Computational Topology for Geometric Design and Molecular Design

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Abstract

The nascent field of computational topology holds great promise for resolving several long-standing industrial design modeling challenges. Geometric modeling has become commonplace in industry as manifested by the critical use of Computer Aided Geometric Design (CAGD) systems within the automotive, aerospace, shipbuilding and consumer product industries. Commercial CAGD packages depend upon complementary geometric and topological algorithms. The emergence of geometric modeling for molecular simulation and pharmaceutical design presents new challenges for supportive topological software within Computer Aided Molecular Design (CAMD) systems. For both CAGD and CAMD systems, splines provide relatively mature geometric technology. However, there remain pernicious issues regarding the 'topology' of these models, particularly for support of robust simulations which rely upon the topological characteristics of adjacency, connectivity and non-self-intersection. This paper presents current challenges and frontiers for reliable simulation and approximation of topology for geometric models. The simultaneous consideration of CAGD and CAMD is important to provide unifying abstractions to benefit both domains. In engineering applications it is a common requirement that topological equivalence be preserved during geometric modifications, but in molecular simulations attention is focused upon where topological changes have occurred as indications of important chemical changes. The methods presented here are supportive of both these disciplinary approaches.

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1 Introduction

Topology is the branch of mathematics that studies the properties of geometric objects which are preserved under continuous deformation [26]. Whereas geometry is concerned with rigid form, size and location of objects, topology is concerned with deformation, connectivity, and associativity of objects.

The field of computational geometry as its own discipline has been pervasive in CAGD, computer graphics, and robotics for more than twenty years [29]. The term 'computational topology' first appeared in 1983 to emphasize the role of the topological adjacency relationships within CAGD [23]. More recently, efforts have arisen to formalize computational topology into its own discipline [28], so as to improve reliability in geometric computing, varying in scales from the atomic to the astronomical.

This paper simultaneously considers topological issues in CAGD and CAMD, offering new perspectives and research directions for advancing these fields. It does so by first exploring the motivation and use of topology for CAGD applications, and by formalizing communication about topology for the field of CAGD in Section 2. Next, contemporary uses of topological methods for CAMD are discussed in Section 3 within the context of the formalisms introduced for CAGD. Possibilities and motivation for improving CAGD and CAMD are discussed throughout with an emphasis placed on topological equivalence. Section 4 provides conclusions and future directions for applications for CAGD and CAMD.

2 Challenges in Computational Topology for CAGD

Surprisingly, all contemporary CAGD systems lack the reliability and robustness required for automation of engineering analysis tasks such as computational fluid dynamics (CFD), finite element analysis (FEA) and optimization of design processes. These engineering applications rely heavily on the accuracy of the model provided by the original CAGD system. An intermediate step between CAGD and analysis is the generation of a piecewise linear (PL) mesh which introduces added errors from the mesh approximation of a free-form surface. While meshing is typical in CAGD, it is expected to become more prominent in CAMD as more sophisticated surface models of molecules evolve. During model approximations for engineering analysis, topological anomalies that now arise include extraneous self-intersections, unwarranted gaps, and incorrect connectivity – all of which can cause problems in a subsequent analysis. According to Farouki [12], a core problem with modern CAGD systems is in the underlying mathematics used for representing models, and the source of many of these problems arise from the algorithmic issues inherent in computing approximations. The mismatch between approximate geometry and faithful topology has historically caused reliability problems not only in CFD and FEA, but also for scientific visualization and engineering applications. As CAMD matures, with more sophisticated geometric models, the accompanying visualizations and simulations are expected to experience similar approximation problems. Hence, it is useful to consider this approximation problem from the viewpoints of CAGD and CAMD simultaneously, while preserving topology during these approx-

imations by meshed representations.

An important challenge for the computational geometry and topology communities is the development of rigorous, robust and tractable methods for guaranteeing that computational approximations of curves and surfaces preserve critical topological characteristics. The emphasis here is upon geometric models having at least C^2 continuity. However, the approach presented is consistent with a broader perspective where important model discontinuities should also be preserved to maintain topological equivalence during approximation. For example, too much algorithmic smoothing on a geometric model with curvature discontinuities could lead to topological changes, just as well as too coarse an approximation could result in topological changes. Both types of topological changes could result in inaccuracies in the associated analysis.

The 'topology' of a CAGD model is frequently expressed as a critical property for reliable engineering simulation. However, the use of the term 'topology' is often informal, sometimes even to the point of being misleading. There is little use in speaking universally of the topology of a model. Rather, it is crucial to decide which topological characteristics of a model should be preserved or changed to support effective engineering simulations. Hence, the use of precise topological terminology is important. The following subsections propose a foundation for communication about topological equivalence for both CAGD and CADM. An article of this length cannot presume to be comprehensive about modeling topology. Hence, selective attention will be given to those specific topological properties that the authors judge to be most central to modern industrial modeling.

2.1 Combinatorial and point-set topology

In CAGD, combinatorial topology[1] is used to represent the adjacency relations between constituent geometric elements of a model [43]. The topological instantiations are typically known as vertices, edges, and faces, which correspond to the geometric entities of points, curves, and surfaces, respectively.

The combinatorial topology provides no information about how an object is embedded in 3-dimensional space. For example, Figure 1 shows that the same combinatorial data can describe a completely different embedding. Note that each object would have exactly the same adjacency graph, even though one object is topologically a circle and the other object describes a trefoil knot, as described further in the next subsection.

A central definition in point-set topology [26] is that any two subsets A and B of $\mathbb{R}^3$ are *topologically equivalent* if there exists a function $f : A \to B$, such that f is continuous, $1-1$, has a continuous inverse and maps onto all of B. Such a function is known as a homeomorphism. The two objects in Figure 1 are also homeomorphic.

The important summarizing observation is that neither combinatorial topology nor point-set topology provides sufficient capability for more subtle topological characteristics that are crucial for today's increasingly sophisticated geometric models. The new frontiers in topological modeling are presented in the next subsection.

[1] Combinatorial topology is often referred to as symbolic topology or adjacency topology in the CAGD literature

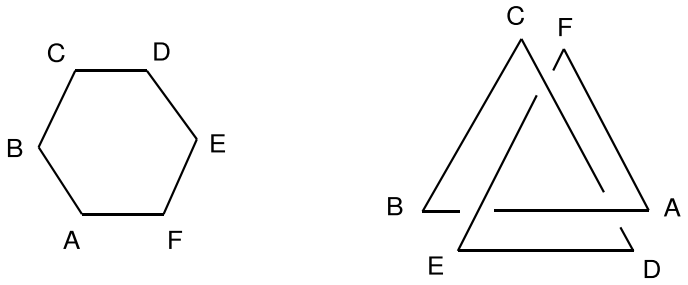


Figure 1. *Same combination represents different objects.*

2.2 Topological Equivalence

While the relations of combinatorial topology and the equivalence relations defined by homeomorphisms are quite powerful and useful, they fail to distinguish how an object is embedded in three-dimensional space. To expand upon the discussion of Subsection 2.1, consider a very simple closed curve, the circle. It is the special planar case of an unknot, which is pictured in Figure 2(a). The important intuitive generalization from the planar circle to the unknot is that the unknot is any closed curve in $\mathbb{R}^3$ formed from certain permissible deformations of the circle, where the types of permissible deformations will be formally described in the following definition of ambient isotopy. A more complex knot, the trefoil is depicted in Figure 2(b). Its essential distinguishing characteristic is the presence of 3 crossings, as shown by the hidden surface rendering in Figure 2(b). The knot with four crossings is shown in Figure 2(c), and is called the figure-8 knot. It is easy to see that all these knots are homeomorphic to each other, yet it is often important to distinguish among these curves [2]. Indeed, this can be accomplished with additional topological techniques. Such techniques are based on a stronger notion of topological equivalence than homeomorphism, known as an *ambient isotopy*. The formal definition of an ambient isotopy follows.

Definition. *If X and Y are subsets of $\mathbb{R}^3$, then X and Y are* **ambient isotopic** *if there exists a continuous function $H : \mathbb{R}^3 \times [0,1] \to \mathbb{R}^3$ such that for each $t \in [0,1]$, $H(\cdot, t)$ is a homeomorphism such that*

- $H(\cdot, 0)$ is the identity and
- $H(X, 1) = Y$.

Consider the unknot, the trefoil knot and the figure-8 knot in Figures 2(a), 2(b) and 2(c), respectively. None of these knots can be continuously deformed into the other without breaking a strand. Hence, none of these three knots are ambient isotopic, but they *are* homeomorphic.

It is worth noting that the existence of an ambient isotopy between two sets can be very hard to detect. Consider the tangled mess in Figure 3, and note that

[2] For a listing of standard knot types, the reader is referred to [1, 32].

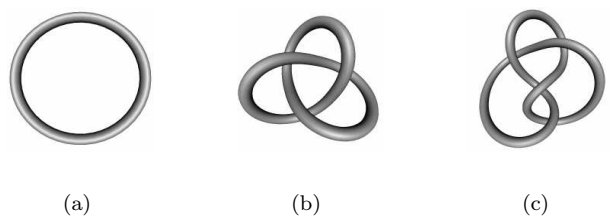


Figure 2. *(a) Unknot. (b) Trefoil knot. (c) Figure-8 knot.*

it *is* ambient isotopic to the circle, meaning it can be 'untangled' without breaking a strand to form the circle [3].

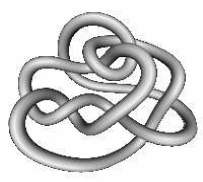


Figure 3. *This tangled mess is ambient isotopic to the unknot.*

Recently, considering generation of self-intersections during perturbations of geometric objects has been fundamental for effective algorithms to preserve isotopy class during these perturbations [3, 4, 5]. This recent work on computational ambient isotopy builds upon the considerable computational geometry literature for detection of self-intersections in curves and surfaces [19, 20, 44].

3 Frontiers in Computational Topology for CAMD

This section describes integration of theory for useful molecular modeling. It is composed of four sub-sections. Subsection 3.1 describes how the abstract mathematics of knots has been useful in forming conceptual models of molecules. Subsection 3.2 then describes an example of how some of this abstract theory could be used as the theoretical basis for molecular simulation algorithms. Subsection 3.3 then points out the difficulties in implementing efficient algorithms for even some relatively simple problems in knot theory, leading to reasonable pessimism about the effectiveness of knot theory for practical implementations. The section is concluded in Subsection 3.4 with an alternative approach to overcome that expressed pessimism. The proposed focus then becomes on approximations to create practical models, such that these approximations maintain topological equivalence under ambient isotopy.

[3] An animation of the knot in Figure 3 can be seen using Robert Sharein's KnotPlot tool [36]. Knot images in Figures 2, 3, and 5 are partially created from KnotPlot.

The authors' specific mathematical contributions are then articulated, suggesting how these approximations can be useful in molecular simulations.

3.1 The Conceptual Role for Knots

For CAGD and computer graphics, static models are often sufficient to represent complex shapes for product design. However, form and function are integrally related in the life sciences, and form is rarely static. Biochemical processes are dominated by dynamic changes which modify function. Existing geometric methods for simulating these dynamics are computationally intensive. While geometry is the correct mathematics for capturing static form and rigid motion changes, topology is more focused upon how an object deforms in time. Hence, the faithful integration of computational topology and geometry is emerging to model dynamic changes in molecular function within the domain of CAMD, and such simulations have the opportunity to leverage and improve more than two decades of experience with geometric models within CAGD.

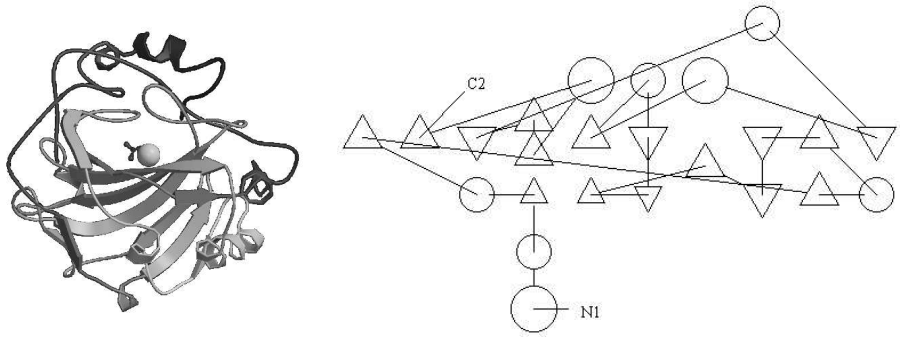
The same formalisms about topology discussed in Section 2 may be equally well suited for advancing CAMD. Note that contemporary use of computational topology for CAMD by the bio-molecular community is mostly combinatorial, particularly when simulating molecules by traditional 'ball-and-stick' models. Such combinatorial models are composed topologically of vertices and edges, where the vertices correspond to individual atoms and the edges represent the bonds between atoms[4]. Current 'textbook' methods classify protein structure as a hierarchy of four subset structures (See [8, 34]), where the secondary structure contains critical combinatorial topology information.

A model of the protein, carbonic anhydrase I, is shown in Figure 4(a), and its corresponding secondary structure topology diagram of its peptide chain is shown in Figure 4(b). The $N1$ and $C2$ represent the ends of a fragment of the chain. The circles represent alpha and 3_{10} helices, and the triangles represent beta strands. (The interested reader can obtain more information on these diagrams from [24], and can easily produce such diagrams on the internet [40] directly from protein structural information contained in the Protein Data Bank(PDB) [31]. The PDB ID for this particular protein is 1hcb. For the reader who wishes to see a more detailed color image of the carbonic anhydrase I protein in Figure 4(a), an online image can be viewed from the PDB.)

In addition to the combinatorial approach to macro-molecular modeling, the mathematics and computer science communities have also begun to formulate a topological perspective of bio-molecules. For example, Edelsbrunner and his associates create new computational topology algorithms to model macro-molecules [9, 10, 21].

The role of knots in understanding molecular dynamics in DNA was discovered nearly two decades ago by Wasserman et. al. [41, 42] and Sumners [38]. These researchers applied topology to predict knots in DNA molecules, and confirmed their results with experimentation. They also showed that specific enzymes can

[4]Geometrically, these are well known as simplicial 1-complexes [6].



(a) (b)

Figure 4. *(a) Carbonic anhydrase I (1hcb). (b) Topology diagram.*

cause a change of knot type, and advocated the use of topology to characterize the role of enzymatic action on DNA structure, since no matter how much a DNA molecule is twisted or distorted, without 'breakage' caused by reaction with specific enzymes, the DNA topology remains invariant.

Although DNA is commonly thought of as a long, thin double helix, in reality, DNA mostly exists in a *supercoiled* form – meaning it is twisted and tangled in order to be in a state of minimum energy [37]. Furthermore, two or more strands of supercoiled DNA can also be *linked* together to form what biologists call catenanes. Note that links are simply a generalization of knots in the mathematical knot theory literature [1, 32]. Such linking and supercoiling of DNA is studied in the life sciences, and presents challenges to the modeling of DNA structure and function [35].

It is interesting to note that knots have been found to naturally occur in the primary structures of proteins. Taylor [39] describes an algorithm which he used to scan 3,440 protein structures in the Protein Data Bank, and found that eight of these contained knots. The protein in Figure 4 is one of these, and contains the trefoil knot. Since knot theory is emerging as useful mathematics for research in the disciplines of molecular modeling and geometric design, some related questions about efficiency for knot recognition algorithms are presented in the next section.

3.2 Algorithmic Efficiencies for Knots

A knot can be visualized as a closed loop of string. The way in which the strands of a knot are entwined is far more important than the size or shape of the knot, and helps distinguish different types of knots. Examples of knots are shown in previous sections of this paper. The important point to note is that topological equivalence of knots is determined by the notion of ambient isotopy. The interested reader is referred to the excellent text by Adams [1] for the introductory details of knot theory that are not included in this article.

A fundamental question in knot theory is how to determine when two knots are equivalent. An active area of research in knot theory today is finding mathematical methods that determine topological invariants of knots. Such invariants are useful for classifying and distinguishing different types of knots, and are typically given by a polynomial of one or two variables. For example the well-known Jones polynomial [18] of the simple trefoil knot depicted in Figure 2(b) is given by $V(t) = -t^{-4} + t^{-3} + t^{-1}$. However knot invariants are typically very hard to compute, and may become intractable as the knot complexity increases. Computation of the Jones polynomial is known to be **#P-hard** [17]. In addition, it is known that even the problem of determining whether an object is knotted or not is in **NP** [14], which presents challenges for developing practical applications. Hence, these authors have shifted their attention to determining when an object and its approximation are ambient isotopic, *even while the knot type of either may not be known*. Both effective theory and algorithms for determination of knot equivalence have been developed [3, 4, 5, 33] and should gain an increasing prominence in CAGD and CAMD.

3.3 Knot representations

Computations for knots must be performed on some representation of the knot. Typically, knots are represented combinatorially by identifying crossings with their adjacent crossings on an oriented knot projection. An example of an oriented projection of the trefoil knot is shown in Figure 5. Note that each crossing is labeled numerically, and the sign on the crossing indicates whether it is an over crossing or under crossing.

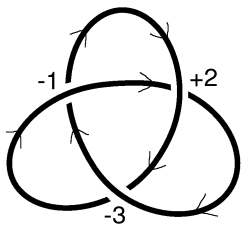
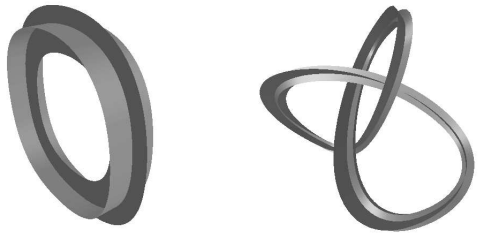


Figure 5. *An oriented projection of the trefoil knot with labeled crossings.*

These knot representations are important for algorithms to distinguish between geometric objects in differing isotopy equivalence classes. For example, the intersection between two surfaces could result in a knotted intersection curve, yet current methods for surface intersections do not specify the isotopy class of the intersection set. This is shown in Figure 6, where the intersection curve of the two surfaces in Figure 6(a) would result in the unknot, and the two surfaces in Figure 6(b) would result in the trefoil knot. In these surface intersection examples it is important to produce a knot, but in other instances, a knot may be an unwanted artifact of a poor approximation. The next subsection discusses how an approxi-

mation algorithm can change the isotopy class of a geometric object, a predicament that has only recently been considered in the literature [2, 3, 5, 22, 33].



(a) (b)

Figure 6. *Surface-to-surface intersection resulting in the (a) unknot. (b) trefoil knot.*

3.4 Algorithms for isotopically equivalent approximations

Approximations are central to geometric modeling and molecular design for computational efficiency, and problems can arise in preserving the isotopic equivalence during an approximation [2, 22, 33]. The relevant summary of the previous material of this section is to advise the reader that fundamental knot computations are not likely to be efficient for practical computations. In particular, performing *explicit* computation of the isotopy class of a knot and its approximant in order to determine isotopy equivalence is unlikely to be tractable. Hence, a more subtle approach is required, which includes additional specific information about the type of approximation process being undertaken. The goal then becomes to demonstrate that specific approximation processes will produce isotopic approximations. Note that this is similar, in spirit, to an approach throughout topology. Namely, topology has many theorems that discuss which topological characteristics (e.g., compactness, connectedness, closure, Euler number) are preserved under specific types of functions (e.g., continuous, homotopic, homeomorphic, diffeomorphic).

To motivate that approach, the difficulties that can arise if approximation is done without incorporating specific topological constraints are shown now. Then, recent work by these authors, as well as others will be summarized to indicate progress on this problem.

Consider the smooth cubic-spline curve in 3-dimensions shown in Figure 7(a). Note that spline curves are often approximated by piecewise linear or piecewise polynomial curves for display and analysis. A good piecewise linear approximation that maintains equivalent topology is shown in Figure 7(b). However, it is easy to see that a poor approximation, shown in Figure 7(c), can result in a different knot. This particular example results in the figure-8 knot.

Hence, a poor approximation as shown in Figure 7 could be detrimental to

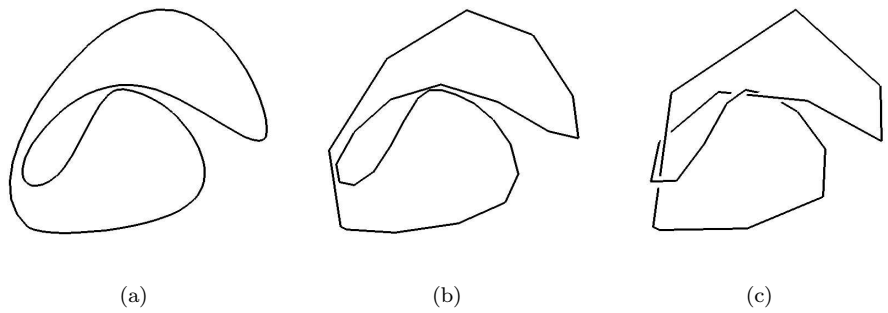


Figure 7. *(a) Smooth spline. (b) Good approximation. (c) Knotted approximation.*

many analyses. Therefore it is important to consider ambient isotopy as the relevant topological equivalence relation. Recent work [2, 3, 5, 22, 33] develops sufficient conditions for preserving ambient isotopy of manifolds, with quantitative bounds on piecewise linear approximations, which may be useful for practical computational applications. Developing algorithms to preserve the isotopy class on resultant approximants is expected to have an important role in both CAGD and CAMD. Recent results in that regard are now stated.

Approximation of spline curves is fundamental for visualization and simulations, where these approximations are often obtained by subdivision methods. Hence, it becomes important to understand when the control points obtained under repeated subdivision form a PL curve that is ambient isotopic to the original spline. Sufficient conditions are given in the following theorem by the present co-authors. The details of the proof are contained in a pre-print by the present authors [25].

Theorem 1: *Let* **B** *be a non-self-intersecting C^2 Bézier curve with regular Bézier parametrization in $\mathbb{R}^3$. Then subdivision will produce a control polygon of B that is ambient isotopic to B,* **provided that nontrivial knots are not introduced during this approximation process.** *(Note that* **B** *may be open or closed.)*

The criterion about nontrivial knots is, admittedly, informally expressed, above. The interested reader is referred to the full paper [25] for a rigorous formulation of this condition about knots. However, the role of this non-knotting hypothesis was unexpected. After all, the intuition is that the control polygon can be made arbitrarily close to the curve, so after sufficiently many subdivisions one would naïvely expect them to have the same topological characteristics. However, the authors do not see how to eliminate the non-knotting hypothesis. This will continue to be investigated, but it has implications for the broad use of subdivision to approximate curves and surfaces. Namely, there is some risk, that if this non-knotting condition is violated, then that specific approximation will not have the same topological characteristics as the original geometric object. The authors know of no geometric design or molecular design system that now explicitly checks this

criterion. Hence, this observation has broad software design implications, since the problem of recognizing when a PL knot is the unknot continues to attract considerable theoretical interest [7, 13, 14], but the development of practical algorithms remains elusive.

Note that subdivision is a recursive algorithm. Theorem 1, as stated, provides the valuable insight that subdivision can be used to create an ambient isotopic approximation. However, the stopping criterion can now only be detected by specific geometric checks for this containment. Since these geometric tests are computationally expensive, ongoing work is exploring if the number of iterations can be analyzed in advance to change the algorithm from its current recursive form into a more efficient iterative style.

For surfaces, the ambient isotopy problem is considerably more difficult. However, there are some initial results, to which co-author Peters has contributed [30, 33]. These are specialized to the circumstances of compact connected C^2 manifolds without boundary, which are embedded in $\mathbb{R}^3$. Such manifolds are broadly assumed within CAGD as the bounding surfaces for design objects containing compact volumes. Similar utilities are expected within CAMD. Again, the proof relies upon a recursive approach to determine if the approximation error is within a specific upper bound. However, the resulting surface is no longer from subdivision, but is a PL surface created with rectangular patches that are parallel to the standard three co-ordinate planes associated with a right-hand co-ordinate system within $\mathbb{R}^3$. In the re-statement of that theorem, below, this will be referred to as a *piecewise box approximation*.

Theorem 2: *Let M be a compact connected C^2 manifold without boundary, which is embedded in $\mathbb{R}^3$. Then for an appropriately chosen value of $\epsilon > 0$, there exists a piecewise box approximation of M such that the approximation error is less than ϵ and is ambient isotopic to M.*

While it is easy to see the applicability of these theorems to CAGD, their usefulness to CAMD remains speculative, but promising. The proposed path to that transition is to consider that ball-and-stick models have been common in molecular modeling. Recently, such models have even been integrated with fast methods for computing their orbitals [11], where the coupling with a static model of a benzene molecule is used as an example. However, simulation algorithms must extend beyond these restrictions on two fronts

1. by replacing the ball-and-stick models with surface and solid models that more fully capture volumetric and physical properties of macro-molecules, and

2. by replacing static models with dynamic ones.

Arguably, the fulfillment of objective #1, above, could be achieved for static molecular models with current spline modeling capabilities of existing CAGD systems. However, the creation of accurate molecular models would either entail the use of high degree splines or multiple intersecting lower degree splines. Hence, the efficiency demands for objective #2, above, would lead naturally to approximation of these models with PL models, including the approximation of knotted intersection

curves that were discussed in Subsection 3.3. The coiled nature of macro-molecules (proteins, DNA, RNA), some of which are known to contain knots, will provide challenging test cases for algorithms based upon the above theorems to deliver ambient isotopic approximations merely for the static cases. Moreover, during simulations, it is expected that life scientists will either require that the isotopy class of a molecule be preserved, or that they will be informed when the isotopy class changes as a result of a chemical or biological process. There remain significant challenges to support such simulations, but the preceding two theorems are presented as fundamental foundations towards that goal.

4 Conclusion

This paper was motivated by the authors' observation that communication about topology is often ambiguous in the literature concerning geometric and molecular modeling. The importance of guaranteeing topological equivalence during approximation is stressed. The criterion proposed for topological equivalence is stronger than the traditional usage based upon homeomorphism. This stronger criterion of ambient isotopy additionally characterizes how an object is embedded in $\mathbb{R}^3$. This permits distinguishing between different types of knots, which are all homeomorphic. The isotopy equivalence class of a design model is an important topological aspect of a model. However, computations to determine knot type are known to be intractable, thereby presenting major algorithmic challenges to determining the isotopy equivalence class of a geometric model. Because of this problem, these authors present sufficient conditions for approximations to be isotopically equivalent to the original model, instead of trying to *explicitly* determine the isotopy equivalence class of each approximation. This comparative approach holds great promise for both CAGD and CAMD.

While CAGD models are typically static, it is noted that in the life sciences form and function are inextricably related, and form is rarely static. Topology is more suited than geometry to capture the increased emphasis upon dynamic change in macro-molecular simulations. Hence, it is important to be precise about which topological specializations should be modeled for simulation and preserved during approximation for both CAGD and CAMD. Opportunities exist to leverage topological issues in CAGD and CAMD to benefit both domains, where the transition to support CAMD is discussed in detail in the immediately preceding section. The development of sophisticated algorithms capable of correctly capturing all topological characteristics for simulation is a challenge, and remains on the frontiers of modern computational and mathematical sciences.

Bibliography

[1] C. C. Adams, The Knot Book: An Elementary Introduction to the Mathematical Theory of Knots, W.H. Freeman and Company, 2001

[2] N. Amenta, T. J. Peters and A. Russell, *Computational topology: ambient isotopic approximation of 2-manifolds*, Theoretical Computer Science, 305, 2003, 3–15.

[3] L.-E. Andersson, S. M. Dorney, T. J. Peters, N. F. Stewart, *Polyhedral perturbations that preserve topological form*, Computer Aided Geometric Design, (12)8, 1995, 785–799.

[4] L.-E. Andersson, T. J. Peters, N. F. Stewart, *Self-intersection of composite curves and surfaces*, Computer Aided Geometric Design, (15)5, 1998, 507–527.

[5] L.-E. Andersson, T. J. Peters, N. F. Stewart, *Equivalence of topological form for curvilinear geometric objects*, International Journal of Computational Geometry and Applications, (10)6, 2000, 609–622.

[6] R. H. Bing, The Geometric Topology of 3-Manifolds, American Mathematical Society, Providence, RI, 1983.

[7] J. S. Birman and M. D. Hirsch, *A new algorithm for recognizing the unknot*, Geometry and Topology, **2**, 1998, 175 – 220.

[8] C. Branden and J. Tooze, Introduction to Protein Structure, 2nd edition, Garland, 1999.

[9] T. K. Dey, H. Edelsbrunner and S. Guha, *Computational topology*, Invited paper in Advances in Discrete and Computational Geometry, B. Chazelle, J. E. Goodman and R. Pollack eds. Contemporary Mathematics, AMS, Providence, 1998.

[10] H. Edelsbrunner, *Biological applications of computational topology*, Chapter 63 of Handbook of Discrete and Computational Geometry, eds. J. E. Goodman and J. O'Rourke, CRC Press, Boca Raton, Florida, to appear.

[11] G. Fann, G. Beylkin, R. J. Harrison, K. E. Jordan, *Singular operators in multiwavelet bases*, IBM J. Res. Dev. 48, 2004, 161-171.

[12] R. T. Farouki, *Closing the gap between CAD model and downstream application*, SIAM News, 32(5), June 1999.

[13] W. Haken, *Theorie der Normalflachen*, Acta. math, **105**, 1961, 245 – 375.

[14] J. Hass, J. C. Lagarias and N. Pippenger, *The computational complexity of knot and link problems*, Jounal of the ACM, 46, 1999, 185-211.

[15] M. W. Hirsch Differential Topology, Springer, New York, 1976

[16] C. M. Hoffman, Geometric and Solid Modeling, Morgan Kaufman, 1989.

[17] F. Jaeger, D. L. Vertigan and D. J. A. Welsh, *On the computational complexity of the Jones and Tutte polynomials*, Proc. Cambridge Philos. Soc., 108, 1990, 35-53.

[18] V. F. R. Jones, *A polynomial invariant for knots and links via Von Neumann algebras*, Bulletins of the American Mathematical Society, 12, 1985, 103-111.

[19] S. Krishnan and D. Manocha, *An efficient surface intersection algorithm based on lower-dimensional formulation*, ACM Transactions on Graphics, (16)1, 1997, 74-106.

[20] D. Lasser, *Calculating the self-intersections of Bezier curves*, Computers in Industry, (12)3, 1989, 259-268.

[21] J. Liang, H. Edelsbrunner, P. Fu, P. V. Sudhakar and S. Subramaniam, *Analytical shape computation of macromolecules: II. inaccessible cavities in proteins*, PROTEINS: Structure, Function, and Genetics, 33, 1998, 18-29.

[22] T. Maekawa, N. M. Patrikalakis, T. Sakkalis and G. Yu, *Analysis and applications of pipe surfaces*, Computer-Aided Geometric Design, 15(5), 1998, 437-458.

[23] M. Mäntylä *Computational topology: a study on topological manipulations and interrogations in computer graphics and geometric modeling*, Acta Polytechnica Scandinavica, Mathematics and Computer Science Series 37, Finnish Academy of Technical Sciences, Helsinki, 1983.

[24] I. Michalopoulos, G. M. Torrance, D. R. Gilbert and D. R. Westhead, *TOPS: an enhanced database of protein structural topology*, Nucleic Acids Research, 32, 2004, 251-254.

[25] E. L. F. Moore and T. J. Peters, *Integration of computational topology and curve sudivision*, pre-print, `www.cse.uconn.edu/~tpeters`.

[26] J. R. Munkres, Topology, 2nd Edition, Prentice Hall, 1999.

[27] M. Neagu, E. Calcoen, and B. Lacolle, *Bézier curves: topological convergence of the control polygon*, in Mathematical Methods in CAGD: Oslo 2000, T. Lyche and L. L. Schumaker (eds.), Vanderbilt University Press, Nashville, TN, 2001, 347–354.

[28] *Emerging challenges in computational topology*, Report from the NSF-funded Workshop on Computational Topology, Miami Beach, FL, June 11-12, 1999.

[29] J. O'Rourke, Computational Geometry in C, Cambridge, 1998.

[30] T. J. Peters, J. Bisceglio, R. R. Ferguson, C. M. Hoffmann, T. Maekawa, N. M. Patrikalakis, T. Sakkalis and N. F. Stewart, *Computational topology for regular closed sets (within the I-TANGO project)*, invited article, Topology Atlas, vol. 9, no. 1 (2004) 12 pp., `http://at.yorku.ca/t/a/i/c/50.htm`.

[31] *Protein Data Bank*, http://www.pdb.org/

[32] D. Rolfsen, Knots and Links, AMS Chelsea Publishing, Providence, 2004.

[33] T. Sakkalis, T. J. Peters and J. Bisceglio, *Application of ambient isotopy to surface approximation and interval solids*, CAD, Solid Modeling Theory and Applications, G. Elber & V. Shapiro (ed.), 36 (11), 1089 – 1100.

[34] T. Schlick, Molecular Modeling and Simulation: An Interdisciplinary Guide, Springer, 2002, 61-89.

[35] T. Schlick, *Modeling superhelical DNA: recent analytical and dynamic approaches*, Current Opinion in Structural Biology, (5), 1995, 245-262.

[36] R. Sharein, http://www.pims.math.ca/knotplot/

[37] R. R. Sinden, DNA Structure and Function, Academic Press, 1994.

[38] D. W. Sumners, *Lifting the curtain: Using topology to probe the hidden action of enzymes*, Notices of the AMS, 42(5), May 1995, 528-537.

[39] W. R. Taylor, *A deeply knotted protein structure and how it might fold*, Nature, 406, 2000, 916-919.

[40] *Toplogy of Protein Structure*, http://www.tops.leeds.ac.uk/

[41] S. A. Wasserman, J. M. Dungan and N. R. Cozzarelli, *Discovery of a predicted DNA knot substantiates a model for site-specific recombination*, Science, 229, 1985, 171-174.

[42] S. A. Wasserman and N. R. Cozzarelli, *Biochenmical topology: applications to DNA recombination and replication*, Science, 232, 1986, 951-960.

[43] K. J. Weiler, Topological Structures for Geometric Modeling, Ph.D. Thesis, Comput. Syst. Engin., Renselaer Polytechnic Inst., 1986.

[44] C. Wonjoon, T. Maekawa and N. M. Patrikalakis, *Topologically reliable approximation of composite Bezier curves*, Computer Aided Geometric Design, (13)6, 1996, 497-582.