doi:10.20944/preprints202204.0156.v1

Review

Living Cell’s Feeling of Holes: The Mathematics of Cavities in Biophysical Structures

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Abstract: Mechanical properties such as shape, volume and size affect the dynamics of biological systems. Most of the current methodological approaches are inclined to remove the existence of holes and impurities from systems’ description, regarding them as routes toward mechanical failure. On the contrary, we suggest that the occurrence of holes might be of utmost functional importance, allowing reversible transformations of cellular structures. The focus here is on the widespread occurrence of intracytoplasmic holes, that deeply modifies the topology of living cells and provides researchers with novel operational tools to investigate intracellular dynamics. We take as example the prokaryotic gas vesicles, i.e., intracellular cavities filled with gases spreading from the nearby medium. The mechanical and topological cellular properties dictated by intracytoplasmic holes are investigated, focusing on the physical constraints imposed by their very existence. For instance, the presence of gas vesicles breaks the cytoplasmic homogeneity, leading to inhomogeneity in functional activities and modifications in intracellular flows. Also, a topological approach to cytoplasmic holes suggests novel physiological roles for gas vesicles. For example, the gas vesicles’ ability to increase/decrease cellular volumes provides a mechanism that counteracts the detrimental effects of the surface/volume ratio. In conclusion, a structural/methodological approach based on the occurrence of holes testifies once again how the simple biophysical structure alone can dictate the function.

Keywords: nanovesicles; flow; homology; vortex; Betti number; Borsuk–Ulam theorem

1. Introduction

From the allometric studies of Otto Snell and D’Arcy Wentworth Thompson onwards, there has been a growing interest towards the mechanical properties of biological structures (Bull et al., 2021a). Changes in shape, size, volume, polarity, orientation, charges, medium, etc. drive numerous cellular activities. For example, at subcellular level the metamorphic proteins quickly change their folds to perform different jobs (Lella and Mahalakshmi, 2017), while hydrogen-bond networks of water molecules induce large-amplitude conformational motions of proteins (Oroguchi et al., 2016) and massive structural reorganization in hepatic endoplasmic reticulum provides both adaptive homeostasis and tissue health (Parlakgül et al., 2022). The intracellular environment shapes the multi-megadalton structure of the nuclear pore complexes (Schuller et al., 2021), while modifications in cytoplasmic crowding influence the clustering behavior of intramembrane ion channels (Duncan et al., 2017). The intricate three-dimensional organization of eukaryotic chromatin drives crucial biological processes (Zheng and Xie, 2019), while icosahedral and octahedral surfaces provide evolutionary advantages to enveloped viruses (Twarock and Luque, 2019). Geometric constraints play crucial functional roles in HIV-1 capsids (Christensen et al., 2020), engineered intestinal organoids (Gjorevski et al., 2022) and even plants’ extensibility, that emerges from the mechanical action of fibril-fibril sliding in aligned cellulose networks (Zhang et al., 2021). Concerning neuroscience, biomechanical interactions among ciliary cells coordinate collective movements in simple animals devoid of neurons (Bull et al., 2021), while mechanosensory processes in the presynaptic boutons contribute to synaptic transmission (Ucar et al., 2021). The last, but not the least, mechanically driven cycles of cell deformation contribute to tissue morphogenesis through actomyosin contraction (Bailles et al., 2019).

Despite the recent advances, we still do not understand the general rules shaping cellular function (Bull et al., 2021b). In this paper, we will focus on the relationships between mechanical and topological changes in the cytoplasm of living cells. Cellular features affecting both morphology and topology, such as, for instance, material stiffness, location, number and connectivity of nodes and compartments, can deeply modify biophysical and biochemical properties, as well as heat, fluid and particle transport (Li et al., 2021). We will explore only one topic, namely the mathematics of holes in biophysical systems. By the rather vague term "hole" we mean nucleations, aggregates, breaks, cavities, closed orbits that are theoretically able to modify the homogeneity of the medium in which they are embedded. Our notion of hole includes not just structural elements such as e.g., sponge cavities and eukaryotic organelles scattered in the intracellular medium, but also functional activities such as, e.g., occurrence of vortices, mechanical turbulences and so on.

We will proceed as follows. At first, we will provide examples of holes in physical and biological systems, taking as a paradigmatic example intracellular gas vesicles. Then, we will characterize the mathematical features of holes by a topological standpoint. Further, we will describe the physical effects of cytoplasmic cavities and suggest their novel feasible functions. We will conclude that the mathematical analysis of intracytoplasmic holes displays intriguing operational implications.

2. Holes in Physical and Biological Systems

A crucial question arises: what does the appraisal of holes bring on the table in the scientific investigation of biophysical systems? Here follow some examples testifying the utmost operational importance of holes in numerous scientific fields, being the hole either cause or consequence of quantifiable phenomena.

The occurrence of holes is very frequent in physics (Afriat 2012). The topology generated by the temperature fluctuations of the cosmic microwave background radiation can be approached in terms of number of holes, formally described by Betti numbers (Pranav et al., 2019). Vortices standing for topological holes are generated in several physical phenomena, such as skyrmions' ultrafast collective polarization dynamics (Li et al., 2021) and quasiparticles' superposition of plasmonic fields in topological plasmonic spin texture (Dai et al., 2020). In condensed matter physics, bound vortex-antivortex pairs are turned at critical temperatures into unpaired vortices/anti-vortices, due to the Berezinskii–Kosterlitz–Thouless phase transition (Beekman et al., 2017; Bighin et al., 2019; Padavić et al., 2020). It is noteworthy that physical matter often contains holes and impurities. For instance, the spontaneous transition from disordered to crystalline states in real atomic systems leads to heterogeneous nucleation of nanocrystals (Jeon et al., 2021).

Concerning biology, many examples of holes can be found. The backbone chains of biomolecules, such as base pairs in RNA chains or native interactions in proteins, can be described by the genus of an auxiliary two-dimensional surface diagram (Zając et al., 2018). Bacterial suspensions display turbulence-like spatiotemporal dynamics producing irregular microvortices (Beppu et al., 2021), while vortex-like defects in the ciliary field contribute to locomotive behavior in organisms without muscles and neurons (Bull et al., 2021b). Examining the three-dimensional locations of individual birds in airborne flocks (Ballerini et al., 2008), it is easy to notice the occurrence of transient vortices that can be described by Betti numbers. It can be safely stated that the vascular system, with vessels diameters ranging from hundreds of microns (arteries/veins) to few microns (capillaries) (Song 2020), stands for a gigantic hole inside the human body. Vortices do exist also inside the vascular system since, contrary to the common belief, the physiological peripheral and intracranial blood flow is turbulent rather than laminar (Saqr et al. (2020).

Concerning neuroscience, neural activities measured by different techniques generate vortices that can be measured in terms of Betti numbers. BOLD signals in triangulated rs-fMRI videoframes display topological vortex structures that rise and fall over time during the spontaneous activity of the brain (Don et al., 2020), while electrocorticograms display brain_waves' vortices that contribute to stabilize patterns (Freeman 2009). In is noteworthy that the brain, rather than being homogeneous, is punctured by countless, uniformly placed anatomical and functional "cavities" (Tozzi et al., 2021).

Concerning human diseases, the self-organized dynamics of vortex-like rotating waves are the basis of the formation of complex spatiotemporal patterns in many excitable biological systems. To provide two examples, cardiac filament-like phase singularities seem to be linked to life-threatening cardiac arrhythmias (Christoph et al., 2018), while intracellular phase separation of proteins produces aggregates resembling oil droplets in water likely correlated with amyotrophic lateral sclerosis and frontotemporal dementia (Yu et al., 2020).

In conclusion, the occurrence of holes in biophysical systems testifies once again that the simple structure alone can dictate the function. In the sequel, we will focus on a paradigmatic example of holes in cellular systems, i.e., the gas vesicles.

Gas vesicles come into play. Gas vesicles are gas-filled, proteinaceous, intracytoplasmic structures, either spindle-shaped or cylindrical, that transiently aggregate in periodic structures and progressively fill the intracellular space. The size varies according to the different species: the wall thickness ranges between 1.8-2.8 nm, the length between 100-1400 nm and the diameter between 45–120 nm (Pfeifer 2012). Eight-fourteen genes encoding different structural and regulatory gas vesicle proteins have been identified in distinct species (Beard et al., 2002). The single-layer wall is mainly composed of the 8-kDa GvpA, one of the most hydrophobic known proteins (Knitsch et al., 2017; Jost et al., 2021). Protein shell makes gas vesicle impermeable to liquid water, but highly permeable to gases passively diffusing from the surrounding environmental/cytoplasmic medium such as oxygen, nitrogen, hydrogen, carbon dioxide, carbon monoxide, methane and even perfluorocyclobutane (Pfeifer 2012). Gas vesicles' production and maintenance is influenced by environmental factors such as light intensity, UV radiation, temperature, ultrasonic irradiation, intracellular accumulation of glucose, maltose, sucrose, and extracellular concentration of salt, glucose, oxygen, pH levels (Pfeifer 2012; Pfeifer 2014).

Gas vesicles are common in aquatic planktonic prokaryotes, especially among anaerobic and aerobic heterotrophic bacteria (Staley 1980). Numerous Haloarchaea retain genes encoding gas vesicles, but only a few halophilic species can produce them (Oren 2012; Völkner et al., 2020). Even yeasts are able to produce intracellular gas bubbles, providing the missing link between intracellular CO_2 production by glycolysis and subsequent CO_2 release from cells (Swart et al., 2012). Little information is available concerning gas vesicles in eukaryotes. Eukaryotes don't have the GvpA gene but are equipped with basic leucine-zipper proteins bearing similarities with the archaeal gene regulator GvpE (Krüger et al., 1998).

Different biological functions have been suggested for gas vesicles. Since the hollow cylinder is liable to collapse when the surrounding pressure increases too much, gas vesicles are used by aquatic organisms as flotation devices to provide buoyancy (Pfeifer 2012). Vesicles' inflation and deflation modifies the overall cell density, allowing microorganisms to float vertically in the aqueous environment (Pfeifer 2014). The ability to reach different depths of the water column allows halophilic microorganisms either to prevent osmotic shock in high-salted environments (Oren 2012), or to reach higher light intensities for the optimal functioning of the light-driven proton pump (Oren 2012). It has been demonstrated that every oceanic microorganism (from Chaetoceros socialis colonies to zooplankton) prefers peculiar locations at different depths of the water columns (Talapatra et al., 2013). Further, it has been hypothesized that the highly conserved gas vesicle may have been an early organelle of prokaryote motility (Staley 1980).

In the sequel, we will describe the mechanical and topological properties of intracellular "holes" using the gas vesicles as a typical example.

3. Physical Effects of Topological Holes

We showed how intracellular gas vesicles increase the number of cytoplasmic holes in various prokaryotic species. Cytoplasmic holes produce two experimentally detectable effects that can be assessed at the whole-cell scale:

1. Physical modifications, such as changes in density, viscosity, etc., that alter intracellular dynamics.
2. Topological modifications, that are correlated with the mathematical structure of the subtending manifold.

Here we will focus of the topological modifications dictated by gas vesicles and their effect on living cells. In this chapter, by the term "hole" we will specifically mean the prokaryotic intracytoplasmic gas vesicles able to modify intracellular melieu's homogeneity, dynamics and topology. The step from hole to mathematics is straightforward, since the very count of the holes number is one of the hallmarks of topology. The topological fields of homology and homotopy differentiate shapes by examining and categorizing their holes, i.e., the mathematical entities that prevent objects from being continuously shrunken to a point. There are many ways to assess and measure holes in a topological space. Mathematical holes can be described in terms of e.g., genus, boundaries, closed manifolds, group cycles, cell complexes, Betti numbers, dysconnectivity, cohomotopy groups, bordism groups, K-theory, closed orbits, vortex nerve complexes, etc. (Peters 2018; Syed Musa, 2021). For instance, the genus of a sphere is 0, the genus of a donut is 1 and the genus of the number eight's shape is 2. By the Nash embedding theorems, every Riemannian manifold can be embedded into some Euclidean space preserving the length of every path (Nash 1956). This means that the three-dimensional living cells and their intracytoplasmic medium can be described in terms of topological manifolds, as we shall see in the next paragraphs.

Topological homogeneity and continuity are disrupted by holes. With few exceptions (Dobro et al., 2017; Monteil et al., 2019), prokaryotes do not have intracytoplasmic segregated structures such as membrane-bound compartments, organelles, assemblies of macromolecular machines, etc. By a topological standpoint, these living cells without holes are finite, closed manifolds equipped with topological genus 0. In touch with the Heine–Borel theorem, which emphasizes the concept of manifold's uniform continuity (Williamson and Janos, 1987), the intracellular medium surrounded by a membrane stands for a continuous topological object. This suggests that living cells devoid of holes are homogeneous three-dimensional spaces where continuous operations take place. In mathematics, a function is continuous when its graph is a single unbroken curve, while a continuous manifold displays either periodicity, homogeneity, isotropy or ergodicity. This means that there no discontinuities i.e., abrupt changes in values, are allowed. A continuum model assumes that the substance of a physical object is continuously distributed and fills the entire space it occupies, regardless of the occurrence of discrete atoms, cracks and discontinuities on a microscopic level. The continuum assumption is very useful by a methodological standpoint, permitting to wipe out molecular discontinuities by averaging the microscopic quantities on a small sampling volume (Colin 2014). It is no coincidence that the most useful macroscopic quantities in fluid mechanics, such as density, velocity, pressure, etc. are assumed to vary continuously from point to point within the flow (Colin 2014).

When dealing with topological spaces of genus 0, deformation retraction stands for a mapping that captures the idea of continuously shrinking a space. Though, the occurrence of intracytoplasmic gas vesicles unavoidably alters the manifold's topology. The existence of holes leads to increases in genus, so that the more the gas vesicles, the higher the genus (and the Betti number) of the intracellular melieu. The question here is: do cytoplasmic increases in number of holes alter the functional features of a manifold like a living cell? Most of the operational approaches, regarding holes as a route toward failure, tend to remove from the methodological evaluation unwanted factors such as e.g., swelling instabilities and compartment shape alterations (Bertoldi 2017). Therefore, scientists tend to encourage coarse methodological approaches framed on the continuum assumption in an effort to analyse the large-scale properties of systems' topological spaces and overlook small-scale details such as the holes. On the contrary, we suggest an opposite line of thinking: in our opinion, the occurrence of holes might be of utmost functional importance for many cellular activities. Indeed, the fact that gas vesicles do NOT preserve the connectivity features of the original genus-0 topology, gives rise to reversible and vital microstructures transformations.

When dealing with topological spaces of genus ≥1, retraction is banned and dysconnectivity starts to catch on. In mathematical jargon, dysconnectivity can be treated in terms of disjoint sets. Two sets are disjoint if they have no elements in common, or in other words, if their intersection is an empty set such that such that $a \cap b = \varnothing$ (Cormen et al., 2001). An example of topological manifold containing disjoint subsets is provided by the Borsuk–Ulam theorem, which describes two opposite antipodal points that cannot meet on the surface of the genus-0 n-sphere (Matoušek 2003; Peters 2016). Since manifolds of genus ≥1 must contain at least some disconnected elements, the very existence of intracellular gas vesicles rules out the possibility of continuity and indivisibility among the elements of the cellular physical manifold. Once the homogeneity is lost, continuous operations are not allowed in cell equipped with holes. The intracellular space is not any longer continuous and cannot be studied anymore by continuous functions. On the contrary, the intracellular space requires to be operationally split in subsets that are different from each other. We suggest that a cell with holes can be just treated by discrete operational approaches. Gas particles do not exhibit chemical intracellular effects, rather stand for a physical barrier that may be conceptually assimilated to inorganic nanoparticles disrupting cytoplasmic continuity. It is well-known that differences in nanoparticles' morphology affect physiological outcomes such as hyperthermia effectiveness, drug loading, escape from the immune system, etc. (Williams et al., 2021). Since the biological efficacy of microparticles varies according to their size, it is tempting to speculate that variations in gas particles' size might lead to different biological outcomes. For example, it could be hypothesized that gas vesicles of_different sizes provide structural reinforcement to the whole cell. In touch with this observation, a glass sponge's skeleton displays a square-grid-like architecture of open and closed cells (i.e., holes) able to withstand compression and bending in the deep waters of the Pacific Ocean (Fernandes et al., 2021).

In conclusion, when a choice is performed, e.g., a gauge (or a hole) is introduced in a symmetric manifold (Sengupta et al., 2016), disjoint subsets are generated such that manifold connectedness and continuity get lost. This leads to biophysical consequences, as we will see below.

Gas vesicles cause discontinuity in intracellular flows. Intracellular flows can be studied through recently-introduced synthetic, multicellular gas–liquid–solid interfaces able to assess gas transport pathways in porous media (Dudukovic et al., 2021). A variety of particles is physically transported through the intracellular milieu to enhance solutes mixing, delivery and target search (Mogre et al., 2020). Diffusive motion, motor-driven transport and advection by cytoplasmic flow are the preferred mechanisms in eukaryotic cells (Mogre et al., 2020), while some algal species use cytoplasmic rotational streaming boosted by molecular motors at the cell periphery (Goldstein et al., 2008). Localized active internal forces sculpt lipid membranes from within, leading to remarkable shape fluctuations and deformations (Vutukuri et al. 2020) that drive intracellular fluid flow and contribute to dispersion of cytoplasmic particles on timescales above seconds (Koslover et al., 2017). Further, the microorganisms living in water columns are subjected to additional dynamical forces. For instance, the flow regimes in horizontal gas-liquid flow under heaving motion show significant differences compared to steady state flow (Chang and Zhou, 2019). We suggest that the occurrence of high amounts of intracellular gas vesicles could be capable of modifying intracytoplasmic flows. Studying polymer solutions' flow through porous media, Browne and Datta (2021) found that the macroscopic flow resistance increases in a porous medium, but not in bulk solution. In touch with this finding, it might be hypothesized that gas vesicles contribute to increase the overall intracellular flow resistance, functioning as nanometric "obstacles" that generate elastic instability and inertial turbulence. By an operational standpoint, we have various possibilities to cope with the mathematic of intracellular flows:

1) The net flow can be mathematically assessed through the exterior derivative on a differentiable manifold.
2) Every phase space of Lagrangian manifolds contains a minimum number of loops, i.e., configurations in which the system comes back to the starting point (Frauenfelder 2004). The Arnold conjecture suggests that this minimum number is at least equal to the number of closed orbits (i.e., of holes) in the overall phase space. This also means that the Hamiltonian motion is correlated with the number of holes (Abbondandolo. 2001; Abouzaid and Blumberg, 2021).

According to the continuum assumption of fluid mechanics, fluids can be modeled as a continuous mass, even though they are composed of discrete molecules on a microscopic scale (Murphy et al., 2022). However, the continuum hypothesis leads to inaccurate results in circumstances like molecular flows on nano scale. In our case, the occurrence of intracellular holes leads to failure in manifold homogeneity and subsequent impairment of intracytoplasmic flows. When the continuum assumption of fluid mechanics is no longer a good approximation, statistical mechanics comes into play (Barber and Emerson 2002). Therefore, we suggest to treat intracellular flows in genus ≥1 manifolds just in terms of statistical approaches, leaving apart the approaches based on the continuum assumption. Notably, living cells are also able to produce intracytoplasmic turbulent flows under unusual circumstances such as, e.g., arrhythmogenic heart diseases (Fan et al., 2011; Kalmár-Nagy and Bak, 2019). These nonlinear, self-organized, flows generate energy transfer between large vortices that break up to form smaller ones. When the smallest scales in turbulent flow (termed Kolmogorov microscales) are reached, viscosity prevails and kinetic energy is dissipated into heat (Ortiz-Suslow and Wang, 2019). Given this premise, since gas vesicles alter the cellular density, it might be speculated that they are able to influence these turbulent intracytoplasmic flows too.

In conclusion, topological considerations lead us to hypothesize that gas vesicles could be able to affect the dynamics of intracellular flows.

Gas vesicles cause the failure of many topological theorems. Notable topological theorems have been proven useful to investigate a large array of physical and biophysical issues. The most used are the hairy ball theorem (colloquially stating that "whenever one attempts to comb a hairy ball flat, there will always be at least one tuft of hair at one point on the ball"), the Brouwer fixed point theorem ("no matter how you slosh the coffee, some point is always in the same position that it was before the sloshing began") and the Borsuk-Ulam theorem ("at any moment, there is always a pair of antipodal points on the Earth's surface with equal temperatures and barometric pressures"). For a survey of their applications in physical and biophysical issues, see Tozzi and Papo (2020). Yet, these theorems describe just genus-0 convex spheres and cannot be used to treat manifolds of genus ≥1. Therefore, the occurrence of cytoplasmic gas vesicles forbids the use of these useful theorems in the evaluation of intracellular affairs. To provide an example, the ability of the Borsuk-Ulam theorem to evaluate living beings' symmetries is lost under the circumstances of a living cell filled with holes.

Betti number's approaches to cytoplasmic cellular structures permit the assessment to cellular dynamics not just by the narrow standpoint of the Euclidean metric spaces, but also by the sophisticated standpoint of the algebraic manifolds. The occurrence of topological holes gives us the theoretical possibility to assess living cell's dynamics in terms of, e.g., a Hilbert space equipped with its own algebra, groups and operators. The operators that provide the metric structure might stand for vortices expressed in terms of Betti numbers. One might be tempted to hypothesize that the occurrence of countless intracytoplasmic gas vesicles gives rise to manifolds of almost infinite genus. This would pave the way to use the powerful mathematical approaches related to infinite-genus manifolds. This would allow to compare the living cell to infinite-genus manifolds such as the Loch

Ness monster surface, i.e., an infinitely long surface with only one end and infinite number of loops (Valdez 2009; Arredondo and Ramírez Maluendas, 2017), or to the Jacob's ladder, i.e., a surface with two ends (Ghys 1995), or to groups with no planar ends and with self-similar end spaces (Aougab et al., 2021), or to the Weierstrass' one-ended, periodic minimal surfaces (Edward 1995). Infinite-genus manifolds are also correlated with Veech groups of tame translation surfaces (Ramírez Maluendas and Valdez 2017), with blooming Cantor trees with infinite number of handles, with wild translation surfaces (Randecker 2018). However, despite these intriguing speculations, the definition of a living cells as a manifold displaying infinite genus cannot be pursued. Indeed, a manifold with infinite genus must be open, since an infinite number of discrete holes cannot be constrained by borders. This goes against the possibility that a living cell, which is delimited by a membrane surface, could be equipped with infinite topological genus.

In conclusion, the occurrence of cytoplasmic holes deeply modifies the topology of the living cells, providing us with unusual methodological tools to investigate their dynamics.

4. Conclusion

We explored the role of holes in biophysical systems, focusing especially on the physical and topological consequences of the existence of gas vesicles in the cytoplasm of many prokaryotes. Our main conclusions are the following:

a. Holes are able to modify intracytoplasmic fluid dynamics.
b. Holes allow to use underrated topological weapons for system's evaluation.

Topology of manifolds ≥1 concerns disjoint objects such as disjoint shapes, functions, vectors, energies, and so on (for a survey, see Tozzi et al., 2017). Therefore, in physical and biological systems provided with holes such as, e.g., vortices/antivortices (Padavić et al., 2020), nanoscopic materials with topological defects or features of fragile topology (Po et al., 2018) and cytoplasmic gas vesicles, the regions surrounding the holes must display at least some inhomogeneous shapes/functions/vectors/energies. The presence of holes not just encodes remarkable biophysical information about a given cellular structure and its three-dimensional structural complexity, but also permits to predict the cooperative folding pattern in multi-domain structures (Zając et al., 2018).

Artificial gas vesicles find a wide range of applications in biotechnology and medicine. Gas vesicles from different species have been successfully bioengineered as recombinant nanoparticles for proteins extracted from eukaryotic, bacterial and viral pathogens. These recombinant structures act as antigen presenters, generating strong immune responses (Hill and Salmond 2020). The bioengineering potential of these nanoparticles has been also extended to catalytically active enzymes. The addition of synthetic gas vesicle-forming proteins improves the responsiveness of mammalian cells to low-power ultrasound (Ibsen et al., 2015). Being able to retain gas within a stable, rigid structure that produce contrast upon exposure to ultrasound, artificial gas vesicles can be used as contrast agents for biomedical purposes (Pfeifer 2014; Shapiro et al., 2014; Hill and Salmond 2020). For example, they have been used to sonicate primary neuron with the aim to evoke non-invasive neuromodulation in deep-seated brain regions (Hou et al., 2021). Exposed to in an ultrasound beam, gas-filled lipids contract and expand, generating enhanced mechanosensitivity in mammalian cells (Blomey et al., 2001). The propensity of gas vesicles to collapse when exposed to high pressures has been proposed as an environmental biocontrol mechanism to disperse cyanobacterial blooms (Hill and Salmond 2020). The last, but not the least, gas vesicles-producing yeasts may serve as model in fermentation biotechnology to study CO_2 behavior under pressurized conditions (Swart et al. (2012).

Apart from these applications, we suggest that gas vesicles could be artificially inserted in specific target cells when an increase in cellular dimensions is pursued. Lessons learned from the study of sponge skeletal systems imply the possibility to build square lattice geometries optimized to selectively increase the volume of preferred nodes (Fernandes et al., 2021). For instance, an artificially induced increase in cellular volumes could

doi:10.20944/preprints202204.0156.v1

be useful either to build biological scaffolds for bone fractures healing, or to enlarge normal cells confining with tumoral cells to stop their growth, or to achieve cosmetic anti-ageing treatments.

Apart from the topological effects, we suggest another biological role for gas vesicles. It is well-known that intracytoplasmic increases in gas-filled holes may have impact on the allometric relationships governing cellular biophysics (Beaulieu-Laroche et al., 2021). The link between size and function has been deeply investigated: for example, the progeny number of the regenerative flatworms Planarians is strictly correlated with parent size (Arnold et al., 2020). In the aqueous three-dimensional medium of the prokaryotic colonies, volume expansion may lead to beneficial effects such as, e.g., improved sphere packing (Hales at al., 2071). Here we propose a further, peculiar role for gas vesicles, namely the ability to increase or decrease the cellular volume and to modify the surface/volume ratio in a distinctive, unusual way. The amount of surface area per unit volume, termed surface-to-volume ratio (S/V), has been used to assess heat transfer, animal water loss and thermoregulation, artificial bone tissue, etc. (Glazier 2010; Nguyen et al., 2019). It is noteworthy that a wide range of bacterial species exhibit robust S/V homeostasis (Harris and Theriot 2018), suggesting once again that cell size, shape and S/V are mathematically interconnected.

Since every intracytoplasmic volume is served by a surface membrane area, S/V is usually disadvantageous for living cells. Let's see why. Since increases in cell radius lead to decreases in S/V, the internal volume expands faster than the surface area, leading to a detrimental event: the relative amount of membrane available to hand out nutrients and substances to a unit cellular volume progressively decreases. Therefore, big size (and subsequent small S/V) impairs the uptake of nutrients across the plasma membrane. Concerning gas vesicles, one might be tempted to believe that increases in their number lead to increases in cytoplasmic volume and decreases in S/V, and vice versa (Oren 2012). Nevertheless, we hypothesize that things are more complex. We suggest that gas vesicles might allow an increase in cellular volume not followed by a corresponding S/V decrease (Pfeifer 2012). Indeed, increases in the number of empty holes at the expenses of the intracytoplasmic medium might cause the paradoxical effect of increasing S/V. Whilst increases in gas vesicles expand the size of the cellular surface, on the other hand they reduce the volume occupied by the cytoplasm. Therefore, increases in intracytoplasmic gas-filled holes might lead to significant increases in cellular surface, but not in cytoplasmic volume. This would mean that microorganisms equipped with gas vesicles have the positive outcome to enlarge their surface area for adsorption, catalysis and reactions, without the detrimental outcome of enlarging too much the cellular volume. In conclusion, gas vesicles provide living cells with a mechanism that counteracts the criticalities linked with the severe constraints dictated by S/V.

We want to bring to an end with a speculation concerning human diseases. Pneumatosis intestinalis is a clinical sign in which gas is found in the bowel wall (Heng et al., 1995). It has been detected in a vast range of diseases, from necrotizing enterocolitis in premature infants, to obstructive pulmonary disease and progressive systemic sclerosis in adults (Ho et al., 2007). The diagnosis is performed looking at the occurrence of linear or cystic cavities in the submucosal or subserosal layers. We suggest looking also at the possible occurrence of intestinal intracytoplasmic cavities, both inside enterocytes and submucosal/serosal cells.

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