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WHY ONLY SOME BACTERIA DEVELOP MULTI-DRUG RESISTANCE

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A sample bottle containing E. coli bacteria | Photo Credit: REUTERS

During evolution, the fitness costs experienced by bacteria under constant and fluctuating environments pose a problem that has not be solved. One way of seeing this is through the example of multi-drug resistance. It is not clear why some bacteria evolve multi-drug resistance while others do not. New research from the Population Biology Lab at IISER Pune could hold a key to this and a similar class of puzzles.

Multi-drug resistance is a menace in public health, however it is a fascinating problem to an evolutionary biologist who sees it from this angle: possessing multi-drug resistance implies that the bacteria is adept at handling multiple antibiotics simultaneously. This would increase its fitness appreciably. Given that antibiotics exert a very strong selection pressure, it would appear that every bacteria in nature can become multi-drug resistant, which is not the case. “One of the reason given for why that does not happen is fitness cost,” says Sutirth Dey, in whose lab the study was carried out. When bacteria become fit in one environment, they either lose fitness or fail to increase fitness in other environments. “Our study is showing that when the environment is fluctuating, large (but not small) populations can by-pass this effect,” he adds.

Yashraj Chavhan, Sarthak Malusare, and Sutirth Dey studied populations of small and large sizes across different constant and fluctuating environments and then subjected the evolved populations to whole-genome, whole-population sequencing analysis. They found that small populations acquire a certain set of mutations which allow them to survive in one environment while paying a cost in others. Large populations also develop these mutations but, in addition, have certain compensatory mutations that together give them fitness to survive in different environments. Thus, population size determines the kind of mutations available to the bacteria, which in turn, leads to the type of fitness costs they evolve.

In the paper, which has been published in the journal *Ecology Letters*, the group studied approximately 480 generations of *E. coli* in four types of steady environments consisting of different carbon sources, namely, galactose, thymidine, maltose and sorbitol, and one fluctuating environment in which the carbon source changed unpredictably between these four. Bacteria cannot use all carbon sources similarly. “Which carbon source is available impacts the bacterium’s ability to survive and grow. Since this is a very basic requirement for survival and growth, we decided to study what the availability of different kinds of carbon sources does to their evolution,” says Prof Dey.

The study showed that, all else being equal, whether the bacteria pay fitness costs or not will depend on the population size they evolve in.

Further, on doing whole-genome, whole population sequencing, the researchers found that the larger populations contained greater number of mutations. The smaller populations only had mutations related to metabolism of one kind of carbon source whereas the larger populations had known mutations for metabolism of multiple types of carbon sources. “We believe that this is the reason that the larger populations were able to bypass the costs while the small populations were not,” clarifies Prof. Dey.

The group plans to engineer these mutations in bacteria to formally show that they demonstrate antagonistic pleiotropy or compensation, in a confirmatory step.

Though the paper gives a very strong prediction about how population size interacts with fluctuating environments, it is not yet clear at what size the effect flips from cost to no-cost? “It will obviously differ from species to species. It would be interesting to figure out theoretically (and validate empirically) where these bounds are for different kinds of organisms,” he says.

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