EVOLUTIONARY BIOPHYSICS

Space-saving tips to lower stress

Understanding how some single cells evolved into multicellular life means figuring out how they overcome the stresses associated with crowding as they multiply. New insights from yeast suggest that changes in the shape of cells may provide an answer.

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Without multicellularity, Earth would have no plants or animals — including people — and would therefore be indescribably different from the planet on which we actually live. The evolutionary transition from unicellular to multicellular life has happened many times, in different biological lineages, in the history of life on Earth[1,2]. The persistence of multicellular life since its origins, in most cases, at least 600 million years ago demonstrates that multicellularity can confer a strong competitive advantage[2]. However, the details of how life overcame the challenges associated with the transition to multicellularity are largely hidden by the mists of the distant past. In particular, little is known about how reproducing multicellular clusters were able to evolve to contain larger numbers of rigid cells, circumventing the tendency of crowding to cause stresses sufficient to break intercellular bonds. Now, writing in *Nature Physics*, Shane Jacobeen and co-workers[3] have presented one possible solution by demonstrating that yeast cells, under selection pressure to grow in clusters of increasing size, evolve such that their shape changes and the stresses from crowding are reduced.

Earlier work showed that yeast that usually bud and separate into discrete single cells can evolve to instead form multicellular clusters as a result of the yeast not separating after budding[4]. In that study, the researchers imposed a daily selection pressure for multicellularity by choosing only yeast that settled rapidly under gravity to propagate forward to the next day's culture. Clusters of cells settle faster than single cells, and large clusters settle faster than small clusters. Under this selection pressure, the yeast evolved into a multicellular 'snowflake' form. Snowflake clusters reproduce by splitting into two smaller clusters, which then grow as yeast bud but do not separate.

Jacobeen et al. characterized the shapes of yeast cells isolated at different time points during the evolutionary process[3]. They showed that as yeast evolve, the individual cells become more elongated, and the snowflake clusters contain a lower volume fraction of yeast. This may seem counterintuitive in the context of classical packing problems. Mangoes pack more efficiently than oranges because of their relative excluded volume and their tendency to rearrange and align with one another (Fig. 1a,b). But yeast cells differ in that — even as they elongate — they are attached to fixed budding sites and therefore cannot rearrange. This results in a decreased volume fraction of cells in the snowflake clusters. As evolutionary time increases, snowflake clusters grow to larger sizes before splitting under internal stresses because reduced crowding leadings to lower internal stresses in the cluster.

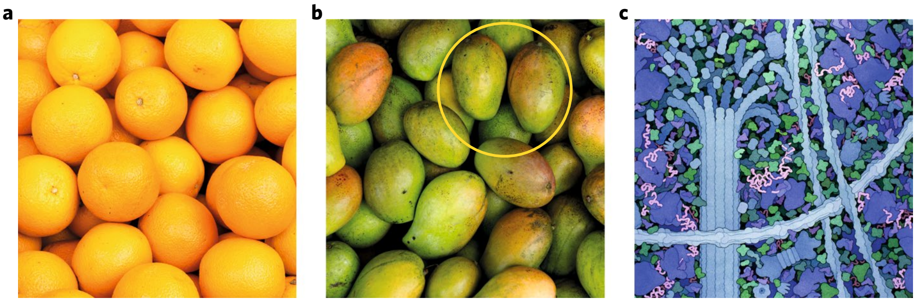

Fig. 1 | Packing problems. a, An orange, with an aspect ratio of about 1, has an excluded volume that extends one orange radius outside the orange, for a total excluded volume of eight orange volumes. **b**, An elongated fruit, such as a mango with an aspect ratio of about 1.5, has an excluded volume that, as a fraction of the fruit's own volume, decreases with increasing aspect ratio. This, combined with the ability of discrete elongated objects to rearrange and align (as for the mangoes circled in yellow), can allow elongated objects to pack more efficiently to achieve a greater volume fraction. **c**, Inside cells, the high density of biological molecules results in crowding, which impacts biochemical and biophysical properties. Image credits: Jens Ickler/Alamy Stock Photo (**a**); Ariadne Van Zandbergen/Alamy Stock Photo (**b**); and David S. Goodsell, the Scripps Research Institute (**c**).

Crowding is often important in the biological physics of intracellular processes[5,6] (Fig. 1c). Perhaps the easiest way to understand this is in terms of the depletion attraction[7]. The volume excluded by one molecule is not available to other molecules, which reduces their entropy. Larger molecules exclude more volume than smaller molecules. If two or more large molecules come close together, so that their excluded volumes partially overlap, more volume is accessible to the small molecules and, as there is often a greater number density of small molecules than large molecules, this is entropically favourable. Biological systems benefit from this crowding-based effect because it can help to bring together and spatially organize interacting partners.

In contrast, in the intercellular interactions considered by Jacobeen and colleagues, crowding does not give rise to a benefit — rather, crowding increases internal stresses that limit the size to which snowflake yeast can grow. Instead of using crowding to their benefit, as for many intracellular biophysical and biochemical processes, snowflake yeast have greater evolutionary fitness when crowding is minimized.

Distinguishing correlation from causation is often a challenge. In particular, assessing the connection between genetic or phenotypic changes and the evolutionary response to selection pressure is not at all straightforward. Evolution can lead to characteristics that do not themselves confer any fitness benefit, but rather are a byproduct of selection for other adaptations that do provide a benefit. Such corollary, non-adaptive changes are known as 'spandrels'[8]. An example is found in our own recent work, in which we showed that chronic biofilm infections evolve in vivo in such a way as to promote mechanical toughness and elasticity[9]. We think it likely that mechanical toughness and elasticity help to protect biofilms against clearance by the immune system. However, the evolving mechanical properties of these biofilms arise from changes in the production of matrix polymers, which are already known to provide chemical protection against antibiotics and the immune system. The degree to which mechanical enhancement per se could produce an adaptive benefit, and therefore might directly be selected for by evolution, is not known and is a topic of current research in our lab.

Jacobeen and collegaues used simulations to show that it is plausible that changes in the aspect ratio of individual yeast cells give rise to less-crowded, and therefore larger, snowflake yeast. If this interpretation is correct, then the change in aspect ratio is not a spandrel — but was rather being selected for, albeit indirectly, via its effect to reduce internal stresses. This is at least strongly suggestive that, in the case of evolving snowflake yeast, life found an elegant solution to an evolutionary problem using basic principles of geometry. ❐

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