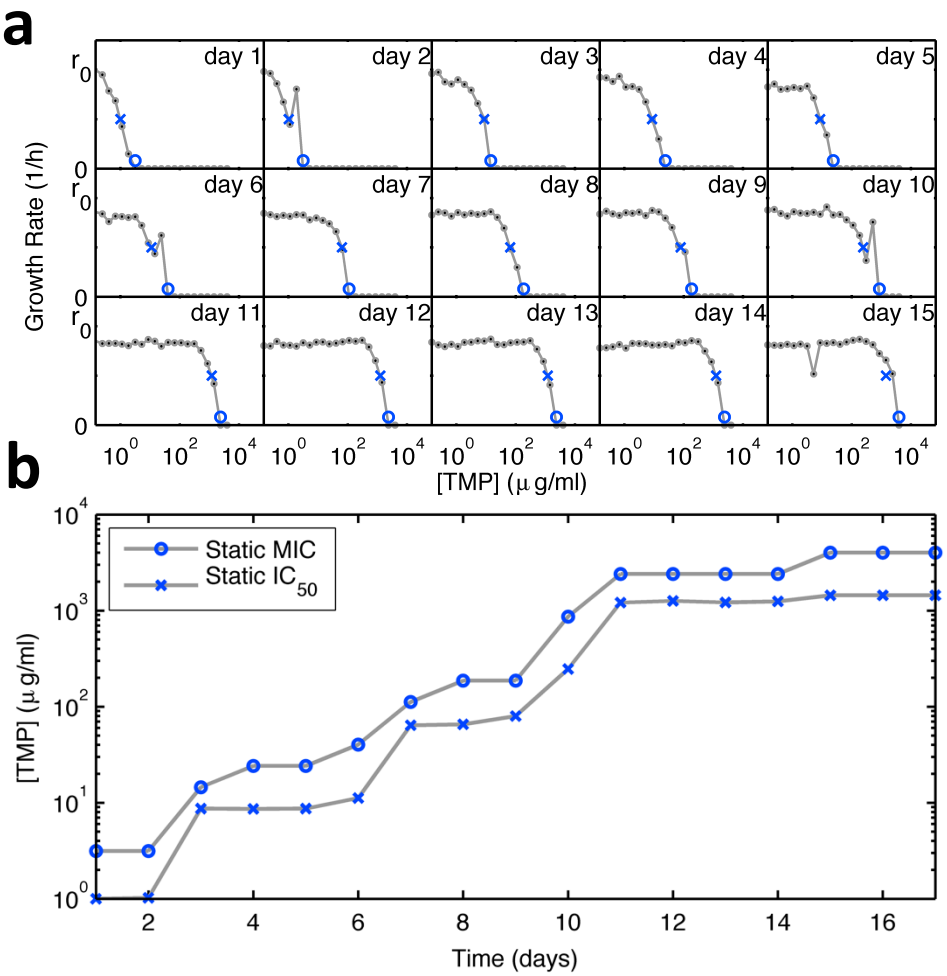

Supplementary Figure 3: Procedure for calculating static MIC and IC_{50} values. **a,** Cells from the daily time course of the evolution experiment were grown in 20 different concentration of drug, and their growth rate was measured. Static IC_{50} values (blue cross marks) and static MIC values (blue circles) are defined as the drug concentration at which the growth rate is 50% and 10% of the maximal growth rate (exponential growth rate in the absence of drugs) respectively. **b,** The temporal changes of static IC_{50} and MIC values

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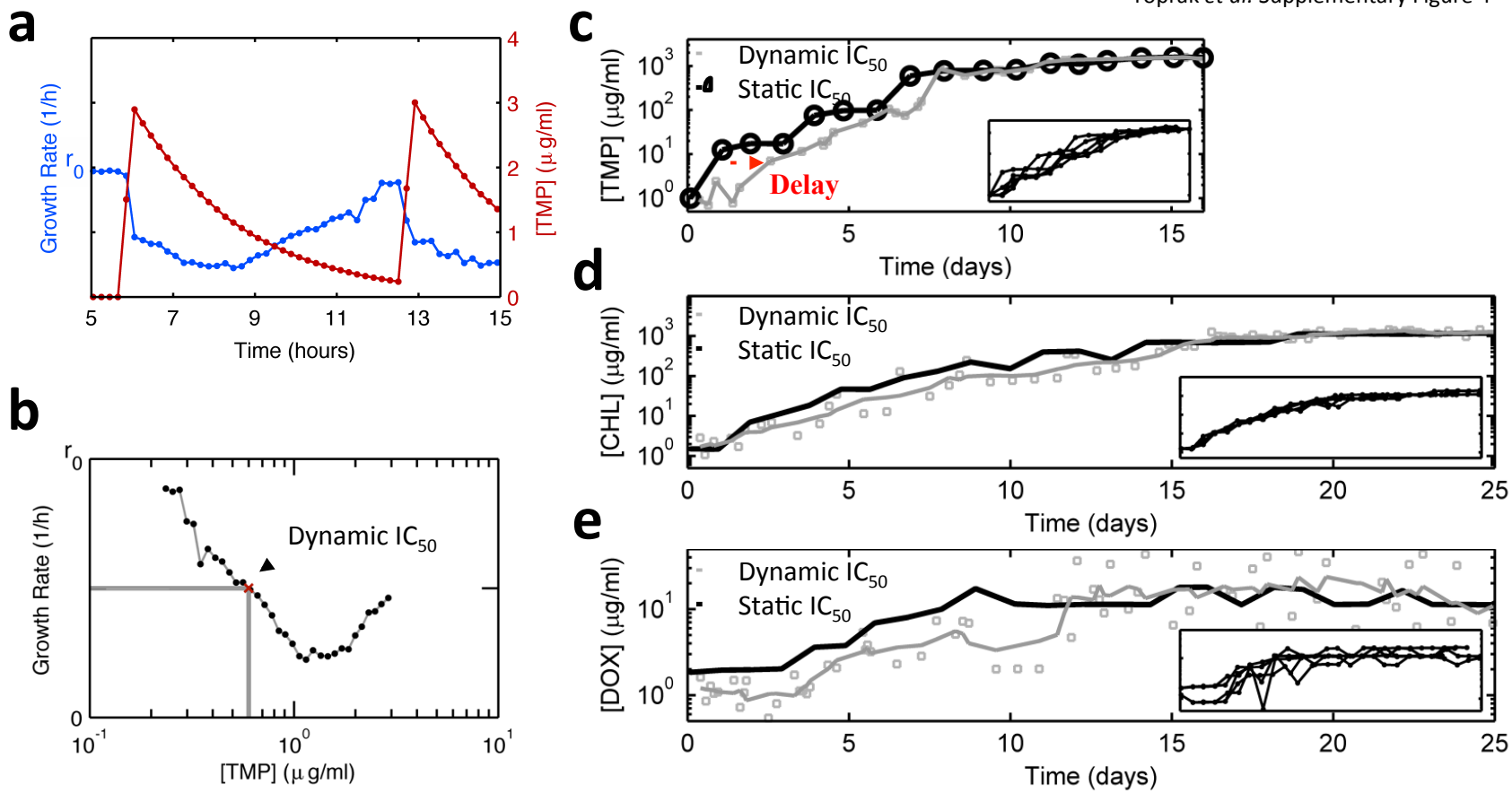

Supplementary Figure 4: Phenotypic changes of drug resistant cultures. a, Growth rates (blue) and calculated drug concentrations (red) corresponding to the time period of Fig. 1c. **b,** Growth rate is plotted as a function of drug concentrations, and the drug concentration that reduces growth by ~50% is defined as the dynamic IC50 (red dot, arrow). **c,** Dynamic (gray line) and static IC50 (black line) values for the strains TMP-1; **d,** CHL-1; and **e,** DOX-5 respectively. Insets show the static IC50 values for all five parallel evolving strains. Dynamic IC50 values trail static IC50 values as shown with the red arrow in panel c.

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strain	drug used	[Drug] (µg/ml)	cell size (µm)
Parental drug sensitive MG1655	none	0	2.19 ± 0.47
Parental drug sensitive MG1655	Chloramphenicol	1.6	2.35 ± 0.54
Parental drug sensitive MG1655	Doxycycline	0.6	2.71 ± 0.56
Parental drug sensitive MG1655	Trimethoprim	0.8	3.59 ± 0.87
Chloramphenicol resistant strain	none	0	2.32 ± 0.58
Chloramphenicol resistant strain	Chloramphenicol	800	2.47 ± 0.64
Doxycycline resistant strain	none	0	2.37 ± 0.82
Doxycycline resistant strain	Doxycycline	10	2.69 ± 0.90
Trimethoprim resistant strain	none	0	2.33 ± 0.51
Trimethoprim resistant strain	Trimethoprim	1250	2.39 ± 0.69

Supplementary Table 1: Cell size changes of drug resistant mutants. Wild type drug sensitive and evolved *E. coli* strains were grown overnight in a drug gradient using a 96 well plate. Cells that are grown in sub-inhibitory drug concentrations close to IC50 were imaged on 3% agar pads under phase illumination. Cell sizes were measured using a custom matlab code. Cell size = median value ± standart deviation. 200 cells are profiled for every experimental condition.

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Populations	Drug Used	Day	Site	SNP	Mutation	Gene	Gene Name	Function (UCSC genome browser)	fraction of mutants	Uniprot Ref	Impact
TMP-1	Trimethoprim	16	484838	G→T	N2K	b0463	acrA	multidrug efflux system	**4/4**	ACRA_ECOLI	low
CHL-2	Chloramphenicol	22	480628	C→A	Q1000H	b0462	acrB	multidrug efflux system protein	**2/5**	ACRB_ECOLI	high
CHL-1,4	Chloramphenicol	22	480645	C→A	silent	b0462	acrB	multidrug efflux system protein	**6/6,5/5**	ACRB_ECOLI	NA
CHL-3	Chloramphenicol	22	481726	C→A	W634C	b0462	acrB	multidrug efflux system protein	**4/5**	ACRB_ECOLI	high
CHL-5	Chloramphenicol	22	481757	G→A	T624I	b0462	acrB	multidrug efflux system protein	**3/5**	ACRB_ECOLI	medium
TMP-1	Trimethoprim	16	480624	C→T	A1002T	b0462	acrB	multidrug efflux system protein	**4/4**	ACRB_ECOLI	high
DOX-1	Doxycycline	22	485022	G→A	R13H	b0464	acrR	acrAB operon repressor	**5/5**	ACRR_ECOLI	high
DOX-2	Doxycycline	22	3409525	C→T	A78V	b3261	fis	transcriptional regulator	**5/5**	FIS_ECOLI	high
TMP-1,2	Trimethoprim	16	49884	C→T	P21L	b0048	folA	DNA Synthesis	**4/4,4/4**	DYR_ECOLI	high
TMP-1,2,3	Trimethoprim	16	49905	T→G	L28R	b0048	folA	DNA Synthesis	**4/4,4/4,4/4**	DYR_ECOLI	high
TMP-3,5	Trimethoprim	16	49910	T→A	W30R	b0048	folA	DNA Synthesis	**4/4,4/4,4/4**	DYR_ECOLI	medium
TMP-4	Trimethoprim	3	49912	G→T	W30C	b0048	folA	DNA Synthesis	**4/4**	DYR_ECOLI	medium
TMP-5	Trimethoprim	16,19	49910	T→G	W30G	b0048	folA	DNA Synthesis	**4/4,4/4**	DYR_ECOLI	medium
TMP-1,3,5	Trimethoprim	18,16,16	49898	G→A	A26T	b0048	folA	DNA Synthesis	**4/4,4/4,4/4**	DYR_ECOLI	medium
TMP-2	Trimethoprim	17	49899	C→T	A26V	b0048	folA	DNA Synthesis	**4/4**	DYR_ECOLI	medium
TMP-4	Trimethoprim	18	49898	G→T	A26S	b0048	folA	DNA Synthesis	**1/4**	DYR_ECOLI	medieum
TMP-4,5	Trimethoprim	16	50102	A→C	I94L	b0048	folA	DNA Synthesis	**4/4,4/4**	DYR_ECOLI	medium
TMP-1,2,4,5	Trimethoprim	16	49765	C→T	promoter	b0048 promoter	folA promoter	DNA Synthesis	**4/4,4/4,4/4,4/4**	NA	NA
TMP-3	Trimethoprim	16	49791	G→A	promoter	b0048 promoter	folA promoter	DNA Synthesis	**4/4**	NA	NA
DOX-3	Doxycycline	22	1937284	G→A	Q312* (end)	b1855	lpxM	acyltransferase	**5/5**	MSBB_ECOLI	NA
DOX-5	Doxycycline	22	1901304	G→A	G67S	b1818	manY	mannose-specific enzymeS	**6/6**	PTNC_ECOLI	high
CHL-1	Chloramphenicol	22	1617423	C→T	R94C	b1530 marR	marR	repressor of mar operon	**6/6**	MARR_ECOLI	NA
DOX-2	Doxycycline	22	1617394	T→G	V84G	b1530 marR	marR	repressor of mar operon	**5/5**	MARR_ECOLI	NA
DOX-3	Doxycycline	22	1617423	C→T	R94C	b1530 marR	marR	repressor of mar operon	**5/5**	MARR_ECOLI	NA
DOX-4, 5	Doxycycline	22	1617349	G→A	G69E	b1530 marR	marR	repressor of mar operon	**5/5, 6/6**	MARR_ECOLI	NA
CHL-3,5	Chloramphenicol	22	882839	T→G	promoter	b0842 promoter	cmr	multidrug efflux system protein	**5/5,5/5**	NA	NA
CHL-4	Chloramphenicol	22	882870	G→T	promoter	b0842 promoter	cmr	multidrug efflux system protein	**4/5**	NA	NA
CHL-5	Chloramphenicol	22	882886	A→G	promoter	b0842 promoter	cmr	multidrug efflux system protein	**2/4**	NA	NA
CHL-3	Chloramphenicol	22	3534420	C→A	G63C	b3405	ompR	DNA-binding response regulator	**4/5**	OMPR_ECOLI	high
CHL-4	Chloramphenicol	22	4632550	C→T	E262K	b4396	rob	DNA-binding transcriptional activator	**5/5**	ROB_ECOLI	high
CHL-4	Chloramphenicol	22	3450121	T→G	K63T	b3319	rplD	50S ribosomal subunit protein L4	**4/5**	RL4_ECOLI	high
TMP-1	Trimethoprim	16	4180843	C→T	H526Y	b3987	rpoB	RNA polymerase, beta subunit	**4/4**	RPOB_ECOLI	low
CHL-1	Chloramphenicol	22	2069404	A→G	NA	b4435	isrC	Novel sRNA, function unknown	**6/6**	NA	NA
DOX-2	Doxycycline	22	485118	G→A	R45H	b0464	acrR	acrAB operon repressor	1/5	ACRR_ECOLI	medium
DOX-1	Doxycycline	22	2037277	C→A	L100I	b1970	yedX	Hydroxyisourate hydrolase	1/5	HIUH_ECOLI	low
DOX-4	Doxycycline	22	4180465	G→C	V400L	b3987	rpoB	RNA polymerase, beta subunit	1/5	RPOB_ECOLI	high

Supplementary Table 2: The complete list of SNPs and their predicted effects. Each row corresponds to a culture that was sequenced with both Illumina and Sanger sequencing.

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Mutant	[Trimethoprim]	SNP	Observed in morbidostat
5_1	94µg/ml	49905 T→G (L28R)	**yes**
5_2	94µg/ml	49905 T→G (L28R)	**yes**
5_3	94µg/ml	none	
6_1	47 µg/ml	none	
6_2	47 µg/ml	none	
7_1	24 µg/ml	none	
8_1	12µg/ml	none	
8_2	12µg/ml	none	
8_3	12µg/ml	none	
8_4	12µg/ml	none	
8_5	12µg/ml	none	
8_6	12µg/ml	none	
8_7	12µg/ml	none	
8_A	12µg/ml	49765 C→T (promoter -35C>T)	**yes**
8_B	12µg/ml	49765 C→T (promoter -35C>T)	**yes**
9_1	6 µg/ml	49912 G→T (W30C)	**yes**
9_2	6 µg/ml	49912 G→T (W30C)	**yes**
9_3	6 µg/ml	49912 G→T (W30C)	**yes**
9_4	6 µg/ml	49912 G→T (W30C)	**yes**
9_5	6 µg/ml	none	
9_6	6 µg/ml	49912 G→T (W30C)	**yes**
9_7	6 µg/ml	49912 G→T (W30C)	**yes**
9_8	6 µg/ml	none	
9_9	6 µg/ml	49912 G→T (W30C)	**yes**
9_10	6 µg/ml	none	
10_1	3 µg/ml	none	
10_2	3 µg/ml	none	
10_3	3 µg/ml	49791 G→A (promoter -9G>A)	**yes**
10_4	3 µg/ml	49795 C→A promoter (-5C>A)	**no**
10_5	3 µg/ml	49912 G→T (W30C)	**yes**
10_6	3 µg/ml	none	
10_7	3 µg/ml	none	
10_A	3 µg/ml	49765 C→T (promoter -35C>T)	**yes**
10_B	3 µg/ml	49765 C→T (promoter -35C>T)	**yes**
10_C	3 µg/ml	49903 t → g (D27E)	**no**
10_D	3 µg/ml	none	

Supplementary Table 3: DHFR mutations found using a plate based selection assay. Drug sensitive *E. coli* cells were plated on agar Petri dishes with different trimethoprim concentrations (10^9 cells per plate) and grown for 3 days. Mutants that appeared after 3 days were Sanger sequenced to identify mutations on the DHFR. Gray color is used for -35C>T and -9G>A promoter mutations, green is used for W30C, and magenta is used for L28R mutations. Novel mutations that were never observed in the morbidostat experiments are highlighted by yellow.

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Supplementary Note

Genomic Amplification

Instances of gene amplification were observed in a total of four strains evolved in the morbidostat. To identify regions likely to have been duplicated during the evolution process, the number of Illumina sequencing reads covering each position of the MG1655 genome were counted using the SAMTools software. The reads per position for each of the sequenced strains are plotted in **Supplementary Fig. 1**. The average number of reads per genome position was calculated for each strain and two-fold deviations in reads per position of continuous regions on the genome were identified. For the chloramphenicol-resistant strain CHL-1, a region between positions ~873,000-889,000 of the genome was duplicated in both sequenced replicates (**Supplementary Fig. 1a,** first two panels). This region contains the *cmr* multidrug resistance-related gene, whose promoter region is mutated in the CHL-3, CHL-4 and CHL-5 strains of the experiment. In the case of the two doxycycline resistant strains DOX-4 and DOX-5, our analysis picked up a much larger region (~3580000-3840000) of which multiple parts were amplified during the evolutionary process (**Supplementary Fig. 1b,** last three panels). Although several genes potentially related to doxycycline resistance exist in this region of the genome, no SNPs identified in the remaining DOX strains appear within the amplified region. Lastly, a single instance of gene amplification in the trimethoprim resistant strain TMP-3 was identified using the outlined procedure (**Supplementary Fig. 1c,** fifth panel). The ~40,000-55,000 region of the genome, which contains the DHFR gene and regulatory sequence, is strongly amplified. TMP-3 is the only strain with the -9G>A mutation in the promoter mutation, unlike the four other trimethoprim strains which exhibit the -35C>T promoter mutation. Although comparison of the average number of reads per position of the DHFR region and rest of the genome suggests that the region may be as much as 7-fold amplified, the SNPs present in the DHFR gene span all aligned Illumina reads. Given the unlikelihood that divergent copies of the DHFR gene evolve identical SNPs during the experiment, this indicates that the gene amplification process should have occurred late in the evolutionary path of TMP-13. These results highlight the potential of genomic amplifications to contribute to resistance phenotypes, similarly to single nucleotide polymorphisms. The role of genomic amplification seems to remain secondary to that of point mutations in the acquisition of resistance for the studied drugs.

Morbidostat Schematics

The morbidostat is a custom-designed automated microbial selection apparatus which can grow 15 independent bacterial cultures in parallel. Bacterial cells are grown in flat-bottomed glass tubes (www.chemglass.com, CG-4902-08). A custom-designed cap (www.chemglass.com, CV-3750-0024) with a Teflon insert which has five through holes (www.chemglass.com, HMS-0909-151GC) is used to

Nature Genetics: doi:10.1038/ng.1034

keep cultures sterile. Five pieces of PEEK (polyether ether ketone; www.fishersci.com, 05-701-6) tubing are inserted into these holes for adding or removing liquids. Three of these holes are used to inject fresh media and drug solutions. One of the holes is used to remove liquid from the culture for keeping the cell volume constant, and the last hole is used as an entrance for filtered air. The entire culture tube assembly is made out of autoclavable materials (**Supplementary Fig. 2a**). Fresh media and drug solutions are injected by the use of peristaltic pumps (http://www.clarksol.com, m045) that are operated at 1ml/minute flow rate. A separate 16 channel peristaltic pump is used as a waste pump (www.harvardapparatus.com, 73-3154). All of the pumps are computer-controlled by the use of relay switches (www.mccdaq.com, USB-ERB24). Autoclavable silicon tubing is used for liquid transfer purposes (www.vwrlabshop.com, 60985-708). Cells inside the glass tubes are continuously mixed by spinning a Teflon coated magnetic stir bar (http://www.stirbars.com, SBM2003MIC) by a 15 position magnetic stirrer (www.neutecgroup.com, F203A0177). The magnetic stirrer generally runs at 200 rpm. The magnetic stirrer is modified such that it can hold fifteen custom-made tube holders made out of black polycarbonate. Each tube holder has an integrated infrared light source and photodiode (www.radioshack.com, 276-0142) used to measure optical density. The final assembled apparatus,, shown in **Supplementary Fig. 2b,** sits in a temperature controlled incubator (VWR, cat # 1535).

Measuring optical density

The optical density of bacterial cells is measured via a matched pair of infrared LED and a phototransistor (www.radioshack.com, 276-0142). The angle between the optical axis of infrared light source and the detector is 135 degrees. The light emitted from the light source gets scattered by the cells inside the tube and falls onto the photodiode. The light-induced voltage changes on the detector are measured with a multichannel data acquisition device (www.mccdaq.com, USB-1616FS). The illumination and detection circuits are shown in **Supplementary Fig. 2c**. The components of the circuits were chosen such that 1 OD change in a culture would generate 2 volts. The voltage values are later converted to optical density (OD) by the calibration protocol described below.

Calibration of detectors

A linear mapping function ($OD=C.(V-V_{background})$) is used for calculating the optical density (OD) of cell cultures where C is the calibration factor, V is the voltage measured by the detection system for a cell culture, and $V_{background}$ is the voltage measured by the detection system for a culture tube filled with plain growth media. A cell culture with an optical density (OD) around 0.5-0.7 was used for calibrating the detection system. First, the voltage created by the cell culture was measured with our detection system. Immediately after this, the corresponding OD value of the cell culture was recorded with a conventional fluorometer. The cell culture was then diluted by ~25% and corresponding OD and voltage values were recorded. This procedure was repeated until the optical density of the cells went below 0.05. Voltage readings and corresponding OD values were than plotted against each other and a

Nature Genetics: doi:10.1038/ng.1034

line (OD=C.V+ offset) was fitted to find the calibrations factor 'C' as shown in **Supplementary Fig. 2d** (red line). This calibration procedure was done weekly for all fifteen detector systems. The weekly variation of the calibration factors even after several weeks of operation was typically less than 5%. The background ($V_{background}$) readings were done daily immediately before starting an experiment for every individual glass tube used. A sample growth curve in the morbidostat tube is shown in **Supplementary Fig. 2e**.

Drug solutions

Drug solutions (in M9 minimal media supplemented with 0.4% glucose and 0.2% amicase) were made from powder stocks and filtered. They were kept at room temperature in glass bottles wrapped with aluminum foil to avoid light induced drug degradation. Drug solutions were periodically tested by measuring the MIC of drug sensitive *E. Coli*. All drug solutions were stable over two weeks under these conditions. Each culture tube was connected to two separate drug solution containers (stock A and stock B). The drug concentration of stock A was generally 10 times MIC (of the wild type drug sensitive ancestor strain) at the beginning of the long term evolution experiment, and the drug concentration of stock B was generally 50 times MIC. All drug injections into morbidostat tubes are normally done from stock A. However, if the evolving population gained resistance and the growth of evolving cells could not be slowed even though the drug concentration inside the morbidostat tube was more than 60% of the concentration of stock A, then the injections were made from stock B. If the system ended up controlling the growth by making injections from stock B, we replaced stock A with stock B and stock B with a new drug solution that was five times more concentrated than the old stock B. All of these adjustments were made in order to control bacterial growth with a small number of drug injections.

Morbidostat Assay

We started morbidostat experiments with wild type (drug sensitive) isogenic E. Coli cells that were frozen at -80˚C. We thawed and diluted the cells 1:1000 in minimal growth media and transferred ~12 ml of the solution into autoclaved morbidostat culture tubes. These tubes were then placed into the tube holders. The optical density of the starting culture was calculated after subtracting the average voltage value within the first 30 seconds. We did not make any injections of drug solutions or fresh media into the culture until the OD of the culture exceeds 0.03 in order to allow cells to adapt their environment. This waiting time is usually around two hours. After this waiting time, there are injections of fresh media or drug solutions every twelve minutes. Each injection takes one minute and is followed by eleven minutes of growth cycle. Waste pump continuously runs during growth cycle but is turned off when injections are made into the culture to avoid suction of the injected liquid. The total volume inside the culture tube is ~12 ml and injection pumps are operated at 1ml/min flow rate. Each injection generates ~8% dilution of the growing cultures. After every growth cycle, we calculated the growth rate of the cell population, initial and final OD values during the growth cycle, and the drug concentration

Nature Genetics: doi:10.1038/ng.1034

inside the culture tube (**Fig. 1**). By using these values, the computer decided to inject fresh media or drug solution. Drug solution is injected if the final OD (OD_{final}) value is higher than $OD_{threshold}$ (0.15) and the net growth trend is positive. Otherwise, fresh media will be injected. We used a simple PID (proportional–integral–derivative controller) controller algorithm for making these decisions. P value is the difference between OD_{final} and $OD_{threshold}$ ($P^k = OD^k_{final} - OD_{threshold}$). I value is the sum of five previous P values ($I^k = P^{k-4} + P^{k-3} + \ldots + P^k$) and D is the difference between OD_{final} and previous OD_{final} ($D^k = OD_{final}^k - OD_{final}^{k-1} = P^k - P^{k-1}$). PID value is calculated using the formula: $PID^k = P^k + 0.001 * I^k + D^k$ (We chose to multiple I^k by 0.001 since I^k seemed to be unimportant both in our simulations and experiments.). Drug solution from stock A was injected if $PID^k \geq 0$, otherwise fresh media was injected. Drug injections were made from stock B if the drug concentration inside the culture tube exceeded 60% of the concentration of stock A. After 24 hours, the experiment was paused and a sample from the evolving cell culture was immediately frozen at-80˚C in 15% glycerol. After waiting about 30 minutes, a small sample (~300µl) from the frozen cells was transferred into a new sterile culture tube filled with minimal growth media. This daily transfer procedure was done to enable the collection of frozen samples from every daily time point of the experiment, and to avoid biofilm formation inside the culture tubes.

Selection of trimethoprim resistant mutants using agar plates

In order to compare the evolution of drug resistance in the morbidostat and in constant drug concentrations, we performed a selection experiment using agar plates with different trimethoprim concentrations and sequenced the DHFR genes of the surviving mutants (Methods). The identified mutations and the drug concentrations used for selection are listed in **Supplementary Table 3**. About half of the mutants had only a single DHFR mutation and the rest had no DHFR mutation. The mutants surviving in the strongest selection condition ([trimethoprim]=100µg/ml) had L28R mutations whereas the mutants selected in more dilute trimethoprim had either W30C or a promoter mutation (-35C>T, -9G>A, -5C>A). Consistent with the morbidostat experiments, -35C>T was the most abundant promoter mutation (4 out of 6) and was mostly observed in lower trimethoprim concentrations. These results suggest that evolution in fixed drug concentrations is limited to single resistance-conferring mutations unless further selection cycles are performed.

Clonal interference

Three examples of clonal interference were observed in the populations evolving resistance to trimethoprim. The first example was found in the TMP-3 population. The promoter mutation -9G>A and W30R competed in two separate clones isolated from third day of TMP-3 population (**Fig. 4b**, panel 3, gray and green appear in different quadrants), but only -9G>A was fixed while W30R became extinct or less prevalent in the population. Later, on day 7, the W30R mutation emerged once again, but this time on the -9G>A background causing a further increase of trimethoprim resistance. The second case of

Nature Genetics: doi:10.1038/ng.1034

similar clonal interference was also found in TMP-5 mutations, where A26T and W30G co-appeared in separate clones (**Fig. 4b**, fifth panel from top. In days 10-12, cyan and green appear in different quadrants). In following days, both of these mutations appeared in the same clones, likely due to one of them reappearing on the background of the other (day 13). The third and an extreme example of clonal interference was observed in TMP-4, where a mutation W30C (green square) initially became abundant in the population but then disappeared after the promoter mutation -35C>T (dark grey) appeared on day 9, although all four of the colonies we sequenced from day 8 had W30C mutation (**Fig. 4b**, fourth panel from top). We verified this exclusivity by sequencing the DHFR region of 23 more colonies from days 8, 9, and 10 (**Fig. 4e**, inset). None of the 15 colonies had W30C mutation on day 9 (when -35C>T appeared) although all ten colonies had W30C mutation on day 8. Later, on day 10, 6 out of 10 colonies acquired W30R (green diamond) mutations.

Sequence Read Archive (SRA) sample number

Whole genome sequencing data from the morbidostat-evolved strain are publicly available in the National Center for Biotechnology Information (NCBI) Sequence Read Archive (SRA). The submission's accession number is SRA046097. The sample accessions numbers are as follow, SRS265129 (CHL-1a), SRS265130 (CHL-1b), SRS265131 (CHL-2), SRS265132 (CHL-3), SRS265133 (CHL-4), SRS265134 (CHL-5), SRS265135 (DOX-1), SRS265136 (DOX-2), SRS265137 (DOX-3), SRS265138 (DOX-4), SRS265139 (DOX-5a), SRS265140 (DOX-5b), SRS265141 (TMP-1a), SRS265142 (TMP-1b), SRS265143 (TMP-1c), SRS265144 (TMP-2), SRS265145 (TMP-3), SRS265146 (TMP-4, SRS265147 (TMP-5), SRS265148 (MG1655 wild type sample).

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