Model Checking in Space with Applications to Medical Image Analysis*

Invited Abstract

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Abstract. Model checking has traditionally focused on the analysis of the *behaviour* of concurrent systems. In this invited abstract, instead, we focus on *spatial* model checking. We briefly motivate its development and its application in the domain of medical imaging, providing a gentle guide to our recent work on that topic and future research lines.

Keywords: Spatial logics · Closure spaces · Spatial model checking · Medical imaging · Polyhedral models

1 Introduction

The purpose of this brief invited abstract is to provide the reader with a concise guide to our recent work on spatial model checking, and, in particular, to its innovative application to medical image analysis. Traditionally, model checking techniques have been developed for the analysis of the behaviour in time of system models. The focus in that context is on the discovery of errors early on in the software development process, in particular software for safety-critical concurrent systems and control systems. Many variants of temporal aspects have been investigated, ranging from discrete and continuous time, hybrid forms combining both, to stochastic time and probabilistic behaviour (see e.g. [4] and references therein). Only recently, spatial aspects and spatio-temporal aspects have received

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attention from the Formal Methods community. Early examples in the Computer Science literature concern situations in which modal operators are interpreted "syntactically", i.e. against the structure of agents in a process calculus (see [22, 24] for some classical examples). The object of discussion in that research line are operators that quantify, for example, over parallel sub-components of a system, or the hidden resources of an agent. Furthermore, logics for graphs have been studied in the context of databases and process calculi (see [23, 40], and references therein). However, the relationship with physical space is often not made explicit, if considered at all. There has been work on studying the influence of space on the interaction between agents in the literature on process calculi using *named locations* (see for example [39]). Variants of spatial logics have also been proposed for the symbolic representation of the contents of images, and, combined with temporal logics, for the analysis of sequences of images [16]. In our current work we use the terminology *spatial logics* in the "topological" sense, starting from a spatial interpretation of modal logics.

In our work we extend the topological semantics of modal logics to *closure spaces*. A closure space (also called *Čech closure space* or preclosure space in the literature), is a generalisation of a standard topological space, where idempotence of the closure operator is not required. This choice is motivated by the need to treat (general) graphs and topological spaces in a *uniform way* so that we can reason on both discrete and continuous models of space in the same general framework. Closure spaces have also been proposed as an alternative foundation of digital imaging by various authors, in particular Smyth and Webster [52] and Galton [41]. Our work continues that line of research, enhancing it with a logical and a model checking perspective. We have developed the Spatial Logic for Closure Spaces (`SLCS`) [32, 33], interpreting the diamond operator of modal logics as a closure operator as in closure spaces, and adding a spatial conditional reachability operator to the logic that is inspired by a first brief mention of such an operator for a topological space in the work by Aiello [1] and in that by van Benthem and Bezhanishvili [11]. The latter paper is included in the Handbook of Spatial Logics [2], which formed a further source of inspiration for the introduction of additional spatial logic operators to `SLCS` such as a distance operator [5, 9], operators for collective spatial logic `CSLCS` [33, 34] and the combination of `SLCS` with branching time temporal logic, leading to the Spatial-Temporal Logic for Closure Spaces (`STLCS`) [30, 29]. In [34] we showed that the well-known discrete variant of the Region Connection Calculus (RCC8D) could be expressed in terms of `CSLCS`. `SLCS` also inspired the development of a spatial version of the Signal Temporal Logic (SSTL) [50]. More recently, `SLCS` was also given a *polyhedral semantics* [12, 15, 14, 13]. This allows for the expression of properties of continuous spatial models, in particular polyhedra. Such spatial models are widely used in the field of computer graphics where they are known as 2D triangular surface meshes or 3D tetrahedral volume meshes.

For all the variants of `SLCS` we have developed efficient *spatial model checkers*. The first model checker, `topochecker`, is actually a spatio-temporal model checker [30, 33, 29]. It also deals with the collective version of `SLCS`. `topochecker` has been applied in case studies in public transportation [35, 29]. In [35, 46] it has been combined with a stochastic simulation model of bike sharing systems. The approach has been extended in [36] with statistical model checking, exploiting its combination with MultiVesta [51]. `topochecker` has also been used in first experiments with spatial model checking the medical field [5]. The success of the latter work was one of the reasons to focus on the development of a purely spatial model checker, `VoxLogicA` [9, 10]. This model checker was built on top of the Insight Toolkit (ITK) [47], which is an open-source, cross-platform software library providing advanced and efficient algorithms for medical image analysis and supported by the National Library of Medicine (NLM) in the United States, which is the world's largest biomedical library. This choice not only considerably improved the efficiency of spatial model checking, but also allowed for the introduction of a suitable image query language (`ImgQL`), having `SLCS` as its core logic, extended with (possibly derived) operators that are familiar to domain experts in medical image analysis. Furthermore, `VoxLogicA` is able to deal with the common NifTy (Neuroimaging Informatics Technology Initiative) format for storing brain imaging data like 3D MRI (Magnetic Resonance Images) scans. A hands-on tutorial for `VoxLogicA` model checking is provided in [27]. Finally, the third spatial model checker we developed in the context of `SLCS` is `PolyLogicA` [12]. This is a polyhedra model checker that can also analyse surface and volume meshes [12, 15, 14, 3] and, in the future, could also play a role in the analysis of 3D meshes of medical images.

To the best of our knowledge, our work is the first to explore the application of (spatial) model checking techniques to the analysis of medical images. This idea emerged in an informal discussion between the co-authors of this abstract trying to find a common ground of understanding of medical image analysis in the clinical practise on one hand, and spatial model checking on the other hand. The discussion took place in the context of the segmentation (contouring, delineation) of High-Grade Glioblastoma (HGG), a very serious form of brain tumours. For the treatment of glioblastomas, neuro-imaging protocols are used before and after treatment of a patient to evaluate the effect of treatment strategies and to monitor the evolution of the disease. Radiotherapy is often part of such treatments and legal aspects about the accountability and justification of particular treatments as well as the quality of life of a patient are all serious issues to be taken into consideration. This makes the accurate contouring of lesions in the brain an important but challenging and safety-critical task, which, in the current practise is also rather time-consuming as delineation is mainly performed manually with the help of computer-assisted drawing tools. Although the actual trend is the use of Deep Learning methods for fully automatic medical image analysis (see for example [49] for a recent overview), the lack of explainability and accountability and a meaningful human control of these methods form a problem in the clinical practise. We have applied spatial model checking on three different case studies in the medical domain: contouring HGG [9, 5, 10], identifying white and grey matter in the brain [8, 10] and contouring potentially harmful lesions of the skin (nevi) [6]. Furthermore, we have studied a neuro-symbolic approach to the contouring of HGG [7, 10].

In the subsequent sections we provide some further details on spatial models and logics, the spatial model checker `VoxLogicA` and its application to the analysis of medical images, providing relevant pointers to the literature.

Synopsis: Section 2 presents an overview of closure models, the main spatial models used in our work, the *Spatial Logics for Closure Spaces*, and variants thereof. Section 3 presents some further information on the various spatial model checkers, Section 4 gives an overview of the application of `VoxLogicA` in medical imaging. Finally, Section 5 concludes the abstract providing some lines for future research.

2 Models of Space and Spatial Logics

Topological spaces are a foundational framework for, among others, a mathematical representation of physical space and for reasoning about its properties. Central in the theory of topological spaces is the notion of *closure* of a set of points. If a set of points is an open set, for example all points on the line segment between 1 and 2, but without its endpoints, the closure operator adds these endpoints to the set. If the set of points is already closed, i.e. including such endpoints, then the closure does not add any further points, i.e. topological closure is idempotent. This implies that topological spaces are not well suited for the representation of other kinds of "spaces", like, e.g., general graphs — even if some restricted classes of graphs can still be represented as topological spaces.

Closure spaces are a *generalisation* of topological spaces where idempotence of the closure operator $\mathcal{C}$ is instead not required. Furthermore, for a certain subclass of closure spaces, namely *quasi-discrete closure spaces* — that includes finite graphs — it can be shown that there is always a binary relation R on the set of points of the space that characterises the closure operator. More specifically, in this case, it can be shown that, letting X denote the set of points of the space, the function $\mathcal{C}_R : \mathbf{2}^X \to \mathbf{2}^X$ defined as follows for any $A \subseteq X$

$$\mathcal{C}_R(A) = A \,\cup\, \{x \in X \mid a\,R\,x \text{ for some } a \in A\} \tag{1}$$

is a closure operator, according to the axiomatic definition of closure spaces of Čech [25]. Similarly, this also holds for the converse relation R^{-1}, which induces the *converse closure* $\mathcal{C}_{R^{-1}}$.

Mathematical logic, and in particular modal logics, have long been a successful framework for formal reasoning about space. In their seminal paper of 1944, Tarski and McKinsey proposed a topological interpretation of the classical necessity modality and its dual modality, the possibility modality [48]. There, the necessity modality, often denoted by $\Box$, is interpreted as *topological interior* — and the possibility modality, i.e. the $\Diamond$ operator, is interpreted as topological closure. In other words, given a formula Φ and a point x of a topological model — i.e. a topological space enriched with an evaluation function $\mathcal{V}$ associating a set of points to each element of a given set PL of *predicate letters* — satisfies formula $\Box \Phi$ if and only if x lays in the (topological) interior of the set of points satisfying Φ. Similarly, x satisfies $\Diamond \Phi$ if x belongs to the closure of the set of points satisfying Φ. Since then, a flourishing field of research in mathematical logic has been developed that focussed on the study of logical operators interpreted on models of space, namely the field of "Spatial Logics" [2].

In [32, 33] the *Spatial Logic for Closure Spaces* (`SLCS`) has been proposed that includes, besides predicate letters, negation and conjunction, a *proximity* modality $\mathcal{N}$ and a *surrounded* modality $\mathcal{S}$. The logic is interpreted on closure models — a closure model is a closure space enriched with an evaluation function $\mathcal{V}$ as in the case of topological models.

A point x of a closure model satisfies a formula $\mathcal{N}\Phi$ if it lays in the closure of the set of points satisfying formula Φ. Note that in `SLCS` the closure operator is that defined for *closure spaces* and not necessarily the topological one. For instance, in the case of a Kripke model — seen as quasi-discrete closure model — the closure operator will be that of (1) above, computed with respect to the accessibility relation R of the Kripke model. In particular, idempotence of the closure operator will depend on the structure of the model.

A point x of a closure model satisfies a formula $\Phi_1 \mathcal{S} \Phi_2$ if it lays in a set of points all satisfying Φ_1 that is surrounded by a set of points satisfying Φ_2. In other words, there is no path in the space, starting from x that can reach a point satisfying neither Φ_1 nor Φ_2 without first passing from a point satisfying Φ_2. Of course, the notion of "path" depends of the nature of the closure space one is considering: in the case of continuous spaces a path is a continuous function from $[0, 1]$ to the space whereas for discrete spaces, e.g. graphs, it is a function π from a set $\{0, \dots, \ell\}$, for some natural number ℓ, such that $\pi(i+1) \in \mathcal{C}(\{\pi(i)\})$ for all i such that $0 \leq i < \ell$.

Several additional operators have been incorporated in `SLCS`. We will briefly discuss some of them. From the above informal description of the surrounded operator, it should be clear that reachability plays a crucial role in the study of properties of space. For this reason, a specific *conditional reachability* operator ρ has been introduced: a point x satisfies $\rho\, \Phi_1[\Phi_2]$ if a path π exists from x such that the end-point of π satisfies Φ_1 while all intermediate points of the path satisfy Φ_2. The surrounded operator can be expressed using the reachability modality and negation, as follows: $\Phi_1 \mathcal{S} \Phi_2$ is equivalent to $\Phi_1 \wedge \neg \rho \neg(\Phi_1 \vee \Phi_2)[\neg \Phi_2]$. When interpreting the logic on a quasi-discrete closure space, the "direction" of the underlying relation R induces a splitting of ρ into two distinct operators: a direct, or "forward", reachability operator $\overrightarrow{\rho}$, and a converse, or "backward" reachability operator $\overleftarrow{\rho}$. The semantics of $\overrightarrow{\rho}$ are the same as those of ρ above, whereas x satisfies $\overleftarrow{\rho}\ \Phi_1[\Phi_2]$ if a point y exists that satisfies Φ_1 and from which a path π exists such that the end-point of π is x while all intermediate points of the path satisfy Φ_2. In other words, while whenever x satisfies $\overrightarrow{\rho}\ \Phi_1[\Phi_2]$ we have that x *can reach* a point satisfying Φ_1 via points (of a path) all satisfying Φ_2, when x satisfies $\overleftarrow{\rho}\ \Phi_1[\Phi_2]$ we have that x *can be reached* from a point satisfying

Φ_1 via points (of a path) all satisfying Φ_2. This difference is quite important when reasoning about space: just think, for instance, of a graph modelling the road system of a city where there are one-way roads. Another example could be the need to express the fact that, from a certain location of a building, via a safe corridor, a rescue area can be reached (forward reachability) that cannot be reached by (backward reachability) smoke generated in another area of the building. Note that for quasi-discrete closure models $\mathcal{N}\Phi$ can be expressed as $\overleftarrow{\rho}\ \Phi[\mathtt{false}]$ and that, whenever R is symmetric, $\overrightarrow{\rho}\ \Phi_1[\Phi_2]$ and $\overleftarrow{\rho}\ \Phi_1[\Phi_2]$ coincide: in this case we simply use the notation $\rho\,\Phi_1[\Phi_2]$ [6]. The case of R being symmetric is of great importance in the context of the present paper since digital images, of which medical images are only a special case, are just finite regular grids, which, in turn, can be modelled as finite, thence quasi-discrete, closure models where points are related by a binary symmetric relation — the so-called *adjacency relation*.

When reasoning about space, it is often useful to make reference to the distance between points. For this reason, in [9, 5] variants of `SLCS` have been equipped with a *distance operator* $\mathcal{D}^I$ and are interpreted on distance closure models, i.e. closure models extended with suitable distance functions[4]. A point x satisfies $\mathcal{D}^I\,\Phi$ if the distance of x from a point satisfying Φ falls in the interval I of the real numbers.

In the context of (medical) image analysis, texture analysis plays an important role. For that purpose, in [9] the statistical correlation operator $\triangle\!\!\!\triangle\,\Phi$ is introduced that compares the correlation between the histogram of a given *area of interest* and that of the set of points satisfying Φ with a given threshold; the specification of the histogram of the area of interest as well as the threshold are given as additional parameters, not shown above (see [9, 6, 10] for details).

3 Spatial Model Checking with `VoxLogicA`

The spatial model checker `VoxLogicA`[5] (Voxel-based Logical Analyser) [9, 10] provides a rapid-development, declarative, logic-based approach to image analysis and segmentation and is a free and open source tool. It is particularly suitable to reason at the “macro-level" by exploiting the *relative* spatial relations between regions of interest in multi-dimensional digital medical images. The input language of `VoxLogicA`, the Image Query Language (`ImgQL`), has `SLCS` at its core, but also encompasses several domain oriented operators to accommodate the level of abstract spatial reasoning by domain experts such as neuro-radiologists. Examples of such operators are region growing, region touching and the surrounded operator (all derived from the reachability operator), distance operator and a texture similarity operator, as well as additional operators to specify similarity measures (e.g. Dice, specificity, sensitivity), primitives for images man-

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[4] In the simplest case, a distance function is a real-valued function d such that for all points x and y $d(x, y) = 0$ if and only if $x = y$. Distance functions generalise metric functions.

[5] Available from: https://github.com/vincenzoml/VoxLogicA

agement (loading and saving results) and mechanisms for the definition of new (derived) logical operators. This choice provides powerful building blocks to develop concise, human readable and explainable image segmentation methods. A tutorial on `VoxLogicA` and `ImgQL` can be found in [27].

4 Application to Medical Imaging

So far we have applied spatial model checking to three different case studies in the medical domain. The first one concerns the contouring of HGG in 3D MRI images from a public dataset of the BraTS (Brain Tumour Segmentation) 2017 Challenge [49]. In these experiments we have been using the spatial model checker `topochecker` for the contouring of the gross tumour volume, consisting of tumour tissue and the surrounding cerebral oedema [5]. The first results with `topochecker` were encouraging as we obtained a similarity (Dice) score of 0.76 with respect to the manual contouring performed by experienced neuro-radiologists. A Dice score of 0.76 roughly means that there is an overlap of 76% between our contouring result and that made by domain experts (providing the ground truth). This number may not look that high at first sight, but one has to take into account that there is a relatively high intra-expert and inter-expert variance estimated between 20(±15%) and 28(±12%), respectively. This means that a similarity score between 80-90% would actually be excellent. With the dedicated `VoxLogicA` spatial model checking approach we have obtained Dice scores in that range. With a 10 lines long `ImgQL` query on the larger BraTS 2020 training dataset considering 276 multi-institutional pre-operative MRI scans of patients affected by HGG we obtained an average Dice similarity score of 0.85(±0.11 standard deviation) [10]. An example of a HGG contouring is shown in Fig. 1.

The second case study concerned the automatic identification of tissues in the brain. We looked in particular to white matter and grey matter. The analysis with `VoxLogicA` on the public BrainWeb[6] dataset containing 20 cases of healthy brains (synthetic MRI scans) gave a similarity of 0.93(±0.02 std) for white matter and 0.91(±0.16 std) for grey matter [8, 10]. An example of the identification of white matter in a healthy brain is shown in Fig. 2.

The third case study addressed the contouring of nevi, which are possibly malicious lesions of the skin [6]. The challenges here are the enormous variation in colour and shape and the presence of additional elements such as hairs and ink annotations on the skin that were added by clinicians to indicate the location of a lesion. For the evaluation of the approach we used the ISIC 2016 training and test sets of dermascopic images [45], originally designed for machine learning approaches. We obtained a Dice similarity score of more than 0.8 in 70% of the cases, both in the test set (379 cases) and in the training set (900 cases). Of course, a spatial model checking approach does not require any training or learning phase, but we did use a small sample of the set of images

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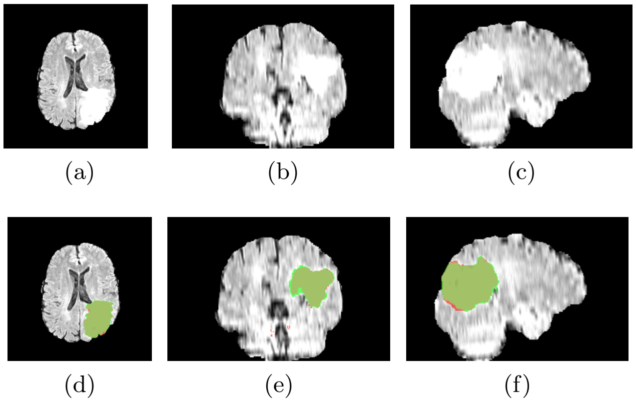
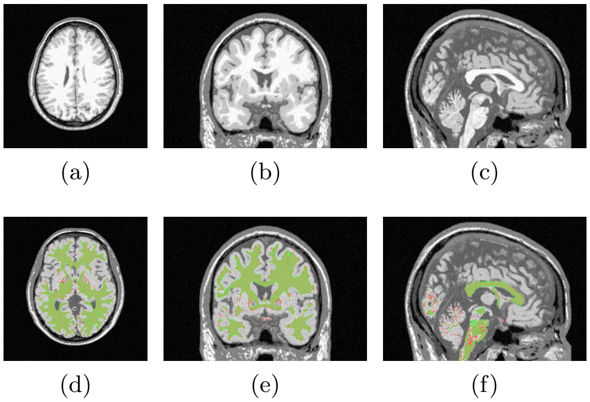
[6] See the following link: http://www.bic.mni.mcgill.ca/brainweb/


(a) (b) (c)

(d) (e) (f)

Fig. 1: First row: original MRI images of case BraTS17_TCIA_335 case. Second row: segmentation result of tumour and oedema with `VoxLogicA` (green) and largely overlapping ground truth (red). Images from [10].


(a) (b) (c)

(d) (e) (f)

Fig. 2: First row: Original Images for the pat_4 case of the BrainWeb dataset. Second row: white matter segmentation (green) and largely overlapping ground truth (red). Images from [10].

for the development of the logic specification. To analyse the complete test set of 379 cases with `VoxLogicA` took approximately 30 minutes on an AMD Ryzen 7 2700 Eight-Core processor with 32GB of memory, i.e. 4 seconds per image on average. A few examples of nevi contouring are shown in Fig. 3.

Finally, in [10], we have also proposed a neuro-symbolic approach to the segmentation of HGG glioblastoma. This hybrid approach combines the symbolic `VoxLogicA` approach to contouring with nnU-Net, a deep-learning technique. The main motivation for that approach was to investigate whether the symbolic

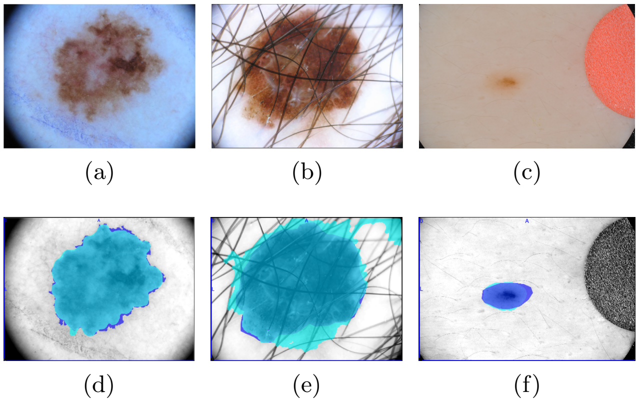


Fig. 3: First row: Original images. Second row: segmentation (cyan) and ground truth (dark blue): Case ISIC_0000002 (3a) resp. (3d), case ISIC_0000043 (3b) resp. (3e) and case ISIC_0004309 (3c) resp. (3f). Images from [6].

approach could provide a high-level, explainable spatial logic based description for a contouring result obtained using nnU-Net, that showed a sufficient overlap with the spatial model checking result. This would provide two results, obtained with completely different techniques, but in case of sufficient similarity, one could be used as the explanation for the other and having two similar results would increase the confidence in the reliability of the contouring. We used a trained nnU-Net model to estimate two threshold values that were directly relevant for the `ImgQL` specification. We then used these values in the symbolic model checking procedure and compared the results using the Dice similarity index. If the results were sufficiently similar, we accepted the result. The hybrid approach showed slightly higher accuracy than a symbolic approach alone. This approach can also be used when no contouring by experts is available, such as in the clinical case. In this approach there would also be space for meaningful human control as the two threshold values could be adjusted manually and the result checked visually by neuro-radiologists.

5 Conclusion and Future Research

The various case studies with `VoxLogicA` in medical imaging show promising results, reaching levels of accuracy that are in line with the state-of-the-art reached with other methods in the literature as published in the leaderboard scores of the various segmentation challenges. This paved the way to many new avenues for research in this field. In the following we briefly mention the currently activities and future challenges.

Concerning the `VoxLogicA` model checker, work has started to develop a version that exploits Graph Processing Units (GPU) computing [18]. Logic specifications in `ImgQL` are such that they often consist of many independent subformulas. In the CPU-version of `VoxLogicA` such sub-formulas can be computed in parallel, upto the number of available cores. Adding GPU computing would allow for many more parallel computations and a consequent speed-up of the analysis. It also opens the way to analyse video streams [20]. The challenge here is the transformation of the spatial model checking algorithm problem for the various operators into suitable parallel counterparts. Extensions of `SLCS` and `CSLCS` with spatial quantification operators are studied in [21, 19]. The former concerns the existential quantification over points in a space, the latter amounts to a form of quantification over atomic propositions. The development of further case studies and the wider take-up of the approach in medical image analysis would greatly benefit from a suitable Graphical User Interface for `VoxLogicA` (`VoxLogicA`-UI) that would neatly fit into and support the workflow of different user classes, such as `ImgQL` specification developers, clinicians and neuroradiologists. Work in this direction can be found in [17, 53] and a prototype implementation of `VoxLogicA`-UI can be found online.[7]

Since spatial models, and in particular 3D medical images, can be rather large, work has been carried out on the development of suitable spatial model reduction techniques. In particular, minimisation techniques based on spatial bisimulation [26, 37] have been investigated [31]. More specifically, a notion of "path-compatibility" for quasi-discrete closure models has been proposed that gives rise to a spatial bisimilarity which enjoys the Hennessy-Milner property with respect to (a variant of) `SLCS` [26, 37]: two points in space are bisimilar if and only if they satisfy the same logic formulas. In [31], it has been shown that an encoding exists of finite quasi-discrete closure models into labelled transition systems such that two points in space are spatially bisimilar if and only if their encodings are branching-bisimulation equivalent [38]. The encoding allows to exploit efficient branching-bisimulation minimisation tools [42, 44] for spatial model minimisation.

A further line of research [43] involving `VoxLogicA` concerns the definition of a comprehensive benchmark framework designed to systematically evaluate spatial reasoning capabilities in neural networks, with a particular focus on morphological properties such as connectivity and distance relationships. In this context the capabilities of nnU-Net are studied, exploiting the spatial model checker `VoxLogicA` to generate two distinct categories of synthetic datasets: one relates to maze connectivity problems for topological analysis, and the other addresses spatial distance computation tasks for geometric understanding. Preliminary experimental results demonstrate significant challenges in neural network spatial reasoning capabilities, revealing systematic failures in basic geometric and topological understanding tasks.

Finally, in [12] `PolyLogicA`[8] is presented that is a model checker supporting `SLCS` for finite polyhedra models. Thus (a restricted form of) continuous spatial models can be checked against `SLCS` formulas. The result of polyhedral model

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[7] Available at: https://github.com/VoxLogicA-Project/VoxLogicA-UI

[8] Available at: https://github.com/vincenzoml/VoxLogicA

checking can be visualised by the visualisation tool `PolyVisualizer`, an ad-hoc 3D visualiser for polyhedral models. Also for polyhedral model checking notions of spatial bisimulation and minimisation [28, 15, 14] have been developed.

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