An Antibiotic Does Not Create Resistance; It Selects the Few That Were Already There

— With 10^9 bacteria and a mutation rate of 10^{-9}, 1.000000 resistant cell is present before the drug is taken — the separator is whether the mutation precedes the drug or the drug causes it — [Paper 819]

Yuuki YAMAGISHI (山岸 勇輝)
Yamagishi Complexity Torus Lab, Japan
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— *From thinking to syncing.* —

Abstract

“Using antibiotics creates resistant bacteria” can be read as the drug changing the bacteria or as the drug selecting those already present.This paper counts, under the selecting reading alone, how the numbers move as two populations.No new theorem or law is claimed. First, resistant cells are there before the drug——10^9 bacteria at a mutation rate of 10^{-9} give exactly 1.000000 in expectation (Section 2). **Second, the drug lowers the number while raising the share——the resistant share is 3.412070×10^{-7} at 2 hours, 3.929258×10^{-2} at 6 and 9.999994×10^{-1} at 12** (Section 3). **Third, there is an hour at which the majority changes hands——resistance becomes the majority 7.110000 hours in, when 5.842775×10^{2} resistant cells are present** (Section 3). **Fourth, and this is the core. Stopping early divides into recovering and not——after 48 hours without the drug, stopping at 6 hours brings the share back to 3.516740×10^{-4}, while stopping at 12 leaves it at 9.999284×10^{-1}** (Section 4). **Fifth, what pushes it back is the cost resistance pays——without the drug the susceptible grow 2.718282 times an hour and the resistant only 2.459603** (Section 4). **Sixth, the separator is whether the mutation precedes the drug or the drug causes it——one and the same observation, “resistant bacteria increased”, reads both ways** (Section 5).
Keywords: antibiotic, resistance, selection, mutation rate, population turnover, representative values.

Scope of this paper (scope note): No new theorem or law is claimed——that mutations arise before exposure (known from the Luria--Delbrück experiment), that selection raises the resistant share, and that resistance carries a cost without the drug, are all known.The values are representative——10^{9} bacteria, a mutation rate of 10^{-9}, a kill rate of 2.0, a growth rate of 1.0 and a cost of 0.10 are values chosen for comparison.No real organism or drug is claimed——particular species, particular drugs and clinical outcomes are not treated.No advice on use——how long to take a drug, and when it may be stopped, are medical judgements; only numbers inside the model are shown.Spread is not treated——horizontal transfer by plasmids, combinations of drugs and the movement of drug concentration in the body are not included.No stochasticity——extinction by chance at small numbers is not treated; the model is deterministic.Relation to earlier papers: Paper 364 showed that selection alone raises the mean by 1.52 standard deviations and shrinks the spread to 0.45——this paper stands beside it: there the upper tail of a distribution is chosen, here one of two populations is killed, and both select without creating.Paper 300 showed that whether two things share a root is decidable——"the drug creates resistance" and "the drug selects resistance" are distinct roots readable from one observation.What is added is counting the pre-existing resistant cells as 1.000000 in expectation, measuring at 7.110000 hours the time when the share crosses, separating recovery from non-recovery at 3.516740×10^{-4} against 9.999284×10^{-1}, and placing the separator on whether the mutation or the drug comes first.

1. Notation and the Question

Setting: let n_s be the number of susceptible bacteria and n_r the number of resistant ones.Under the drug the susceptible fall at a rate of 2.0 per hour, while the resistant grow at 1.0 less a cost of 0.10 for being resistant.

$$\frac{dn_s}{dt} = -2.0\, n_s \ \text{(with the drug)}, \qquad \frac{dn_r}{dt} = (1.0 - 0.10)\, n_r$$

There are 10^{9} bacteria and the mutation rate is 10^{-9} per division.

Question: does the drug create resistance or select it, and how far do the numbers move under selection alone?

2. They Are There Beforehand

Computation 2.1: 10^{9} bacteria times a mutation rate of 10^{-9} gives 1.000000 resistant cell in expectation.

> **Observation 2.2**
>
> resistant cells are there before the drug.The mutation happens without reference to the drug, and the drug picks from what is there——once the number of bacteria in one body reaches the reciprocal of the mutation rate, having no resistant cell becomes the unusual case.

3. While the Drug Is Taken

Computation 3.1: both numbers and the resistant share were computed at several hours.

hours	susceptible	resistant	resistant share
0	1.000000×10^{9}	1.000000	1.000000×10^{-9}
2	1.758795×10^{7}	6.001133	3.412070×10^{-7}
6	5.331771×10^{3}	2.180675×10^{2}	3.929258×10^{-2}
12	2.900794×10^{-2}	4.712926×10^{4}	9.999994×10^{-1}

> **Observation 3.2**
>
> the drug lowers the number while raising the share.The susceptible fall from 10^{9} to 10^{-2} in twelve hours while the resistant rise from 1 to 4.712926×10^{4}——the total is falling all the while the contents are changing.

> **Observation 3.3**
>
> there is an hour at which the majority changes hands.It is 7.110000 hours in, with 5.842775×10^{2} resistant cells present——that hour is fixed by the kill rate and the cost alone.

4. Stopping Early

Computation 4.1: the drug was stopped and the share computed after 48 hours without it.

hours taken	share on stopping	share 48 hours later
6	3.929258×10^{-2}	3.516740×10^{-4}
12	9.999994×10^{-1}	9.999284×10^{-1}
24	1.000000	1.000000

Observation 4.2

this is the core. Stopping early divides into recovering and not.Stopping at 6 hours brings the share back to 3.516740×10^{-4}, while stopping at 12 leaves it at 9.999284×10^{-1}——recovery needs someone left to push back.

Observation 4.3

what pushes back is the cost resistance pays.Without the drug the susceptible grow 2.718282 times an hour and the resistant 2.459603——that difference is what drives the share down again.

5. The Separator

Observation 5.1

the separator is whether the mutation precedes the drug or the drug causes it.In this model the mutation is placed before the drug and the drug only kills, yet the resistant share moves from 10^{-9} to 1——an observation that looks like “the drug made resistant bacteria” can be produced by selection alone.

Observation 5.2

placed beside Papers 364 and 300.Paper 364 showed that selection alone raises the mean by 1.52 standard deviations——there the upper tail of a distribution, here one of two populations, and both select without creating.Paper 300 showed that sharing a root is decidable——“creating” and “selecting” are distinct roots behind one observation.

Observation 5.3

what is not said.Real organisms and drugs, clinical instructions, horizontal transfer, drug concentration in the body and chance at small numbers are not treated——what is shown is that selection alone carries the share from end to end.

6. Census and Closing

1. $\mathbf{1.000000}$ **cell beforehand** (Computation 2.1): **the mutation comes first.**
2. $\mathbf{3.412070 \times 10^{-7}}$ **at 2 hours** (Computation 3.1): **the share starts up.**
3. $\mathbf{3.929258 \times 10^{-2}}$ **at 6 hours** (Computation 3.1): **still a minority.**
4. $\mathbf{9.999994 \times 10^{-1}}$ **at 12 hours** (Computation 3.1): **changed over.**
5. **majority at** $\mathbf{7.110000}$ **hours** (Observation 3.3): $\mathbf{5.842775 \times 10^{2}}$ **cells.**
6. **stopping at 6:** $\mathbf{3.516740 \times 10^{-4}}$ (Computation 4.1): **the core; it recovers.**
7. **stopping at 12:** $\mathbf{9.999284 \times 10^{-1}}$ (Computation 4.1): **it does not.**
8. **susceptible** $\mathbf{2.718282}$ **times an hour** (Observation 4.3): **without the drug.**
9. **resistant** $\mathbf{2.459603}$ **times an hour** (Observation 4.3): **paying the cost.**
10. **mutation first or drug first** (Observation 5.1): **the separator; Papers 364, 300.**

Closing: **An antibiotic does not create resistance; it selects the few that were already there.With 10^{9} bacteria and a mutation rate of 10^{-9} there is 1.000000 resistant cell in expectation, and although the drug only kills, the resistant share runs 3.412070×10^{-7} at 2 hours, 3.929258×10^{-2} at 6 and 9.999994×10^{-1} at 12, with the majority changing hands at 7.110000 hours——the total falls while the contents change.Stopping early and waiting 48 hours, the six-hour case falls back to 3.516740×10^{-4} while the twelve-hour case stays at 9.999284×10^{-1}——recovery needs someone left to push back.The separator is whether the mutation precedes the drug or the drug causes it.Placed among the earlier papers——standing beside Paper 364's "selection alone", and keeping Paper 300's discipline between creating and selecting.To be honest——every value is representative, and no real organism, drug or clinical instruction is treated.**

References

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