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Origami-Inspired Engineering: Math behind DONs

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Abstract Origami, an ancient art of paperfolding, has evolved beyond its traditional use for cultural and entertainment purposes and has found its way into artistic, scientific, and engineering realms. This research paper explores the mathematical foundations of origami, and later focuses on a specific application in biomedical engineering. This study is intended to illustrate several aspects of origami that are relevant to engineering structures, namely: geometry, pattern generation, flat-foldability, and the ability of origami tessellations to fit specific target shapes. This review further examines DNA Origami Nano-structures (DONs) which provide numerous benefits, including lower biotoxicity, increased stability, and superior adaptability, making them an excellent choice for Drug Delivery Systems.

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1 Introduction

Origami, an ancient and captivating art form, has truly transcended its humble beginnings to become a source of inspiration and innovation in various domains. Its history can be traced back centuries to Japan, late Showa Era (1926-1989)[ ] [1]. The word "origami" is a combination of "oru," meaning "fold," and "kami," meaning "paper" [2]. However, the art of folding paper has a long and diverse history, known by various names like "orisue" [3] and "orikata" [4] throughout its tradition. The exact origins of origami remain a topic of scholarly debate. While some believe it was an inherent outcome of paper's discovery, others propose Chinese or even European connections to its beginnings. The European tradition, known as "paperfolding," and Japanese origami developed independently for centuries until cultural exchange and the opening of Japan during the Meiji Restoration [5] brought them together, enriching both traditions and contributing to what we recognize as modern origami today. One of the earliest known origami books is

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"Senbazuru Orikata," published in 1797. This book contained instructions on how to fold one thousand paper cranes, which are considered a symbol of good luck and longevity in Japanese culture. Another significant figure in the history of origami is Akira Yoshizawa, often referred to as the father of modern origami. He developed a system of notation and symbols to represent folding techniques, which greatly contributed to the widespread popularity and understanding of origami as an art form. Originally, origami served religious and recreational purposes, often utilizing scarce paper resources [6] . Models were created by folding uncut sheets of paper, typically squares, into abstract or realistic shapes. Over time, the art form expanded and developed practical applications, particularly in the past 50 years [7] . Today, origami is not only limited to the traditional square sheets but is explored across scales, from nano to meter, and applied in various engineering fields [8]. The cross-disciplinary nature of origami has led to a multitude of engineering applications, giving rise to a plethora of origami-based designs. This newfound versatility has garnered interest in the engineering community, leading to innovative solutions in different fields. As origami continues to evolve and integrate into modern applications, the term "origami-based" is used to describe its engineering applications in this article, in accordance with previous studies. The marriage of tradition and innovation has brought origami to new heights, making it a fascinating subject of study and exploration across cultures and disciplines.

1.1 Mathematics behind Folding Art

Origami models exhibit a strong connection to Euclidean geometry, leveraging the inherent properties of a flat surface and employing folding techniques reminiscent of straight-edge-and-compass constructions. When we fold paper, the act itself mirrors the creation of a straight line, while folding the paper in half allows us to establish distances between points, akin to the functions of a compass. The magic lies in the fact that various angle values and numerical relationships, such as sines and cosines, can be meticulously constructed based on the chosen set of basic construction rules, thereby expanding the possibilities within paper folding. In the realm of origami, a complex model's description can be partially deduced from the intricate network of folds displayed on the unfolded paper. This fascinating aspect comes into play particularly when exploring straight-edge folds and the planar developable case. Understanding how these folds interact and intertwine unveils the hidden geometrical brilliance behind the seemingly simple art of origami. We will now focus on how math is applied in origami in ways that most impact origami's applications in our respected field.

2 Creases and Flat-foldability

The core of origami lies in understanding two primary types of creases: mountain and valley creases. A mountain crease creates a fold where the two ends of the paper go down, resulting in a pointed fold resembling a mountain. Conversely, a valley crease is formed when the fold is at the bottom, and the ends of the paper are facing upwards, resembling a valley. The point where mountain and valley creases meet is called a vertex, akin to a corner or a point in a geometrical solid where sides intersect. Origami artists follow certain laws or principles when working with crease patterns. One of these principles, known as Maekawa's Theorem, states that the difference between the number of mountain and valley folds at any vertex is always two (Remember to leave out negative numbers). For example, 5 mountain creases and 3 valley creases would be accurate, since 5-3=2. However, 6 mountain creases and 2 valley creases wouldn't work because 6-2=4 [9]. This rule is essential when learning how to read and fold crease patterns, as it can save you a lot of time trying to fold 6 mountain creases and 5 valley creases since that's an impossible feat.

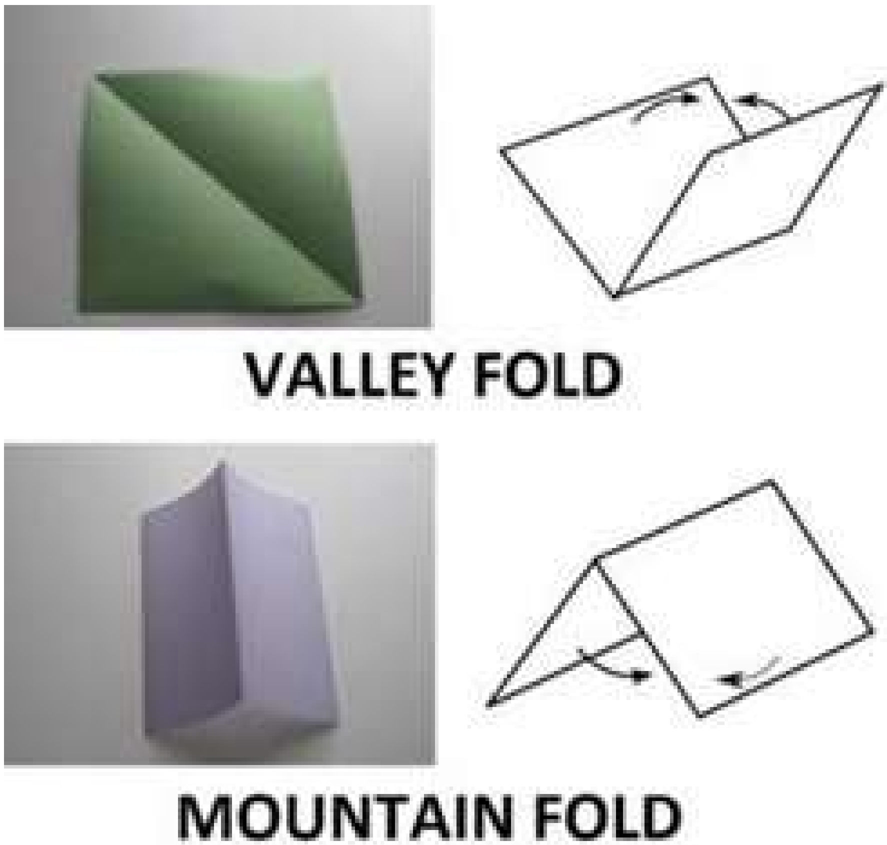

Figure 1. Two types of creases: a) Valley Fold. b) Mountain Fold

The term used to define an origami model solely by the representation of the creases with their type on the unfolded flat piece of paper is known as its 'crease pattern.' Japanese astrophysicist Koryo Miura, using his knowledge of crease patterns, revolutionized the art form with his groundbreaking invention known as the Miura map fold, or Miura-ori. This remarkable innovation showcases an origami tessellation, where a single shape is ingeniously repeated across a surface with no gaps, creating a mesmerizing pattern that adheres to the rules of flat-folded origami [10].

The Miura-ori crease pattern comprises a carefully arranged tiling of parallelograms. Parallelograms are quadrilaterals with opposite sides parallel, and they possess several mathematical properties that contribute to the fold's strength and flexibility. By using parallelograms, the crease pattern ensures that the model can be folded and unfolded seamlessly without deformation or crease interference. This characteristic makes it a perfect fit for folding maps, as it allows for convenient and efficient usage; however, the implications of the Miura-ori stretch far beyond its application in cartography: Dr. Miura used this design as a way to deploy large solar panels into outer space.

Now let's dig a bit deeper into valley folds, mountain folds and Miura-ori crease patterns.

Within the crease pattern, we encounter key elements like creases, vertices, and facets. A crease rep-

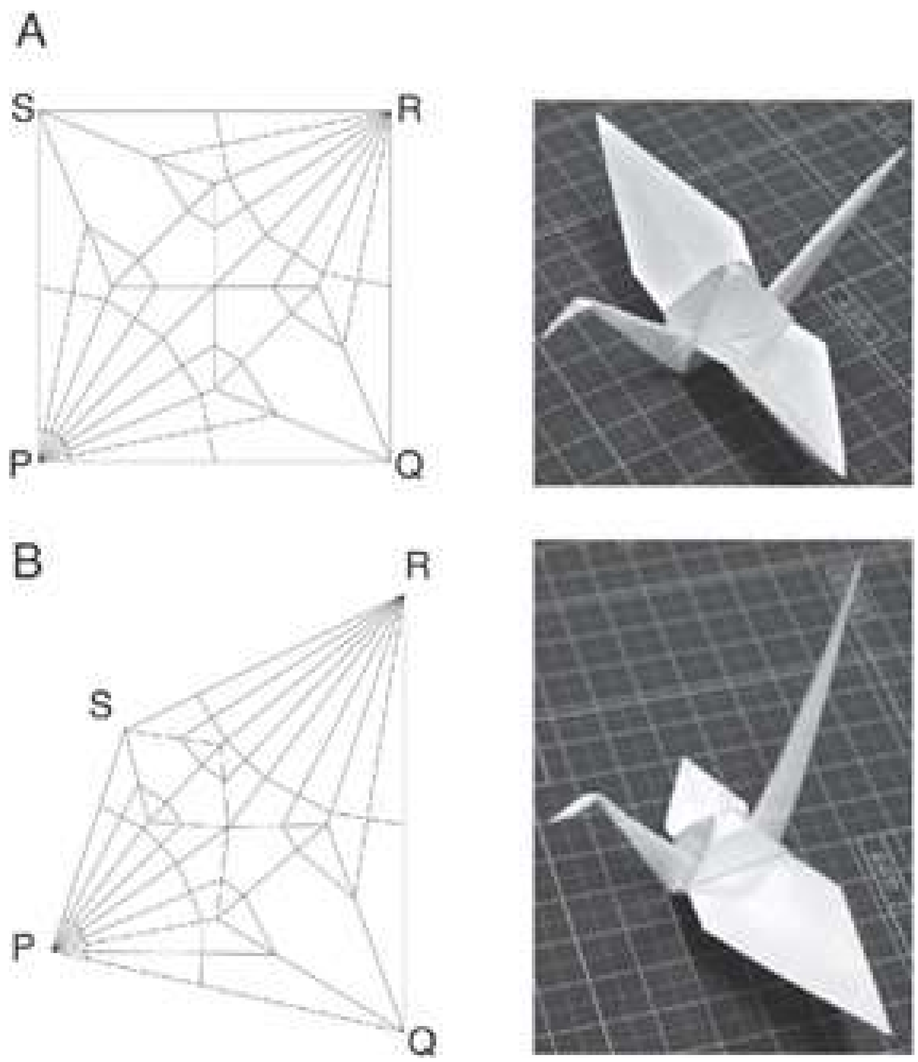

Figure 2. Crease patterns for origami cranes (left) and photographs of actual folded models (right). A: Square. B: Quadrilateral satisfying JK condition.

resents a line along which a fold occurs, and its mathematical properties include the concept of a straight-line segment connecting two points on the paper. Vertices, the points where multiple creases intersect, hold significant mathematical implications in origami design. Facets, referring to the regions bounded by creases, introduce mathematical considerations in terms of planar geometry and topology. The angles formed at the facets and the relationships between adjacent facets are vital aspects that demand mathematical precision to achieve harmonious folding.

The vertex degree holds significance in origami, as it represents the number of creases converging at a vertex, influencing the complexity and structural possibilities of the model which is increased by every fold. Each fold is characterized by a fold angle, which denotes the deviation from the flat state of the paper concerning a plane perpendicular to the fold. The already mentioned two distinct types of folds are most important when looking at the paper from a consistent face of the reference plane where it stands: the mountain fold, which creates a convex shape with an angle ranging from < 0° to -180°, and the valley fold,

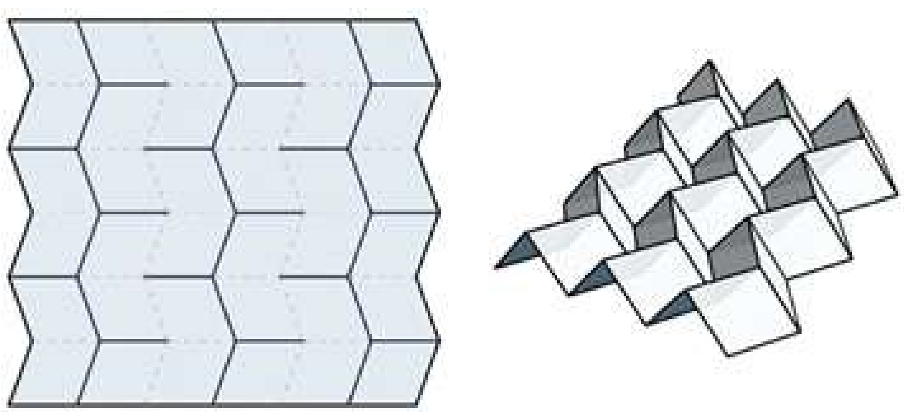

Figure 3. Example of a Miura-ori crease pattern

which produces a concave shape with an angle ranging from > 0° to 180° [11].

The Yoshizawa-Randlett notation system, often utilized in origami diagrams, represents mountain folds as chain lines and valley folds as dashed lines. This notation system simplifies the representation of folds and provides a standardized method for communicating origami designs. However, for intricate crease patterns, conventions tend to represent mountain folds as solid dark lines and valley folds as saturated dashed lines for clarity and readability [11].

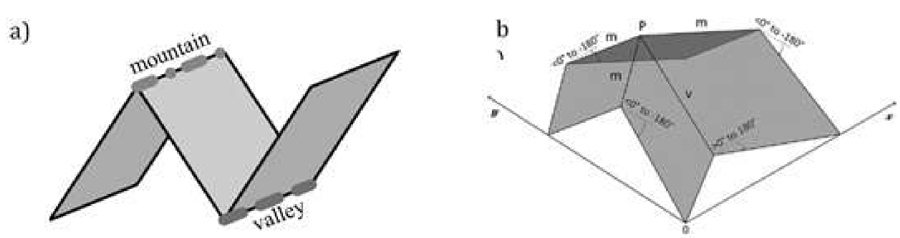

Figure 4. a) single vertex Miura-ori crease pattern. Mountain and valley folds are represented as chain and dashed lines, respectively; P is the single degree-4 vertex. b) folded configuration of the Miura-ori crease pattern; m and v represent mountain and valley folds, respectively.

An origami model is deemed "flat-foldable," also known as flat origami, when it adheres to a specific condition regarding the fold angles of both mountain and valley folds. In this context, the term "flat-foldable" refers to the remarkable property of being foldable in a way that preserves the flatness of the original sheet of paper. This condition sets a maximum limit for the fold angles, where the mountain fold angles range from - (negative pi radians) to (pi radians), and the valley fold angles also conform to the same limit [12].

The significance of this flat-foldability property lies in the practicality and elegance it brings to origami designs. When an origami model is flat-foldable, it can be transformed from its initial flat state into a three-dimensional sculpture through a series of well-defined and precise folding maneuvers. From a mathematical perspective, the constraints imposed on the fold angles make flat origami an intriguing area of study. The notion of fold angles ranging from - to introduces the concept of angular measures in radians. This angular representation allows origami artists to precisely quantify the degree of rotation involved in the

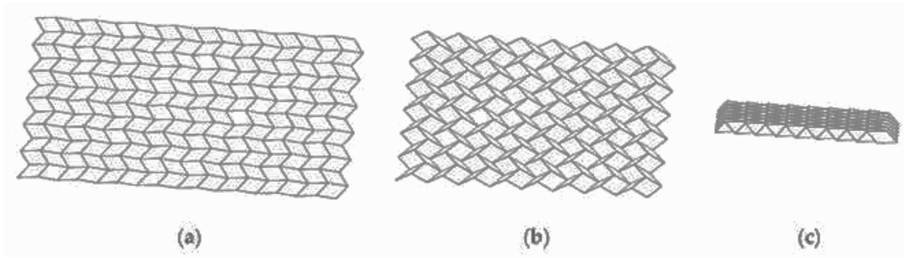

Figure 5. Flat-foldability of a Miura-ori origami. (a) initial fully deployed configuration, (b) intermediate partially-folded configuration, (c) final flat-folded configuration.

folding process. As they manipulate the paper's edges to create mountain and valley folds, the fold angles play a pivotal role in determining the final shape of the origami model. Using this knowledge, Maekawa, Kawasaki, and Justin jointly established a pair of theorems that precisely delineate the prerequisites for achieving local flat-foldability:

- **The Kawasaki-Justin Theorem:** According to this theorem, when considering the alternating angles formed by consecutive mountain and valley folds around a vertex in an origami crease pattern, their sum will always equal 180 degrees [13–15].
- **The Maekawa-Justin Theorem:** Already mentioned above, this theorem proves that the number of mountain folds and valley folds will always differ by two [16]. This implies that the vertex degree, which corresponds to the total number of creases converging at a vertex, is always even. Now, let's investigate the implications of the even vertex degree and its connection to color ability. When a crease pattern adheres to the Maekawa-Justin Theorem, it exhibits a distinct pattern of alternating mountain and valley folds at each vertex. This alternating pattern leads to a fascinating property known as two-color ability. Two-color ability means that it is possible to color the facets of the crease pattern using only two distinct colors, such that no two adjacent facets share the same color. To illustrate this concept, envision a crease pattern with alternating mountain and valley folds at each vertex. Now, assign one color, let's say red, to all the mountain folds, and another color, say blue, to all the valley folds. Since the vertex degree is even, there will be an equal number of red and blue creases converging at each vertex. As a result, the colors red and blue will not meet at any facet border, ensuring a consistent and harmonious coloration of the crease pattern. This property is crucial in the precise execution of complex origami designs, where color-coding the creases facilitates the folding process and enhances the understanding of the model's structure.

These theorems specifically tackle the concept of local flat-foldability, focusing on the folding behavior at individual vertices. However, it should be noted that exploration of global flat-foldability has occurred, which involves multiple vertices, by Bern and Hayes in their seminal work [17].

The Huzita-Justin axioms are a set of seven geometric properties related to origami constructions. They were introduced by mathematicians Z. Huzita and J. Justin in 1989 and play a fundamental role in the field of origami mathematics [18]. Flat-foldability in origami can be characterized by the Maekawa-Justin theorem, which states that any origami pattern constructed using only the first six Huzita-Justin axioms is flat foldable if and only if every interior angle formed by three creases at a point is an integer multiple of /2 (i.e., right angles).

The addition of the seventh Huzita-Justin axiom (Axiom of a Circle through Three Points) further expands the set of possible folding operations, enabling the creation of circles passing through three non-collinear points [19]. This additional axiom provides more flexibility and creative potential in designing flat-foldable origami models, allowing for the incorporation of curved elements and circular patterns. Here are the seven Huzita-Justin axioms:

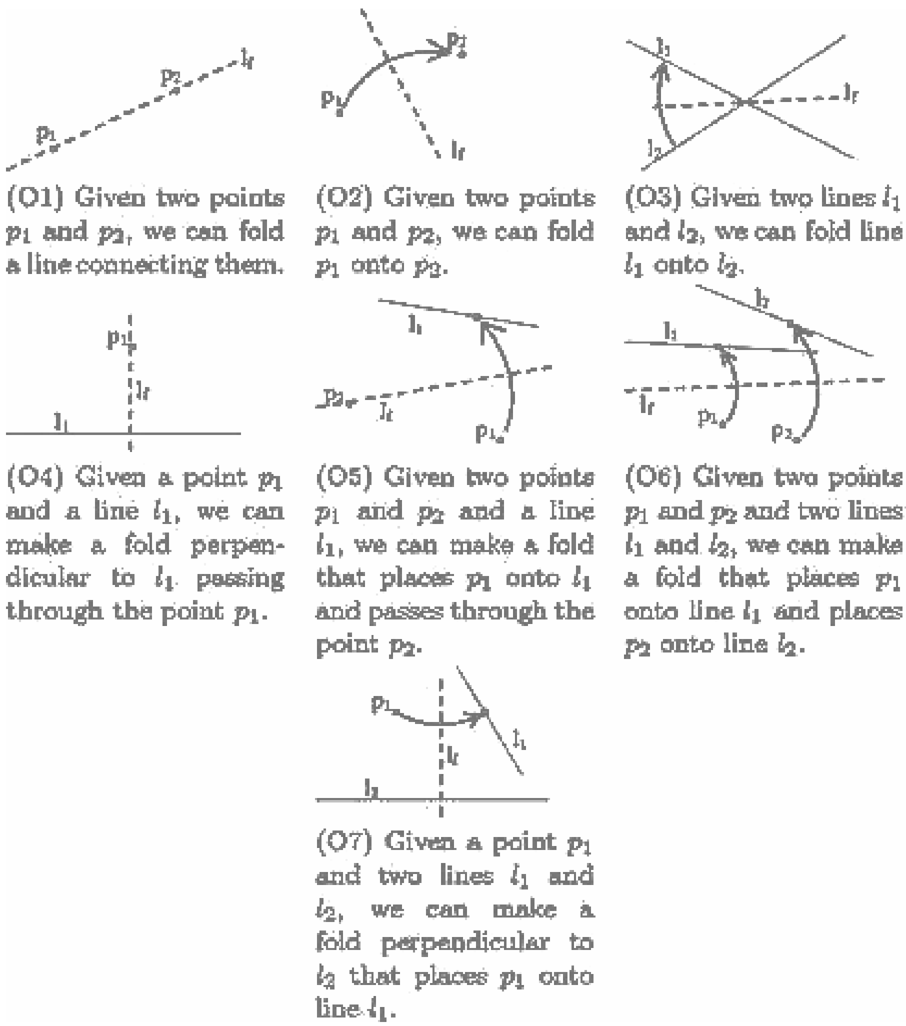

Figure 6. The Huzita-Justin axioms.

2.1 Origami Tessellations and Curvature

Until now, our discussion has revolved around Origami and folding structures using patterns and creases on a flat sheet. However, it hasn't addressed the process of designing patterns that conform precisely to specific target shapes. Origami tessellations represent a mesmerizing class of textured morphing shell structures [10]. These tessellations involve folding the paper in a way that results in a repeating geometric motif, covering the entire surface with the same pattern. While the initial description indicated that we have been working with origami to create folded structures from flat patterns, origami tessellations extend this concept by exploring the art of designing these patterns to fit desired target shapes. What sets them apart is their extraordinary ability to undergo intricate folding and unfolding mechanisms on a local scale, which in turn aggregate and induce significant changes in shape, curvature, and prolongation on a global scale. These global deformation modes enable them to conform seamlessly to specific target shapes, igniting inspiration for their application in diverse fields like structural engineering, architectural design, and beyond.

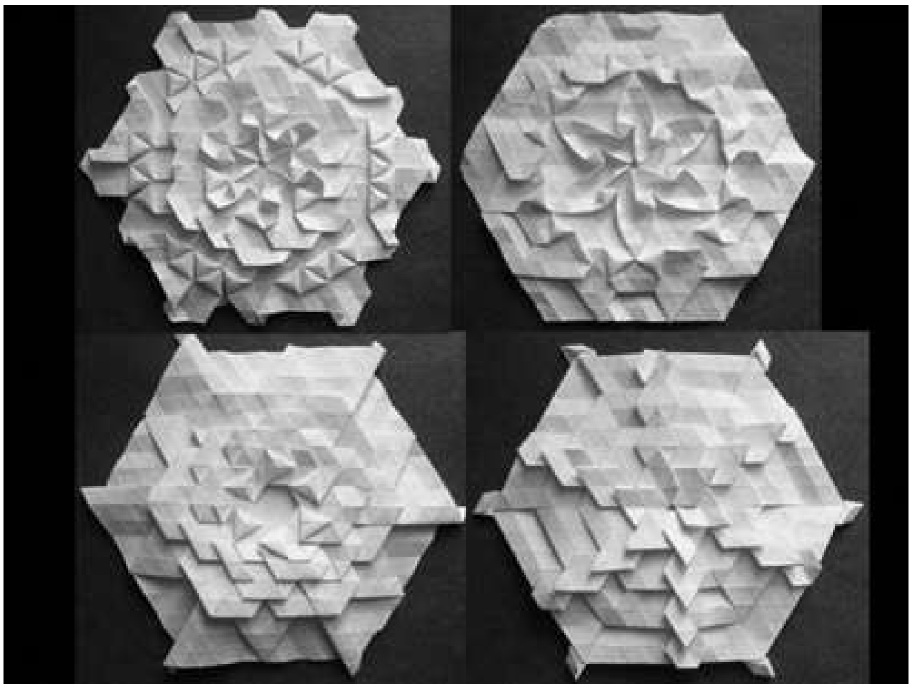

Figure 7. Origami Tessellations

Again, it all boils down to the Geometry of Miura-ori. The exceptional suitability of the Miura-ori for engineering deployable or foldable structures arises from its remarkable degree of symmetry, showcased through its periodicity, and four fundamental geometric properties. These properties play a pivotal role in enabling the Miura-ori to be seamlessly transformed from a flat, planar state to a folded configuration:

1) **Rigidity in Folding:** The Miura-ori demonstrates a unique ability to be rigidly folded, allowing continuous and isometric deformation from its initial flat state to the folded form.
2) **Single Degree of Freedom:** Remarkably, the entire structure's shape is dictated by the folding angle of just one crease, making it an elegant and efficient design.
3) **Negative Poisson's Ratio:** Folding the Miura-ori leads to a decrease in its projected extent in both planar directions, revealing the intriguing property of negative Poisson's ratio.
4) **Flat-Foldability:** At the peak of its folding along the single degree of freedom, all faces of the Miura-ori pattern align in a coplanar fashion.

The simplicity and versatility of the Miura-ori pattern naturally prompt us to ponder if similar tessellations exist for other surfaces with intrinsic curvature. Specifically, one may wonder whether a Miura-ori-like tessellation of the plane can be devised to approximate the folding of an arbitrary curved surface and specific target shapes. For this, we will now discuss inverse origami design framework. To develop our inverse origami design, we will utilize the concept of rigidly and flat-foldable quadrilateral mesh origami (RFFQM). RFFQM is a special class of origami with two fundamental properties that make it particularly suitable for our purposes. Firstly, RFFQM allows us to design and manufacture the origami on a flat reference domain. We can then deploy it to its intended target state and subsequently fold it back to a compact, folded flat state, all without any stretching or bending of the panels throughout the entire process. This feature ensures that the origami maintains its structural integrity during transformation, making it robust and reliable for real-world applications involving repeated deployments and folding. Moreover, the compact folded state achieved in RFFQM can be unfolded back to the target state, which is essential for scenarios involving storage and portability. This reversibility enables us to create deployable structures that can be easily packed and transported when not in use, and effortlessly unfolded to their functional configurations when needed. Secondly, RFFQM exhibits folding kinematics with only one degree-of-freedom (DOF). During the folding process, all the folding angles vary in a coordinated manner, simplifying the design of a mechanical control system or actuation strategy. This inherent simplicity in the folding motion allows for more straightforward and efficient mechanisms to control the origami's deployment, further enhancing its practicality and ease of use. Given these unique properties, we find RFFQM to be an exceptionally promising template for the design of deployable structures. More knowledge about the designs and deformations of quadrilateral mesh origami can be gained by a research paper by Fan Feng, Xiangxin Dang, Richard D. James, and Paul Plucinsky [21]. They also proved that it is possible to march algorithmically and discover that: *For a given set of input data, there exists precisely one or no RFFQM that is consistent with this particular data set.* In their research, they also obtain an explicit marching algorithm that either discovers a unique RFFQM pattern or fails due to incompatibility at some point during iteration. It is recommended to check out this algorithm as in itself it is too detailed to get into here.

Rigidly and Flat-Foldable Quadrilateral Mesh Origami (RFFQM) is an exclusive category of quad-mesh origami patterns, where a quad-mesh crease pattern comprises quad panels arranged in a 2D plane and interconnected along creases. The deployment capabilities of RFFQM are unparalleled, but they impose distinct constraints on their design process.

To precisely define a RFFQM crease pattern with $M \times N$ panels, we focus on the characteristics of each vertex. At every vertex (indexed by $i = 0, 1, \ldots, M$ and $j = 0, 1, \ldots, N$), there exist two sector angles, $\alpha_{i,j}$ and $\beta_{i,j}$, each constrained within the range $0 < \alpha_{i,j}, \beta_{i,j} < \pi$. However, this is just the beginning of the constraints placed on the vertices.

Further restrictions are imposed on the remaining two sector angles at each vertex to ensure the origami's deployability. The sum of all four sector angles at a vertex must be precisely 2π, preserving the concept of developability, which is vital for RFFQM structures. Additionally, the sum of opposite sector angles at a vertex must be exactly π, satisfying the famous flat-foldability condition, also known as Kawasaki's condition [22].

In our scenario, we start with compatible input data $(\alpha_0, l_0, \sigma_0)$, which enables us to effectively compute the overall crease pattern using a sophisticated marching algorithm. This algorithm guarantees that the resulting pattern exhibits a unique and highly desirable single Degree of Freedom (DOF) folding motion. During this folding motion, each individual folding angle evolves from 0 to π (or $-\pi$) in a strictly monotonous manner, adhering to the prescribed M-V (Mountain-Valley) assignments.

To comprehensively understand and characterize this folding motion, we introduce a crucial folding parameter denoted as ω. This parameter acts as a key descriptor, allowing us to capture and analyze the complete evolution of the crease pattern. When ω is set to 0, the crease pattern is essentially flat, representing the starting configuration. On the other end of the spectrum, when ω takes the value of π, the crease pattern transforms into the folded-flat state, signifying the final folded configuration.

It's important to note that this folding parameter, ω, operates on a continuous scale between 0 and π. As such, intermediate values of $0 < \omega < \pi$ correspond to progressive stages of the pattern's transformation, smoothly evolving the crease pattern from its flat state to the fully folded state. By manipulating this folding parameter, we can effortlessly control the crease pattern's evolution, seamlessly transitioning it from a flat arrangement to a compact folded state, culminating in an extraordinary and versatile deployable origami structure. As a result, the kinematics of the origami structure are parameterized by:

$$\text{Eq. (1)} – \{y^{i,j}(\alpha_0, l_0, \sigma_0, \omega) \mid i = 0, 1, \ldots, M, j = 0, 1, \ldots, N\},$$

where $y^{i,j}$ are the vertex positions (in 3D) on the deformed origami structure (determined by $\alpha_0, l_0, \sigma_0, \omega$).

In the context of inverse design, a pivotal aspect concerning the marching algorithm lies in its efficiency. The process of uncovering a Rigidly and Flat-Foldable Quadrilateral Mesh (RFFQM) pattern and computing its kinematics using Eq. (1) proves to be remarkably time-effective. Both the pattern itself and any of its potential folded states can be determined through computations that exhibit a linear scaling with the number of panels, denoted by (O(MN)). This remarkable efficiency is a result of the explicit iterative nature of the procedure, which contributes to swift and accurate calculations.

2.2 Inverse Design Strategies

The inverse design of origami structures deals with the innovative challenge of creating crease patterns that fold into desired structures with specific properties. Here, we present a comprehensive and versatile framework that focuses on the inverse design of deployable origami structures using the principles of Rigidly and Flat-Foldable Quadrilateral Mesh (RFFQM) origami.

Consider a set of vertices $y_{i,j}$ in 3D space, representing a collection of points $y_{0,0}$, $y_{1,0}$, ..., $y_{M,N}$. Our objective is to arrange these vertices in a manner that corresponds to an origami deformation of a Rigidly and Flat-Foldable Quadrilateral Mesh (RFFQM) crease pattern with $M \times N$ panels. In addition, we seek to minimize an objective function that aligns with a specific inverse problem we aim to solve.

Tachi's Theorem[**?**], a significant mathematical result in this context, serves as a fundamental guideline for enabling rigid motion in general quadrilateral

$$\min f_{\text{obj}}(\mathbf{y}^{i,j}) \tag{1}$$

subject to

In the context of our origami design and optimization, we introduce the objective function, denoted by f_{obj}, which captures the essence of our specific design goals. This function is carefully chosen to incorporate desired properties of some or all vertices $\{y_{i,j}\}$ in our origami structure.

Two pivotal constraints are vital to the successful design of deployable origami structures: the developability constraint (g_{dev}) and the flat-foldable constraint (g_{ffold}). The developability constraint ensures that the sector angles at each vertex sum to 2π, preserving the flatness and smoothness of the origami surface. Meanwhile, the flat-foldable constraint guarantees that the sum of opposite sector angles at each

Eq.(2) -

$$\min_{\{y^{i,j}\}} f_{obj.}(\{y^{i,j}\})$$

$$\text{subject to } \begin{cases} g_{dev.}(y^{i,j}, y^{i+1,j}, y^{i,j+1}, y^{i-1,j}, y^{i,j-1}) = 0 & \text{if (i, j) indexes an interior vertex,} \\ g_{ffold.}(y^{i,j}, y^{i+1,j}, y^{i,j+1}, y^{i-1,j}, y^{i,j-1}) = 0 & \text{if (i, j) indexes an interior vertex,} \end{cases}$$

vertex equals π, allowing for the feasibility of smooth folding. As indicated, these constraints can be written in terms of five neighboring vertices on $\mathbb{R}^3$ via the formulas:

Eq.(3) -

$$g_{dev.}.(v_0, v_1, v_2, v_3, v_4) = \sum_{i=1,\ldots,4} \arccos\left(\frac{v_i - v_0}{|v_i - v_0|} \cdot \frac{v_{i+1} - v_0}{|v_{i+1} - v_0|}\right) - 2\pi$$

$$g_{ffold.}.(v_0, v_1, v_2, v_3, v_4) = \arccos\left(\frac{v_2 - v_0}{|v_2 - v_0|} \cdot \frac{v_1 - v_0}{|v_1 - v_0|}\right) + \arccos\left(\frac{v_4 - v_0}{|v_4 - v_0|} \cdot \frac{v_3 - v_0}{|v_3 - v_0|}\right) - \pi$$

In the former formula, $v_5 = v_1$ and the side lengths $|v_i - v_0|$ are assumed to be positive in order to apply the formulas correctly. In a more precise manner, Tachi's theorem provides a valuable result: If we are able to find vertices $\{y_{i,j}\}$ that satisfy all the $2(M-1)(N-1)$ equality constraints mentioned in Eq. (2) for an $M \times N$ crease pattern, and these vertices are not all confined to a single plane in $\mathbb{R}^3$, then set $\{y_{i,j}\}$ represents the vertices of a rigid origami deformation for an $M \times N$ Rigidly and Flat-Foldable Quadrilateral Mesh (RFFQM) crease pattern. In other words, any solution that satisfies Eq. (2) corresponds to an origami structure that can be designed on a flat reference crease pattern and deployed through a folding motion or mechanism to achieve the desired objective.

2.3 Formulating the optimization

Our primary approach revolves around eliminating the equality constraints entirely, leveraging the insightful characterization provided by the marching algorithm for Rigidly and Flat-Foldable Quadrilateral Mesh (RFFQM) crease patterns. As previously discussed, this algorithm efficiently parameterizes a RFFQM crease pattern based on angles, lengths, and mountain-valley assignments along the "L"-shaped boundary represented by the arrays $(\alpha_0, l_0, \sigma_0)$. Simultaneously, it effectively parameterizes the kinematics of the origami using a folding parameter ω.

With these valuable insights at our disposal, we can seamlessly replace the optimization process in Eq. (2) with a more direct and efficient formulation:

In our approach, we introduce a simple yet powerful modification to the objective function f_{obj} by replacing it with $f_{obj}(\alpha_0, l_0, \sigma_0, \omega) = f_{obj}(\{y_{i,j}(\alpha_0, l_0, \sigma_0, \omega)\})$. Essentially, we maintain the same general objective function, but now the vertices $\{y_{i,j}\}$ are explicitly parameterized by the marching algorithm using the arrays $(\alpha_0, l_0, \sigma_0, \omega)$.

Eq.(4) –

$$\min_{\alpha_o,\, l_0,\, \sigma_0,\, \omega} \tilde{f}_{obj.}(\alpha_o, l_0, \sigma_0, \omega)$$

$$\text{subject to} \begin{cases} (\alpha_0, l_0, \sigma_0) \text{ is compatible input data,} \\ \omega \in (0, \pi). \end{cases}$$

While Eq. (4) defines a general optimization scheme equivalent to Eq. (2) for the family of Rigidly and Flat-Foldable Quadrilateral Mesh (RFFQM) crease patterns, we encounter a challenge with the variable σ_0. As an array of discrete variables, σ_0 poses numerical optimization difficulties. To address this practical implementation issue, we adopt an alternative strategy and proceed with the optimization problem under a prescribed value, denoted as $\overline{\sigma_0}$:

Eq.(5) -

$$\min_{\alpha_o,\, l_0,\, \omega} \hat{f}_{obj.}(\alpha_o, l_0, \omega) = \tilde{f}_{obj.}(\alpha_o, l_0, \bar{\sigma}_0, \omega)$$

$$\text{subject to} \begin{cases} (\alpha_0, l_0, \bar{\sigma}_0) \text{ is compatible input data,} \\ \omega \in (0, \pi). \end{cases}$$

In this context, the nature of compatible input data lends itself to seamless numerical implementation, offering valuable properties for optimization. Suppose we have already identified a set of compatible input data ($\bar{\alpha}_0, \bar{l}_0, \bar{\sigma}_0$) that corresponds to a well-known Rigidly and Flat-Foldable Quadrilateral Mesh (RFFQM) origami structure, such as the renowned Miura-Ori pattern. Now, with the Mountain-Valley (M-V) assignment indicated by $\bar{\sigma}_0$ held fixed, we can rigorously demonstrate that there exists an open neighborhood around ($\bar{\alpha}_0, \bar{l}_0$) where the data remains compatible.

Furthermore, we can establish that the formulas governing the vertex positions $y_{i,j}(\bar{\alpha}_0, \bar{l}_0, \bar{\sigma}_0, \omega)$ are smooth for ($\bar{\alpha}_0, \bar{}_0$) within this neighborhood and for $\omega \in (0, \pi)$. This smoothness property ensures that the optimization process described in Eq. (5) becomes a standard nonlinear programming problem over an open subset of $\mathbb{R}^{3M+3N+2}$. Consequently, with the

3 Biomedical engineering

The biomedical industry stands at the forefront of origami-based device research and application, making remarkable strides in harnessing the potential of origami-inspired designs. This unlikely marriage has given rise to a host of ingenious devices and structures that are making significant waves in the field. These origami-inspired creations possess a unique set of properties that make them stand out. They can seamlessly transition between various shapes, display auxetic behaviour (which is basically a fancy way of saying they expand when stretched), and have the flexibility to adapt their geometry and mechanical characteristics to suit different needs. Moreover, they're relatively easy to manufacture and can be scaled up as required, making them incredibly versatile for both in vivo and ex vivo applications.

However, while the potential is vast, there are still some hurdles to overcome. These challenges revolve around issues like material compatibility, the efficiency of actuation methods, and the overall reliability and durability of these origami-based systems, particularly in demanding clinical scenarios.

What's truly intriguing about origami-based structures is their adaptability. They can be scaled and optimised to meet specific design constraints, offering a canvas for inventive and flexible solutions. The ability of origami to smoothly transition from a folded state to a fully deployed one is particularly promising, especially in the context of minimally invasive medical procedures. Recent advances in self-folding technologies have added an exciting dimension to this concept. Additionally, researchers have been exploring optimised 3D assembly methods that employ bending, curving, and folding, opening up exciting possibilities for biomedical applications. In the realm of synthetic biosystems, where the goal is to mimic natural biological systems, origami has emerged as a game-changer. It simplifies the design process, reduces costs, and adds an element of disposability. This involves applying mathematical and technological principles known as origamics to decode complex biosystems. Key to this are the six Huzita Axioms and one Hatori Axiom, which define various folding methods and expand the potential applications of origamics. These 3D structures can be further fine-tuned using simulation software and 3D printing to achieve precise patterns and customization.

Looking ahead, the future of origami-based enhancements in biomedical applications appears incredibly promising. I anticipate breakthroughs that will allow for the creation of intricate 3D structures, enhanced biocompatibility, and dynamic shape-shifting capabilities. This research will provide a glimpse into the world of an important modern origami application in the medical field: Drug Delivery.

3.1 Drug Delivery Design

3.1.1 DNA Origami Overview

A DNA molecule is a remarkable polymer composed of two continuous single strands of deoxyribonucleotides running in parallel but opposite directions. These strands are built from four types of bases: adenine (A), guanine (G), thymine (T), and cytosine (C). They pair up in complementary pairs—A-T and C-G—creating stable links between the strands and forming the iconic double helix structure of DNA. This elegant base pairing property allows DNA molecules to be folded and assembled, and their sequence arrangement and template shape can be manipulated to construct complex three-dimensional structures. In 2006, Professor Rothemund [23] from the California Institute of Technology introduced the groundbreaking concept of DNA origami. Using this ingenious approach, DNA sequences are meticulously designed and arranged to fabricate artificial shapes such as triangles and stars. DNA origami is a revolutionary bottom-up technique for crafting nanoscale structures, driven by the self-assembly properties of DNA. The method leverages nucleic acid sequence hybridization and relies on two main components: a long single-stranded DNA scaffold (typically the genome of M13 phage) and numerous short single-stranded DNA staple strands. These short DNA strands act akin to staples in a book bind, strategically crossing multiple binding domains on the DNA scaffold to engineer the intended 2D or 3D structure. Subsequently, heating the mixture of short and long DNA strands in an alkaline solution leads to their automatic and stable binding, giving life to the initially designed structures.

The creation of DNA origami nanostructures (DONs) typically begins with designing the sequence using specialized software like caDNAno [24], ATHENA [25], or Adenita [26]. Once the template strand and auxiliary folding strands are meticulously designed, they are blended in specific ratios to facilitate annealing.

Subsequent steps involve functional modifications and purification of the resulting structures. Over the past two decades, scientists have harnessed this technology to craft an array of 2D and 3D DNA folding structures, each with unique potential applications. DNA origami is a programmable and versatile technique that allows for the precise design and manufacturing of DNA nanostructures tailored to specific needs. These structures hold immense promise across various domains, including drug delivery, sensing technology, and nanocircuits.

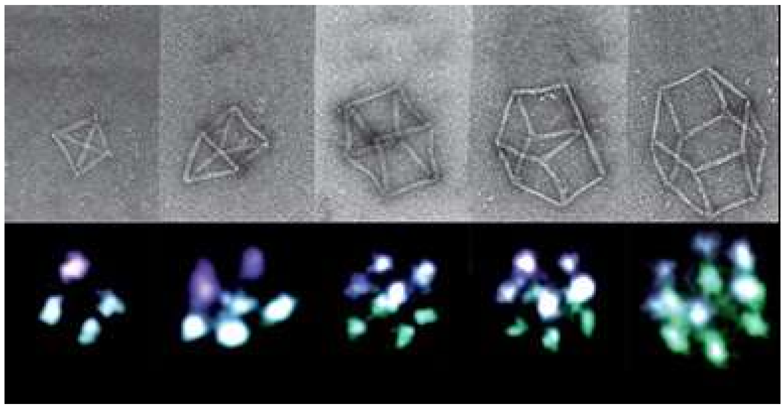

Figure 12. DON for Drug Delivery

3.1.2 Efficient Drug Loading onto DONs

To optimize drug delivery using DONs, it's essential to load drugs efficiently. This involves selecting the appropriate loading method based on the drug's properties. [26]. The choice of method can significantly impact the success of drug delivery using DONs.

- **Intercalation:** This method involves inserting drug molecules, such as doxorubicin (DOX), between the base pairs of DONs. DOX can form stable bonds with the G-C base pairs or fit snugly into the grooves of A-T rich regions within the DONs' double-stranded DNA structure. This intercalation creates a robust complex ready for drug delivery [27].
- **Chemical Bonding:** For larger drugs or those with specific ligands, chemical bonds can be established between the drug and DONs. These bonds ensure a secure connection and help maintain the drug's integrity during delivery.
- **Covalent Connection:** In some cases, drugs can become an integral part of the DNA structure within DONs. This covalent connection ensures that the drug is an inherent component of the DONs' intricate design.
- **Complementary Single-Strand Extensions:** Nucleic acid drugs like cytosine-phosphonothioate-guanine (CpG) and small interfering RNA (siRNA) can be loaded onto DONs by adding complementary single-strand extensions. These extensions act as bridges, connecting the drug to the DONs, facilitating effective drug delivery [28].

Selecting the right loading method is akin to composing a symphony, ensuring that the drug harmonizes seamlessly with DONs for efficient drug delivery.

3.1.3 Targeted Drug Delivery

Utilizing the DNA origami technique for constructing nanostructures expands their functional capabilities beyond basic drug delivery. For instance, these structures can accommodate various medications, such as combinations of anti-tumor drugs and adjuvants or different types of anti-tumor agents, enhancing treatment comprehensiveness and therapeutic effectiveness while minimizing side effects. Additionally, employing DNA origami to load multifunctional nanocarriers enables concurrent support for drug delivery, imaging, and therapy, offering substantial potential for enhancing treatment outcomes [29] . Targeted therapy, a treatment approach that identifies and selectively attacks specific cancer cells while sparing normal cells, has demonstrated clinical promise. However, many drugs used in such therapies often suffer from limitations such as multiple targets, high cell toxicity, and poor in vivo stability, resulting in various side effects and suboptimal therapeutic outcomes [29]. Yet, by employing suitably designed DNA nanostructures constructed using DNA origami, drugs can be loaded onto these DNA-based vehicles. This approach reduces in vivo drug loss, facilitates precise delivery to target cells, enables precise targeting of specific cellular markers, minimizes toxic side effects, and enhances therapeutic efficacy. Numerous studies have illustrated that DNA origami-based drug carriers are effective for targeted delivery, particularly for chemotherapeutic agents, nucleic acid drugs, proteins, and peptides. DNA origami allows the precise folding of DNA molecules into diverse nanoscale structures, such as nanotubes and nanoboxes, offering notable advantages for targeted drug delivery. These nanostructures are highly controllable, with shape and size readily adjusted by modifying the folding sequence and length, facilitating accurate drug targeting and delivery. Furthermore, DNA origami exhibits excellent selectivity, enabling specific cell or tissue targeting by designing DNA sequences with distinct affinities. Additionally, DNA origami boasts a high drug-carrying capacity, efficiently encapsulating and releasing multiple drug types by manipulating spatial structure and size. Lastly, utilizing naturally occurring DNA molecules in the body ensures exceptional biocompatibility, minimizing adverse effects on the human body.

Consequently, DNA origami has gained extensive utility in targeted drug delivery, significantly enhancing delivery efficiency and precision while opening new avenues for drug treatment research. Research has illuminated the process of DNA origami nanostructures' internalization by tumor cells, involving mechanisms like cell membrane engulfment and endocytic vesicle formation. The internalization process typically includes four primary steps: adsorption, endocytosis, early endosome formation, and late endosome formation. During adsorption, DNA origami nanostructures interact with scavenger receptors on the cell membrane surface, tightly adhering to it. Subsequently, the cell membrane undergoes stretching movements, encapsulating the nanostructures in endocytic vesicles. These vesicles then fuse with the endoplasmic reticulum, transforming into late endosomes or lysosomes where decomposition occurs [30]. Notably, the uptake and intracellular localization mechanisms can be structure and coating-dependent. Various types of DNA origami nanostructures, along with distinct modifications, can significantly influence cellular uptake. Nevertheless, a consensus on the cellular uptake process of DNA origami nanostructures is yet to be established, warranting further research for clarity in this regard.

3.1.4 Multifunctional Drug Delivery System

A multifunctional drug delivery system leverages DNA origami, a highly versatile and customizable tool, to create carriers for multiple drugs with distinct therapeutic effects. This approach enables comprehensive treatment strategies, encompassing various modalities like photoacoustic diagnosis, photothermal therapy, chemotherapy, immunotherapy, and gene therapy. DNA origami plays a pivotal role in advancing multifunctional drug delivery systems, transforming modern medicine. Recent breakthroughs have successfully utilized DNA origami to produce these innovative carriers. In cancer treatment, drug resistance poses a significant challenge. Gold nanomaterials (AuNPs), known for their unique properties and biocompatibility, are used as drug carriers, delivering drugs precisely to tumor cells while harnessing photothermal effects [31]. Incorporating gold nanorods and drugs into DNA origami nanostructures (DONs) allows targeted delivery to drug-resistant tumor cells, effectively eliminating them. Researchers have also combined chemotherapy drugs with DONs, achieving remarkable results. To reach deeper into tumor tissues, researchers like Gu et al. have ingeniously combined DOX, gold nanoparticles (GNP), and tetrahedral DNA nanostructures (TDNs) [32]. This approach capitalizes on pH variations within the tumor microenvironment, allowing for precise drug release at specific depths. DONs have shown promise in co-delivering different therapeutic agents, enhancing treatment efficacy without causing systemic toxicity. Furthermore, the optimization of DNA origami structures for specific surfaces has been significantly enhanced through inverse design strategies, with equations like Eq. (5) ensuring rigid and flatfoldable origami structures. This approach guarantees deployability and directly encodes the dimensionality of the design space, offering advantages over vertex-based approaches like Eq. (2). These advanced techniques hold immense potential in tailoring DNA origami structures for drug delivery systems, enhancing their effectiveness in targeted therapies.

Conclusion

This research delves into the intricate world of origami, showcasing its evolution from a traditional cultural and entertainment practice to a pivotal component in artistic, scientific, and engineering domains. By dissecting the mathematical foundations of origami, this study sheds light on its relevance to engineering structures, emphasizing crucial aspects such as geometry, pattern generation, and flat-foldability. The focus on origami tessellations and their ability to conform to specific target shapes highlights the versatility of this ancient art form. Moreover, the exploration of DNA Origami Nano-structures (DONs) in the realm of biomedical engineering unveils a promising avenue for innovation. DONs, with their lower biotoxicity, heightened stability, and exceptional adaptability, emerge as a groundbreaking choice for Drug Delivery Systems. This research underscores the transformative potential of origami-inspired designs in the advancement of various scientific and engineering applications, demonstrating the fusion of tradition and innovation for a brighter future.

Compliance with Ethical Standards

It is declare that all authors don't have any conflict of interest. Furthermore, informed consent was obtained from all individual participants included in the study.

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