

Multiscale biological systems converge toward universal topology

Daria S. Roshal¹, Renaud Lebrun^{2,3}, Kirill Fedorenko¹, Ivan Golushko¹,
Sergei B. Rochal^{1,*} and Stephen Baghdiguian^{2,†}

¹Faculty of Physics, Southern Federal University, 344090 Rostov-on-Don, Russia

²Institut des Sciences de l'Evolution-Montpellier, Université de Montpellier, CNRS, Ecole Pratique des Hautes Etudes, Institut de Recherche pour le Développement, Montpellier 34095, France

³Montpellier Ressources Imagerie, Biocampus, Université de Montpellier, CNRS, INSERM, Montpellier, France



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As has been known for almost 20 years, topological characteristics of polygonal proliferative epithelial cells of various animal and plant species are universal. Here, we address the question of whether this universality paradigm is applicable to the level of colonial organisms, i.e., at a significantly higher level of life organization than cell populations. By comparing the cellular structure of the epithelium with the arrangement of individual polyps in coral colonies, we discover common topological patterns at distinct levels of life structuring. We hypothesize that the mechanism behind this universality is a repulsion between structural units limited by a certain critical distance. By minimizing the corresponding repulsive energy, we produce packings, which are similar to the epithelial and colonial systems in the distribution of structural units by both the number of their neighbors and their area. The surprising analogies between the systems together with the developed theoretical approach could provide an efficient tool for further studies on morphogenesis, development, and evolution of living systems.

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I. INTRODUCTION

Free energy minimization tends to generate similar patterns at diverse levels of structural organization in various physical, chemical, and biological systems. This theoretical principle serves as a golden thread connecting different areas of research. It plays a fundamental role in understanding various quantum-mechanical and atomic systems, it is important for the development of different materials [1–4], and its combination with ideas about neuron packing led to the creation of the first neural networks [5,6]. Similar approaches can explain the morphogenesis of biological objects with interesting symmetry, geometry, and shape [7–9]. For example, hexagonal packing is characteristic not only of honeycombs but also of the epithelium in the eyes and wings of *Drosophila* [10–12]. The discoveries of complex DNA structures and highly symmetrical protein viral capsids were also inspired by the principles of simplicity and minimality of information required to reproduce these objects [13,14].

In the last two decades, approaches based on energy minimization were actively applied to the epithelial structures [15–17]; however, the polygonal shape of cells has interested

scientists much earlier, since Hooke's studies in the 17th century. The first step in cellular topology—the calculation of cell distributions by the number of the cell neighbors—was made in 1926, while at the beginning of the 21st century it was shown that these distributions are invariant for most proliferative epithelia of plants and animals [18]. This topological invariance is closely related to the physiological invariance of the normal epithelium: In all metazoans and plants, the epithelium acts as a selective barrier that controls fluxes of nutrients, regulates ion and water balance, and protects the host from antigens and microbes.

To date, it is commonly accepted that the patterns related to energy minimization are most clearly expressed in the simplest living systems like virus capsids and cell monolayers. In this study, we show for the first time that the topologically similar structural patterns emerge both in the cell monolayers and at a higher level of biological organization, namely, in corals that are colonies of individual polyps (i.e., organism population).

Here, we consider the corals of the Faviidae, Montastraeidae, and Merulinidae families. Note that due to quite different morphology, we distinguish between Merulinidae species with fused (FCW) and separate corallite walls (SCW). All the considered corals are massive, colonial organisms with flat or hemispherical surfaces, common for all coral reefs from the Red Sea to the West Indies. These corals have striking similarities with the proliferative epithelia. Like cells, individual polyps have a polygonal shape that is clearly delimited by corallite contours. In addition, growth occurs through the intercalary division of preexisting polyps [19], while efficient healing of wounds and injuries takes place via the same

*Contact author: rochal_s@yahoo.fr

†Contact author: stephen.baghdiguian@umontpellier.fr

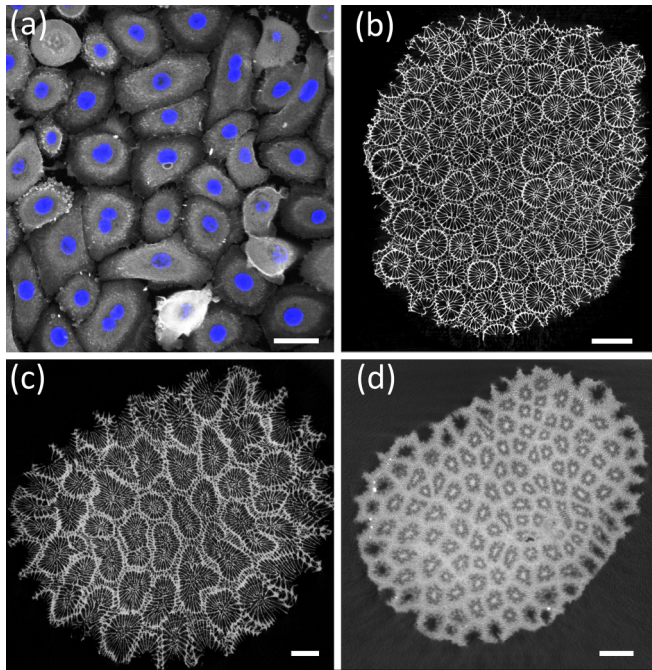


FIG. 1. Similarity in morphology of epithelial monolayers and slices of corals. (a) Fragment of flat monolayer of primary Human Cervical Epithelial Cells (HCEpiC). Cell nuclei are stained with blue dye (Hoechst 33342). (b) Slice of *Montastrea* sp., Montastraeidae. (c) Slice of *Dipsastraea favus*, Merulinidae SCW. (d) Slice of *Favites abdita*, Merulinidae FCW; see coral No. 5 in Table I. Scalebars in panels (a)–(d) are 50 μm , 5 mm, 10 mm, and 5 mm, respectively.

process of asexual reproduction [20]. Also, polyp skeletons accurately reflect the shape and position of each living polyp, which then permits the precise analysis of the number of the nearest neighbors of each individual within the colony. Thus, the considered corals represent an ideal model for rationalizing the nature of the invariant distribution of polygon classes previously observed in epithelial proliferative systems.

The observed similarity between the structures of the epithelium and the coral slices (see Fig. 1 and Supplemental Material [21]) is remarkable for a number of reasons. First, these systems belong to the different levels of biological organization: the cellular level and the level of organism population, accordingly. This change in scale is accompanied by a dramatic change in kinetic parameters of the system. While in the epithelium the unit of analysis is a 10 μm diameter single cell, in species of Faviidae family, this unit is a centimetric polyp consisting of 50 000 to 100 000 cells. Second, the cell membrane has an average thickness of 7.5 nm, is fluid, constantly renews itself, and deforms, whereas the skeleton of a coral colony is extremely rigid (made of aragonite), has a thickness of 1 mm, and is constantly growing. Third, a mother epithelial cell gives birth to two daughter cells in approximately 20 h, while the intratentacular division generates two or three new polyps every year (see movies in the Supplemental Material [21]), and a colony grows at an extremely low rate of 1–5 mm per year [22]. Consequently, relaxation times, which play a decisive role at the epithelial level [23,24]

and are of the order of the cell cycle duration (i.e., 20 h), are extremely long in *Dipsastraea favus* colonies where the growth rate is around 0.1 mm² per month [25]. Fourth, there is a subtle balance between the cell proliferation and apoptosis in developing epithelia, where apoptotic cells are extruded or phagocytized by neighboring cells, which is not the case for dying polyps, whose skeletons persist throughout coral growth. Finally, the forces that organize cells in the epithelium and polyps in the coral are of completely different nature. In the epithelium, these forces are mainly caused by mechanical interactions between neighbors (cell-to-cell adhesion), as well as the tendency of cells to preserve their volume and minimize total area. In contrast, in corals, the mechanism of polyp organization, which occurs during the slow growth of tubular polyps and their division, is associated with optimal positioning of all polyps according to the colony's immediate environment within a coral reef (light, current, food, etc.).

Coral reefs are the basis of biocenoses containing rare and endangered species while simultaneously being powerful global carbon storage systems. Unfortunately, the area of coral reefs is constantly decreasing due to global warming and associated coral bleaching, which makes studying the structure of corals, as well as creating models of their vital activity (and their response to external influences), an important task not only for biology, but also for ecology. All these factors motivate studies of coral morphology [26,27], their physical and mechanical properties [28,29] as well as ability to regenerate damage [20,30], and the development of theoretical models of coral growth [31,32].

As we show in the first part of this work, the distribution of cells by the number of their neighbors, which is invariant for most proliferative epithelia of plants and animals, is close to the analogous distribution of polyps in the colonies of corals Merulinidae SCW, Faviidae, and Montastraeidae, although, on average, the relative spread of areas per individual polyp in the colonies of Montastraeidae is somewhat smaller. The fact that biological systems that are so different in terms of their properties and represent different levels of living matter organization adopt the same topological pattern seems particularly surprising and suggests that in both cases there is a hidden universal mechanism responsible for the life structuring. So, in the second part of our paper, we hypothesize that the energy associated with the mechanism may stem from a simple repulsion between structural units (SUs), provided that this interaction is limited by a certain critical distance. Then, we justify our assumption by comparing the topological characteristics of an *in silico* model and pavements observed in the biological systems.

II. MATERIALS AND METHODS

The corals used in our study were collected in the Red Sea and come from the University of Montpellier collection managed by the Institut des Sciences de l'Évolution-Montpellier-UMR CNRS 5554. In addition, two specimens were collected in the Antilles (Grenadines Archipelago) and Reunion Island, respectively. The specimens have different shapes: mainly flat (encrusting colony), quasihemispherical, convoluted, and even more complex. The taxonomy adopted is based on the World Register of Marine Species [33].

TABLE I. Topological characteristics of corals from two morphotypes of Merulinidae (SCW and FCW) family, and families Montastraeidae and Faviidae. The first column is the colony number. The second column represents coral species and families. The third and fourth columns indicate the number of slices studied and the total number of Voronoi cells in these slices for which the number of neighbors can be accurately determined. The fifth column shows the half-width of the Voronoi cell area distribution. Columns 6–10 represent the fractions P_i of cells with i neighbors; also, these columns show the standard deviations of the P_i values. The value Δ characterizes the topological balance and is calculated using Eq. (1). Average values with the weight equal to the number of Voronoi cells are shown in bold in columns 5–11. The values in columns 6–11 are multiplied by 100. The total/averaged characteristics are given in bold.

No.	Species, family (morphotype)	N_S	N_V	$\Delta S/S_{av}$	$100P_4$	$100P_5$	$100P_6$	$100P_7$	$100P_8$	100Δ
1	<i>Dipsastraea favus</i>	9	131	0.29 ± 0.11	3 ± 3	27 ± 4	46 ± 11	19 ± 7	4 ± 5	5
2	<i>Dipsastraea favus</i>	19	502	0.33 ± 0.1	4 ± 5	24 ± 6	45 ± 11	21 ± 7	4 ± 4	2
3	<i>Dipsastraea favus</i>	8	272	0.27 ± 0.09	2 ± 1	25 ± 3	51 ± 7	19 ± 7	1 ± 2	9
1–3	Merulinidae SCW	36	905	0.31 ± 0.1	4 ± 4	25 ± 5	47 ± 9	20 ± 7	3 ± 4	4
4	<i>Favites abdita</i>	18	8180	0.28 ± 0.09	1 ± 1	22 ± 2	55 ± 3	19 ± 2	1 ± 1	4
5	<i>Favites abdita</i>	12	1805	0.3 ± 0.07	3 ± 1	23 ± 2	51 ± 4	19 ± 2	2 ± 1	4
6	<i>Favites complanate</i>	7	2587	0.33 ± 0.03	3 ± 1	25 ± 2	45 ± 2	21 ± 1	3 ± 1	2
4–6	Merulinidae FCW	37	12 572	0.30 ± 0.07	2 ± 1	24 ± 2	53 ± 3	20 ± 2	2 ± 1	4
7	<i>Montastrea</i> sp.	25	416	0.21 ± 0.07	2 ± 3	30 ± 9	47 ± 11	19 ± 5	2 ± 3	11
8	<i>Montastrea</i> sp.	22	1908	0.22 ± 0.05	2 ± 2	27 ± 3	44 ± 4	22 ± 2	3 ± 2	2
7–8	Montastraeidae	47	2324	0.22 ± 0.05	2 ± 2	28 ± 4	45 ± 6	22 ± 3	3 ± 2	4
9	<i>Favia fragum</i>, Faviidae	9	158	0.27 ± 0.1	0	32 ± 5	42 ± 7	24 ± 5	2 ± 2	4

The specimens were imaged using an EasyTom 150/RX Solutions x-ray microtomograph (Montpellier Ressources Imagerie platform, ISEM, Montpellier, France). Scans were performed using a 1-mm-thick aluminum filter and at voltages ranging from 100 kV for the smallest specimens up to 130 kV for the largest ones. For each specimen, a series of virtual slices of isotropic voxel size (ranging from 28 up to 163 μm depending on the size of the colony) was produced.

Culture cells and labeling: COS cells [COS-1 (ATCC CRL-1650), gift from the Institut de Biothérapie, Montpellier, France] were seeded on standard Petri dishes in minimum essential medium alpha medium supplemented with 10% fetal bovine serum, 20 ng/ml hepatocyte growth factor, 10 ng/ml epidermal growth factor, 25 mM glucose, 1 μM thyrotropin-releasing hormone, 1 μM hydrocortisone, 10 $\mu\text{g}/\text{ml}$ insulin, 50 $\mu\text{g}/\text{ml}$ albumin-linoleic acid, 0.1 μM selenium acetate, 0.5 $\mu\text{g}/\text{ml}$ ferrous sulfate, 0.75 $\mu\text{g}/\text{ml}$ zinc sulfate, 10 mM nicotinamide, 100 $\mu\text{g}/\text{ml}$ streptomycin, and 100 U/ml penicillin.

Normal primary cervical epithelial cells (HCerEpiC) isolated from human uterus were purchased from ScienCell Research Laboratories (Clinisciences S.A.S., Nanterre, France). Cells were grown, processed for fluorescence microscopy, and examined under a Leica TCS SPE confocal microscope as previously described [23].

III. RESULTS

A. Structural characterization of the coral colonies

We obtained and studied about 10 000 virtual slices of nine corals (see Sec. II for more details on the coral characterization and origin of the collection). The slices were made approximately parallel to the surface of the colony attachment; the distances between the nearest slices ranged from 28 to 163 μm , depending on the dimensions of the colony. A detailed topological analysis of 129 slices was performed. The slices for this analysis were selected with gaps such that the

structure of colony varies evenly, and more than 20 individual polyps were present in the image.

The nine studied corals belong to three different families: six corals of the Merulinidae family (three *Dipsastraea favus*, two *Favites abdita*, and one *Favites complanate* specimens), two corals of the Montastraeidae family (*Montastrea* sp. specimens), and one coral of the Faviidae family (*Favia fragum* specimen). In Merulinidae FCW, each polyp shares its wall with its nearest neighbors, while in Faviidae, Merulinidae SCW, and Montastraeidae, each polyp has a well-individualized wall. As for the difference between Faviidae and Montastraeidae, *Montastrea* polyps form a peripheral bead on the surface and are generally smaller in size.

The analysis of the slices studied was performed using the original software written in python. Similarly to our previous analyses of epithelial monolayers [23,34], where the Delaunay triangulation centers were chosen at the centers of cell nuclei, the Delaunay triangulation of coral sections was performed based on the geometric centers of each individual polyp [see Figs. 2(a) and 2(b)]. We recall that the edges of the Delaunay triangulation [35] connect points closest to each other, so the number of the nearest neighbors for a polyp was found from this triangulation. Then, the Voronoi tessellation [36] was constructed [see Figs. 2(c) and 2(d)]; the edges of the tessellation are the bisectors of the perpendiculars to the edges of the Delaunay triangulation. Since we used the polygonal model of the slice structure, the visible areas of polyp sections were (re)calculated as the areas of the polygonal cells of the Voronoi tessellation, as was done earlier in the works [34,37,38], where the areas of the cells were understood as the areas of the corresponding Voronoi cells. We note that the slices are finite, and thus, only those polyps, which correspond to the Voronoi cells with all vertices presented in the slice region, were taken into account.

As an example of the above processing, slices of corals of the *Dipsastraea favus* and *Favites complanata* species (No. 2 and No. 6 in Table I) are shown in Figs. 2(a)–2(d). These

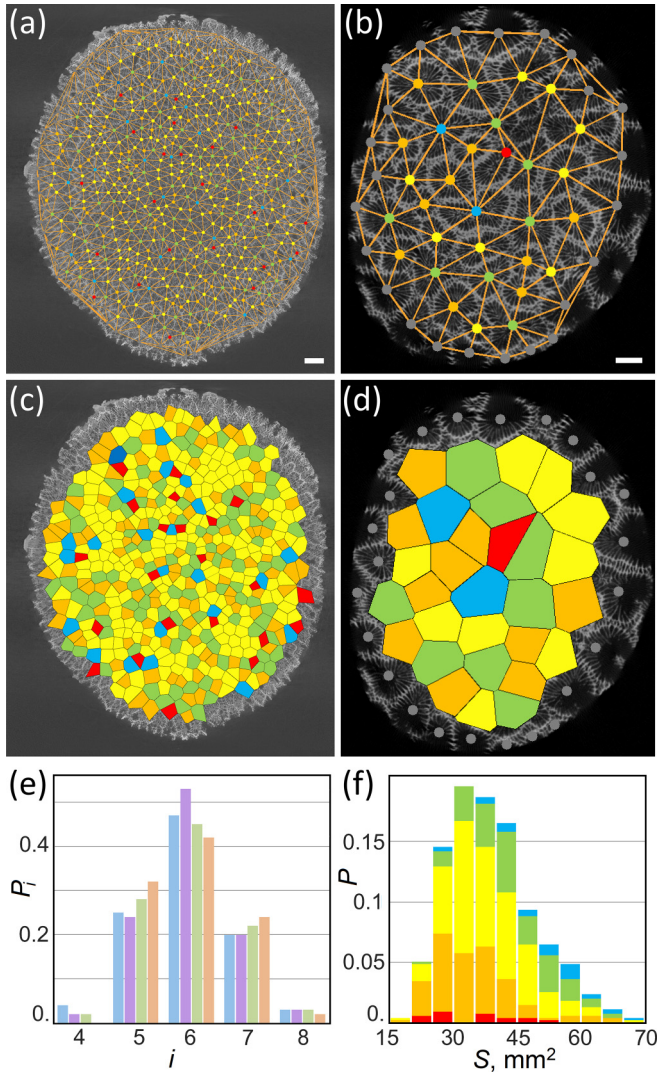


FIG. 2. Topological characteristics of slices of corals. (a) and (c) *Favites complanata* slice containing 641 polyps. (b) and (d) *Dipsastraea favus* slice containing 62 polyps. (a) and (b) Delaunay triangulations are superimposed on the slices. Scalebars are 10 mm. (c) and (d) Voronoi tessellations corresponding to the triangulations. The triangulation nodes are the geometric centers of polyps. Red, orange, yellow, green, and blue colors correspond to polyps/Voronoi cells with four, five, six, seven, and eight neighbors, respectively. (e) Distribution of polyps by the number of their neighbors for three coral families including two morphotypes of Merulinidae family. Blue, violet, green, and orange colors correspond to our results on Merulinidae SCW, Merulinidae FCW, Montastraeidae, and Faviidae, respectively. (f) Distribution of polyps by the areas of Voronoi cells for the slice, shown in panel (a). This asymmetric type of area distribution is typical for both corals and normal epithelial monolayers.

slices contain 641 and 62 polyps, respectively. The determined centers of the polyps are marked with circles, which are the vertices of the Delaunay triangulation [see Figs. 2(a) and 2(b)]. The numbers of Voronoi cells with a reliably obtained number of sides for these slices are 555 and 38, respectively. Only these cells are taken into account when calculating the values of $P_i = N_i / \sum_j N_j$, where P_i is the fraction of cells with

the number of sides i and N_j is the number of cells with j neighbors.

The topological properties of all considered slices are summarized in Table I. The averaging is carried out for slices of each colony separately. The distributions of P_i values averaged with weights equal to the number of Voronoi cells over all corals belonging to one family are shown in Fig. 2(e). In order to assess the reliability of the obtained distributions, we note that in the case of a flat infinite nondegenerate Voronoi tessellation, the fractions P_i strictly satisfy the topological balance equation [39]:

$$\sum_i P_i q_i = 0, \quad (1)$$

where $q_i = 6 - i$ is the topological charge of a cell with i neighbors. Note that the expression (1) is satisfied by any infinite flat polygonal packing, at each vertex of which exactly three edges of the polygonal tessellation converge. As shown in the works [39,40], the right-hand side of the equation $\Delta = \sum_i P_i q_i$ can characterize the error in determining the topology of the monolayer. For experimental P_i distributions obtained in Refs. [18,41,42], $\Delta \leq 0.05$, and in Ref. [37], $\Delta \sim 0.15$. In this work, due to the finiteness of the samples and the simplified method of processing of the image boundaries, the average value of Δ in some cases reaches 0.11. The value of Δ for different colonies can be seen in the last column of Table I. Thus, our results show that the range of distributions [18] typical of many proliferative epithelia of plants and animals, $P_4 \approx 0.02-0.03$, $P_5 \approx 0.25-0.27$, $P_6 \approx 0.41-0.47$, $P_7 \approx 0.22$, and $P_8 \approx 0.03-0.05$, is fulfilled for Faviidae, Merulinidae SCW, and Montastraeidae. The $P_6 \approx 0.53 \pm 3$, corresponding to Merulinidae FCW, lies slightly outside of the range. The biological reason behind this fact may be that the polyps in Faviidae and Montastraeidae (unlike Merulinidae FCW) have individual walls and therefore their structure is more similar to that of epithelium.

The second most important characteristic (after the distribution of structural units by the number of their neighbors), characterizing packings of similar objects on a plane, is the spread of the areas of these objects [23]. In our case, this spread is conveniently characterized by the half-width of the Voronoi cell distribution by area. Due to the asymmetry of this distribution [see Fig. 2(f)], following the work [23], we define the half-width as $\Delta S / S_{av}$, where S_{av} is the average area of cells and ΔS is the difference between the smallest and the largest cell areas among the half of the cells with the areas closest to the S_{av} value. This value, averaged with weights proportional to the number of Voronoi cells in each analyzed coral slice, is equal to 0.27–0.31 in Faviidae and Merulinidae (see Table I), which practically coincides with the experimental data on the *Cucumis* proliferative epithelium [41], where $\Delta S / S_{av} \sim 0.29$ [23]. At the same time, in Montastraeidae, $\Delta S / S_{av} \sim 0.22$, which is due to the fact that the polyps in this family are smaller in size and have a narrower distribution by area. Note that, according to our previous calculations [23], for other proliferative monolayers, the half-width of the area can also vary. For example, in the monolayers of Human Cervical Epithelial Cells (HCerEpiC) and African green monkey kidney cells (cell line COS), the spread of cell areas is larger: $\Delta S / S_{av} \sim 0.34$ and 0.44, respectively; see the cell

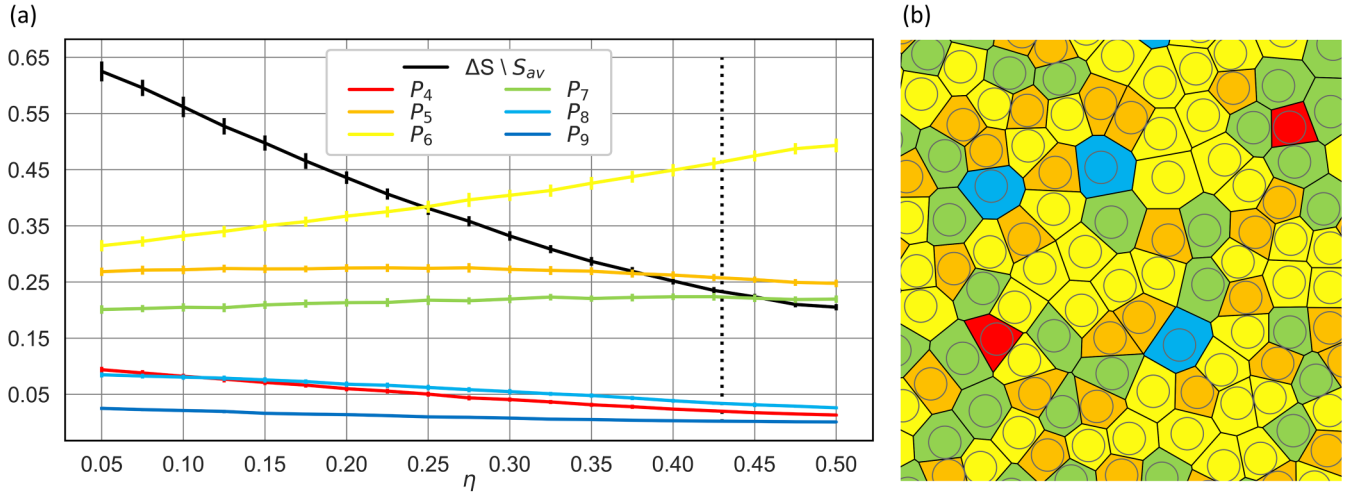


FIG. 3. Topological properties of model polygonal packings obtained by the RSA algorithm. (a) Dependences of fractions P_i (colored lines), the spread of areas $\Delta S/S_{av}$ (black line), and their standard deviations on coverage fraction η in the model of random polygonal packings. The vertical dotted line shows the point $\eta = 0.43$, at which the packings are closest in their topological characteristics to the slices of *Montastrea sp.* (b) Fragment of the polygonal packing corresponding to $\eta = 0.43$. The gray circumferences show the disks used within the method. The polygons are colored according to the number of their sides, similar to Fig. 2.

origin in Sec. II and more structural data in Supplemental Material [21].

B. Model polygonal packings, their optimization, and topological characteristics

Since the morphology of the considered systems is substantially irregular, we start the construction of the model polygonal packings from the known algorithm of random sequential adsorption (RSA) of disks [43]. According to this algorithm, N disks of the same radius are sequentially placed in a given square (fundamental) region with the periodic boundary conditions. The nonzero size of the disks reflects the limitation on the minimum size of an individual cell or polyp of the biological structures under consideration. When attempting to place a disk, its coordinates are chosen randomly. If the disk does not intersect with the existing ones, it is placed on the plane; if it does intersect, the placement attempt is repeated, which makes the algorithm not completely random. The region is filled until a given coverage density η is reached. This density, defined as the ratio of the total area of all placed disks to the area of the fundamental region A , is the main parameter in the model.

Let us discuss the mathematical expectation of the maximum limit on the coverage density η . Thanks to the discovery of different types of disordered structures and the continuous increase of available computing power, this limit, also known as the jamming limit [43,44], has been extensively studied in literature over the past 35 years for various shapes and dimensions of adsorbed particles [43–47]. In the case of the random sequential adsorption of equivalent disks, the average ratio of the area occupied by them to the area of the fundamental region tends to $\eta_{RSA} \approx 0.547$ [43]. Note that this value is significantly less than the coverage density of the hexagonal packing of disks $\eta_{hex} = \pi/2\sqrt{3} \approx 0.9069$.

For the construction of dual polygonal packings, we use the centers of disks as centers of the Voronoi cells and study

dependences of the topological properties on the coverage density η [see Fig. 3(a)]. With the increase of η , the fraction of hexagonal cells P_6 increases, while the spread of area $\Delta S/S_{av}$, on the contrary, decreases. Each point of the graph in Fig. 3 is obtained by averaging the results of 48 numerical experiments with $N = 2500$ points in the fundamental region; coverage density η is varied by changing the area of the fundamental region A . The obtained standard deviations [the vertical segments in Fig. 3(a)] are less than 0.018, and the fact that these deviations decrease with the increase of the number of numerical experiments confirms that the discussed topological characteristics of the obtained packings are functions of η . In this context, we stress again that the resulting polygonal packings are not completely random due to specific way of their construction.

The above model reproduces the topological characteristics of the *Montastraea* coral very well [see Fig. 3(a) and Table I]. Namely, for the coverage density $\eta \approx 0.43$ [vertical line in Fig. 3(a)], the model produces polygonal packings with the spread of areas $\Delta S/S_{av} \approx 0.23 \pm 0.01$ and the proportion of hexavalent cells $P_6 \approx 0.47 \pm 0.01$, which is within the experimental measurement error (see Table I). Note that at $\eta \approx 0.43$, the obtained distribution of polygons by the number of their sides practically coincides with the topologically invariant (orange and gray) distributions shown in Fig. 2(e). Also, we stress that for a pair of polygonal distributions to be close, it is sufficient that P_6 values are close; the remaining fractions P_i in this case become approximately equal due to the balance equation (1).

However, the topological characteristics of the slices of other coral families considered in this paper, as well as normal (proliferative) epithelial monolayers (see the previous section), substantially deviate from the plots in Fig. 3(a). The value of η found from the dependence $\Delta S/S_{av}(\eta)$ leads to a smaller value of P_6 than that obtained from the corresponding experimental data. If η is found from the dependence $P_6(\eta)$, then the spread of areas $\Delta S/S_{av}$ is underestimated. The above

oversimplified model can be improved by introducing some short-range repulsion between the centers of cells (epithelial cells or individual polyps) and minimizing the corresponding effective energy. The biophysical nature of such interaction can vary depending on the system; along with purely physical mechanisms that ensure the optimal shape of the cells and the intercellular interface, these interactions may stem from, for example, a tendency to optimize exchange surfaces with the surrounding environment. In any case, it seems reasonable to assume that the SUs that form the system try to be no closer than a certain critical distance from each other, beyond which the interaction disappears.

When constructing the model, we did not take into account possible anisotropy, for example, associated with the direction of cell division, and to describe the interaction between a pair of SUs, we used the repulsive part of the Lennard-Jones potential, writing our potential as

$$V_{ij} = \begin{cases} \left(\frac{2\sigma}{r_{ij}}\right)^{12} - 1, & r_{ij} \leq 2\sigma, \\ 0, & r_{ij} > 2\sigma, \end{cases} \quad (2)$$

where i and j are the indices of the interacting SUs, r_{ij} is the distance between their centers, and 2σ is the critical distance at which the SU interactions vanish. Accordingly, the total energy of the system U has the form

$$U = \sum_{i>j} V_{ij}. \quad (3)$$

In the case when $\sigma < R$, where R is the radius of the disks used in the initial construction of polygonal packings, there is no interaction between the particles and the minimization of Eq. (3) does not affect the system. In the case of $\sigma > R$, the original structure is additionally ordered. We use a nonlinear conjugate gradient descent algorithm [48] implemented in *scipy* package for the energy minimization. Even though the precise configurations of the resulting packings may strongly depend on the initial positions of SUs, our analysis shows that some essential characteristics of the packings are mainly controlled by the value of σ and the coverage density η of the initial structures. If the value of $N\pi\sigma^2$ is less or in the vicinity of $A\eta_{\text{RSA}}$, then after the minimization, energy (3) turns out to be very close to zero, since the absolute majority of the SUs stop interacting with each other. Accordingly, in this case, σ is the effective radius of the disk in the optimized packing, and the achieved coverage area by identical nonoverlapping disks is $\sim N\pi\sigma^2/A$.

With a further increase of σ when $N\pi\sigma^2 > A\eta_{\text{hex}}$, its value obviously loses the meaning of the effective radius of the disk. In order to analyze in more detail how the topological characteristics of the packings change after minimization of Eq. (3) depending on values of σ , we introduce parameter α , changing from 0 to 1, and determining σ as follows:

$$\sigma = R \left(1 + \left(\sqrt{\frac{\eta_{\text{hex}}}{\eta_0}} - 1 \right) \alpha \right), \quad (4)$$

where η_0 is the coverage density at which the initial packing was constructed. Then, at $\alpha = 0$ the energy minimization does not change the packing at all, whereas $\alpha = 1$ corresponds to the ideal hexagonal close packing. However, since packings are constructed by the minimization of energy (3) from (quasi)random point distributions, in practice, the ideal

hexagonal order emerges only for specific and relatively small numbers of disks.

An example of the polygonal packing optimization within the framework of the model is shown in Figs. 4(a) and 4(b). Figure 4(a) shows a fragment of the initial polygonal packing with $\eta_0 = 0.17$. Next, the value of σ is determined for the chosen value of $\alpha = 0.61$, and energy (3) minimization is performed using the gradient descent method. Here, parameters $\langle \eta_0, \alpha \rangle$ were selected so that after the energy minimization, the optimized polygonal packing morphologically similar to the normal proliferative epithelium of *Cucumis* emerges.

Figures 4(c) and 4(d) show how the topological characteristics of the packings $\Delta S/S_{\text{av}}$ and P_6 depend on parameters $\langle \eta_0, \alpha \rangle$. The 3D graphs were constructed using 378 points in the space of these parameters with steps $\Delta\eta_0 = 0.025$ and $\Delta\alpha = 0.05$. The values of $\Delta S/S_{\text{av}}$ and P_6 at each point were obtained by averaging over the results of energy minimization of 48 different initial structures (each structure has $N = 2500$ SUs in the fundamental region). The values of $\Delta S/S_{\text{av}}$ and P_6 are shown by a color gradient, while contour lines were obtained using *mpl2014* algorithm from *MATPLOTLIB* package (PYTHON). The points closest to the corresponding topological characteristics of corals and cell monolayers are shown as ellipses with the first two letters of their names. Figure 4(e) shows the dependences of $\Delta S/S_{\text{av}}$ and P_6 on the value of η_0 , plotted at a constant value of parameter α . The values of α are chosen to correspond to the structures under consideration.

In Table II, we summarize the average characteristics of the model polygonal packings obtained for parameters η_0 and α that best correspond to the seven analyzed biological structures. To obtain the data in the last two columns of Table II, we analyzed the counterparts (formed from disks) of the polygonal packings. We calculated the effective coverage fraction η_{eff} of disks with the effective radius σ : $\eta_{\text{eff}} = N\pi\sigma^2/A$. Also, we determined a quantitative characteristic of possible disk intersection in the packing. For each model packing, we calculated the linear intersection L_{nm} as l_{int}/RN , where $2R$ is the minimum distance between the disk centers and $N = 2500$ is the number of disks in the fundamental region. In turn, the value of the total intersection length l_{int} was calculated as $l_{\text{int}} = \sum_{i>j, 2\sigma>r_{ij}} (2\sigma - r_{ij})$, where the summation is carried out over pairs of disks with numbers i and j ; r_{ij} is the distance between their centers. Table II presents the average values of L_{nm} .

IV. DISCUSSION

As we have shown, the obtained optimized packings reproduce well the topological characteristics of both the coral families and the normal epithelial monolayers: Compare the values of $\Delta S/S_{\text{av}}$ and P_6 in Tables I and II. Moreover, the characteristics of cell monolayers and Merulinidae SCW, Faviidae, and Montastraeidae corals appear to be very close, in spite of the fact that these systems represent different scales of living matter organization (i.e., cell/organism populations).

In contrast to the other considered corals, Merulinidae FCW species, for which the observed average value of P_6 is ~ 0.53 , deviate from the invariant polygonal topology typical of the normal proliferative epithelia. In our opinion, it is because in this case all polyps in a colony collectively share the

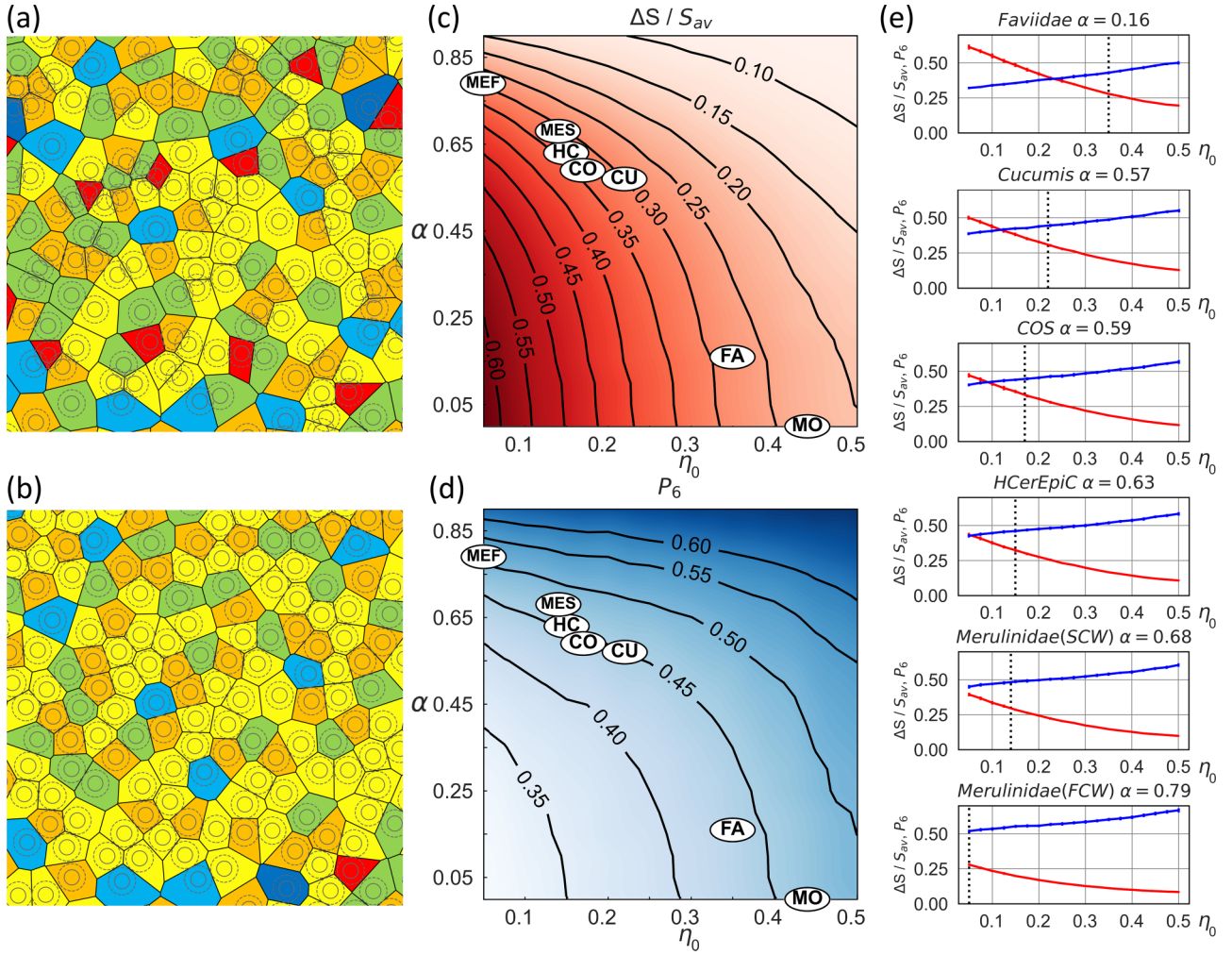


FIG. 4. Topological characteristics of the optimized model polygonal packings and real biological systems. (a) and (b) Optimization of random polygonal model packing. (a) Initial structure with $\eta_0 = 0.17$. (b) The same packing after energy (3) minimization, where the effective radius σ corresponds to the parameter $\alpha = 0.59$. Dashed gray lines show the location of disks with the effective radius σ , while solid gray lines show the size of the disks (with radius R) used in constructing the initial polygonal packing. (c) Dependence of the spread of areas $\Delta S/S_{av}$ on the model parameters. (d) Dependence of the proportion of cells with six nearest neighbors P_6 on the model parameters. Points of the parameter space corresponding to the experimentally measured topological characteristics of corals (Montastraeidae, Merulinidae, Faviidae) and epithelia monolayers (COS, *Cucumis*, HCEpiC) are shown as ellipses with the first two or three letters of their names. (e) Dependences of the topological characteristics of the model packings on the initial coverage density η_0 for the values of α corresponding to the discussed biological systems. The blue and red lines show P_6 and $\Delta S/S_{av}$, accordingly, and the dashed black lines show the values of η_0 corresponding to the experimentally studied systems. Abbreviations: MEF, Merulinidae FCW; MES, Merulinidae SCW; FA, Faviidae; MO, Monstraeraidae; HC, HCEpiC; CO, COS; and CU, *Cucumis*.

same corallite wall, whereas in other considered coral species each polyp has its own wall (which is also the case for the cell membrane). This particular feature of the Merulinidae FCW is similar to the “honeycomb” structure of the beehive, where each cell shares the same wax wall with its neighbors and where the polygonal pattern is exclusively hexagonal [49].

The model structures corresponding to the coral of the Merulinidae FCW species match the experimental data the least: The confidence intervals of the experimental and theoretical model values of P_6 and $\Delta S/S_{av}$ overlap near the interval edges [see Tables I and II]. Accordingly, in this case, we obtain the highest values of $\eta_{eff} = 0.64$ and $L_{nrm} \approx 10^{-2}$.

In all other cases, the model describes the data with a better accuracy (the centers of the corresponding confidence

intervals coinciding almost perfectly) since the simulated packings fulfill the following relations: $\eta_{eff} \lesssim \eta_{RSA}$ and $L_{nrm} \simeq 0$, where not exact vanishing of L_{nrm} is due to the stop condition in the gradient descent algorithm used. Exact zero $L_{nrm} = 0$ for Montastraeidae family is due to the fact that corresponding model packings are obtained exclusively through the RSA algorithm (without subsequent minimization). For the cases when the model fits the data well, the law, according to which the short-range potential (2) tends to zero, is insignificant, since after the energy minimization, the interactions between the structural units practically disappear and energy (3) vanishes. One can check that the topological characteristics of the polygonal packings optimized with potential (2) with different exponent values

TABLE II. Topological characteristics of model packings fitted to corals and normal proliferative monolayers. The first and second columns are abbreviations and species/families. The next two columns indicate the parameters of the model. The fifth column shows the half-width of the Voronoi cell area distribution. Column 6 represents the fractions P_6 of cells with six neighbors. Also, the fifth, sixth and last columns show the standard deviations of the corresponding values. The next column shows the effective coverage fraction $\eta_{\text{eff}} = N\pi\sigma^2/A$ of the optimized packing, while the last one represents the normalized linear intersections L_{nm} of effective disks. All topological characteristics were obtained by averaging the results of 48 simulations with 2500 points each.

	Species/family/morphotype	η_0	α	$\Delta S/S_{\text{av}}$	P_6	η_{eff}	L_{nm}
FA	Faviidae	0.35	0.16	0.28 ± 0.01	0.43 ± 0.01	0.42	$(1 \pm 4) \times 10^{-7}$
MO	Montastraeidae	0.44	0	0.23 ± 0.01	0.47 ± 0.01	0.44	0
MEF	Merulinidae (FCW)	0.05	0.79	0.29 ± 0.01	0.51 ± 0.01	0.64	$(2 \pm 1) \times 10^{-2}$
MES	Merulinidae (SCW)	0.14	0.68	0.31 ± 0.01	0.47 ± 0.01	0.59	$(3 \pm 2) \times 10^{-3}$
CO	COS	0.17	0.59	0.34 ± 0.01	0.44 ± 0.01	0.53	$(5 \pm 5) \times 10^{-4}$
CU	<i>Cucumis</i>	0.22	0.57	0.3 ± 0.01	0.45 ± 0.01	0.55	$(4 \pm 4) \times 10^{-4}$
HC	HCerEpiC	0.15	0.63	0.33 ± 0.01	0.45 ± 0.01	0.55	$(1 \pm 1) \times 10^{-3}$

(varying from 1 to 20) are extremely close provided that $\eta_{\text{eff}} \lesssim \eta_{\text{RSA}}$.

The relative softness of the latter condition makes the model applicable to multiscale biological structures: Both normal proliferative epithelial monolayers and the considered families of coral polyp colonies are topologically equivalent to the optimized pseudorandom flat polygonal packings resulting from our model.

Note that we consider biological monolayers, in which the equilibrium order is maintained dynamically, due to the growth, division, and death of structural units. Due to various biological mechanisms driving the development of monolayers, their topological characteristics vary depending on the system. Therefore, the two parameters of our model are necessary to account for this diversity. Recall that the initial RSA structure is determined by the first parameter η_0 , while the second parameter α defines the additional ordering of the system due to the tendency of its elements to be sufficiently distant from each other. Thus, both parameters are essentially distances reduced to the sizes of the SUs under consideration.

Morphogenesis of many biological structures organized in a regular paving starts from genetically controlled units [50] whose self-organized spatial configuration emerges from a “Turing-like” biochemical system [51,52] with the integrated mechanical and molecular feedback [53,54]. For example, the organization of fish spots requires a Turing reaction-diffusion dynamics produced by chemical interactions between activating and inhibiting morphogens acting at various but critical spatial distances [55].

At the same time, many aspects of patterning in biological tissues are not directly related to genetic control and can be described within the framework of relatively simple physical models representing SUs as deformable polygons. In the models describing cell monolayers, the corresponding energy is often determined through the interactions between polygonal cells [56–60] and depends on the deviation of their area, perimeter, and/or lengths of intercellular boundaries from some equilibrium values. These essentially mechanistic interactions are usually associated with the surface tension energy of the cell membrane, intercellular adhesion, and the rigidity of the actomyosin skeleton, as well as the condition of constancy of the cell volume [56,60,61]. The energy of a monolayer in such polygonal models is minimized either by

moving individual vertices of the polygons (vertex models) [58,60] or only by changing the positions of the cell centers, followed by the construction of different triangulations (models based on Voronoi triangulation) [56,57]. Multiple phenomena occurring in the confluent monolayers were examined within the framework of the polygonal models [61]. For example, with the help of the Voronoi-based model, it has been shown that the fraction of six-valent cells in a monolayer is associated with the so-called mesenchymal-to-epithelial transition, which causes the transformation between liquidlike and solidlike cell phenotypes [56,57].

Unlike the abovementioned models, in which the spread of polygonal cells by area is not explicitly taken into account, our approach demonstrates that the distributions of polygons by the number of neighbors and by area are closely related. Concurrently, the interaction energy between SUs in the model we propose is extremely simplified. We take into account only the simplest isotropic repulsion between the SUs accompanied by the periodic boundary conditions, which limits the area available to the system. However, we do not consider such idealization to be a drawback of our approach. The proposed simple phenomenological model, unlike those discussed above, is not associated with the specific interactions and properties of structural units, which, as we have demonstrated, makes it applicable to a variety of biological systems. We also note that the combination of the RSA algorithm with the used repulsive potential makes the approach we developed similar to more complex approaches used in colloid and interface sciences to describe the processes of colloid particle deposition (irreversible adsorption) in polydisperse soft and solid systems [62].

The next step in the development and application of the proposed model to the abiotic and biological systems may be the explicit consideration of the different sizes and shapes of the structural units. For example, in Merulinidae SCW and Faviidae families, polyp sections are often concave, especially during their division (see movies in the Supplemental Material [21]). It is also of interest to consider dynamic processes within the model, accompanied by a change in the number of structural units and their geometric characteristics. We emphasize that the size of both cells and polyps increases monotonically during their life and changes quite sharply during their division or death. With the simplest modification

of the model (without introducing anisotropy), each structural unit can be characterized by its own time-depending effective radius σ_i , while the value of 2σ in potential (2) can be replaced with $\sigma_i + \sigma_j$. Thus, repulsion potential allowing to obtain more diverse patterns can include the effective sizes of each structural polygonal unit. However, naturally, the packings obtained in this manner will no longer be dual to pseudorandom packings of identical disks.

V. CONCLUSIONS

Finally, by analyzing experimental data on biological structures and using a conventional physical energy minimization approach, we have revealed and explained the convergent universal topology observed at different levels of biological organization. Topological similarity of the considered multiscale biological systems (cell monolayers and colonial organisms) emerges despite different mechanisms of morphogenesis, growth, and division, different sizes of structural units, and characteristic time periods of their development. In the future, we plan to use computerized tomography scan and mathematical physics modeling to investigate the topological characteristics of fossil coral species from the Ordovician and Devonian periods. During these periods, the physicochemical conditions (pO_2 , pCO_2) of the oceans were very different [63–65]. Comparative analysis of these fossil and present-day species within the framework of more detailed models could provide important insights into the global climate changes currently impacting the planet.

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S.B. conceptualized the work. R.L. obtained images of the systems. K.F. performed image analysis and collected statistical data. D.R., K.F., and I.G. developed software, performed formal analysis, and validated results. S.R. managed the project and together with the help of S.B. wrote the main part of the MS. All authors participated in writing and editing the MS.

DATA AVAILABILITY

The data that support the findings of this article are not publicly available. The data are available from the authors upon reasonable request.

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