

On the Shifting Balance: the Case of *Staphylococcus aureus* CC398

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ABSTRACT The recent study by L. Price et al. [mBio, 3(1):e00305-11, 2012] demonstrating the human origin of the livestock-associated CC398 *Staphylococcus aureus* provides an excellent example of how bacterial populations can explore a wide range of potential niches and acquire optimal adaptations for life in alternative hosts. The shifting balance theory proposed by Sewall Wright 80 years ago serves as a perfect model for understanding the observed facts: a possibly large CC398 population optimally positioned on the top of a fitness peak for living in a human host probably began evolving long ago by variation, drift, and migration, until it reached the low fitness edge of a neighboring alternative peak in the fitness landscape, one in a livestock host. The bacterial population then evolved again, moving uphill to reach a novel optimal “top of the peak” position in livestock. In the case of CC398, it is worrisome to think that it might readapt to human hosts without losing fitness in livestock; a double-host-adapted organism could certainly be in an optimal position for increasing its virulence and antibiotic resistance.

The recently published study of Price et al. about the host adaptation of *Staphylococcus aureus* CC398 (1) serves to illustrate the influence of interhost transmission in the evolution and modulation of bacterial fitness. Fitness is understood here as the global reproductive success of a certain bacterial genotype, in this case ST398, compared to that of other genotypes. Accordingly with the classic metaphor proposed in 1932 by Sewall Wright (1889–1988) about the “surface of selective values” (2), evolutionary trajectories can be mentally (and mathematically) visualized as a process in which the populations move from low to high fitness by climbing hills and descending those hills as fitness declines. The top of the peak represents the local optimum for reproduction, and the downhill slopes and valleys represent suboptimal locations. The results presented in the Price et al. study indicate that *Staphylococcus aureus* ST398 was most likely of human origin, was disseminated efficiently among human populations, and was then accidentally transmitted to livestock. When that occurred remains unknown, but it was probably a long time ago.

In general, during long periods of stable coexistence with their hosts, bacteria slowly reach high-fitness states in host-specific peaks, but specific adaptation to a particular host deadapts for other hosts. Most probably the transmission of the human-adapted *S. aureus* ST398 to livestock was a rare event, as the organism moved from an adaptive peak to a valley, a low-fitness region. However, anything rare finally occurs if a multiplicity of occasions is provided, as certainly happens in the case of contacts between farmers and livestock. After the bacterium was contracted by a farm animal, frequent transmission exerted its effects on bacterial adaptation: in the new host, ST398 starts moving uphill in the fitness landscape.

Climbing the fitness peak in a new host is greatly facilitated by frequent transmission, a process that occurs frequently on farms. The multiplicity of contacts between animals means significant increases in the total bacterial population and more potential variability. Many animal-to-animal transmissions represent transmission bottlenecks, which are successfully crossed only by the better-adapted genotypes. Successively, over the course of many transmissions, these best-adapted genotypes increases in absolute number, are better and better transmitted, and move higher up on the adaptive peak, eventually reaching the optimal equilibrium

point. Thus, ST398 was converted into a livestock-adapted organism.

Adaptation to livestock hosts resulted in deadaptation to the human host. This explains why the livestock-associated ST398 strains were so infrequently transmitted from livestock to humans and from human to human. A shift in the adaptive balance has occurred.

Sewall Wright proposed the theory of the “shifting balance” to understand the evolutionary process that propels the trajectory of an organism between two differentiated fitness peaks separated by a saddle area (3, 4). The success of a population in one of the peaks produces an increase in local proliferation of individuals, with consequent increases in both the stochastic variability and dispersion rate of the population. This inevitably increases the possibility of occasional shifts locally across the saddle and eventually to populations that start climbing a separate fitness peak and finally reach a novel optimum position. The result is the differentiation between two separate populations, as in the case of CC398 (Fig. 1).

Interestingly, the shifting balance theory was conceived by Wright during his period of work at the Animal Husbandry Division of the U.S. Bureau of Animal Industry (1915–1925). It is amazing that, almost one century later, a study that addresses bacterial populations in livestock might again lead microbiologists to consider such a hypothesis to understand results obtained using whole-genome sequencing.

In light of the shifting balance theory, there is a final, worrisome aspect of the Price et al. paper to consider. Nothing excludes the possibility that methicillin-resistant *S. aureus* (MRSA) CC398 clones adapted to livestock, and recently sending back migrants to farmers could increase their fitness in the human population without losing their adaptations to the livestock hosts. My colleagues and I recently reported on the case of human and swine hosts sharing *Enterococcus* strains from the same clonal complexes (5).

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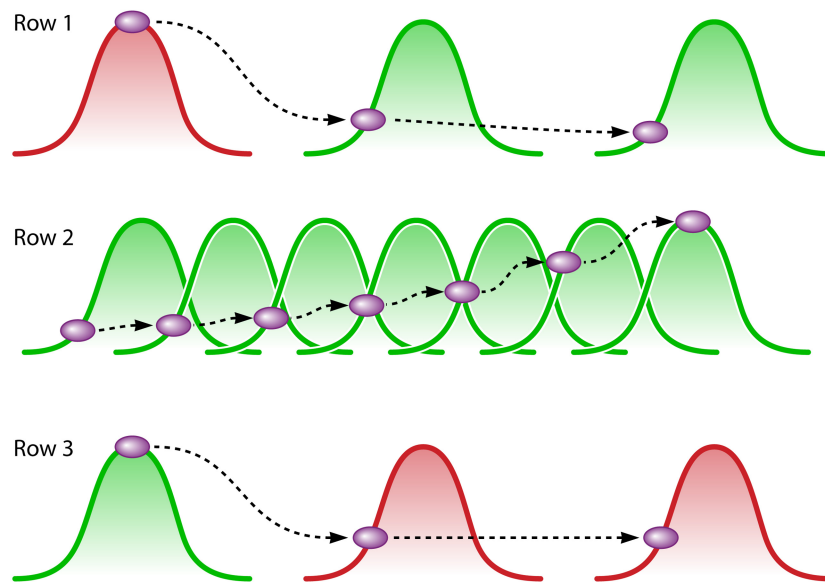


FIG 1 Red (human) and green (livestock) mountains represent fitness peaks for *S. aureus* CC398; the higher CC398 (violet circle) is on the peak, the greater its fitness in the corresponding host. In the first row, when the strain migrates from humans to livestock, the fitness decreases, and low fitness is maintained if the transmission between animals is rare. In the second row, a high density of animals (crowded farming) facilitates up-hill climbing in fitness, until optimal fitness is reached; CC398 is now a livestock-adapted organism. In the third row, CC398 migrates to humans again, but its fitness now is low, and transmission between humans is rare.

These oscillatory phenomena (fitness unification after former diversification) can be expected in bacterial evolutionary biology (6). The possibility that both types of hosts, humans and livestock, could constitute, for bacterial populations, equally advantageous colonizable environments is favored by the strong reduction in diversity of farm animals. Diversity in farm animals represented a strong barrier of multiple bottlenecks preventing the local spread of bacterial organisms. Genetic and nutritional homogenization of animals weakens such a barrier. The resulting unified adaptive landscape, in combination with poor hygienic conditions in farming, will greatly enlarge the possibilities of bacterial evolution toward increased virulence and antibiotic resistance.

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