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Connectome subgraph isomorphisms and graph queries with DotMotif

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Abstract

As connectomics datasets continue to grow in size and complexity, methods to search for and identify interesting graph patterns offer a promising approach to quickly reduce data dimensionality and enable discovery. Recent advances in neuroscience have enabled brain structure exploration at the level of individual synaptic connections. These graphs are often too large to be analyzed manually, presenting significant barriers to searching for structure and testing hypotheses. We combine graph database and analysis libraries with an easy-to-use neuroscience grammar suitable for rapidly constructing queries and searching for subgraphs and patterns of interest. This abstracts many of the computer science and graph theory challenges associated with nanoscale brain network analysis and allows scientists to quickly achieve reproducible findings at scale. We demonstrate these tools to search for motifs on simulated data and real public connectomics datasets, and share simple and complex structures relevant to the neuroscience community. We contextualize these results and provide case studies to motivate future neuroscience questions. All of our tools are released open source to empower other scientists to use and extend these methods.

1 Introduction

Modern nanoscale-connectomics research commonly involves the conversion of microscopy imagery data into a graph representation of connectivity, where nodes represent neurons, and directed edges represent the synapses between them. This process enables researchers to convert terabytes or even petabytes of imagery into megabytes or gigabytes of graph data. This process reduces the cost and complexity of interrogating the data, at the expense of losing morphology information [1, 2]. Though this graph representation uses substantially less storage-space on disk, extracting knowledge about even the seemingly simplest network questions (e.g., identifying local graph structure around a particular neuron, or comparing the downstream targets of a certain cell type) may still exceed the computational power, timelines, and budgets available to many research teams [3].

Connectomics researchers have begun to address this challenge by adopting existing large-scale graph management software, such as graph databases, and by enforcing consistent, well-architected data schemas [4, 5]. These systems provide performant and cost-effective ways to manipulate larger-than-memory graphs, but tend to require familiarity with complex and nuanced graph query programming languages such as Gremlin or Cypher. Though graph databases continue to grow in popularity, the expertise to administer or use these technologies is still not common in the biological sciences.

In order to make the study of connectomes accessible and computationally efficient, we developed *DotMotif*, an intuitive but powerful graph query language designed to reduce the expertise and time required to begin interrogating large biological graphs. DotMotif acts as an interface to common graph management systems such as the networkx Python library or the Neo4j graph database, abstracting the intricacies of subgraph-query design and enabling researchers to focus on field-specific scientific inquiry.

DotMotif assists researchers in query design by ex-

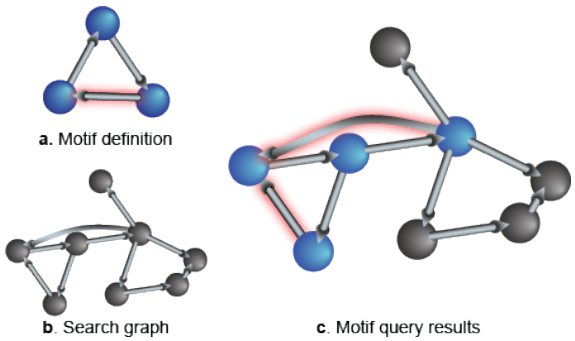

Figure 1: *Subgraph search.* Subgraph search is formally defined in the *Background* section. **A.** A motif query is defined. In this toy example, the query is a simple directed triangle. One edge has been assigned an attribute constraint (perhaps a neurotransmitter type or weight threshold). **B.** A directed search graph, or "host" graph. **C.** The motif is discovered in the search graph. Two unique detections are shown here, in which two of the node participants are "reused".

posing an intuitive, simple syntax that automatically validates and optimizes user queries, and adapts to different graph tool backends without the need for any further user input.

We present the DotMotif Python package and software architecture, which enables researchers to write queries while remaining agnostic to underlying technologies. We demonstrate DotMotif's utility by comparing its advantages over manual query design, and we share several use-cases inspired by ongoing research in the connectomics community.

2 Background

Many of the fundamental questions of modern neuroscience rely upon the study of simple circuits of neural connectivity in the brain. These simple circuits might be likened to individual logic gates in a computer, in that they are hypothesized to be repeated and reused with conserved local network topology. Though they might comprise only a small number of neurons, as shown in **Figure 1**, these graph *motifs* may be critical to unraveling or discovering the existence of larger structures of the brain, such as cortical columns or modules of computational importance [6, 7].

Identifying these motifs is one motivation for the field of *connectomics*, the study of the brain through the lens of its connectivity. Many related research efforts seek to construct graph representations of the brain, commonly represented by the notation $G = (V, E, A)$, where a graph G is made up of nodes V, representing neurons; (directed) edges E, representing synapses between them; and attributes A, which may be associated with vertices, edges, or the graph as a whole. Neuroscience questions may be reformulated as analyses on a graph, and the neuroscientist adds graph theory to the toolbox of strategies with which to understand the brain [6, 8]. Such questions include searching for specific subgraph structures, investigating the connectivity of specific neuron cell types or categories, proofreading connectomes for accuracy, and generating summary statistics on the graph as a whole [9, 10, 2, 11, 12, 13].

Even some of the simplest graphs generated by the connectomics community in recent years have spanned multiple gigabytes of hard drive space, rendering conventional graph toolkits, such as the powerful networkx library [14] (or its counterparts in other programming languages) under-powered to address the needs of the scientific community. These tools, which require all graph data to be stored in RAM, would require impractically expensive compute hardware in order to run fully in-memory, and would require impractically long timelines in order to run while swapping to disk. Instead, some teams [4] have opted to leverage "out-of-memory" tools, such as Neo4j [5] or Cayley [15], graph databases that operate on graph data much like conventional relational databases operate on tabular data. Despite their power, such tools require expertise in specialized query languages such as Cypher or Gremlin, much like relational databases require knowledge of languages such as SQL. Developing or hiring for this sort of domain expertise may be impractical for many neuroscience research laboratories and is a distraction from the core expertise needed to formulate and test neuroscience hypotheses. The need for computationally efficient, accessible, and intuitive neural graph analysis tools motivates this work.

3 Results

We share illustrative DotMotif experiments run on a set of publicly-available, seminal connectome datasets. We first validate our results by comparing against existing online data, and then share a network-analysis result on both partial as well as complete connectomes. Lastly, we share performance benchmarks for graphs of various sizes.

3.1 Datasets

We demonstrate the use of our tool on both complete (all of the organism's neurons are included in the graph) connectomes as well as on partial connectomes. Here, we compare the complete connectome of the invertebrate *C. elegans* worm [16], the partial connectome of the invertebrate fruit fly from the HHMI

Janelia Hemibrain [1] project, and the partial vertebrate mouse visual cortex connectome from the Intelligence Advanced Research Project Activity (IARPA) Machine Intelligence from Cortical Networks (MICrONS) project [17, 18]. These published graphs do not adhere to a particular database schema or storage system, and each has different node and edge attributes. Despite these differences, these graphs may still be analyzed using DotMotif after an ingest process (described in the *Architecture* section).

3.2 Tool validation: Declarative queries

In order to illustrate compatibility with data stored in the neuPrint data format [4], we ran a DotMotif search query on the partial *Drosophila melanogaster* connectome (dubbed *"hemibrain"*) recently published by HHMI Janelia [1]. We then validated these results with the neuPrint API at *neuprint.janelia.org* [4].

In this example query, we wanted to find all *Antennal Lobe* inputs to *Kenyon Cells* with weights within a certain range:

DotMotif Syntax:

```
# Find synapses from ant. lobe to KCs:
src -> kenyon [weight>12, weight<=14]

# Set known cell-type attributes:
src.type contains "mALT"
kenyon.type contains "KC"
```

We identified `src`-neuron instance IDs of 1917188956, 1825085656, 5813063239, 1887163927, 1917188956, 1825085656, 1037293275, and DotMotif returned all available cell metadata for these neurons.

In order to confirm that the query above returned identical results as the canonical neuPrint server, we validated these results with the following Cypher command in the neuPrint web application:

neuPrint Cypher Syntax:

```
MATCH
  (src:Neuron)-[
    synapseSet:ConnectsTo
  ]->(kenyon:Neuron)
WHERE src.type CONTAINS "mALT"
  AND kenyon.type CONTAINS "KC"
  AND synapseSet.weight <= 14
  AND synapseSet.weight > 12
RETURN DISTINCT src, kenyon
```

3.3 Subgraph searches

As an illustration of the minimal configuration requirements of the DotMotif package, we searched the recently-published, human-proofread subgraph from the IARPA MICrONS project [17, 18] for all undirected graphs of size $|V| \leq 6$, with ordering from the *Atlas of Graphs* [19, p. 8–30], and counted the number of times each subgraph appeared. For example, we counted all triangles (*Atlas of Graphs* ID #7) and discovered that there were 267 unique triangle monomorphisms in the MICrONS graph. Graph IDs 191, 195, 175, 52, 208, 187, and 190 occurred *zero* times in the MICrONS connectome (**Figure 2**).

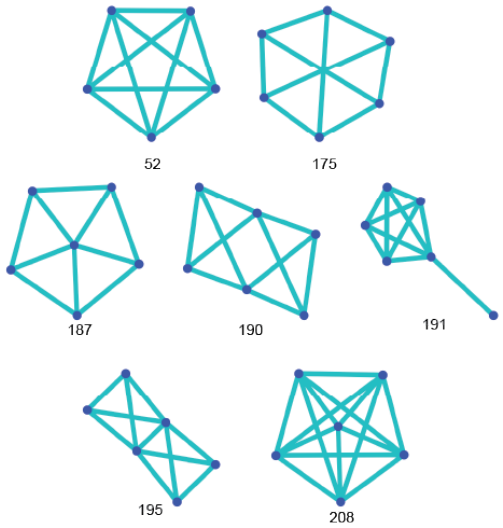

Figure 2: Motifs with no appearances in the published IARPA MICrONS connectome. These seven motifs do not occur at all in the MICrONS connectome. Note that several of these graphs are subgraphs of others in this list. For example, ID 52 is a subgraph of IDs 191 and 208; 190 is a subgraph of 195.

To contextualize these results, we calibrated the parameters of four random graph models (Erdős–Rényi [20], Undirected Geometric [21], Watts-Strogatz [22], and Barbarási-Albert [23]) to match the graph density ($D=\frac{2|E|}{|V|(|V|-1)}$) of each estimated connectome, and ran the same count of subgraph motifs on samples taken from each random graph distribution. The graph densities were computed as 0.030 for the MICRONS graph and 0.060 for the *C. elegans* graph. The code used to compute these values will be made available to the public (see *Supplemental Materials*). In order to compare these results with a complete connectome example dataset, we ran this count-scan on the *C. elegans* connectome [16, 24]. All motifs tested occurred at least once in the *C. elegans* connectome. We discovered the top n most common motifs differed greatly across biological connectomes and their random-graph counterparts. All seven motifs that occurred zero times in the MICrONS graphs were also infrequently or never encountered in the Watts-Strogatz and Erdős–Rényi random graph models, but occurred with high frequency in the *C. elegans* graph as well as the Geometric and Barabási-Albert random

graph models (**Figure 3**).

Queries from this set of experiments were run using both Neo4j and NetworkX executors, as convenient, leveraging our ability to seamlessly switch between executors when using DotMotif.

All data and results from this study will be made publicly available as described in *Supplemental Materials*. These experiments may aid in the design or selection of random graph models to approximate a connectome graph, and in the design or selection of query graphs when studying reconstructed connectomes.

3.4 Benchmarks

We compared the performance of two DotMotif executors available for use in our downloadable Python module. Results shown in **Figure 4** demonstrate that for graphs of $|E| > 10^4$, the `Neo4jExecutor` outperforms the `NetworkXExecutor` in query response-time.

Users may find that different executors suit the needs of different research questions. The *NetworkXExecutor*, which converts DotMotif DSL syntax into a series of Python commands, is preferable for running small numbers of graph queries on a small host graph, due to its low startup-time overhead. The *Neo4jExecutor*, which converts DotMotif DSL syntax into a Cypher query for execution with the Neo4j graph database, has significant data-ingest overhead for the first query on a graph, but in general tends to be much faster than NetworkX for all subsequent queries. For cold-start queries on graphs of sufficient size, the Neo4jExecutor startup overhead becomes trivial compared to the total runtime of the query.

The Neo4jExecutor has the dramatic advantage of caching graph data to disk. Users may find that for a sufficiently large graph, it is not possible to use executors that require the full query to run in RAM. In our experience, even when a user has access to a multi-terabyte RAM node, the Neo4j Java-based executor outperforms the Python-based NetworkX executor on large or high-density host graphs.

DotMotif users may trivially switch between Executors without modifying their queries, as the DotMotif engine stores queries in an intermediate format after parsing and validation steps (**Figure 5**).

All benchmarks listed here were performed on consumer laptop hardware with 16 gigabytes of RAM and a 3.1 GHz Intel core i7 processor.

4 Methods

In developing DotMotif, we aimed to ensure that our software was both accessible — intuitive for new users but powerful enough for power-users — as well as sufficiently computationally efficient to execute most queries on commodity hardware.

In the interest of research flexibility, we also required that the software adapt to best utilize available hardware resources. For this reason, DotMotif includes several *executors*, each of which leverage a different graph analysis technology. DotMotif also includes tools to help researchers decide which executor to use for a graph search. Executors are discussed further in depth in the *Benchmarks* section.

4.1 Formal definition of the subgraph search task

Here we consider the ideas of *subgraph isomorphism* and *subgraph monomorphism*, which have slightly different definitions in graph theory literature. When we refer to a *subgraph*, we always refer to a *node-induced* subgraph, which is inline with the usage in popular subgraph isomorphism research, including research on the commonly used VF2 algorithm [25, 26, 27].

Given graphs $G = (V_1, E_1)$ and $H = (V_2, E_2)$, we say G is isomorphic to H if there exists a bijection $f : V_1 \to V_2$ such that $\{u, v\} \subseteq E_1$ if and only if $\{f(u), f(v)\} \subseteq E_2$ [28]. An extension of this idea is that a subgraph isomorphism exists between G and H if and only if there exists a subgraph G' of G such that G' is isomorphic to H. A monomorphism loosens the bijection requirement to simply injection, meaning the search graph can contain extra edges.

DotMotif finds all subgraphs in a search graph that match a query graph, where the term *match* used here means that one of the above described mappings exists. By default, DotMotif will perform a search for all subgraphs that are monomorphic to the query subgraph. A user may choose to search for exact matches only, in which case DotMotif identifies subgraph *isomorphisms*, rather than *monomorphisms*. This behavior is user-toggleable during the construction of a query.

4.2 Comparison to Random Graph Models

One way to determine if a motif is significant within a real biological dataset is to compare to its frequency within a random graph model. There are several different random graph models, each with different properties and capturing a different aspect of real world data. In this manuscript, we perform subgraph search on four different random graph models.

The Erdős–Rényi random model has parameters n, or the number of nodes, and p, or the probability that any of the potential $\binom{n}{2}$ edges will independently exist within the graph [20]. The Erdős–Rényi model is easy to analyze and understand and thus is included in this analysis. However, the edge independence assumption often fails for real datasets. Thus, other models are required to provide further context.

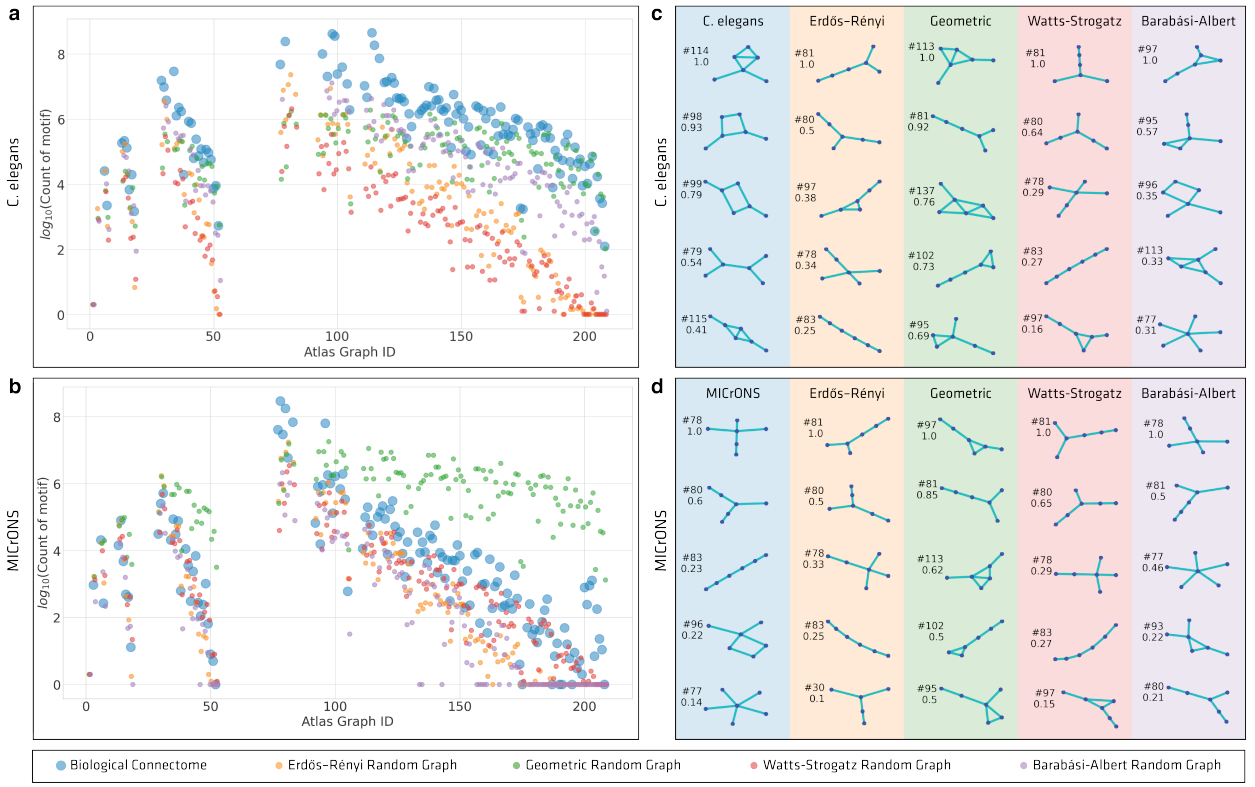

Figure 3: a & b: The count of every undirected subgraph of size $|V| \leq 6$. Each motif was counted in the connectomes, as well as in random graphs calibrated to match the density of each connectome. The x axis is the motif ID from the *Atlas of Graphs* text. Gaps indicate omitted motifs (those with multiple connected components). **a. Comparing *C. elegans* with random graphs calibrated to *C. elegans* density.** The geometric random graph tends to most closely approximate the motif incidence frequency of the biological *C. elegans* connectome. **b. Comparing MICrONS with random graphs calibrated to MICrONS density.** In contrast with the closely matching geometric model calibrated to the *C. elegans* graph, this geometric model almost always overestimates the motif count for the MICrONS connectome. It is interesting to note that many high-density subgraphs of size $|V| = 6$ (far right) are frequently encountered in the MICrONS dataset. **c & d:** The five most common motifs in each graph. The first number is the graph ID (corresponding to the x axis of **A** and **B**). The second number is the relative frequency of that motif compared to the most common motif for that graph. All random graphs in **c** are calibrated to match the *C. elegans* connectome density, and all random graphs in **d** are calibrated to match the MICrONS density. Full-resolution copies of this graphic are available online (see *Supplemental Materials*).

Geometric random graphs are desirable because they naturally capture spatial relationships that occur within the brain. Nodes are uniformly distributed within a region and two nodes are adjacent is they fall within a radius r, which is an adjustable parameter [21]. One potential shortcoming of this model is that it does not capture the fact that some neurons can be long range and others are rather localized, resulting in some spatial relationships that are not captured by the point cloud approach of the geometric model.

The Watts-Strogatz model addresses the edge dependence issue more directly, recognizing that many real world networks have high clustering coefficient, which is a measure of the extent to which two adjacent nodes have similar neighbors [22]. This phenomenon is called *preferential attachment* and intuitively makes sense (I am likely to be friends with my friends' friends). This phenomenon is seen in many real world datasets, even beyond social networks, including complete connectomes such as that of *C. elegans*.

The Barabási-Albert extends Watts-Strogatz to ensure the model also has a power law degree distribution, making it a scale free graph model [23].

Each of the described random models has a set of parameters resulting in different graph properties. These parameters may be selected to generate models that generate graphs "similar" to the real dataset in question. Similarity can mean different things and we try to match the models to a characteristic that

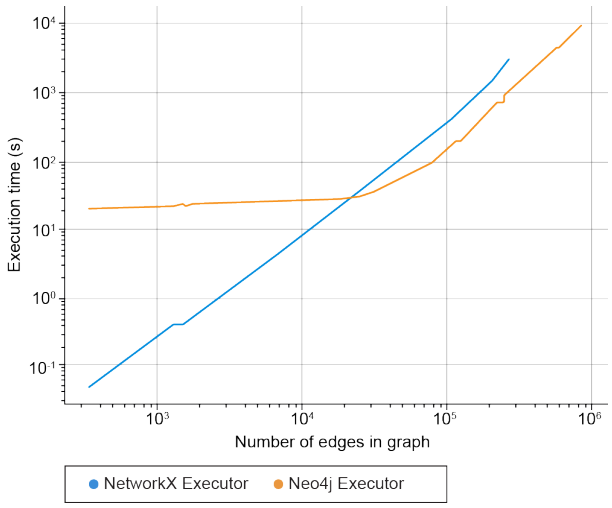

Figure 4: Comparison of executor runtime when counting undirected triangles. Here, two DotMotif *Executors* are compared counting triangle motifs in Erdős–Rényi random graphs. All times are reported from a cold start (i.e. the executor was not running prior to the query) and so all Neo4jExecutor results include start-up overhead that is not a factor for subsequent queries on the same host graph. Axes are on a log-log scale.

is closely tied to motif search. One obvious choice is to match the graph density (D=$\frac{2|E|}{|V|(|V|-1)}$) of each estimated connectome because density is a metric that can be more easily tweaked across models. Furthermore, a density that is too high or too low can result in inflated or underestimated subgraph counts, respectively. Other metrics besides graph density may be considered, such as degree distribution. Note that one implication is that the parameters selected for a random graph model will differ for each connectome being analyzed. More specifically, differences in density for *C. elegans* and MICrONS datasets will result in differently parameterized random graph models.

By performing subgraph search across these four models, tuned or calibrated to some characteristic of the real dataset, we obtain a clearer picture of what it means for a motif to occur at random in the real dataset.

4.3 Architecture

DotMotif is comprised of three submodules: A `parser` module, an `optimizer` module, and finally an `executor` module. In order of use, the `parser` module is responsible for converting the DotMotif domain-specific language into an in-memory representation. The `optimizer` module is then responsible for converting and simplifying the in-memory motif into its simplest possible representation. The `optimizer` module may also optionally check for violations of biological priors, in a validation step. Finally, the `executor` module converts the optimized motif into a query that can be submitted to a graph analysis tool. Each executor is responsible for generating its own target-specific queries. (For example, the `Neo4jExecutor` generates Cypher queries, and the `NetworkXExecutor` converts queries to a sequence of Python commands.)

4.3.1 DotMotif Domain-Specific Language Parser

We identified a disparity between the flexibility of common query languages (such as Cypher [5]) and the needs of the research community, where many research questions require overwhelmingly complex or verbose queries. We opted to develop a domain-specific query language to aid in the construction of queries. This enables research-driven query design agnostic to the underlying frameworks.

The DotMotif domain-specific language (DSL) borrows from DOT-like syntax [29] as well as from SQL-like syntax in order to expose a succinct and user-friendly query language.

For example, the simple query `A -> B` will return a list of all edges in the complete graph (in other words, the list of all subgraphs of $G = (V, E)$ that comprise one edge from a node $A \in V$ to node $B \in V$).

A query of `A -> B; B -> C; C -> A` will return a list of all triangles with edges of the same direction in the complete graph. A query of `A -> B; B !> A` will return a list of all edges in the graph for which the reciprocal edge does not exist.

In order to make queries understandable and maintainable, the DotMotif DSL supports "macros," or composable building-blocks that can be combined to generate more complicated queries. For example, if we wish to identify all inhibitory neurons with an annotated radius of 10 units or more, with a GABAergic synapse onto a node with radius of 5 units or smaller, we can write the following query:

```
Big -> Small [type=GABA]
Big.radius >= 10
Small.radius <= 5
```

If we want to extend this query to find all cases where *two* 'Big' neurons synapse on the same 'Small' neuron, we can use a macro (DotMotif comments are preceded by a `#` character):

```
BigInhibitsSmall(Big, Small) {
  # A macro for a single synapse
  # under investigation
  Big -> Small [type=GABA]
  Big.radius >= 10
  Small.radius <= 5
}
```

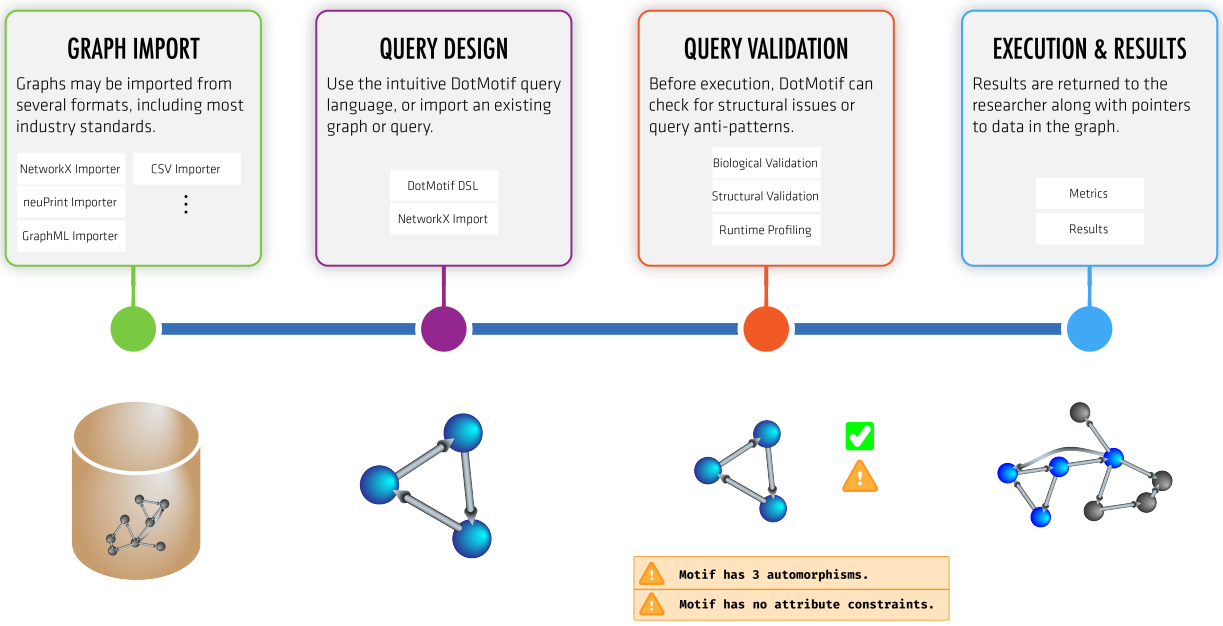

Figure 5: The DotMotif query execution process.
Graph Import. A user may import a search graph (also commonly referred to as a *host* graph) from a variety of industry standard formats, including edgelist CSV, GraphML, numpy adjacency matrix, and any format supported by the NetworkX library. Furthermore, DotMotif is compatible with graphs stored in neuPrint schemas in a Neo4j database [4]. **Query Design.** The user may select from a library of pre-built motifs, or write a novel query. The query may be written in the DotMotif DSL, encoded as a NetworkX graph, or written as text directly in the target graph database query language, such as Cypher. A user may choose to save this query as another standalone file on disk for future use. The .motif file-format stores both the motif itself as well as provenance metadata such as the date of creation, comments associated with the motif, and author information. **Query Validation.** DotMotif supports several pre-execution validation steps in order to fail quickly when asked to perform an impossible or paradoxical query. Several other optional validators may be invoked to check a motif for biological feasibility and warn the user if a potential error is detected. **Execution & Results.** The user may choose from the available DotMotif Executors in order to use the most appropriate subgraph matching tool for the compute resources available. No further query modification is required in order to run the same motif on several different Executors. A user may also choose to simply use DotMotif as a query executor without leveraging the query validation or query design tools.

```
# Search for two of this pattern
# that share a postsynaptic partner:
BigInhibitsSmall(A, C)
BigInhibitsSmall(B, C)
```

These macros minimize "boilerplate" syntax without leading to duplicate notation. By default, DotMotif returns a single representative element of each automorphism group in the result set. An *automorphism* is an isomorphism from a graph onto itself [28]. Returning a single representative of the automorphism group avoids overcounting motifs in the search graph. For example, if a user requests a triangle:

```
A -> B
B -> C
C -> A
```

...then there are three possible automorphisms for each node A, B, and C (the same set of three nodes in the host graph may be assigned to any of the nodes in the motif query). In this case, DotMotif will choose one arbitrarily. In this counter-example,

```
A -> B
B -> C
C -> A
A.brainArea != "CX"
```

...there are no motif automorphisms because the node-attribute constraint on A makes it unique from the unconstrained nodes B and C.

A user may explicitly specify that two nodes in a motif are isomorphic with the `===` notation:

```
A -> B
B -> C
```

```
C -> A

A === B
B === C
```

The DotMotif `===` automorphism operator is transitive and symmetric, so `A===C` is unnecessary in this query.

If the user uses the automatic query automorphism detection (the former example) or notates it manually (the latter example), the DotMotif optimizer will enrich the query motif to lower the space of possible matches, and thus return a result more rapidly. DotMotif considers both semantic as well as syntactic feasibility when automatically determining automorphism mappings [26].

This DSL is formally defined in Extended Backus–Naur Form [30, 31] by the grammar file referenced in *Supplemental Materials*. This syntax is visualized using the railroad-diagram convention in **Figure 6**.

4.3.2 Query Optimization and Validation

After a query has been parsed and ingested, it is passed to an optimization stage in which the query is reduced to a simplified form in order to improve the speed of query execution. Optionally, a user may also enable the automatic detection of impossible structures — or even biologically implausible structures — in a *Validation* step.

For example, the following simple *.motif* file would fail structural validation, because it calls for an edge between nodes A and B to both exist as well as *not* exist:

```
A -> B
A !> B
```

This motif fails with the following error message:

```
DisagreeingEdgesValidatorError:
  Trying to add <[A]-[B] exists=False> but
  <[A]-[B] exists=True> already in motif.
```

This second example fails validation due to the impossible requirements placed on the size of the A neuron:

```
A.size > 50
A -> B
A.size <= 25

DisagreeingNodeConstraintError:
  Trying to add ([A].size <= 25)
  but constraint ([A].size > 50)
  already in motif.
```

These verbose error messages are intended to warn a user quickly and clearly if a graph query is unlikely or impossible, rather than allowing the user to proceed with a long-running query that is destined to fail. In contrast, the equivalent Cypher command running in Neo4j will still go through the process of execution on the full host graph, but will return no results.

DotMotif includes the option to include validators for *biological plausibility*. These allow the user to prohibit motifs that — for example — require inhibition and excitation to be performed by the same neuron. These validators, like all validators in the DotMotif package, are both optional as well as modifiable.

4.3.3 Query execution

A parsed, optimized, and validated query can now be evaluated against a large graph. Where necessary, it is possible to run these queries fully in-memory on consumer hardware. DotMotif includes a `NetworkXExecutor`, which can search a graph for motifs in a pure Python implementation. This is ideal for very small graphs (see *Benchmarks*, below) or for constrained compute environments where more efficient executors cannot be used.

We have also implemented a `Neo4jExecutor`, which leverages the Neo4j [5] database and its built-in subgraph match detection algorithm, an implementation of the *VF2* algorithm [25, 26]. In order to run queries in this environment, our software converts the optimized query to *Cypher*, the database query language used natively by Neo4j. If a user does not have a running Neo4j database, our library also includes routines to provision a Docker container [33] and quickly ingest the data in an appropriate format for Neo4j to use.

5 Discussion

Modern connectomics research currently suffers from a lack of accessible, yet performant, graph analysis and subgraph-search tools. In this work, we present DotMotif, a combined domain-specific language and interface to powerful graph-search tools. Our hope is that this tool and others like it will reduce the barrier-to-entry for researchers unacquainted with graph theory or graph databases, and will enable researchers to interrogate increasingly-common connectome datasets with ease.

Though the undirected graphs found in the graph atlas study here may not point to specific results that directly illuminate neuroscience answers, this broad search can narrow down where it may be most impactful to dig deeper, perhaps leading to more interesting directed graph searches or neural simulations over smaller directed version. Future work may in-

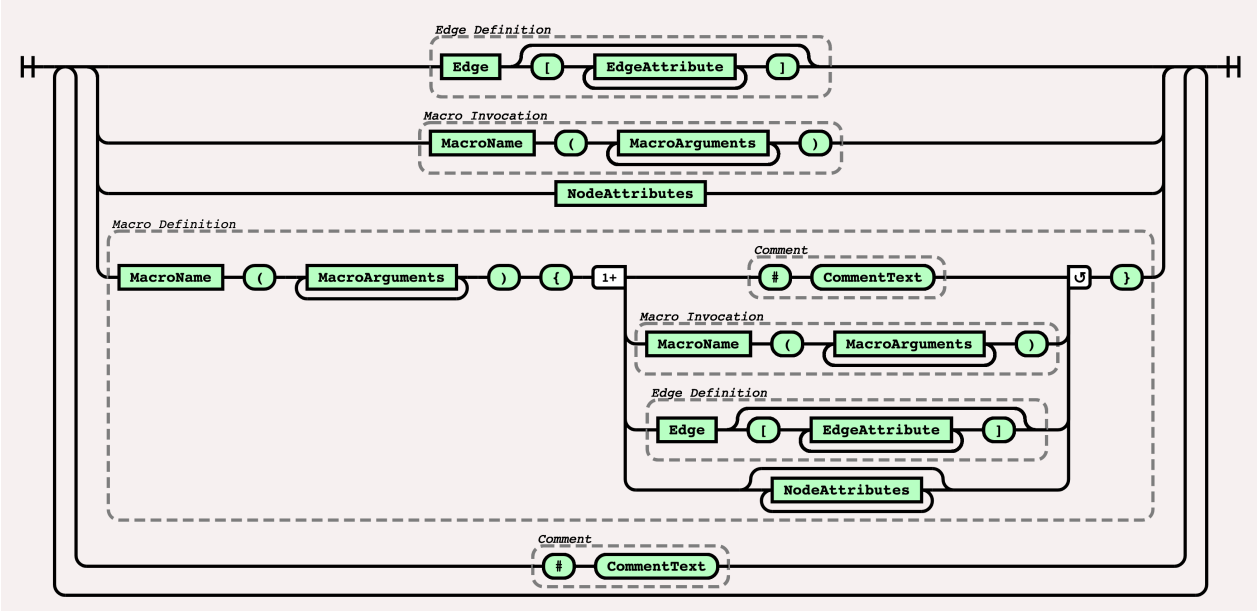

Figure 6: The DotMotif Syntax in railroad-diagram form. The DotMotif DSL is a whitespace-agnostic language with hash-symbol comments and curly-brace bracketed macros. Edges are defined with `->`-arrowlike syntax; edge attributes may be listed in JSON-like syntax. Node attributes may be listed in object dot-notation syntax. For example usage of this syntax system, refer to *Architecture*. This syntax is formally defined in Extended Backus-Naur Form. Both this formal definition as well as the language specification will be made available as per *Supplemental Materials*. This figure was generated with the *railroad-diagrams* Node.js package [32].

clude random direction assignment in order to perform an unbiased search across the space of all possible graphs, akin to other random-graph searches [6].

It is interesting to note that the MICrONS dataset closely matched all random graph models but the geometric random graph. Indeed, the Watts-Strogatz graph model, which greatly underestimated motif counts when calibrated to match the *C. elegans* graph, was a much better predictor of motif counts in the MICrONS dataset. We intend to further explore other metrics beyond density for random graph model calibration in the future.

Despite many of the simplifications and optimizations to the subgraph monomorphism task mentioned here, this task in general is NP-complete [34, 27, 35, 36]. Even in a relatively small connectome such as that of *C. elegans*, certain sufficiently common or poorly-optimized motif searches may still remain infeasible to run on consumer hardware. In our experience, the addition of further constraints, such as specifying edge direction, specifying node- and edge-attributes, or searching for query graphs with nodes of high degree, may reduce the execution time of complex queries; but other seemingly helpful modifications, such as increasing the diameter of a query graph, may counter-intuitively increase runtime quite substantially. As a result of such longer query runtimes or more compute-hungry queries, researchers will be able to run fewer queries per study.

In our ongoing work, we hope to help to reduce this barrier by developing more rigorous automated query optimizations and by publishing connectome query results for reuse. We will introduce and refine new validators that aid DotMotif query designers in identifying qualities of a query graph that may lead to long runtimes, and we hope that the atlas results published above may shed light on how to select query graphs for further study in a dataset. We intend to disseminate an open-data *motif encyclopedia* so that long-running or complex queries may be run on a dataset once and then shared with the community.

The field of connectomics is at an inflection point, as technology and neuroscience provide avenues to create and study large datasets at unprecedented scales beyond the analysis capabilities of a single lab. Open, free, and public datasets, as well as accessible and affordable tools to understand those public data, are of paramount importance.

We are releasing the DotMotif codebase, as well as all demonstration code and data in this manuscript, as open-source and open-data tools to support community discovery. We invite collaborators to share questions that allow us extend DotMotif to test scientific hypotheses.

6 Supplemental Materials

Code for the DotMotif Python library, the example snippets in this paper, and all data and code for the experiments run in *Results* are available online at *https://bossdb.org/tools/dotmotif*.

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