Whether Resistance Arises Before the Drug Is Told Apart Not by the Mean Count per Culture but by Its Spread

— the variance-to-mean ratio of resistant counts per culture is **2664.022763** if mutations arise before the drug and **0.999151** if the drug causes them, while medians and zero shares cannot tell them apart — the separator is whether one compares by the mean or by the spread (variance) — [Paper 797]

Yuuki YAMAGISHI (山岸 勇輝)
Yamagishi Complexity Torus Lab, Japan
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Abstract

When a drug is used, resistant cells appear. Did the drug cause the mutations, or were cells already present that were merely selected?The same cultures are simulated under both views, and the mean, zero share, median and spread of resistant counts per culture are compared to count which quantity separates the two.No new theorem or law is claimed. First, zero share and median cannot tell the two apart——zero shares of 0.357250 and 0.333000, median 1 in both (Section 2). **Second, and this is the core. The spread separates the two by orders of magnitude——variance over mean is 2664.022763 if mutations arise before, 0.999151 if the drug causes them** (Section 2). **Third, the pre-existing model occasionally produces jackpot cultures——0.002250 of cultures have 256 or more, with a maximum of 8196; the drug-caused model's maximum is 6** (Section 2). **Fourth, the mean is unreliable——0.400000 of the mean formula 10.485760 comes from early generations that occur perhaps once in 4000 cultures, and the sample mean is 8.057750** (Section 3). **Fifth, if resistance pre-exists, using two drugs at once is highly effective——in 2^{30} cells, the probability of a cell resisting one drug is 0.658273, and the expected number resisting two at once is 1.503239×10^{-8}** (Section 4). **Sixth, the separator is whether one compares by the mean or by the spread (variance)——"the drug creates resistance" and "resistance was already there" are not separated by mean or zero share, and are not decided until the spread is stated** (Section 5). **Keywords**: drug resistance, fluctuation test, Luria-Delbrück distribution, mutation rate, variance, two-drug combination.

Scope of this paper (scope note): **No new theorem or law is claimed——the fluctuation test telling whether mutations arise before or after selection from the spread of resistant counts per culture (Luria and Delbrück), the heavy-tailed, jackpot-containing form of that distribution, and probabilities multiplying when two independent mutations are needed at once are all known (Luria and Delbrück 1943, Lea and Coulson 1949).Cultures are idealized——all cells double in synchrony, and mutation costs, death and generational fluctuations are left out.Mutation rates are representative——10^{-6} per division (10^{-9} in the two-drug calculation) is for comparison; no particular organism or drug is claimed.Two drugs are independent——a single mutation working against both drugs (cross-resistance) is not treated.No treatment is recommended——how drugs should be used is not stated.Relation to earlier papers**: **Paper 692 showed that to carry a longer genome one must first copy more accurately, and that the order is fixed——its scope note stated that evolution was not discussed and that the speed of adaptation and the acquisition of drug resistance were not its subject. There the order of mutation rate and genome length was counted. Here the same mutation rate is counted as distinguishable, by the spread of counts per culture, according to whether it produces resistance before the drug.**What is added is **simulating 4000 cultures under each view and showing that zero share and median do not separate them while variance over mean does, 2664.022763 against 0.999151, deriving the 0.400000 share of the mean formula from early generations and showing the sample mean to be unreliable, deriving the expected number of cells resisting two drugs at once**, and **placing the separator on mean versus spread**.

1. Notation and the Question

Setting: **let 1 cell grow to $N = 2^G$ cells over G generations, with a resistance mutation occurring with probability μ per division. The expected number of mutation events is $m = \mu(N-1)$. Resistant counts per culture are generated under two views.**

$$\text{before the drug: } X = \sum_{g=0}^{G-1} K_g \, 2^{\,G-1-g}, \quad K_g \sim \text{Poisson}(\mu \, 2^g), \qquad E[X] = \mu \, G \, 2^{\,G-1}$$

$$\text{caused by the drug: } X \sim \text{Poisson}(m), \qquad E[X] = m, \qquad \frac{\text{Var}[X]}{E[X]} = 1$$

In the pre-existing model, mutations in earlier generations leave more descendants. Take $G = 20$ and $\mu = 10^{-6}$.

Question: **what should be counted in cultures to tell whether resistance arises before the drug?**

2. Cultures Under the Two Views

Computation 2.1: **4000 cultures were simulated under each view and resistant cells counted ($m = 1.048575$).**

quantity	mutations before the drug	mutations caused by the drug
mean (formula)	8.057750 (10.485760)	1.108250 (1.048575)
variance / mean	2664.022763	0.999151
zero share	0.357250	0.333000
median	1	1
maximum	8196	6
share with 32 or more	0.033500	0.000000
share with 256 or more	0.002250	0.000000

Against the zero-share formula $e^{-m} = 0.350437$ (standard error 0.007544 for 4000 cultures), the pre-existing model is 0.903 standard deviations off; the drug-caused model's variance over mean is 0.038 standard deviations from 1.

> **Observation 2.2**
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> zero share and median cannot tell the two apart.The zero shares are 0.357250 and 0.333000, and both medians are 1——in that about half the cultures have almost no resistant cells, the two views look the same.

> **Observation 2.3**
>
> this is the core: the spread separates the two by orders of magnitude.Variance over mean is 2664.022763 if mutations arise before the drug and 0.999151 if the drug causes them. In the pre-existing model 0.002250 of cultures have 256 or more, reaching a maximum of 8196, while the drug-caused model's maximum is 6——only cultures that drew a mutation in an early generation become jackpots, so pre-existing resistance makes counts per culture vary enormously.

3. The Mean Is Unreliable

Computation 3.1: the pre-existing model's mean formula was split by generation, and the share from generations whose expected event count over 4000 cultures is below 1 derived.

quantity	value
mean formula	10.485760
share from generations 0 to 7 (perhaps once in 4000 cultures)	0.400000
expected mean without that share	6.291456
sample mean	8.057750

Observation 3.2

the mean is unreliable.Of the mean formula 10.485760, 0.400000 comes from early-generation mutations that occur perhaps once even across 4000 cultures, and the sample mean 8.057750 came out below the formula——because rare jackpots set the mean, comparing the two by sample means is at the mercy of whether a jackpot happened to be drawn.

4. Two Drugs at Once

Computation 4.1: for a population of 2^{30} (1073741824) cells with mutation rate 10^{-9}, the probability of at least one cell resisting one drug and the expected number of cells resisting two drugs at once were derived.

quantity	value
probability of at least one cell resisting one drug	0.658273
expected number resisting two drugs at once	1.503239×10^{-8}

Observation 4.2

if resistance pre-exists, using two drugs at once is highly effective.With one drug the probability of a resistant cell being present is 0.658273, but the expected number resisting both at once is 1.503239×10^{-8} ——both mutations must already be present before the drug, so the probabilities nearly multiply.

5. The Separator

Observation 5.1

the separator is whether one compares by the mean or by the spread (variance).Zero share (0.357250 against 0.333000) and median (1 against 1) do not separate them, and the mean is at the mercy of jackpots, but variance over mean separates them by orders of magnitude, 2664.022763 against 0.999151——"the drug creates resistance" and "resistance was already there" are not decided until the spread is stated.

Observation 5.2

beside Paper 692.Paper 692 showed that mutation rate and genome length come in a fixed order, leaving drug resistance aside——here the same mutation rate is counted as distinguishable, by the spread of counts per culture, according to whether it produces resistance before the drug.

Observation 5.3

what is not said.Mutation costs, death, cross-resistance, particular organisms or drugs, and treatment are not treated——what is shown is that the two views are separated not by the mean but by the spread.

6. Roll Call and Closing

1. **zero shares 0.357250 and 0.333000** (Observation 2.2): **indistinguishable.**
2. **medians 1 and 1** (Computation 2.1): **indistinguishable.**
3. **variance over mean 2664.022763** (Observation 2.3): **the core.**
4. **variance over mean 0.999151** (Observation 2.3): **1 if the drug causes them.**
5. **maximum 8196** (Computation 2.1): **a jackpot.**
6. **mean formula 10.485760** (Computation 3.1): **the expectation.**
7. **early-generation share 0.400000** (Observation 3.2): **rarely occurring.**
8. **sample mean 8.057750** (Observation 3.2): **at the mercy of jackpots.**
9. **1.503239×10^{-8} for two drugs** (Observation 4.2): **nearly a product.**
10. **mean or spread** (Observation 5.1): **the separator; Paper 692.**

Closing: **Whether resistance arises before the drug is told apart not by the mean count per culture but by its spread.In cultures growing from 1 to 1048576 cells over 20 generations with mutation rate 10^{-6}, zero shares are 0.357250 and 0.333000 and both medians are 1, so the two views cannot be told apart here——about half the cultures have almost no resistance either way.Variance over mean is 2664.022763 if mutations arise before the drug and 0.999151 if the drug causes them, orders of magnitude apart, and because 0.400000 of the pre-existing mean formula 10.485760 comes from early generations that occur perhaps once in 4000 cultures, the sample mean 8.057750 is unreliable——pre-existing resistance produces jackpot cultures and makes the spread large.The separator is whether one compares by the mean or by the spread (variance).Placed among the earlier papers——Paper 692 counted the order of mutation rate and genome length; this counts how to tell whether the same mutation rate produces resistance before the drug.To be honest——the cultures are idealized, and neither mutation costs, particular organisms or drugs, nor treatment are treated.**

References

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Yuuki YAMAGISHI (山岸 勇輝)

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