Commensal bacteria were critical shapers of early human populations

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Using mathematical modeling, researchers at New York and Vanderbilt universities have shown that commensal bacteria that cause problems later in life most likely played a key role in stabilizing early human populations. The finding, published in *mBio*, the online open-access journal of the American Society for Microbiology, offers an explanation as to why humans co-evolved with microbes that can cause or contribute to cancer, inflammation, and degenerative diseases of aging.

The work sprung from a fundamental question in biology about senescence, or aging past the point of reproduction. "Nature has a central problem—it must have a way to remove old individuals, whether fish or trees or people," says Martin Blaser, microbiologist at New York University Langone Medical Center in New York City. "Resources are always limited. And young guys are ultimately competing with older ones."

In most species, individuals die shortly after the reproductive phase. But humans are weird—we have an extra long senescence phase. Blaser began to think about the problem from the symbiotic microbe's point of view and he came up with a hypothesis: "The great symbionts keep us alive when we are young, then after reproductive age, they start to kill us." They are part of the biological clock of aging.

In other words, he hypothesized that evolution selected for microbes that keep the whole community of hosts healthy, even if that comes with a cost to an individual host's health.

Modeling of early human population dynamics could tell him if he was on the right track. Blaser worked together with his collaborator Glenn Webb, professor of mathematics at Vanderbilt University in Nashville, to define a mathematical model of an early human population, giving it characteristics similar to a time 500-100,000 years ago, when the human population consisted of sparse, isolated communities.

Webb came up with a non-linear differential equation to describe the variables involved, their rates of change over time, and the relationship between those rates. "It can reveal something that's not quite appreciated or intuitive, because it sorts out relationships changing in time," even with many variables, such as age-dependent fertility rates and mortality rates, changing simultaneously, explains Webb.

Using this baseline model, the team could tweak the conditions to see what happened to the population dynamics. For example, they increased the fertility rate from roughly six children per female to a dozen, proposing that this might be one way for populations to overcome the burden of senescence, by boosting juvenile numbers. Instead, they were surprised to see that this created wild oscillations in total population size over time—an unstable scenario.

"You could imagine if something bad happens during a low point, like a drought, then the population crashes or might be extinguished," says Blaser. Over time, the increased fertility rate adds to the pressure that a larger population of older people puts on the juveniles due to limited resources. Likewise, when Blaser and Webb plugged parameters into the model that greatly increased mortality from a microbial infection akin to Shigella, which primarily kills children, the population crashed to zero.

Next they set juvenile mortality to a constant, low level and senescent mortality risk was set to increase each year with age—a condition that mimics certain symbiotic bacteria such as *Helicobacter pylori* that can

become harmful in old age. This model exhibited a stable population equilibrium.

"By preferentially knocking off older individuals, you get a robust population, and this is what Nature is doing," says Blaser. Now, though, the legacy of co-evolving with such microbes has become a burden as longevity stretches out, because some of these microbes contribute to inflammatory and degenerative diseases. Recognizing that our own once-beneficial microbes might be the agents of mortality in later life, could lead to better preventives or treatments for diseases of aging.

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