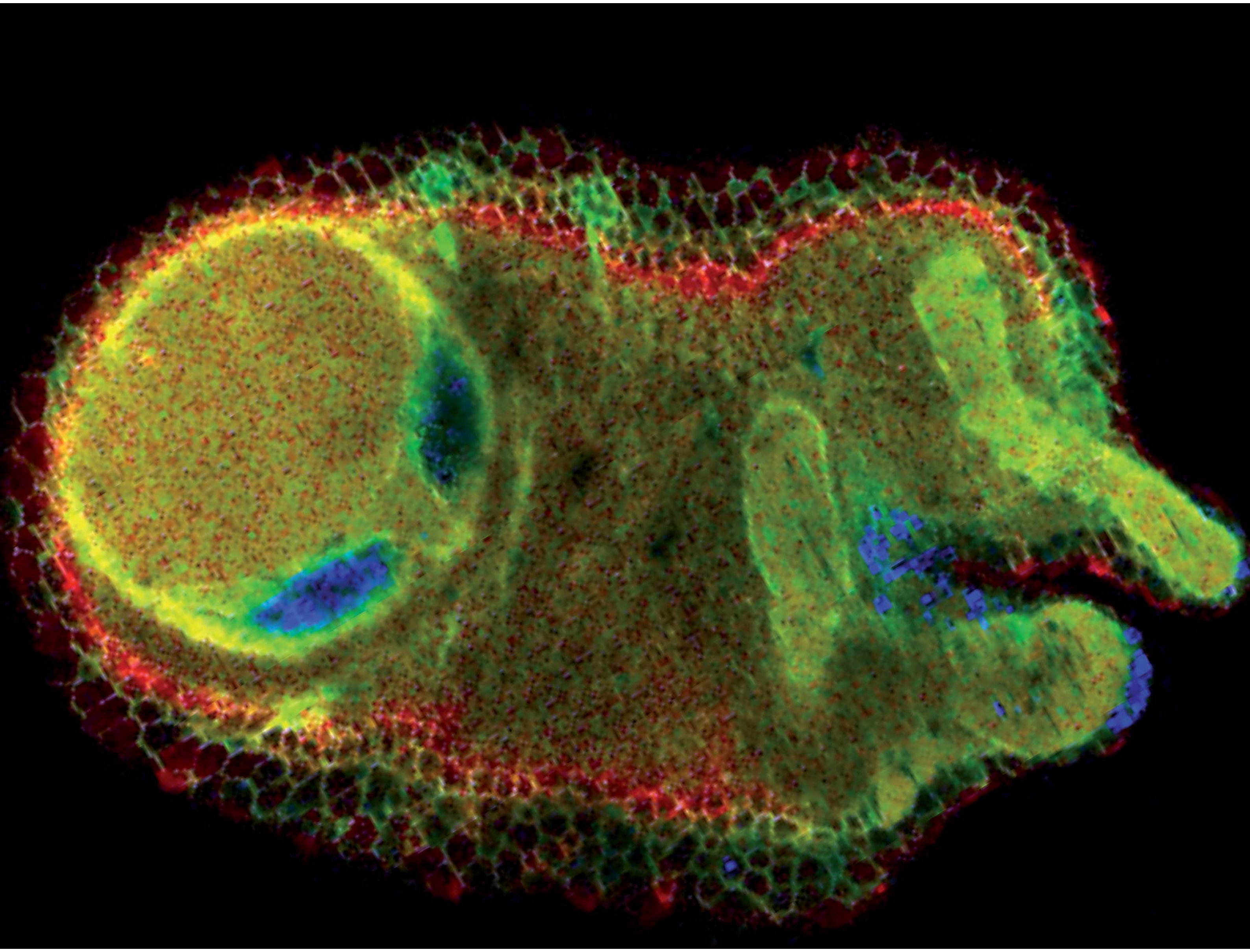
Digital Discovery

Volume 3
Number 2
February 2024
Pages 223-438

rsc.li/digitaldiscovery



ISSN 2635-098X

ROYAL SOCIETY
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PAPER
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Cite this: *Digital Discovery*, 2024, **3**, 249

Machine learning for hypothesis generation in biology and medicine: exploring the latent space of neuroscience and developmental bioelectricity

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Artificial intelligence is a powerful tool that could be deployed to accelerate the scientific enterprise. Here we address a major unmet need: use of existing scientific literature to generate novel hypotheses. We use a deep symmetry between the fields of neuroscience and developmental bioelectricity to evaluate a new tool, FieldSHIFT. FieldSHIFT is an in-context learning framework using a large language model to facilitate candidate scientific research from existing published studies, serving as a tool to generate hypotheses at scale. We release a new dataset for translating between the neuroscience and developmental bioelectricity domains and show how FieldSHIFT helps human scientists explore a latent space of papers that could exist, providing a rich field of suggested future research. We demonstrate the performance of FieldSHIFT for hypothesis generation relative to human-generated developmental biology research directions then test a key prediction of this model using bioinformatics, showing a surprising conservation of molecular mechanisms involved in cognitive behavior and developmental morphogenesis. By allowing scientists to rapidly explore symmetries and meta-parameters that exist in a corpus of scientific papers, we show how machine learning can potentiate human creativity and assist with one of the most interesting and crucial aspects of research: identifying insights from data and generating potential candidates for research agendas.

Received 17th September 2023
Accepted 2nd January 2024

DOI: 10.1039/d3dd00185g

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Introduction

The scientific enterprise depends critically not only on the skills needed to definitively test crisp hypotheses,[1–7] but also on the much less well-understood step of acquiring insights and fruitful research directions.[8,9] Many recent discussions[10,11] have focused on the fact that while modern "big data" methods are generating a deluge of facts and measurements, it is increasingly more important to be "building the edifice of science, in addition to throwing bricks into the yard".[12] In other words, it is essential that we develop strategies for deriving novel insights and deep hypotheses that cross traditional (in many cases, artificial) boundaries between disciplines. We must improve, at a pace that keeps up with technological and data science advances, our ability to identify symmetries (invariances) between sets of observations and approaches – to unify and simplify where possible by identifying large-scale patterns in research literature and thus motivate and enhance new research programs (Fig. 1).

One set of tools that is being rapidly developed and ubiquitously deployed originates in the advances of the field of artificial intelligence.[13–15] Machine learning is clearly poised to help science.[14,16–19] It is becoming widely recognized that "robot scientist" platforms can not only provide number crunching, automation, and high throughput, but could potentially also guide research by identifying what experiments to do next.[20–22] Machine learning tools have been suggested to be essential for progress in the bioinformatics of shape[23–26] (moving beyond molecular information to understand organ- and organism-level form and function), and developmental biology.[27,28] Not surprisingly, much emphasis is currently placed on improving the factuality of the output of AI tools; this parallels the well-developed notions of strong inference and hypothesis-testing in science: the well-established algorithm of falsifying and removing incorrect ideas. What is much less well-understood, but ultimately as crucial, is the process that provides a pool of interesting hypotheses from which to winnow until provisional truths are found. Our contribution attempts to bolster this second component of the scientific process – ideation – with a new AI-based tool for human scientists that provides input into the canonical scientific method.

Recent work in this field includes the AI-based discovery of testable models of regenerative anatomical regulation,[29] which were subsequently empirically validated,[30] and similar efforts in

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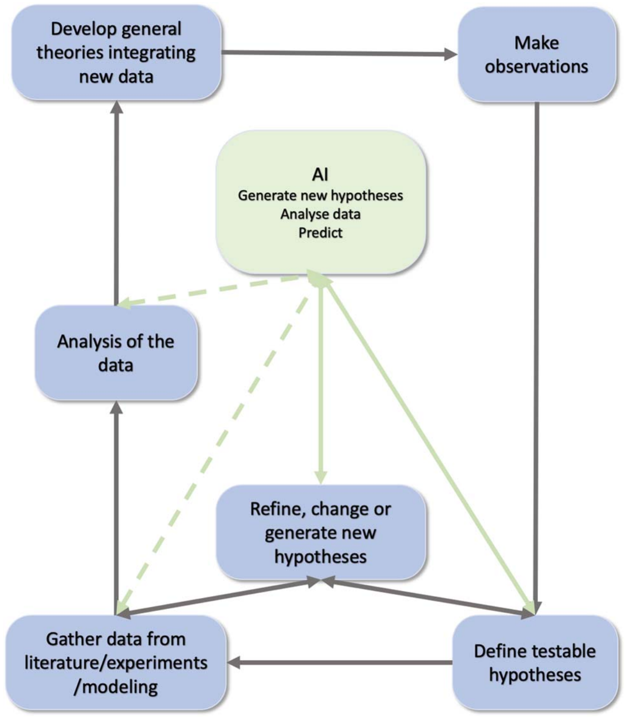

Fig. 1 The scientific discovery cycle and the role of AI within it. Black arrows describe the scientific cycle, green dotted arrow the links with AI and green plain arrows the ones we are interested in this paper. Modified after ref. 111.

genomics,[22] chemistry[31,32] and biomaterials.[33] One of the most potentially important current gaps is the paucity of tools for assisting with the most creative aspect of the work: identifying deep commonalities between disparate functional datasets, to enable generalized insight from the ever-growing literature. Tools are needed that would take meta-hypotheses of human scientists and mine the published studies for information that can be used to turn those conceptual hunches into actionable research programs.

One interdisciplinary area in which computer-assisted discovery would be most welcome is real-time physiology that controls form and function *in vivo*. How large-scale anatomy and behavior arises from the operation of molecular processes is a canonical systems biology problem.[34] It is currently handled by two distinct fields, with their own educational tracks, conferences, journals, funding bodies, and paradigms: neuroscience and developmental biology. Interestingly however, recent work has suggested that these may share an important underlying set of dynamics.[35–37] Neuroscience has long understood that behavior and cognition are driven by the physiological information processing by neural networks, which signal *via* electrical events at their membranes.[38–41] Likewise, a long history of classical work has suggested that bioelectric signaling of all kinds of cells is required as an instructive set of influences that help direct complex developmental and regenerative morphogenesis.[42–44] Interestingly, recent advances in the molecular understanding of developmental bioelectricity[45–47] has begun to blur the boundaries between those disciplines[48,49] (Fig. 2).

Specifically, it has been conjectured that the immense functional capabilities of brains have their origin in the more ancient, and slower, bioelectric networks that began operation at the emergence of bacterial biofilms[50–54] and were heavily exploited by evolution to orchestrate metazoan morphogenesis.[55,56] The idea that the same algorithms for scaling cellular activity into larger competencies (such as regulative morphogenesis and intelligent behavior) are used in the brain and in the body (Fig. 3) has many deep implications, for example with respect to porting methods from neuroscience and behavioral science into biomedicine,[35,57,58] to take advantage of neuroscience's successful paradigms for managing multi-scale causality and inferring effective interventions.

The proposed symmetry between cellular swarms using collective dynamics to solve problems in anatomical morphospace and in 3D classical behavioral space has been empirically tested in specific contexts,[34,47] and has significant implications for biomedicine and evolutionary biology.[59,60] However, there has been no way to derive these hypotheses at scale from the plethora of functional literature of neuroscience and developmental biophysics. Specifically, it has been claimed that the deep similarity between the role of bioelectric networks in control of body shape (cellular collectives' behavior) and cognition (organism-level behavior) enables one to readily read neuroscience papers as if they were developmental biology papers, by only pivoting problem spaces (from 3D space to anatomical morphospace) and time scales (from milliseconds to minutes).[49,56] However, there has never been an efficient way to implement this conjecture and actually explore the latent space of hypothetical papers that could provide candidate hypotheses and potentially fruitful research directions.

Here, we provide a first-generation tool, FieldSHIFT, that helps human scientists explore the mapping between developmental bioelectricity and neuroscience and begins the journey towards exploring the space of scientific studies far wider than what has already been written. FieldSHIFT is an in-context learning framework which uses a large language model to convert existing paper abstracts in neuroscience to the field of developmental biology, by appropriately replacing specific words and concepts. We show that this process generates useful, readable, insightful results that can be used to expand scientific intuition and identify testable hypotheses for novel work at the intersection of two fields. Furthermore, we test some of the resulting predictions using a bioinformatics approach, revealing a remarkable quantitative conservation of genes between developmental morphogenesis and cognitive behavior. The described system is a first step on the road to using AI tools as an imagination enhancing tool for research, deriving novel insights from expensive published experiments and letting scientists explore life-as-it-could be.[61] We tested one of the predictions of its output, finding a quantitatively significant enrichment in overlap between specific genes implicated in both cognitive processes and morphogenesis.

There have been a handful of related research efforts using generative AI for hypothesis generation and cross-domain knowledge discovery. One such approach is MechGPT, a large language model for identifying and probing analogous concepts

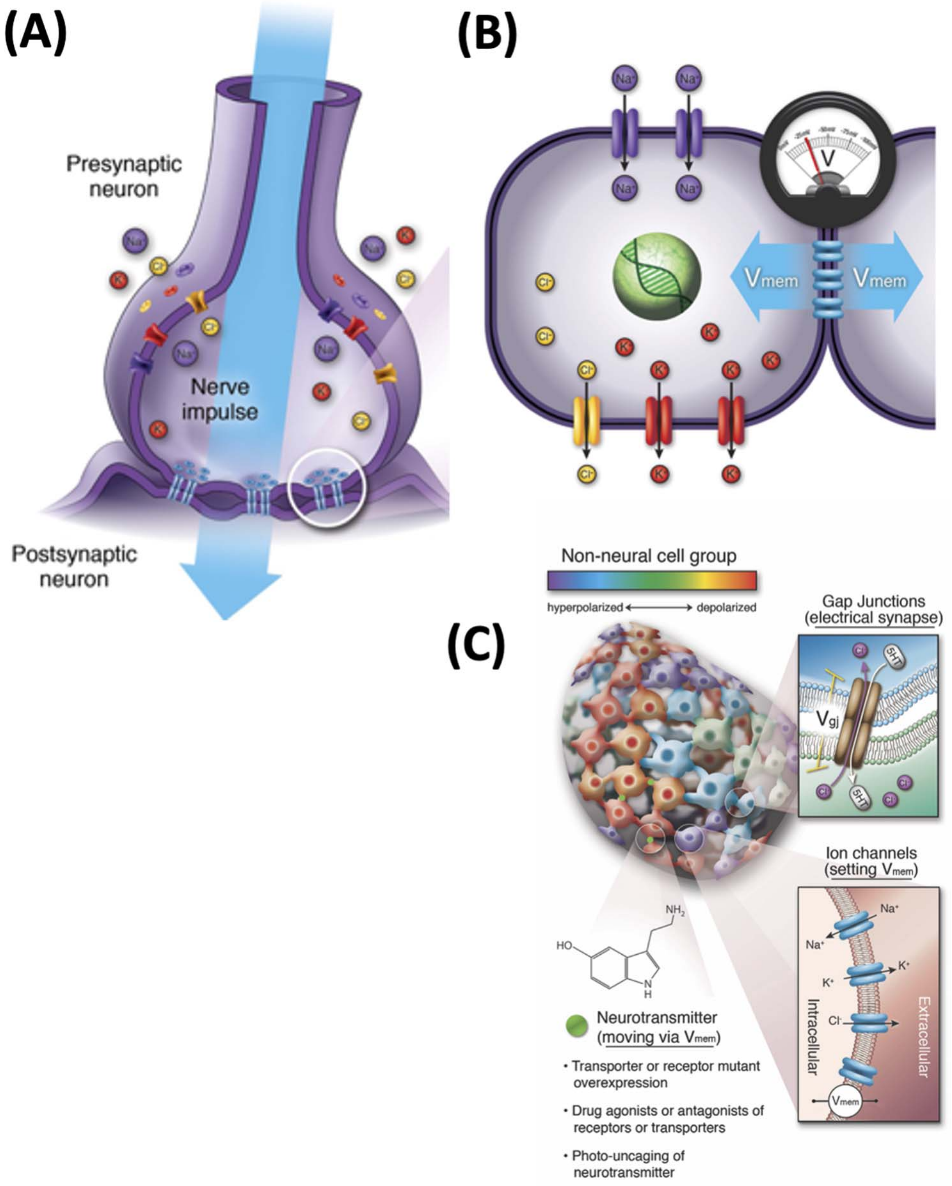

Fig. 2 Bioelectricity of the brain and body. (A) Neuronal signaling that underlies cognition and behavior is implemented by ion channels and gap junctions, which together set the voltage potential of cells and the propagation of these voltage states through neural networks. (B) All cells in the body have ion channels, and most have gap junctional connections to their neighbors, establishing a bioelectrical network outside the brain. (C) Numerous studies[45–47] have taken advantage of the isomorphism of function and mechanistic conservation between neurons and other cell types by exploiting classic tools of neuroscience in developmental biology outside the CNS. Specifically, analogs of synaptic plasticity (altering connectivity between cells by targeting gap junctions), intrinsic plasticity (directly modifying the voltage state of specific cells), and neurotransmitter signaling (which also takes place in non-neural tissues) have all been used. Optogenetics, ion channel mutations, and channel- and gap junction-modifying pharmacological agents have been used to induce specific changes in the processing of morphogenetic information. All images by Jeremy Guay of Peregrine Creative. (A) and (B) used with permission from ref. 36; (C) used with permission from ref. 57.

between scientific domains.[62] Other approaches have focused on knowledge discovery across scientific domains, such as[63] for translating between protein sequences and music note sequences with attention-based deep neural networks and[64] for identifying new designs within the field of mechanical engineering *via* cross-domain patent mining using knowledge graphs and natural language processing. Our method focuses uniquely on generating scientific hypotheses in the form of abstracts *via* text translations.

Methods

We propose FieldSHIFT: a framework for domain translation with modular components in the form of training data and an AI language model for mapping text from one domain to another. We constructed a dataset of neuroscience and developmental biology sentences and associated concepts to test FieldSHIFT with two AI language models. We used trained biologists to both build the dataset and evaluate the model

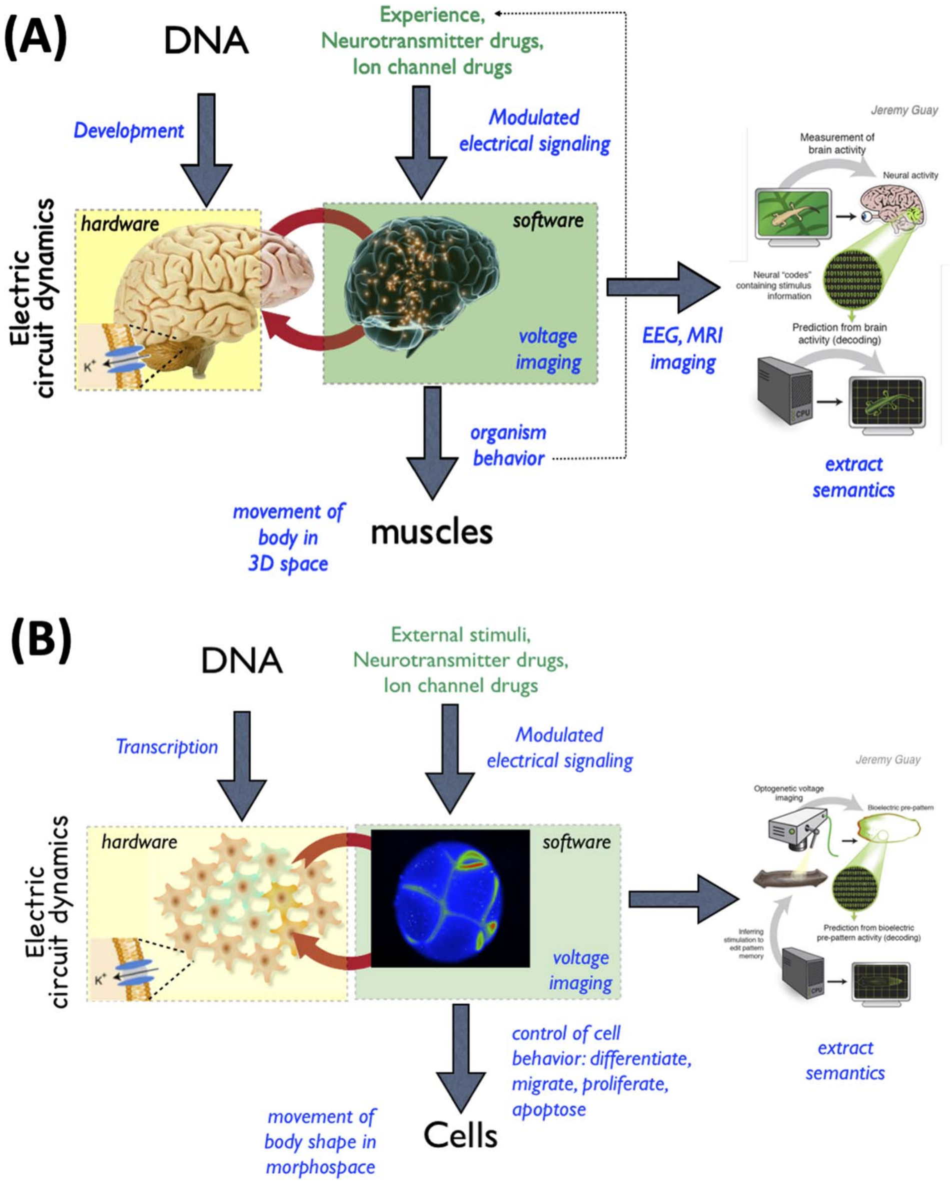

Fig. 3 Functional invariants between neuroscience and developmental biology. The fields of neuroscience and developmental biology are addressed by separate communities, journals, funding bodies, and educational programs. While many details across these domains differ, it is increasingly seen that many tools and concepts used in neuroscience carry over and can be successfully used in developmental biology settings. This is because of a shared evolutionary history and a deep symmetry of both hardware and physiology across these domains. (A) In the nervous system, behavior is implemented in 3-dimensional space by electrical networks that process information so as to control muscle cells. The interplay between the cellular hardware and physiological software is the subject of a field of neuroscience known as neural decoding,[112] where it is hoped that the cognitive content (memories, plans, preferences, *etc.*) of the 1st-person mind implemented by the electrophysiology can be read out by 3rd-person observers (scientists). (B) This same architecture was implemented by an evolutionarily more ancient system in which bioelectric networks in the body processed information so as to control the behavior of all cell types, moving the body configuration through morphospace (during development, regeneration, and remodeling).[55,56] As with the brain, developmental biologists have been attempting to decode these patterns and re-write them,[36,60] to be able to infer and modify the paths that cellular collective will take through morphospace. All images by Jeremy Guay of Peregrine Creative.

translations. While we focused on mapping neuroscience to developmental biology text, we believe a similar approach could be taken to apply FieldSHIFT to other domains.

Data

As an exercise with students and other researchers, the Levin Lab has been translating neuroscience to development biology, by hand, for several decades. They'd do this by changing concepts like "brain" to "body", "millisecond" to "minute", and "neuron" to "cell". We collected 70 such translation pairs. Using these concept pairs, we constructed translations varying from one sentence to abstract-length paragraphs by matching neuroscience passages with corresponding developmental biology passages. These passages include a variety of text from facts about these scientific domains to recently published abstracts from neuroscience and developmental biology articles. We collected 1437 translation samples in total. The average length of a sample input or output passage is 209 characters, and the standard deviation is 375. Below is an example pair pertaining to "brain" as the neuroscience concept and "body" as the developmental biology concept:

Neuroscience: "The brain is a complex system of neurons that are interconnected by synapses."

Developmental Biology: "The body is a complex system of cells that are interconnected by gap junctions."

In addition to translations, in some cases we added the same developmental biology abstract as both input and output examples. The goal was to teach a model trained on these examples not to change anything in the case that development biology text is provided as input. The six abstracts (corresponding to papers[65–70]) we used in this way were selected by choosing developmental biology papers produced by the Levin Lab. We published the full dataset on Hugging Face for re-use by the community: **https://huggingface.co/datasets/levinlab/neuroscience-to-dev-bio/tree/main**.

To train and test models for domain translation, we randomly split the dataset according to the neuroscience concepts associated with each sample. An effective domain translator should be able to generalize beyond the concepts it sees during training, demonstrating general knowledge of both domains and an ability to both identify new concepts within the input domain and an ability to map those concepts to corresponding concepts in the output domain. As such, we split the concepts into 43 training, 6 validation, and 21 test concepts without overlap *via* random sampling. After splitting concepts, we split the passages associated with these concepts into 503 train, 50 validation, and 57 test passages by searching for each concept name within the passage (after normalizing the text by stripping punctuation, lowercasing, and ignoring extra white-space characters). Because some concepts mapped to more passages, we repeated the process until we achieved close to this desired ratio of train, validation, and test samples (roughly 10× the number of train samples as validation and test) without looking at the resulting data until settling on a desirable ratio.

Domain translation with machine learning

We implemented and tested two domain translation approaches for research paper abstracts using pretrained language models to identify a suitable backend model for FieldSHIFT. The first is inspired by neural machine translation (NMT) and abstractive summarization and uses the open-source BART[71] pretrained Transformer language model (LM).[72] The pretrained BART model is designed for summarizing text. Rather than have the model generate a summary of an input sample, we fine-tuned it to map neuroscience text to developmental biology text using the domain translation dataset. The second model we implemented uses in-context learning[73] to prompt the GPT-4 (ref. 74) large language model (LLM) to complete the task of translating neuroscience text into developmental biology text. We used human evaluation from trained biologists to test the effectiveness of these approaches by having each model generate translations and counting successful ones according to expert judgement. For more details on the testing procedure, see the model validation section.

Transformer LMs, and recently, LLMs, which demonstrate emergent capabilities when scaled to billions of parameters,[75] are highly expressive deep neural networks used to represent sequences, especially text data, and have achieved state-of-the-art performance on a variety of natural language tasks.[76–78] LMs are typically pretrained to learn general representations of text from large, unannotated corpora, then fine-tuned for specific, downstream natural language tasks. Both NMT and summarization involve the task of text generation, conditioning on an input text sequence to generate an output text sequence. We exploit this symmetry in our first domain translation approach using BART by continuing to fine-tune an encoder–decoder LM[72] already trained for summarization. This neural architecture embeds discrete textual characters from an input sequence in a vector space. It then generates an encoded representation of the text in a hidden, latent space in a manner that captures word order (encoder layer). Next, it decodes the latent space, conditioning on previously generated words and the encoder hidden state (decoder layer). Finally, it predicts the next word in the output sequence using the decoder output. Greedily predicting the most likely word at each step is unlikely to generate the best overall output sentence, while selecting the most likely output sentence in its entirety is computationally infeasible. As such, we used Beam Search[79] to select the top-k most likely output words given an input sentence and encoder–decoder model parameters.

We continued fine-tuning the pretrained BART LM[71] first fine-tuned as an abstractive summarizer (and available *via* Hugging Face transformers[80]) for domain translation by feeding the summarizer text pairs specific to our translation task. We selected the BART LM for its pretraining procedure designed for text generation, its performance on summarization benchmarks, and its public availability. A key advantage of the BART architecture is the way it combines ideas from other popular and effective Transformer neural networks, specifically bidirectional encoding *via* corruption of input text as in [77] and autoregressive decoding as in the GPT family of models.[81]

Recent decoder-only GPT models such as GPT-3,[81] InstructGPT,[82] and GPT-4 have proven even more powerful than encoder–decoder models when scaled to billions of parameters and trained on sufficiently large corpora.[83] Furthermore, Instruction Fine-Tuning and Reinforcement Learning with Human Feedback[82] have led to human-like, and in some cases, beyond human-level performance on text generation tasks with decoder-only LLMs. The key idea of these models is to frame all downstream tasks as text generation with no intermediate encoding step and align the outputs from the model to human expectations using Reinforcement Learning to reward the model for generating desirable text. Once such a model has been pretrained and instruction fine-tuned, given some starting input, such as a request or a series of patterns, the LLM can generate text which fulfills the request or completes the pattern in a stunningly human-like fashion. We selected and used the GPT-4 LLM based on its superior performance to other LLMs.[74]

Model training

Here we describe the core ideas and training procedures for the two domain translation models we used within FieldSHIFT: fine-tuned BART and GPT-4.

The core idea of the BART-based domain translator is to learn a mapping from one text domain to another. This learning process is illustrated in the top section of Fig. 4. The process for generating new developmental biology text using the trained model is illustrated in the bottom section. During continued fine-tuning of the BART model, we fed two types of text pairs which we call positive and negative samples. Positive samples are neuroscience abstracts/sentences we want to translate into developmental biology abstracts/sentences, and negative samples are developmental biology abstracts/sentences which should remain untouched. This teaches the model to leave existing developmental biology texts as they are. An additional benefit of this strategy is that the model sees more examples of developmental biology text during continued fine-tuning, which comes "for free" as no human-time is required to generate these negative pairs. We sourced both from the domain translation dataset described above.

We used Beam Search with $k = 5$ beams to generate the next output token from the predicted probabilities of each token given by the decoder at each decoding step. We used the final predicted text sequence and the encoded ground truth text consisting of either the same developmental biology abstract as was provided as input text (for negative samples) or the corresponding output developmental biology text from a human-generated pair (for positive samples) to compute cross-entropy loss, then updated the weights of the BART encoder–decoder over many epochs of training using the AdamW optimizer[84] with a learning rate of 0.00005, weight decay of 0.01, batch size per device of 1, and 128 gradient accumulation steps. We selected the final model according to cross-entropy loss on the validation

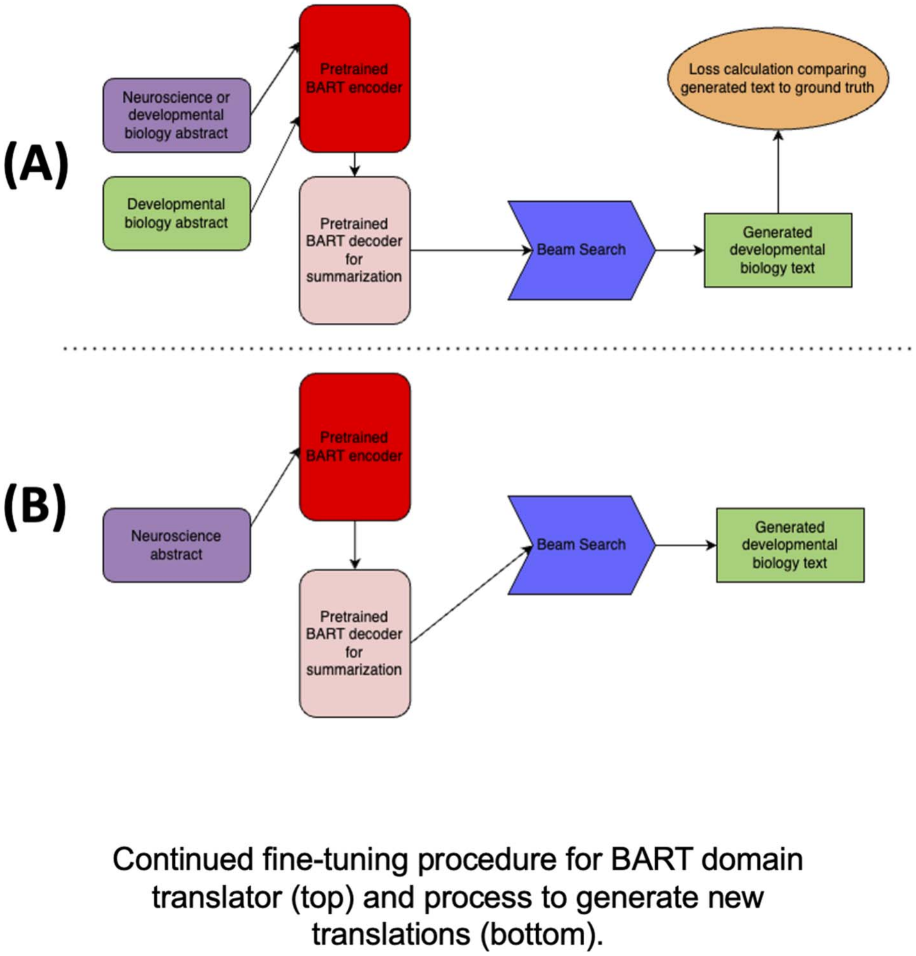

Fig. 4 BART-based domain translator. (A) Neuroscience abstracts are encoded in purple, though in training, sometimes the model sees the developmental biology abstract as both the input and output. For most of the samples, a neuroscience abstract and corresponding developmental biology abstract (green) are provided as input during training. Text is generated using Beam Search (blue), and loss is computed (orange) by comparing the generated developmental biology text to the ground truth developmental biology text. The BART model consists of an encoder (red) and decoder (pink). We start with a BART model fine-tuned for summarization and continue fine-tuning the model to output developmental biology text like the input examples. (B) During inference (bottom), the model receives only a neuroscience abstract and produces a translation in the form of a corresponding developmental biology abstract.

set after 8 epochs of no improvement. The 503 training, 50 validation, and 57 test examples generated *via* our neuroscience concept split were used to train, validate, and test the model.

The core idea of the GPT-4-based domain translator is also to learn mappings from neuroscience to developmental biology text. It does this *via* text generation and in-context learning as shown in Fig. 5. When prompting the model, we provided translation example concept mappings such as those listed below. The full set of concepts was sourced from our domain translation dataset.

- *Neuron > Cell*
- *Neural > Cellular*
- *Behavior > Morphogenesis*

To use the GPT-4 LLM as a domain-translator, we provided in-context examples and asked the LLM to complete the pattern. We did not update the weights of GPT-4, rather we simply ran inference using training examples within the prompt. We sampled these in-context examples from the train concepts of our domain translation dataset and validated the pattern completions on abstracts corresponding to test concepts. In this way, we measured whether GPT-4 can generalize and translate new concepts not seen among the in-context examples. We hypothesized that the very large pretraining set (much of the text on the internet) used to build GPT-4 contains many neuroscience and developmental biology concepts, and thus, the model is able to use information stored within its layers pertaining to these concepts in order to both identify new concepts from the same domain, *i.e.*, a neuroscience concept in the test set but not in the train set, and map these concepts to developmental biology concepts not provided as sample outputs in the in-context examples.

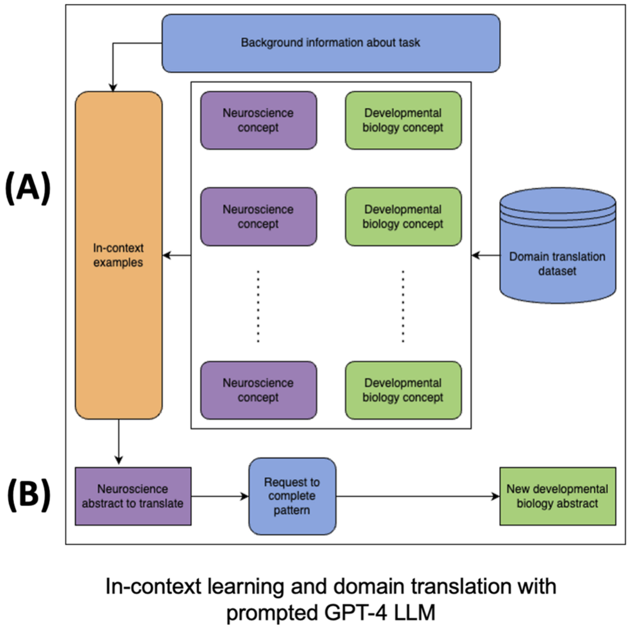

Fig. 5 GPT-4-based domain translator. (A) Neuroscience concepts (purple) are paired with corresponding developmental biology concepts (green) and provided in the GPT-4 prompt (blue). The prompt consists of this set of in-context examples as data (orange), user-provided background information on the task of domain translation (blue) and a user-provided request to complete the pattern (blue). The example concepts provided as data in the prompt are sourced from our domain translation dataset, while the user-provided instructions are described in the methods section. (B) The GPT-4 domain translator completes the pattern according to the user-provided instructions for a new neuroscience abstract (purple), generating a translation in the form of a new developmental biology abstract (green).

The following illustrates how we tested GPT-4. It includes a very simple way to prompt GPT-4 to translate from neuroscience to developmental biology. It consists of our prompts and GPT responses.

Prompt

You are a translator—you translate neuroscience to developmental biology. There are deep symmetries between these fields and we want to use them to create new hypotheses in developmental biology.

The output should read as developmental biology, meaning that any neuroscience concept, such as "hippocampus", should be translated into the most relevant/related developmental biology term.

Make sure the translation makes sense as developmental biology text and is using real terms that exist in developmental biology literature.

Make sure the translation doesn't include any neuroscience words, such as a part of the brain. Do the best you can to find the most relevant translation.

For example, here are some terms and their translations:
Neuron > Cell
Neural > Cellular
Behavior > Morphogenesis
Millisecond > Minute
Msec > Min
… (link to full prompt below dialogue)

And here's some training data. The "prompt" is the neuroscience and "completion" is the developmental biology.

idx,prompt,completion

156,Live 3D Brain Function Mapping,Live 3D Body Function Mapping

397,How many neuroscientists are there in the world that specialize in human behavior?,How many developmental biologists are there in the world that specialize in human morphogenesis?

… (link to full prompt below dialogue)

Are you ready to translate neuroscience into developmental biology?

Typical GPT response

Yes, I am ready to translate neuroscience into developmental biology. Please provide the text or concepts you would like to translate, and I will do my best to provide a relevant and accurate translation in the field of developmental biology.

Prompt

(Developmental biology text here)

GPT response

(Translation)

Link to full prompt: **https://github.com/listenaddress/domain-translator/blob/main/prompt.txt/**.

Link to full dataset from which the examples in the prompt were selected: **https://huggingface.co/datasets/levinlab/neuroscience-to-dev-bio/tree/main**.

We also tested a version of the GPT-4-based domain translator with chain-of-thought prompting and self-critique.[85] This approach takes advantage of the chatbot interface available for GPT-4 and asks questions *via* multiple prompts to arrive at a final translation. We employ self-critique, asking the model to revise its initial translation, to arrive at a final translation from neuroscience to developmental biology text. In the results section, we refer to this variation of the GPT-4 domain translator as GPT-4 with self-critique.

We used the ChatGPT interface for GPT-4 provided by OpenAI with the March 23, 2023, API version. We used the default temperature of 0.7 when generating translations. Note that we used language like "are you ready to translate…" because of OpenAI and Microsoft documentation suggesting that the GPT-4 model is more effective when used in a role-playing fashion, encouraging and preparing the model like one might a human before a test.

Model validation

For each test concept in our domain translation dataset, we searched the term and chose the first abstract that included the term. Specifically, we collected one paper per test concept and selected samples using the following structure in a Google Scholar query: "⟨research domain⟩" "⟨specific topic⟩". For example, to find a paper on neurodegeneration to test, this was our search: "neuroscience" "neurodegeneration". We then selected the first result. There were five test phrases, such as "Control of anatomy by bioelectric signaling", "Change of ion channel expression" and "Axonal-dendritic chemical synapses" that didn't yield any exact matches. For those we did a follow up search for the closest matches with a query like this: "neuroscience" "Axonal-dendritic chemical synapses". We then selected the first result.

To judge the quality of the translations we had two professional cell/developmental biologists grade the text. Both annotators graded real developmental biology abstracts and GPT-4 generated abstracts using the self-critique version of the domain translator. Only one annotator graded BART-generated abstracts following initial results suggesting superiority of the GPT-4 approach. When comparing abstracts, the annotators were given the following instructions:

For each abstract you'll consider the following: does this abstract seem interesting, offering a way to think about an aspect of developmental biology or new ideas that could be investigated? The grade can either be a 1 (yes) or a 0 (no).

To sample developmental biology abstracts, we used the same concept-based search approach described above, *e.g.*, searching for "developmental biology" "cellular". The goal was to provide a baseline understanding of how often developmental biology abstracts are seen as interesting/valuable directions of study. All abstracts were provided without specifying their origin. That is, the annotators did not know which methods generated each abstract they were grading. We report the count of 1 s and 0 s for each method in the results section and *P*-values for these counts using two-sample *T*-tests to compare sample proportions.

Bioinformatics

We extracted the whole set of the unique genes related to gene ontologies 'Developmental process' (GO:0032502) and 'Behavior' (GO:0007610) in humans, *Drosophila*, the zebrafish (*Danio rerio*), and the mice (*Mus musculus*) using Ensembl database and computed the percentage of genes of 'Behavior' included in the set of genes annotated as 'Developmental process'.[86,87] As a control, we also computed the overlap between all the pairs of gene ontologies that are the children at level one of the gene ontology 'Biological process' (GO:0008150) as a control for each organism, or in other words all the gene ontologies at the same level of 'Developmental process'. We removed from the set of combinations the gene ontologies that should not be used for annotation of genes (as defined on the Gene ontology website); the removal includes: 'Regulation of biological processes' (GO:0050789), 'Negative regulation of biological process' (GO:0048519), 'Positive regulation of biological process' (GO:0048518), 'Biological regulation' (GO:0065007), 'Response to stimulus' (GO:0050896), 'Cellular process' (GO:0009987), 'Multicellular organismal process' (GO:0032501), 'Metabolic process' (GO:0008152), 'Growth' (GO:0040007), 'Biological process involved in intraspecies interaction between organisms' (GO:0051703), and 'Biological process involved in intraspecies interaction between organisms' (GO:0044419). We applied a one-sample *T*-test to compare the distribution of genetic overlap between all pairs of gene ontologies we extracted and the genetic overlap between 'Developmental process' and 'Behavior' sets of genes. The code for retrieving and analyzing the data can be found at: **https://github.com/LPioL/DevCog_GeneticOverlap**.

Results

Comparing domain translators

A quantitative evaluation of domain translation methods *via* human annotation suggests the effectiveness of ML-based domain translation. According to both annotators (annotator 1 and 2), the GPT-4-based domain translator with self-critique generated good translations according to the annotation criteria for over half of the neuroscience abstracts provided. The GPT-4 approach performed significantly better than the BART approach ($P = 0.017$) according to annotator 1 who compared ML methods. Both annotators graded more real abstracts as good than ML-generated abstracts, however, this difference was significant only for annotator 1 (Tables 1 and 2).

While there were more false positives when generating abstracts with ML, the approach is far more scalable than humans writing abstracts. The GPT-4-based domain translator

Table 1 Annotator 1 results with two-sample *T* tests to compare methods

Model	Count of good translations (out of 36)	Proportion of good translations	Comparison to real abstracts: *P*-value	Comparison to BART: *P*-value	Comparison to GPT-4 with self-critique: *P*-value
BART	11	0.306	<0.001	1.000	0.017
GPT-4 with self-critique	21	0.583	0.001	0.017	1.000
Real	33	0.917	1.000	<0.001	0.001

performed best of the two ML approaches tested and can output a new abstract in about five seconds. Compared to human-written abstracts, generalizing from our results, the chance of producing a good abstract is reduced by about 39%. We compute this as $1 - 20/33$ where we average the 21 and 19 good translations from GPT-4 from each annotator. However, assuming these abstracts can be quickly verified and that they are sometimes very interesting and very different from humans in their content, we believe this is an incredibly useful system, enabling the generation of thousands of scientific hypotheses within a single day.

Compute budget and limited human oversight (involving less work than writing abstracts) become the main constraints on hypothesis generation using this ML-based approach to domain translation. Additional constraints may include the diversity of input papers and an upper bound on the total number of symmetries between domains of which GPT-4 is aware. While these claims warrant further research and our results represent initial findings, the value of ML-based domain translation is promising given the inherent ability to scale.

The inter-annotator agreement for the combined set of GPT-4 with self-critique and real abstracts was 0.639 with Cohen's Kappa 0.235. The low Cohen's Kappa indicates the subjectivity of this exercise, even when grading real developmental biology abstracts. Future work may look to increase the number of annotators or annotations for comparing domain translation methods (Table 3).

We found no difference between GPT-4 and GPT-4 with self-critique according to an evaluation from the first annotator. It's possible future work on the series of prompts used for self-critique could improve model performance. We leave this as future work.

Examples of abstracts generated

Examining some specific cases, BART and GPT performed the best when translating words in or near the space of words they'd seen before. Specific neuroscience terms that often don't have clear translations such as "trigeminal autonomic cephalalgias" would often be erroneously translated or not translated at all. One of the most interesting translations was the following:

Input: The brain forms cognitive maps of relational knowledge—an organizing principle thought to underlie our ability to generalize and make inferences. However, how can a relevant map be selected in situations where a stimulus is embedded in multiple relational structures? Here, we find that both spatial and predictive cognitive maps influence generalization in a choice task, where spatial location determines reward magnitude. Mirroring behavior, the hippocampus not only builds a map of spatial relationships but also encodes the experienced transition structure. As the task progresses, participants' choices become more influenced by spatial relationships, reflected in a strengthening of the spatial map and a weakening of the predictive map. This change is driven by the orbitofrontal cortex, which represents the degree to which an outcome is consistent with the spatial rather than the predictive map and updates hippocampal representations accordingly. Taken together, this demonstrates how hippocampal cognitive maps are used and updated flexibly for inference.

GPT-4: Morphogenetic gradients are an organizing principle thought to underlie the ability to direct and coordinate cellular behaviors during development. However, how can a relevant gradient be selected in situations where a stimulus influences multiple spatial structures? Here, we find that both spatial and predictive morphogenetic gradients govern the coordination of cell differentiation and tissue organization, with spatial location determining cell fate. Mirroring morphogenesis, the organizer region not only establishes a gradient of spatial relationships but also encodes the transition structure experienced during development. As development progresses, cellular behaviors become more influenced by spatial relationships, reflected in a strengthening of the spatial gradient and a weakening of the predictive gradient. This change is driven by the signaling center, which represents the degree to which a morphogenetic event is consistent with the spatial rather than the predictive gradient and updates organizer region representations accordingly. Taken together, this demonstrates how morphogenetic gradients in the organizer region are used and updated flexibly for directing cellular behaviors during development.

Table 2 Annotator 2 results with two-sample *T* tests to compare methods (no statistically significant difference between methods)

Model	Count of good translations (out of 36)	Proportion of good translations	Comparison to real abstracts: *P*-value	Comparison to GPT-4 with self-critique: *P*-value
GPT-4 with self-critique	19	0.528	0.641	1.000
Real	21	0.583	1.000	0.641

Table 3 Annotator 1 GPT-4 method comparison (no meaningful difference observed)

Agent	Count of good translations (out of 36)	Proportion of good translations
GPT-4	21	0.583
GPT-4 with self-critique	21	0.583

This is a very interesting translation, because it suggests the use of a predictive coding model (a *predictive gradient*) to understand progressive morphogenesis.[88,89] This is testable, as biophysical or biochemical representations of cell expectations (homeostatic setpoints, in the sense of priors[90–96]) can be looked for experimentally.

To illustrate the abilities and struggles of the two domain translation models, below are three translation examples, from easy to difficult. Both approaches correctly translated the first, only GPT-4 correctly translated the second, and neither correctly translated the third.

"Neurogeneration" test – easy

Input: In parallel to recent developments of genetic techniques, understanding of the syndromes of neurodegeneration with brain iron accumulation has grown considerably…
GPT-4: In parallel to recent developments of genetic techniques, understanding of the syndromes of cellular degeneration with tissue iron accumulation has grown considerably…
BART: In parallel to recent developments of genetic techniques, understanding of the syndromes of cellular degeneration with tissue iron accumulation has grown considerably…

"Nervous system" test – medium

Input: We tested the hypothesis that the nervous system, and the cortex in particular, is a critical determinant of muscle strength/weakness…
GPT-4: We tested the hypothesis that the cellular system, and the tissue organization in particular, is a critical determinant of cell behavior regulation…
BART: We tested the hypothesis that the nervous system, and the cortex in particular, is a critical determinant of muscle strength/weakness…

"Autonomic reflexes" test – hard

Input: The trigeminal autonomic reflex is a physiologic reflex that plays a crucial role in primary headache and particularly in trigeminal autonomic cephalalgias…
GPT-4: The trigeminal autonomic reflex is a physiological reflex that plays a crucial role in primary tissue growth and particularly in trigeminal-autonomic tissue formation…
BART: The trigeminal autonomic reflex is a physiologic reflex that plays a crucial role in primary headache and particularly in remodeling of the epithelium and particularly tissues…

The examples above show BART and GPT-4 have an easier time translating words they've seen in the training data than esoteric neuroscience words they haven't seen. They also show the kinds of translations that set GPT-4 apart in our experiments. For example, in the medium case, GPT-4 translated "cortex" into "tissue organization", while our BART model didn't recognize "cortex" as a neuroscience word and attempt to translate it.

Hypothesis testing: molecular conservation between cognition and morphogenesis

One clear hypothesis that can be generated by FieldSHIFT is that the *molecular mechanisms* behind developmental bioelectricity and that of cognitive/behavioral phenomena should be conserved. That is, the same genes should be found as implicated in both roles; this is novel because only the idea of "morphogenesis as behavior in anatomical space"[37,56] predicts any association between genes across what are normally thought of as two very distinct fields of biology. Interestingly, GPT (August 3rd version of GPT-4) itself generated this hypothesis after doing all the translations and being asked to come up with a new idea as follows:

Input: (Base input as described above) You are a translator—you translate neuroscience to developmental biology…

Input: Let's start by generating a hypothesis based on everything you know about developmental biology and genetics; instead of making a translation, generate a novel and testable hypothesis about the genes involved in learning and morphogenesis.

Reply: There exists a set of evolutionarily conserved genes that are activated both during early morphogenetic processes and later in the organism's life during learning and memory formation. These genes mediate cellular plasticity mechanisms, which are vital for both the formation of complex body structures during embryonic development and the flexibility and adaptability of mature organisms to new environmental stimuli.

Thus, we next decided to test this prediction using bioinformatics, focusing for the purposes of this study on the genes thought to underlie phenomena in behavioral science and developmental biology.

We computed the genetic overlap between the set of genes annotated as 'Behaviour' and the set of genes annotated as 'Developmental process' in different species widely dispersed within the phylogenetic tree including *Drosophila*, zebrafish, mice and homo sapiens. We found that 74.1% of the 'Behavior' genes (649 genes) are included in the 'Developmental process' set of genes (6486 genes). From *Drosophila* to humans, this genetic overlap is increasing: 46.5% for *Drosophila*, 60.6% for the zebrafish, 73.8% for the mouse and 74.1% for humans (see Fig. 6A and B). We applied a one-sample *T*-test to compare the distribution of genetic overlap between all pairs of gene ontologies we extracted and the genetic overlap between

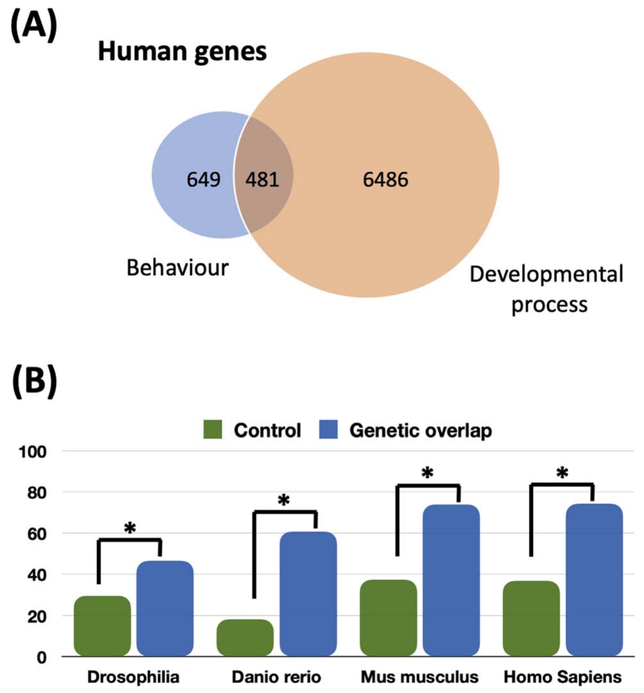

Fig. 6 Bioinformatic tests of the system's predictions. (A) Overlap between the human genes annotated as 'Behavior' (GO:0032502) and the set of genes annotated as 'Developmental process' (GO:0007610). 74.1% of the 'Behavior' genes are included in the set of genes annotated as 'Developmental process'. (B) Overlap between the set of the unique genes related to gene ontologies 'Developmental process' (GO:0032502) and 'Behavior' (GO:0007610) in fruit fly (*Drosophila melanogaster*), the zebrafish (*Danio rerio*), and the mice (*Mus musculus*) and humans (*Homo sapiens*) using Ensembl database. The control represents the mean of the distribution of all overlaps at level 1 of the children of 'Biological process' (GO:0008150). The star represents a statistical significance on a one sample t-test (p-value < 0.05).

'Developmental process' and 'Behavior' sets of genes for each organism. Statistical analysis of overlap among all pairs of gene ontologies (at the same level of 'Developmental process') for these four organisms is significantly smaller ($p < 0.05$) than the overlap we observed among the predictive categories of development and behavior. Thus, we conclude that during evolution there is an increase of the genetic overlap between 'Behavior' and 'Developmental process'. In other words, genes used for development and morphogenesis have been co-opted for cognition. The mapping between behavior and development/morphogenesis can also be seen at the genetic level.

Discussion

Machine learning for domain translation

We proposed FieldSHIFT, a framework for domain translation. To implement FieldSHIFT, we built a domain translation dataset and compared two ML approaches for domain translation using this data and expert evaluation of the translations. Expert evaluation identified that the GPT-4-based approach produced good translations, leading to a useful hypothesis or insight about developmental biology, in about 20 out of every 33 tries. This suggests that new hypotheses in developmental biology can be produced at scale in an automated fashion, using humans to review and extend the initial ideas. We found that curating a high-quality dataset and designing prompts was the bulk of the work for making the system effectively translate between domains.

While the GPT-4-based approach which used in-context learning performed better than the BART-based approach, the recent public release of open-source LLMs such as Llama 2 [97] and Falcon[98] present opportunities to perform domain translation by fine-tuning on arbitrarily many examples of translated text. BART is an early LM for text generation, though its size makes it a cost-effective choice compared to fine-tuning a large, open-source LLM. Still, because the exact implementation of the GPT-4 LLM is not publicly disclosed, and because fine-tuning can provide greater control and performance on specific tasks than in-context learning, future efforts should consider the use of open LLM architectures for domain translation. We note also that multimodal strategies for training and applying LLMs to a mix of image and text data could be valuable for domain translation. In addition to example abstracts or articles, researchers could include images or videos pertaining to experiments or experimental findings as input to a system like FieldSHIFT, or a domain translator could output images or video clips in addition to text as literal visions of scientific hypothesis and their potential outcomes.

Bioelectricity: conserved mechanisms and algorithms between control of body and behavior

It has been previously hypothesized that the *algorithms* of behavior (active inference, perceptual control, collective decision-making, memory and learning, navigation of problem spaces, preferences, pursuit of goal states with degrees of flexible response, *etc.*) are used to direct morphogenesis and may even derive from it evolutionarily.[55,56,99] Here, we produce a tool that can be used to explore the symmetries and commonalities between these two fields, and in fact any other two fields. By translating abstracts of papers from one set of vocabulary into another, we generate new ways to think about data and potential new hypotheses. We show here that this works in the case of the parallels between behavioral science and the science of morphogenesis, and generated a specific new hypothesis: not only the algorithms, but the *molecular mechanisms* (genes) are also conserved. While empirical (functional) testing will be needed to conclusively test this idea, we performed bioinformatics experiments that generated new data supporting the hypothesis: implications of the same genes between the topics of morphogenesis and cognition occurs at a frequency much greater than between other random categories of genes. This finding thus suggests a number of genes and their products to be tested in novel morphogenetic assays using genetic and pharmacological tools. This work is currently under way in our lab.

Latent space of scientific papers

We believe that this work is just the beginning of the AI-guided exploration of the latent space around scientific papers, in the sense of the "adjacent possible".[100,101] Each real scientific paper in the literature provides access to an associated set of possible papers in which one or more aspects are changed – in effect, exploring various symmetries of concepts in specific problem spaces. These papers are not meant to be taken literally, since they do not provide real-world data, but instead as tools to spur creativity, provide testable novel hypotheses, suggest studies to be carried out, and perhaps most importantly, by reflecting approaches from specific studies into different disciplines, dissolve barriers between fields and knowledge silos. These "virtual" papers are not published in scientific journals (which should be reserved for studies that have actually been carried out), but are accessible *via* machine learning and represent another useful repository (whose goal is to advance creativity and novel thinking – a second-order function complementing first order traditional papers containing specific knowledge and data). While it is essential for the scientific literature to be clearly demarcated as to whether a study was actually done or is only hypothetical, we believe that maintaining artificial barriers between the creative ideation and hypothesis testing phases of science is counterproductive. An early example of this realization came from the James V. McConnell (discoverer of the ability of memories to move through tissues[102,103]), who edited a journal called *The Journal of Biological Psychology* which contained peer-reviewed primary papers in one half of each issue, while the second half (printed upside-down) contained perspectives, drawings, poetry, *etc.*

Limitations of the study and next steps

One limitation of the study is the number of papers we were able to manually curate; the machine learning will improve as more papers are added in the future. Especially with the rapid development in large language models, we can expect significant improvements in the quality of output in the future. While a number of ways exist in which machine learning may disrupt current scientific structures,[104] the platform described herein can be safely utilized to generate candidate research programs, as long as it is clearly kept in mind that the system we describe is not claimed to generate truths by analysis of existing data; it is a system for generating novel hypotheses that must be empirically tested.

While the current evaluation is based on human assessments of the quality of translations between the fields of neuroscience and developmental biology, we acknowledge that experimental validation of generated hypotheses would be necessary to fully realize the power of our method. That is, a complete evaluation of FieldSHIFT would require conducting experiments to address hypotheses from our domain translator and assessing the value of the findings relative to human-generated experimental directions. Not only the findings of the experiments but also the methods, complexity, and feasibility of testing FieldSHIFT-generated hypotheses should be compared to human-directed research. Work of this kind is already underway at the Levin Lab, and we look forward to sharing these results in future work.

Conclusion

The increased overlap we observed between genes implicated in morphogenesis and behavior has a number of implications for experimental work on the evolution and biomedical targeting of many of those genes. More broadly, our approach has identified a method for generating testable hypotheses in the space of developmental bioelectricity, which has implications for birth defects, traumatic injury, and cancer.[57,105–107] Future work will incorporate this kind of workflow into machine science pipelines, and empirically test the creative products of exploring the structures of concepts among diverse fields of inquiry. It is clear however that this approach in exploring the latent space around existing scientific literature extends far beyond bioelectricity and can be applied to numerous domains. Machine learning and AI are poised to significantly potentiate every aspect of research.[20,21,108–110] One of the critical roles will be not as mere number crunching, but as an essential aid to the first key step: hypothesis generation. We foresee extremely fruitful collaborations between naturally evolved (human scientists) and engineered (AI) scientists.

Data availability

Data and processing scripts for this paper are available at Hugging Face, at **https://huggingface.co/datasets/levinlab/neuroscience-to-dev-bio/tree/main**.

Author contributions

T. O'B.: conceptualization, data curation, formal analysis, investigation, software, writing. J. S.: conceptualization, data curation, formal analysis, investigation, software, writing. L. P.-L.: conceptualization, formal analysis, investigation, software. P. M.: data curation, validation. C. R.-I.: data curation, validation. M. L.: conceptualization, formal analysis, investigation, writing, project administration, supervision, funding acquisition.

Conflicts of interest

M. L. is a scientific co-founder of two companies (Morphoceuticals, and Astonishing Labs) which explore the symmetries between neuroscience and developmental biology. J. S. is an employee of Optum, a healthcare technology company.

Acknowledgements

We thank Giovanni Pezzulo for helpful discussions, and Juanita Mathews for manually rating AI-derived text. We also thank Julia Poirier for assistance with the manuscript. M. L. gratefully acknowledges support *via* Grant 62212 from the John Templeton Foundation. The opinions expressed in this publication are those of the authors and do not necessarily reflect the views of the John Templeton Foundation.

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