GREATER THAN THE SUM OF ITS PARTS: BUILDING SUBSTRUCTURE INTO PROTEIN ENCODING MODELS

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ABSTRACT

Protein representation learning has achieved major advances using large sequence and structure datasets, yet current models primarily operate at the level of individual residues or entire proteins. This overlooks a critical aspect of protein biology: proteins are composed of recurrent, evolutionarily conserved substructures that mediate core molecular functions. Despite decades of curated biological knowledge, these substructures remain largely unexploited in modern protein models. We introduce Magneton, an integrated environment for developing substructure-aware protein models. Magneton provides (1) a large-scale dataset of 530,601 proteins annotated with over 1.7 million substructures spanning 13,075 types, (2) a training framework for incorporating substructures into existing models, and (3) a benchmark suite of 13 tasks probing residue-, substructure-, and protein-level representations. Using Magneton, we develop substructure-tuning, a supervised finetuning method that distills substructural knowledge into pretrained protein models. Across state-of-the-art sequence- and structure-based models, substructure-tuning improves function-related tasks while revealing that substructural signals are complementary to global structural information. The Magneton environment, datasets, and substructure-tuned models are all openly available[1].

1 INTRODUCTION

Protein representation learning has progressed from models trained on large sequence databases (Rives et al., 2021; Elnaggar et al., 2022) to models incorporating experimentally determined or predicted structures (Gligorijević et al., 2021; Zhang et al., 2022b), enabling advances in folding (Lin et al., 2023), function prediction (Rao et al., 2019), and variant effect prediction (Meier et al., 2021; Brandes et al., 2023). However, these models have largely ignored the recurrent and modular composition of proteins, which introduces substantial technical challenges. Protein substructures occur at multiple spatial and functional scales, from local motifs spanning only a handful of residues to domains that cover large fractions of a protein. They are often non-contiguous in sequence space, making them difficult to encode with standard sequential architectures. A single residue can belong to several overlapping substructures, inducing hierarchical and context-dependent relationships that are not naturally handled by flat representations. Finally, annotated substructures are distributed in a long-tailed fashion, with abundant secondary structure elements but scarce examples of specialized motifs, complicating the design of training objectives and evaluation protocols.

These challenges arise because proteins are not uniform chains but are organized into recurrent, modular substructures that provide a natural multiscale vocabulary for representation. At the finest level are amino acids, which assemble into secondary structure elements such as alpha helices and beta sheets; these in turn combine into higher-order motifs and domains such as beta barrels and zinc fingers (Figure 1A). These substructures are responsible for core molecular functions of proteins, such as coordinating metal ions for reaction catalysis or binding to other proteins as parts of cellular signaling networks, and their importance is underscored by their occurrence in proteins sampled from across the tree of life. Decades of biological research has led to the categorization of these recurrent substructures, resulting in large databases that exhaustively annotate these elements

[1] https://anonymous.4open.science/r/magneton-14F2/README.md

across proteins (Sonnhammer et al., 1997; Paysan-Lafosse et al., 2025; Blum et al., 2025). However, prevailing protein representation learning methods still rely on self-supervised objectives that operate at the scale of single amino acids, such as masked language modeling or structural denoising, or occasionally operate on full proteins (Yu et al., 2023). This is despite abundant evidence that evolutionarily conserved substructures are key components of protein function (Rossman & Liljas, 1974). In this work, we ask, *how should we systematically incorporate decades of biological knowledge about protein substructures into protein encoding models?*

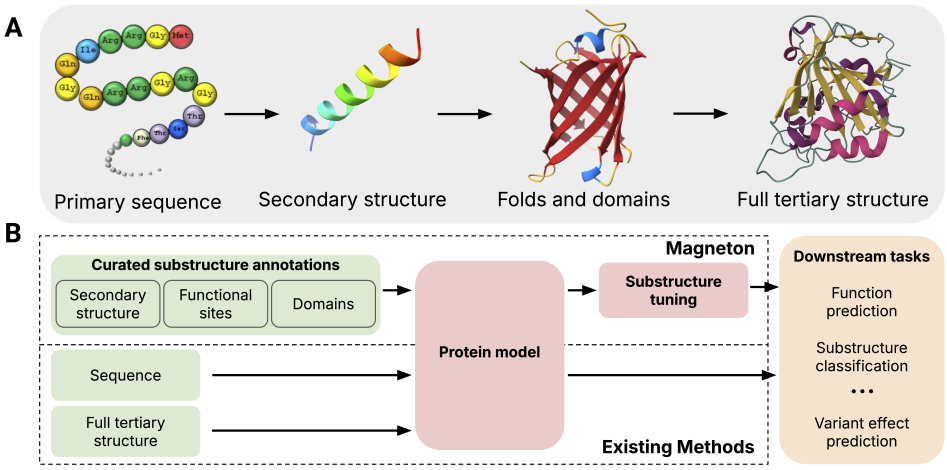

Figure 1: Overview of protein structure and the Magneton environment. (A) Proteins are built from modular substructures that assemble into full structures. (B) Magneton leverages decades of substructure research to provide an environment for developing and evaluating substructure-aware models.

While there exists a growing body of work exploring how to best integrate protein sequence and structure into a single model, either via direct incorporation of structural tokens (Su et al., 2023; Li et al., 2024; Hayes et al., 2025; Lu et al., 2025; Yuan et al., 2025) or finetuning of sequence models to better align with structural representations (Zhang et al., 2024b; Ouyang-Zhang et al., 2025), there are few examples of incorporating substructure information into protein encoding models. Models such as GearNet (Zhang et al., 2022b) use a multi-view contrastive objective and cite recurrent substructures as motivation, but use multiple views of subsets of the same protein rather than considering recurrent substrucutures across proteins. The Functional Community Invariance approach (Wang et al., 2025b) employs secondary structure annotations to guide graph augmentations but ignores higher-order substructures. Other threads of work seek to construct hierarchical representations of proteins, either by connecting residues to their exposed surface areas (Somnath et al., 2022; Zhang et al., 2024c; Mallet et al., 2025), or in models such as ProNet (Wang et al., 2023), by progressing from all-atom graphs to residue graphs, but these works pass over protein substructure as a valuable part of the structural hierarchy.

Present work. To close this gap, we first create a new environment for developing substructure-aware protein models, which we call *Magneton*. Magneton has three main components: (1) a dataset of proteins with curated substructures in an ML-ready format; (2) a framework for using these substructures to train or finetune protein encoding models; and (3) a benchmark of evaluation tasks that probe the learned representations at the residue, substructure, and protein levels (Figure 1B). By curating data from Pfam, InterPro, and DSSP, we create a dataset of 530,601 proteins with over 1.7 million substructural annotations (37 million when including secondary structure) across six substructure classes with 13,075 distinct substructure types.

Using Magneton, we next explore *substructure-tuning*, a supervised fine-tuning strategy that explicitly distills substructural information into protein encoders. Concretely, we formulate substructure-tuning as classification of evolutionarily conserved substructures, where residue-level embeddings produced by a base encoder are pooled to construct substructure representations and optimized with a cross-entropy loss. This objective is model-agnostic, requiring only residue-level embeddings, and naturally extends to multiple structural scales through a multi-task formulation in which each substructure class is assigned its own prediction head and the total loss is the sum across scales.

We systematically vary the substructures used for tuning, exploring configurations ranging from small, highly local elements (e.g., active sites spanning < 10 residues) to larger domains, as well as joint training over multiple scales. Substructure-tuning is evaluated on 13 benchmarking tasks using 6 state-of-the-art base models, including both sequence-only and sequence–structure encoders. Substructure-tuned representations yield consistent improvements of 5% on function-related prediction tasks (e.g., EC and GO terms), while effects on localization and residue-level tasks are neutral or negative. Improvements persist even when base models already incorporate global structural inputs, underscoring that substructural signals are distinct and complementary to global protein structure.

Our key contributions are: ① We present Magneton, a benchmark that combines large-scale curated substructural annotations with an associated Python library and a suite of 13 evaluation tasks spanning residue, substructure, protein, and interaction levels. This environment enables exploration of how substructural priors can be integrated into protein models. ② We introduce substructure-tuning, a supervised fine-tuning method for distilling substructural information into pretrained models. We exhaustively evaluate its design space across six state-of-the-art encoders, covering both sequence-only and sequence–structure models and ranging from 150M to 650M parameters. ③ We show that substructure-tuning improves models' ability to represent protein function: for example, Enzyme Commission (EC) prediction with ESM-C 300M improves from 0.688 to 0.815, and Gene Ontology molecular function prediction increases from 0.429 to 0.525. These results demonstrate that substructural information is complementary to global structure, yielding consistent gains in functional prediction tasks across architectures. We envision that this work will catalyze closer integration of machine learning and biology, motivating new approaches and inductive biases that incorporate decades of knowledge about protein structure across scales.

2 Related Work

Integrating structure- and function-based inductive biases into sequence-based protein models. A large body of work has explored distilling auxiliary modalities into sequence-based protein models. Some methods incorporate free-text descriptions, such as Gene Ontology terms (Zhang et al., 2022a) or SwissProt annotations (Xu et al., 2023). The majority, however, focus on structural information. Explicit approaches integrate structure directly, either through structure graphs (**?**) or structural tokenization (Su et al., 2023; Li et al., 2024). Structural distillation methods instead use structure only at training time, preserving sequence-only inference. For example, Implicit Structure Model (ISM) (Ouyang-Zhang et al., 2025) trains residue-level predictors on tokens from a structural autoencoder, while ESM-S (Zhang et al., 2024b) distills global structural information via fold classification. S-PLM (Wang et al., 2025a) employs contrastive learning to align representations of an ESM encoder with those of a contact-map encoder. Magneton differs by focusing on protein *substructures* rather than only residue-level or global structural signals. It provides large-scale curated annotations of conserved substructures and a framework for supervised fine-tuning on these elements to encode modular, recurrent units of protein organization. This is orthogonal to existing sequence-structure integration and structural distillation approaches.

Substructure-aware training and hierarchical models. Protein substructure admits a hierarchical view, but most hierarchical modeling approaches focus on geometric relations rather than functional substructures. Some methods connect residues to exposed surface areas (Somnath et al., 2022; Zhang et al., 2024c; Mallet et al., 2025), while others connect residues to constituent atoms (Wang et al., 2023). Few approaches incorporate substructural information directly. GearNet (Zhang et al., 2022b) uses a multiview contrastive objective that samples local regions within a protein, but supervision is restricted to intra-protein partitions rather than conserved substructures across proteins. SES-Adapter (Tan et al., 2024) augments sequence models with cross-attention to DSSP-derived secondary structure tokens, but does not extend beyond this single level of annotation. Protein language models such as xTrimoPGLM (Chen et al., 2025) use span-masking, but the masked spans are random residue segments rather than biologically defined substructures. ESM3 (Hayes et al., 2025) introduces multi-track tokenization, including secondary structure and function tracks, where the function track is derived from ontology terms often correlated with substructural annotations. However, the learning remains self-supervised and intra-protein, without supervision on conserved substructures across proteins. Magneton differs by providing annotations of conserved substructures across proteins and by defining supervised training objectives that operate directly on these annotations. This design moves beyond local partitions, random spans, or ontology proxies, enabling

systematic study of substructure-aware modeling across residue-, motif-, domain-, and protein-level representations.

Geometric protein models. Geometric deep learning has been widely applied to proteins, with models developed for folding (Jumper et al., 2021; Abramson et al., 2024), structure design (Passaro et al., 2025; Watson et al., 2023; Huang et al., 2024), and representation learning (Jing et al., 2020; Fang et al., 2025). These approaches operate at the atom scale (Qu et al., 2025; Widatalla et al., 2025) and encode spatial coordinates of all atoms to model global protein geometry. Magneton addresses a complementary problem: representing recurrent substructures that span residues, motifs, and domains, and recur across proteins. Rather than optimizing directly on atomic coordinates, Magneton introduces supervised objectives on conserved substructures, providing functional supervision across structural scales. This supervision captures signals relevant to tasks such as Enzyme Commission classification, Gene Ontology function prediction, and thermostability, where global geometry alone is insufficient. Substructural objectives can also be integrated with atom-scale geometric encoders to yield models that capture fine-grained geometry and functional modularity.

3 METHODS

Preliminaries. Two possible views of a protein P are the residue-level, $P = (a_1, \ldots, a_l)$ where a_i is the i'th residue in the primary sequence, and the substructure-level, $P = (s_1, \ldots, s_n)$ where each s_i represents a substructure contained within a protein. Other views are possible (*e.g.* atom-level), but these two views are the most relevant for our work. In the substructure view, each substructure is a subset of k residues, $s_i = \{a_j\}_{j=1}^{j=k}$, where the residues a_j may or may not be contiguous in the primary sequence. Since substructures exist at multiple scales, a given residue may be a member of multiple, possibly overlapping substructures, *e.g.* a residue may be part of a secondary structure element, such as a beta strand, that is itself part of a larger fold, such as a beta barrel. It is also possible for a given residue to not be included in any annotated substructure. While the substructure view of a protein is common in the biological community, there is a lack of curated datasets for exploring it in the context of protein modeling.

3.1 MAGNETON DEVELOPMENT ENVIRONMENT

Magneton is an environment for developing substructure-aware protein models, and consists of three main parts: (1) a curated dataset of proteins with annotated substructures, (2) a framework for using this dataset for substructure-aware training, and (3) an integrated benchmark of evaluation tasks that probe a model's learned representations at multiple structural scales.

Dataset. We use the `2024_06` release of UniProtKB/TrEMBL (The UniProt Consortium, 2025) as our core protein dataset, containing roughly 254M proteins. We obtain annotations of 8-class secondary structure from DSSP (Kabsch & Sander, 1983; Hekkelman et al., 2025) and annotations of higher-order structures (Homologous superfamilies, domains, conserved sites, active sites, binding sites) from the 103.0 release of InterPro (Blum et al., 2025). We process these raw releases into Magneton's core datatypes representing a protein and its associated substructures, and store these as compressed, binary files which we shard to enable parallel processing and file-level shuffling for large-scale training runs. Due to the scale of the dataset at this stage and the size of protein structure data, we focus our further exploration on the manually curated SwissProt subset of UniProtKB, but make the processed version of the full UniProtKB/TrEMBL dataset available to the community. For each protein, we obtain amino acid sequences from UniProtKB and predicted structures from AlphaFold DB (Varadi et al., 2022). To ensure consistent training and evaluation across sequence-based and structure-based models, we subset the SwissProt dataset to only proteins with calculated structures in the current (Nov 2022) release of AlphaFold DB, leaving 530,601 proteins.

To focus learning efforts on substructures where sufficient data is present, we create a restricted label set of more frequently occurring substructures. We restrict to substructures that occur at least 75 times in the SwissProt dataset, corresponding to to retaining only the top 10% most frequently occurring domains. While this may seem stringent, we find that this retains the vast majority of actual substructure occurrences across types, since many substructures have very few occurrences (Appendix A.1). However, our published datasets retain all substructure annotations, to enable future research by the community. Table 1 summarizes the different classes of substructures, their counts, number of types, and typical span on the protein. As expected for substructural elements,

Substructure class	Unique types (pre-filter)	Total occurrences (pre-filter)	Unique types (post-filter)	Total occurrences (post-filter)	Median protein span
Homologous superfamily	2978	1.09M	1133	1.05M	50% (137 AA)
Domain	9133	389K	917	301K	34.8% (127 AA)
Conserved site	739	175K	356	162K	5.18% (16 AA)
Binding site	67	20.1K	48	19.0K	4.28% (16 AA)
Active site	132	31.1K	82	29.2K	3.47% (12 AA)
Secondary structure	8	35.2M	8	35.2M	0.94% (3.4 AA)
Total w/o secondary structure	13075	17.1M	2542	15.6M	—

Table 1: Summary of Magneton substructure dataset (SwissProt subset). Before and after refers to filtering out rare substructures. Median protein span is the median length of a type of substructure, expressed as a percentage of the protein and as absolute amino acid count.

the majority of the substructures span less than 10% of the annotated protein, with the scale varying by the class of substructure. We then split this dataset into training, validation, and test sets using the AFDB50 sequence-based clusters (Barrio-Hernandez et al., 2023).

Evaluation benchmark. To provide a holistic evaluation of substructure-focused protein modeling within Magneton, we integrate numerous evaluation tasks from the community. These tasks probe a model's learned representations at multiple scales: individual residues, substructures, proteins, and protein interactions (Table 2). At the residue-level, we include contact prediction (Rao et al., 2019), zero-shot prediction of variant effects (Notin et al., 2023), and multiple types of functional residue prediction tasks (Dallago et al., 2021; Yuan et al., 2025); at the substructure-level, we include multiclass substructure classification problems derived from the Magneton dataset itself; at the protein-level, we include function prediction (GO and EC terms) (Gligorijević et al., 2021), subcellular localization (Almagro Armenteros et al., 2017), and fitness prediction (Rao et al., 2019). Finally, we include a human PPI prediction task (Pan et al., 2010; Xu et al., 2022). Full details of evaluation datasets can be found in Appendix A.2.

Scale	Task	Task type	Metric	Data source
Interaction	Human PPI prediction	Binary	Accuracy	Pan et al.
Protein	Gene Ontology prediction	Multilabel	$F_{\max}$	Gligorijević et al.
	Enzyme Commission prediction	Multilabel	$F_{\max}$	
	Subcellular localization	Multiclass	Accuracy	Almagro Armenteros et al.
	Binary localization	Binary	Accuracy	
	Thermostability prediction	Regression	Spearman's ρ	Rao et al.
Substructure	Substructure classification	Multiclass	Macro accuracy	Ours
Residue	Contact prediction	Binary	Precision@L	Rao et al.
	Variant effect prediction	Regression	Spearman's ρ	Notin et al.
	Binding residue categorization	Multilabel	$F_{\max}$	Dallago et al.
	Functional site prediction	Binary	AUROC	Yuan et al.

Table 2: Evaluation tasks contained within Magneton. Grouped by the scale of structural representation they interrogate.

3.2 Substructure representation and tuning

Given the dataset in Magneton, we now have a large collection of proteins $\mathcal{P}$, where each protein has curated substructural annotations, $P = (s_1, \ldots, s_k); P \in \mathcal{P}$. We first use this dataset to assess whether existing protein models can generate meaningful representations of substructures.

Specifically, for a protein model f, we construct a representation of each substructure $s_j \in P$ by calculating residue-level embeddings, $f(P) = (v_1, \ldots, v_l), v_l \in \mathbb{R}^d$ where v_i is the embedding of residue a_i. We then perform a substructure pooling operation over the constituent residues of s, $f(s) = \texttt{pool}(\{v_i \ : a_i \in s\}, f(s) \in \mathbb{R}^d$, where $\texttt{pool}$ can be any arbitrary pooling operation. These substructure-level representations are then input to a classifier over the possible substructure labels for the final substructure classification task. Since a substructure's constituent residues are given to the model, this is a *diagnostic task* meant to probe each model's ability to represent substructures, not a task meant to measure the ability to identify previously unannotated substructures. For the purposes of this diagnostic assessment, we freeze the parameters of the underlying protein model and train only the substructure classification head.

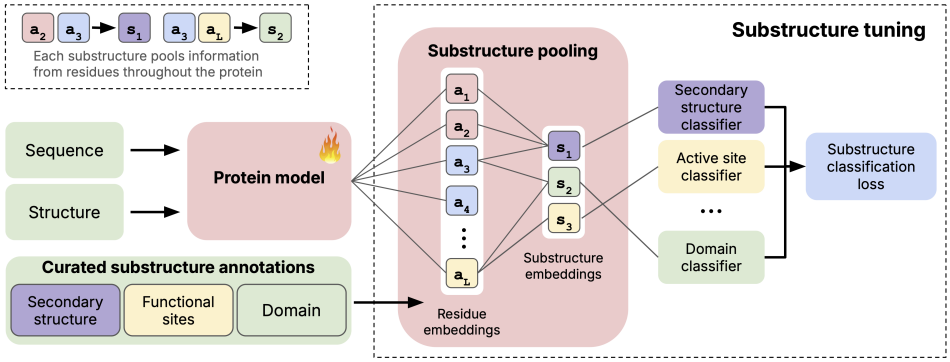

Figure 2: Overview of using Magneton for substructure-tuning. Given a pre-trained protein model, substructure-tuning first pools residue-level embedding to create substructure representations, which are then used for supervised finetuning via substructure type-specific classifier heads.

We next explore imbuing existing protein models with substructural information. In a process we refer to as *substructure-tuning*, we again perform the substructure classification task outlined above, but with finetuning of the original protein model's parameters (Figure 2) Although we use supervised finetuning, other losses, such as a contrastive objective (van den Oord et al., 2019), could also be used. The substructure-tuning process is compatible with any finetuning method, including parameter-efficient methods such as LoRA (Hu et al., 2021) for larger base models. We perform substructure-tuning using the Magneton training set and explore tuning with different substructure types as well as their combinations. When finetuning with multiple substructure classes, each class uses its own predictor module with the cross entropy loss across all types summed to form the final substructure classification loss.

3.3 Implementation Details

For our experiments, we select base protein models that represent state-of-the-art models across a range of model sizes and modality inputs. For sequence-based models, we use ESM2-150M and -650M (Lin et al., 2023) and ESM-C 300M and 600M (ESM Team, 2024). For models that incorporate protein structure, we use SaProt (Su et al., 2023) and ProSST-2048 (Li et al., 2024), both of which use both protein sequence and structure. We opt to exclude purely structural models such as GearNet (Zhang et al., 2022b) as their performance is generally below that of the sequence-structure models we've included.

For substructure classification and tuning, we use single-hidden layer MLPs where the hidden dimension size matches that of the base model as our prediction modules, mean pool for the substructure pooling operation. For substructure-tuning, we perform full finetuning of the base model. To regularize the substructure-tuning process and avoid catastrophic forgetting of the base model's original objective, we use elastic weight consolidation (EWC) (Kirkpatrick et al., 2017). Detailed training methodology is available in Appendix A.3.

For supervised downstream evaluations, we train head models on top of either the original base model or the substructure-tuned base model. For these evaluations, we freeze the base model to focus on evaluating the representations learned during substructure-tuning. Results across all tasks

and models were generated within the Magneton environment and use identical datasets and splits. We unfortunately exclude ProSST from the functional site prediction and contact prediction tasks due to it's incompatibility with experimental structures from PDB. Full training details for all models and tasks are available in Appendix A.4.

4 EXPERIMENTS

4.1 SUBSTRUCTURE REPRESENTATION ASSESSMENT

Table 3 shows that base models are readily able to produce effective representations of substructures across scales, with structure-based models generally outperforming sequence-only models. We also find that models are able to correctly classify substructures within proteins that contain multiple substructures (*e.g.* accurately classifying all domains within a single protein containing multiple domains), indicating that classification relies on local structural cues rather than global structural similarity (Figure 3A). While performance degrades for some rarer substructures, we generally see high accuracy even for rare substructures (Figure 3B).

Model	Homologous superfamily	Domain	Conserved site	Binding site	Active site	Secondary structure
ESM2-150M	0.899	0.969	0.988	1.000	0.995	0.827
+ST	0.925	0.983	0.991	0.999	0.994	0.916
ESM2-650M	0.926	0.982	0.986	1.000	0.995	0.892
+ST	0.902	0.967	0.986	1.000	0.996	0.938
ESM-C 300M	0.913	0.962	0.990	0.998	0.994	0.863
+ST	0.946	0.982	0.983	0.999	0.996	0.757
ESM-C 600M	0.919	0.975	0.992	0.977	0.994	0.891
+ST	0.907	0.966	0.993	0.997	0.996	0.927
ProSST-2048	0.888	0.945	0.995	0.996	0.993	0.927
+ST	0.879	0.976	0.991	0.991	0.995	0.961
SaProt	0.916	0.967	0.992	0.999	0.996	0.955
+ST	0.925	0.980	0.993	0.999	0.996	0.972

Table 3: Comparison of substructure classification performance. Model performance on the *diagnostic task* of classifying substructures given their annotated residues. All values are macro-averaged accuracy.

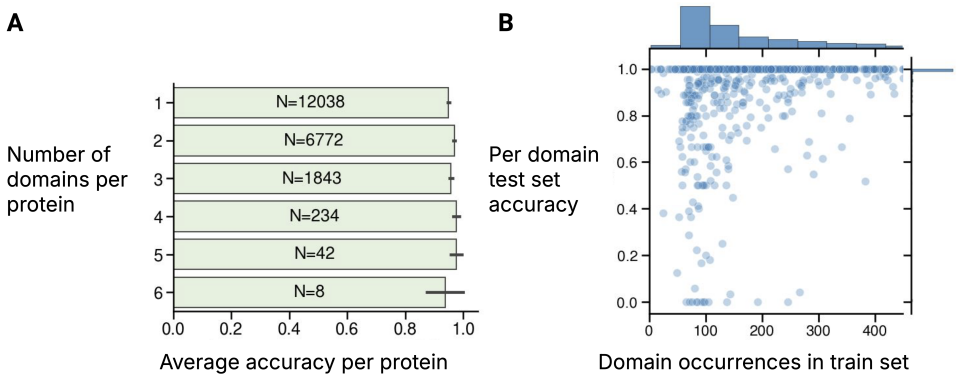

Figure 3: (A) Domain classification uses local cues. Even within proteins containing multiple domains, classification accuracy remains high for all contained domains. Labels within bars show the number of test set proteins containing that number of domains. **(B) Domain classification accuracy as a function of training set representation.** Results shown for ESM-C 300M.

4.2 SUBSTRUCTURE-TUNING

Substructure-tuning configurations. Table 4 shows the results of substructure-tuning with a range of different substructure classes, both individually and their combinations, as measured by downstream evaluation tasks. Due to the large number of possible configurations, we restricted this initial exploration to a single model (ESM-C 300M), a subset of evaluation tasks, and a selection of the 2^6 possible substructure class combinations aimed at exploring combinations of substructure classes across scales.

Substructures used	EC	GO:BP	GO:CC	GO:MF	Localization (Accuracy)		Thermostability (Spearman's ρ)	Zero-shot DMS (Spearman's ρ)
	$F_{\max}$				Binary	Subcellular		
None	0.688	0.307	**0.416**	0.429	0.871	0.703	0.648	**0.432**
H_____	0.805	0.312	0.395	0.518	0.851	0.632	0.662	0.308
_D____	0.776	0.307	0.403	0.501	0.811	0.640	**0.666**	0.340
__C___	0.749	0.318	0.398	0.491	0.870	**0.706**	0.661	0.402
___B__	0.745	0.315	0.415	0.478	0.852	0.686	0.663	0.423
____A_	0.794	0.318	0.403	0.518	0.851	0.639	0.663	0.340
_____S	0.618	0.297	0.379	0.381	0.823	0.587	0.612	0.264
HD____	0.774	0.316	0.388	0.500	0.847	0.606	0.639	0.302
H____S	0.765	0.297	0.395	0.466	**0.883**	0.651	0.644	0.346
HD___S	0.754	0.318	0.413	0.473	0.868	0.633	0.658	0.350
H_CBA_	0.800	0.322	0.389	0.515	0.857	0.611	0.663	0.340
_D___S	0.751	0.308	0.384	0.462	0.872	0.646	0.643	0.369
DCBA	**0.815**	**0.329**	0.395	**0.525**	0.851	0.662	0.659	0.369
__CBA_	0.761	0.325	0.403	0.488	0.879	0.681	0.660	0.410
___BA_	0.740	0.319	0.406	0.467	0.841	0.677	0.656	0.418
__CBAS	0.719	0.313	0.393	0.453	0.839	0.666	0.636	0.379
HDCBAS	0.760	0.315	0.383	0.457	0.832	0.624	0.640	0.359

Table 4: Comparison of substructure-tuning configurations. Performance across tasks for ESM-C 300M with a range of substructure-tuning configurations. For each configuration, the substructures used are indicated by the presence of that substructure type's single-letter code: H=Homologous superfamily, D=Domain, C=Conserved site, B=Binding site, A=Active site, S=Secondary structure; an underscore (_) means that substructure type was not used.

Our exploration of substructure configurations revealed the following: 1) The effects of substructure-tuning are largely consistent across the selected substructure types used, with large performance boosts in tasks related to protein function (GO:MF, GO:BP, EC, Thermostability) and neutral to negative effects on localization tasks (GO:CC, Binary localization, Subcellular localization) and residue-level variant-effect prediction. 2) These effects are present even when tuning with very small substructures, such as active sites, which typically consist of only 12 amino acids (median protein span of 3.47%). Based on these results, we selected the combination of active site, binding site, and conserved site as the substructure-tuning configuration for use on the full set of models and benchmarks, as this configuration represented a balance of positive gains on function-related tasks and neutral effects on localization and residue-level variant-effect tasks.

Substructure-tuning across models. Tables 5 and 6 show how the selected substructure-tuning configuration affects the downstream performance of the full set of base protein models across protein-level and residue-level tasks, respectively. The full evaluation across models and benchmarks led to the following conclusions: 1) Results across models are consistent with the initial exploration: performance boosts in function-related tasks and neutral to negative effects on localization and residue-level tasks. 2) Importantly, these results hold true for models that already incorporate protein structure as an input (ProSST-2048 and SaProt), suggesting complementarity between structural and substructural information.

We additionally explored how substructure-tuning interacts with task-specific finetuning by repeating the evaluations above for a subset of models and tasks with full finetuning of the protein model for each task (Appendix A.5). We found that task-specific finetuning results in similar performance across models trained with and without substructure-tuning, indicating that aggressive task-specific finetuning may dominate the substructural information imbued during the substructure-tuning process.

Model	EC	GO:BP	GO:CC	GO:MF	Localization (Accuracy)		Thermostability (Spearman's ρ)	Human PPI (AUROC)
	$F_{\max}$				Binary	Subcellular		
ESM2-150M	0.727	0.316	0.416	0.441	0.869	0.694	0.627	0.933
+ST	0.742	0.324	0.415	0.473	0.866	0.679	0.582	0.919
ESM2-650M	0.755	0.319	0.431	0.486	0.876	0.710	0.643	0.939
+ST	0.745	0.321	0.440	0.534	0.895	0.749	0.655	0.935
ESM-C 300M	0.688	0.307	0.416	0.429	0.871	0.703	0.648	0.917
+ST	0.761	0.325	0.403	0.488	0.879	0.681	0.660	0.933
ESM-C 600M	0.701	0.312	0.403	0.436	0.863	0.713	0.668	0.927
+ST	0.780	0.319	0.385	0.527	0.872	0.635	0.667	0.902
SaProt (650M)	0.778	0.326	0.453	0.538	0.887	0.784	0.692	0.952
+ST	0.839	0.339	0.446	0.584	0.896	0.741	0.697	0.932
ProSST-2048	0.778	0.317	0.426	0.522	0.878	0.693	0.686	0.925
+ST	0.791	0.314	0.420	0.567	0.853	0.683	0.648	0.883

Table 5: Protein-level task performance for models with and without substructure-tuning.

Model	Binding residue ($F_{\max}$)	Functional site prediction		Contact Prediction			Variant Effect (Spearman's ρ)
		Binding	Catalytic	Short	Medium	Long	
		(AUROC)		(Precision@L)			
ESM2-150M	0.379	0.871	0.910	0.487	0.452	0.289	0.342
+ST	0.327	0.852	0.890	0.460	0.445	0.285	0.262
ESM2-650M	0.366	0.849	0.912	0.551	0.528	0.372	0.359
+ST	0.362	0.851	0.927	0.532	0.518	0.367	0.317
ESM-C 300M	0.367	0.851	0.923	0.339	0.364	0.174	0.432
+ST	0.411	0.866	0.910	0.350	0.374	0.180	0.410
ESM-C 600M	0.357	0.850	0.921	0.329	0.362	0.161	0.434
+ST	0.368	0.852	0.906	0.313	0.315	0.141	0.381
SaProt (650M)	0.423	0.891	0.923	0.788	0.747	0.697	0.457
+ST	0.400	0.871	0.924	0.765	0.726	0.647	0.405
ProSST-2048	0.375	N/A	N/A	N/A	N/A	N/A	0.507
+ST	0.342	N/A	N/A	N/A	N/A	N/A	0.356

Table 6: Residue-level task performance for models with and without substructure-tuning.

5 Conclusion and Future Work

Our study has several limitations and directions for future work. We focused on an intuitive substructure-tuning approach applied to existing state-of-the-art models, which yielded mixed gains across tasks and proved brittle under task-specific finetuning. These results suggest that incorporating substructural information at the architectural level may provide a more stable integration strategy. In addition, our experiments emphasized frequently occurring substructures by restricting to SwissProt proteins and filtering out rare elements. Extending to the full UniProtKB and incorporating the long tail of infrequent substructures could enable deeper insights into poorly characterized aspects of protein modularity.

In this work, we've presented the open problem: *how to best incorporate decades of research on protein substructures into protein models?* To this end, we introduced Magneton, an integrated environment for developing substructure-aware protein models that provides (1) large-scale datasets of proteins with curated substructure annotations, (2) a framework for using these processed datasets for training and finetuning protein models using sequence, structure, and substructure inputs, and (3) a suite of benchmarking tasks that evaluate models across a range of structural granularities. Using Magneton, we explored both how well existing models are able to represent protein substructures and whether a supervised finetuning paradigm can be used to effectively imbue those models with substructural information. We found that while this direct, intuitive substructure-tuning approach improves model performance on molecular function-related tasks, it has a neutral to negative effect on others. Our work lays the foundation for development of substructure-aware protein models.

6 ETHICS STATEMENT

This work involves the analysis of publicly available protein sequence and structure data from established databases (UniProtKB/SwissProt, AlphaFold DB, InterPro, and Pfam). All data used in this study is derived from previously published sources and does not involve human subjects, animal experiments, or the generation of new biological data requiring ethical oversight. Our work improves computational methods for understanding protein function, which could contribute to advances in drug discovery and biotechnology. We encourage responsible use of our methods and datasets, which are publicly available to promote scientific reproducibility and advancement.

7 REPRODUCIBILITY STATEMENT

To ensure the reproducibility of our work, we provide the following:

1. All code for Magneton, including data processing pipelines, model training scripts, and evaluation benchmarks, is available at `https://anonymous.4open.science/r/magneton-14F2/`. The processed datasets will be made publicly available following the anonymous review period.
2. We provide comprehensive implementation details including model architectures and hyperparameters, training procedures, optimization details, and data splitting procedures (Methods 3.3).
3. We specify all experimental details including dataset statistics and preprocessing steps such as substructure filtering criteria and thresholds (Table 1, Appendix A.2), as well as evaluation metrics and protocols for all benchmark tasks (Table 2).
4. All experiments can be reproduced using 1-4 NVIDIA A100 GPUs.

The modular design of Magneton facilitates easy plug-and-play usability of our benchmark suite, supporting not only reproducibility but also future research in this area.

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A Appendix

A.1 Substructure dataset filtering

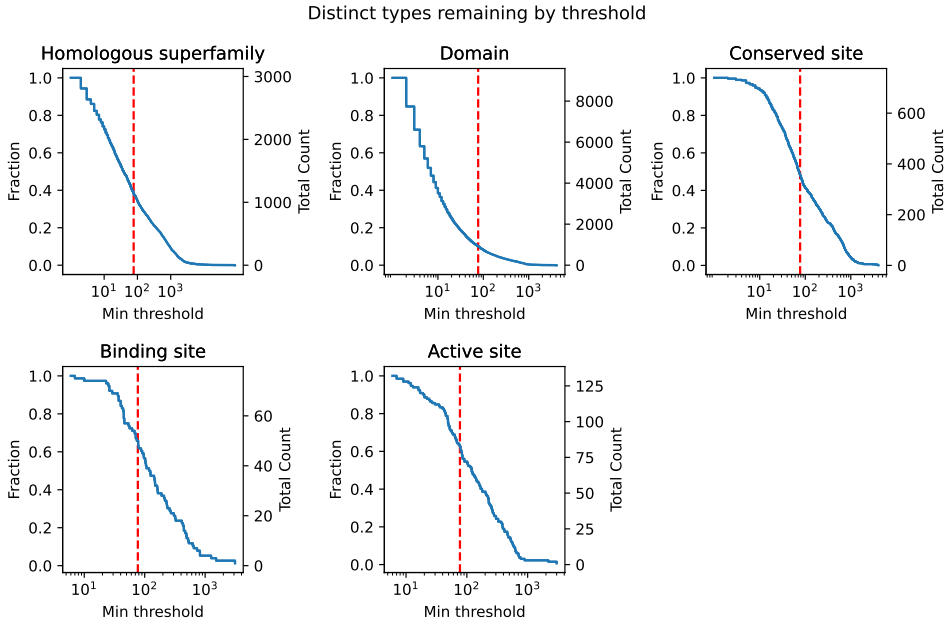

Figure A.1: Inverse CDF of **unique types** retained at a given count threshold. The x-axis specifies the minimum count for a substructure type to be retained, the left y-axis shows the fraction of all unique types retained at the given threshold, and the right y-axis shows the absolute count of unique types retained. Facets show different classes of substructural elements. The vertical dashed red lines show the threshold selected for downstream substructure-tuning.

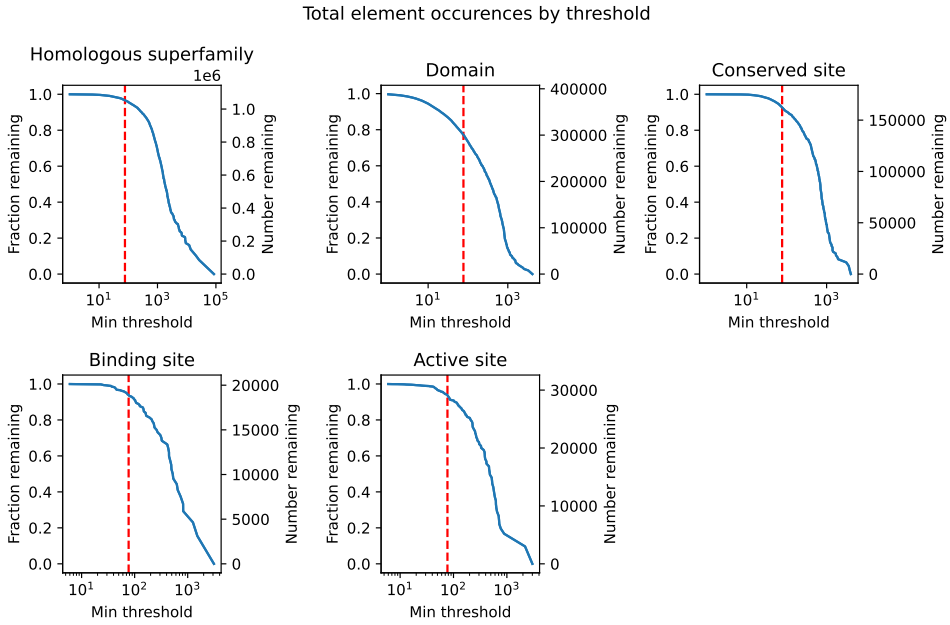

Figure A.2: Inverse CDF of **total occurrences** retained at a given count cutoff. This is analogous to Figure A.1 above, but showing total occurrences of substructures rather than unique types, demonstrating that for classes like domains, the majority of annotations come from a small number of domain types.

A.2 MAGNETON EVALUATION DATASETS

Magneton contains eleven different benchmarking datasets, comprising 14 evaluation tasks. These evaluation tasks represent years of work from the scientific community, both in their original generation and later processing that we build upon, and we acknowledge and thank all of those involved. The included tasks are:

- **Human PPI prediction.** The goal of this task is to predict whether or not two proteins form an interacting pair. This is a binary classification task where the input is two proteins and the output is a binary label indicating interaction or no interaction. The evaluation metric is accuracy. The original dataset is sourced from Pan et al. (2010). We build off of processed data files from Su et al. (2023).
- **Gene Ontology and Enzyme Commission prediction.** The goal of these tasks are to predict the Gene Ontology (GO) or Enzyme Commission (EC) annotations for a protein. There are three categories of GO annotations: Molecular Function (MF), Cellular Component (CC), and Biological Process (BP), each of which captures a different aspect of protein biology and is treated as a separate benchmarking task, giving a total of four tasks. These are multilabel classification tasks where a protein can have multiple annotations. The evaluation metric is $F_{\max}$, the maximum F_1 score over possible thresholds. We source original data from Gligorijević et al. (2021).
- **Subcellular and binary localization.** The goal of these tasks is to predict a protein's localization either within multiple cellular compartments (subcellular localization) or whether the protein is membrane-bound or soluble (binary localization). The input is a single protein and this is either a multiclass or binary classification task. The evaluation metric is accuracy. The original dataset is sourced from Almagro Armenteros et al. (2017). We build off of processed data files from Su et al. (2023).
- **Thermostability.** The goal of this task is to predict the stability of a protein under extreme temperatures. The output is a continuous value indicating the thermostability, and the goal is to rank-order proteins according to their experimental values. The evaluation metric is Spearman rank correlation (Spearman's ρ) calculated against the experimental values. The original dataset is sourced from Rao et al. (2019).
- **Binding residue categorization.** The goal of this task is to predict whether a given residue binds three different types of ligands: metal ions, small molecules, or nucleic acids. This is a residue-level multilabel classification task. The evaluation metric is $F_{\max}$. The original dataset is sourced from Dallago et al. (2021).
- **Binding and catalytic site prediction.** The goal of these tasks are to predict whether a given residue is part of an annotated binding or catalytic site. This is a residue-level binary classification task. The evaluation metric is AUROC. The original datasets are sourced from experimentally determined structures curated by Zhang et al. (2024a). We build off of processed data files from Yuan et al. (2025).
- **Contact prediction.** The goal of this task is to predict whether two residues within the same protein are "in contact" with each other, which is defined as having alpha-carbon atoms within 8 angstroms of each other in the tertiary structure. The input is a single protein of length L and the output is a $L \times L$ contact map, where element i, j of the contact map is the predicted probability that residues i and j are in contact. The evaluation metric is Precision@L, which calculates precision over the top L most confident contact predictions where L is the protein length. This metric is further stratified into short, medium, and long-range contacts in which the possible residue pairs considered are those whose pairwise separation along the primary sequence is either in $[6, 10]$, $[12, 22]$, or $[24, L]$, respectively. The underlying data are experimentally determined structures from PDB, originally curated by Rao et al. (2019).
- **Zero-shot DMS variant effect prediction**. The goal of this task is to predict the effect of a single or multiple amino acid mutations on a protein's function. The input is the mutated sequence and the output is a continuous value representing fitness. The evaluation metric is Spearman's ρ against the experimentally-determined fitness values from deep mutational scans (DMS) experiments. These tasks are zero-shot in that no supervised training for

variant effect prediction is performed. For each model, we use the author's recommended methods for VEP. The data is sourced from Notin et al. (2023).

For all datasets, protein structures are sourced from AlphaFold DB (Varadi et al., 2022) unless otherwise specified. Accounting of samples per split in each dataset are available in Table A.1.

Task	Train	Validation	Test	Number of classes	Task type
EC	14,466	1,599	1,715	538	Multilabel
GO:BP	21,470	2,393	3,394	1,943	Multilabel
GO:CC	9,793	1,118	3,394	320	Multilabel
GO:MF	22,621	2,495	3,394	489	Multilabel
Subcellular localization	8,741	2,190	2,744	10	Multiclass
Binary localization	5,473	1,335	1,728	2	Binary
Thermostability	5,020	636	1,329	N/A	Regression
Binding residue categorization	890	102	286	3	Multilabel
Binding site prediction	8,231	2,389	5,182	2	Binary
Catalytic site prediction	2,856	603	1,165	2	Binary
Contact prediction	20,653	209	40	2	Binary
Variant effect prediction[1]	N/A	N/A	217	N/A	Regression
Human PPI prediction[2]	26,313	234	180	2	Binary

Table A.1: Dataset sizes (in proteins) and number of classes for each benchmarking task.

[1] This is a zero-shot task, hence the lack of training and validation data. Samples correspond to assays, covering 2.3M mutations.

[2] Samples correspond to *pairs* of proteins rather than individual proteins.

A.3 Substructure classification and tuning

For our substructure prediction modules, we use single hidden-layer MLPs where the dimensionality of the hidden layer matches that of the underlying base model. We extract residue-level embeddings from the final hidden layer of the base model, and use mean pooling across a substructure's constituent residues to construct a single embedding per substructure. When training with multiple categories of substructures, we use a separate prediction module for each category. The training loss is the sum of the classification losses across all categories.

We train using AdamW (Loshchilov & Hutter, 2019) ($\beta_1 = 0.9, \beta_2 = 0.999$), learning rates of 10^{-3} and dropout rate of 0.1 for the prediction heads, learning rate of 10^{-5} for the base model, and EWC weight of 400 (as used by original authors). Training proceeded until convergence of validation loss. All runs used batches of 32 proteins with a variable number of substructures per protein. All training was performed using `bfloat16` on one to four NVIDIA A100 GPUs.

Elastic weight consolidation. Briefly, EWC uses the diagonal of the Fisher information matrix $\mathcal{F}$ as weights on a loss that regularizes towards the original model parameters, θ_0:

$$L = L_c(\theta) + \sum_i \frac{\lambda}{2} F_i \left(\theta_i - \theta_{0_i}\right)^2$$

where L_c is the substructure classification loss. $\mathcal{F}$ can be estimated at the beginning of training as the squared gradients of the original loss with respect to the model parameters using the training set. In our case, the original loss corresponds to the training objective of the underlying model (*e.g.* masked amino acid prediction for ESM models, masked amino acid prediction in presence of structure tokens for ProSST or SaProt). In practice, the $\mathcal{F}$ is estimated by making a single pass over the training set, running backwards passes using the original loss, and averaging the squared gradients over minibatches.

While similar to a L_2 loss, EWC has two advantages over a simple L_2 or weight decay regularization: (1) weights are decayed towards the original weights of the base model, (2) per-parameter weights are applied which correspond to the importance of that parameter for the original task. We selected EWC due to its simplicity and ease of use, as the estimate of $\mathcal{F}$ can be calculated a single

time and used for the remainder of training or for other training runs using the same base model, as opposed to alternate methods like replay buffers. For more details, please refer to Kirkpatrick et al. (2017).

A.4 Downstream task training details

We use different head models for different scales of supervised downstream tasks:

- **Protein-level.** For protein-level tasks such as GO term prediction, we construct a protein-level representation for each protein following author's recommendations. For ESM-2, we use the final embedding of the `CLS` token as the protein-level embedding. For all other models, we mean pool the final hidden layer representations of all residue tokens (*i.e.* excluding `CLS`, `EOS` , and `PAD` tokens). Prediction heads are then single hidden-layer MLPs with hidden dimensionality matching the hidden dimension of the underlying model.
- **Residue-level.** For residue-level tasks such as binding site prediction, we use a head model consisting of a single 1-dimensional convolutional layer with zero-padding and filter width 5, followed by a nonlinearity and linear layer to the final output.
- **Protein-protein interaction.** For protein-protein interaction prediction, we extract protein-level embeddings as above, concatenate the embeddings for the two input proteins, and pass into a single hidden-layer MLP.
- **Contact prediction**. For contact prediction, we use the `EsmContactPredictionHead` from the `transformers` Python package, which trains a linear regression on top of attention weights from all attention heads in the underlying model.

To train the models, we used AdamW ($\beta_1 = 0.9, \beta_2 = 0.999$) with a learning rate of 10^{-2}, weight decay of 10^{-2}, dropout rate of 0.1, and a batch size of 32. Training proceeded for a maximum of 20 epochs, selecting the best model based on validation set performance. When performing full task-specific finetuning, we use a learning rate of 2×10^{-5} for the base model and scale the number of GPUs and gradient accumulation steps accordingly to maintain a batch size of 32. All training was performed using `bfloat16` on one to four NVIDIA A100 GPUs.

A.5 TASK-SPECIFIC FINETUNING

Model	EC	GO:BP	GO:CC	GO:MF	Localization (Accuracy)		Thermostability (Spearman's ρ)
	$F_{\max}$				Binary	Subcellular	
ESM2-150M	0.911	0.352	0.451	0.658	0.928	0.810	0.694
+ST	0.910	0.349	0.444	0.658	0.936	0.791	0.702
ESM2-650M	0.910	0.356	0.446	0.662	0.933	0.824	0.703
+ST	0.914	0.360	0.457	0.665	0.930	0.793	0.703
ESM-C 300M	0.916	0.368	0.470	0.667	0.932	0.806	0.693
+ST	0.920	0.355	0.454	0.669	0.941	0.804	0.693
ESM-C 600M	0.920	0.374	0.469	0.669	0.917	0.812	0.705
+ST	0.924	0.372	0.468	0.667	0.931	0.828	0.699
ProSST-2048	0.911	0.319	0.439	0.631	0.912	0.760	0.673
+ST	0.901	0.336	0.427	0.638	0.923	0.744	0.670

Table A.2: Evaluation task performance for models with and without substructure-tuning, and **full finetuning for the downstream task.** In this regime, we find that task-specific finetuning largely results in similar models, showing that imbuing substructural information via supervised finetuning may be brittle in the face of aggressive task-specific finetuning.