Self-Organizing Models of Brain Wiring: Developmental Programs for Evolving Intelligence

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Abstract

In developing brains, axonal projections follow chemical gradients shaped by local interactions. This paper asks whether such a process can be inferred from its outcome: For instance, given observed mouse brain connectivity, can one recover the developmental program that produced it? If such developmental programs can be recovered, they not only explain how biological connectivity arises, but also offer a biologically grounded search space for artificial intelligence, in which architectures emerge through the evolution of genetic encodings that produce plausible wiring diagrams. A framework is proposed that uses the biological connectome itself as a beacon to guide this search, referred to as the Connectome-Generating, AI-Generating Algorithm (*CONGA*). Implemented as neural cellular automata (NCA), a model was trained to reproduce axon-tracing data in the mouse connectome, and its internal representations were compared to gene expression patterns measured in the same spatial coordinates. The result demonstrates how the brain of an intelligent organism may self-assemble through an indirect encoding of connectivity. The model outperformed a static linear baseline, but only when constrained in size, suggesting that compact developmental programs better align with biological mechanisms.

CCS Concepts

• **Applied computing** → *Systems biology*; • **Computing methodologies** → *Randomized search*; *Multi-agent systems*; *Unsupervised learning*.

Keywords

Neural Cellular Automata, Connectomics, Development, Indirect Encoding, Gene Expression, Mouse Brain, Self-Organization, Evolutionary Algorithms, Generative Modeling

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1 Introduction

This work investigates whether NCA can serve as an explanatory developmental model for real biological data, specifically the wiring architecture of the mouse brain. These models provide a powerful framework for simulating systems in which structure emerges through localized, iterative processes. Originally applied to synthetic pattern formation tasks such as emoji regeneration, NCA were simultaneously proposed as models of morphogenesis [26]. Building on that proposal, this work applies them to the domain of real developmental data. To produce the connectivity data, the NCA is extended with a dot-product *decoder* to convert its voxel-level state vectors into a connectivity estimate. This decoding mechanism reflects homophilic wiring rules, where connectivity is determined by the similarity between genetic expression signatures at source and target sites [2].

The central question of this work is whether an NCA, when trained to reproduce the voxel-level connectivity of the mouse brain, also captures features of the biological developmental process that gives rise to that connectivity. The NCA's internal state variables, treated as a candidate mechanism for generating connectivity, are compared to aligned in situ hybridization (ISH) gene expression data using a gene score metric that quantifies how much of the transcriptomic variation is explained by the learned representations. High scores indicate that the model has not merely fit the data, but has inferred a biologically meaningful generative process.

To benchmark the developmental model, it is compared to a static alternative that directly learns latent state variables to fit the observed connectivity. Unlike the developmental model, which constructs state through a sequential local process, the static model optimizes each latent vector independently, without regard for spatial structure. As a result, it serves as a baseline for evaluating whether spatially grounded dynamics provide additional explanatory power. The developmental model yields higher gene-expression predictivity, indicating a closer alignment with the biological processes that shape brain organization.

Having established that developmental models capture a biologically grounded link between genetics and phylogeny, this work proposes that the same link can support the evolution of intelligent architectures by enabling direct comparison between model connectivity and biological data. This provides a way to validate whether evolved structures reflect principles of biological intelligence. The idea is formalized in the *Connectome-Generating, AI-Generating Algorithm* (*CONGA*) framework, which evolves AI models in an emergent task environment and uses biological connectomic data as a reference point for evaluating candidate architectures derived from that process. Because models like NCA produce spatially structured connectivity shaped by developmental rules, their outputs

can be meaningfully compared to biological connectomes. When a model solves a task while also exhibiting strong correspondence to brain connectivity, it suggests convergence on principles that underlie biological intelligence.

This paper proceeds in two parts. The first presents a developmental modeling approach to brain connectivity and evaluates its correspondence with genetic expression. The second proposes CONGA as a framework for using developmental models and biological data to guide the evolution of artificial neural architectures. Together, these contributions demonstrate how developmental and evolutionary principles can be integrated to inform the design of brain-like AI systems.

2 Related Work

This work sits at the intersection of developmental biology and neuroevolution. In developmental biology, computational methods have been used to explain neural wiring from transcriptional data, often via supervised models that predict connectivity based on gene expression, revealing key genes involved in brain organization. Neuroevolution approaches, meanwhile, explore indirect encodings that generate structure through development-inspired representations, enabling more efficient exploration of neural architecture design spaces. This section reviews related methods from both fields to situate the NCA as both a model of brain connectivity and an implementation of indirect encoding.

2.1 Linking Gene Expression to Connectivity

Computational models have helped reveal how developmental processes give rise to brain wiring architecture. These studies leveraged spatially aligned datasets (at the neuron or region level) that combine transcriptomic and connectomic data, enabling models to explore how gene expression shapes circuit formation. This subsection reviews work modeling the link between gene expression and brain connectivity.

The idea that brain wiring is guided by chemical signals dates back decades. A foundational theory, the chemoaffinity hypothesis, posits that neurons form precise connections using molecular markers. Early experiments showed that regenerating optic nerves in amphibians reconnected to their original targets despite inverted orientation, suggesting axonal guidance by chemical cues rather than learning [35]. These findings established the chemoaffinity hypothesis, now widely accepted: axons and targets express complementary molecular markers shaped by differentiation, guiding connectivity during development [25]. Subsequent research identified key families of attractant and repellent molecules [8], and revealed that large-scale wiring patterns are shaped by gradients of signaling molecules known as morphogens [32]. These principles laid the foundation for computational models linking genetic expression to wiring behavior.

The nematode *C. elegans* was one of the first organisms used to explore computational models linking gene expression to connectivity. Early studies showed that a neuron's gene expression profile could predict its synaptic partners [19]. The Connectome Model (CM) proposed that wiring motifs such as bicliques emerge from gene-gene compatibility rules, identifying these network-level patterns computationally and using them to infer genes involved in circuit formation [2]. This model was later extended to incorporate physical constraints and biological noise, recovering plausible gene interactions in both *C. elegans* and mouse retina data [21]. Another approach, based on bilinear factorization, treated gene expression profiles as input to a recommender system for predicting pairwise connection strength [30]. Collectively, these models supported the idea that genetic signatures can encode wiring rules and highlighted candidate genes likely to influence circuit assembly.

In mammals, limited neuron-level resolution has led researchers to focus on region-level data when relating gene expression to connectivity. Early studies found that brain regions with similar gene expression profiles were more likely to be connected [13], and that classifiers trained on gene expression could predict anatomical connectivity in mice and rats [43]. Later work leveraging the Allen Mouse Brain Connectivity Atlas (MBCA) demonstrated that voxel-level connectivity could be predicted with high accuracy from local gene expression [11, 18]. The most predictive genes were involved in synaptic function and neural development. Other studies identified transcriptomic features that distinguish network hubs in both mouse and human brains, suggesting potential conservation of wiring principles across species [1, 12].

While most prior studies used supervised learning to predict connectivity from gene expression, this paper adopts a latent variable formulation. Rather than learning a direct mapping (gene expression $\rightarrow$ connectivity), the model infers voxel-level latent variables, or "barcodes," from the connectivity matrix, which are then compared to observed gene expression patterns (connectivity $\rightarrow$ barcodes $\rightarrow$ gene expression). This approach enables testing of competing hypotheses about how connectivity may be genetically encoded. Unlike supervised models, which are constrained to define connectivity only in terms of the genetic expression already observed, latent variable models can uncover spatial codes *de novo*. When such codes align with gene expression, they offer compelling candidate explanations for the genetic basis of neural wiring.

Supported by this latent variable framework, this work introduces a new connectivity model: an NCA-based developmental model that incorporates biological constraints through a morphogenesis-inspired growth process. Drawing on classical theories such as reaction-diffusion systems [39] and positional information gradients [44], the NCA generates structure through sequential, local interactions that mimic intercellular chemical signaling. The resulting spatially organized barcodes are then used to estimate connectivity, as detailed in Section 3.3.

2.2 Indirect Encodings and Developmental Programs

The developmental model presented here defines connectivity through a learned growth process, placing it within a broader class of neuroevolutionary approaches that use indirect encodings to construct neural architectures [37]. Rather than specifying connectivity directly, these methods generate structure through biologically inspired processes that yield compact and regular wiring patterns. A notable example is HyperNEAT [36], which uses compositional pattern-producing networks (CPPNs) to generate neural weights from spatial coordinates. The NCA model applied here can be viewed as a conceptual successor: whereas HyperNEAT relies on

fixed pattern generators, NCAs implement dynamic, local growth processes that construct networks through sequential interactions, more closely mirroring biological development.

Several recent models adopt developmental encoding using NCAs as the generative engine of connective weights, though they differ in key ways from the approach presented here. HyperNCA grows the weights of a policy network from a seed state, interpreting the final NCA state vectors directly as connection weights [27]. In contrast, the present model uses a dot-product-based connectivity rule, which better reflects homophilic wiring principles observed in biological systems [2]. Both Developmental Graph Cellular Automata (DGCA) and Neural Developmental Programs (NDPs) modify graph structure directly; DGCA, in particular, has been used to fully reconstruct the *C. elegans* connectome through evolved local rules [28, 40, 41]. These approaches rely on evolutionary search, whereas the present model uses backpropagation for greater sample efficiency and scalability to region-level mouse brain data. As a proposed next step, evolutionary optimization is introduced only at the task level, as outlined in Section 6.

3 Methods

To investigate how brain connectivity might emerge from biological principles, this analysis uses combined transcriptional and anatomical data from the adult mouse brain. Two generative models are applied, each estimating connectivity from latent variables—or "barcodes"—that define a three-dimensional spatial pattern. The baseline static model directly learns barcodes that reproduce the observed connectivity, illustrating how independent encodings, without spatial or developmental structure, can account for wiring patterns. The developmental model, implemented as an NCA, extends this by modeling the emergence of barcodes through a morphogenetic process. In doing so, it incorporates biological constraints and offers a framework for explaining the origins of gene expression patterns in a developmental process.

3.1 Dataset and Preprocessing

This work uses transcriptomic [23] and connectomic [29] datasets from the Allen Institute for Brain Science, which offer extensive whole-brain measurements. All data are aligned to a common coordinate system, allowing latent representations derived from connectivity to be directly compared with voxel-level gene expression. For tractability, both data types were downsampled to a $20 \times 20 \times 20$ grid, resulting in 1,544 interior brain voxels used in the analysis. Downsampling was performed using cubic interpolation. Voxels corresponding to invalid regions, such as outside the brain or within ventricles, were assigned a value of zero.

Gene expression data were obtained from the Allen Mouse Brain Atlas [23], which uses in situ hybridization (ISH) to measure mRNA transcript levels for over 20,000 genes. Expression energy values were extracted, capturing both the volume and intensity of expression within each voxel of the grid. The resulting matrix assigns each voxel a high-dimensional gene expression vector representing local transcriptional activity.

Connectivity data were derived from the Allen Mouse Brain Connectivity Atlas [29], which reports voxel-level axonal projections from viral tracer experiments. The raw dataset includes scans taken both immediately after tracer injection ("injection") and after axonal transport ("projection"). Following the approach of [29], a voxel-to-voxel connectivity matrix was estimated by regressing projection activity onto injection activity using L2-regularized linear regression ($\alpha = 0.001$). The resulting weights were log-transformed to normalize scale, thresholded to remove values below 10^{-5}, and shifted to ensure all retained values were positive, with absent connections set to zero. The final matrix, aligned to the same $20 \times 20 \times 20$ voxel grid as the gene expression data, served as the modeling target.

Given a model estimate of connectivity, the coefficient of determination (R^2) provides an interpretable measure of performance, quantifying the proportion of variance in the observed connectivity explained by the model. Since only 4.3% of voxel pairs exhibit nonzero connectivity, the total variance is dominated by the contrast between connected and unconnected pairs. A variance decomposition shows that 86% of the total variance arises from the mean difference between these two groups, while only 14% reflects variation in edge strength among connected voxels. As a result, R^2 primarily evaluates the model's ability to predict the presence or absence of connections, rather than their precise magnitude.

3.2 Gene Score Evaluation

To evaluate whether the models capture developmentally meaningful structure, a gene score metric quantifies the correspondence between the learned spatial representations and measured gene expression. This metric provides an assessment of how well the barcodes align with biological development, independent of their ability to reconstruct connectivity.

Given a set of voxel-level latent representations, produced by either the static or developmental model, the gene score quantifies how well these vectors predict the spatial distribution of gene expression. This metric adapts the "brain score" framework from neural representation analysis [4], repurposed here for genetic data. For each gene, a linear model is trained to predict expression levels across voxels from the latent vectors, using a leave-one-region-out cross-validation scheme. Voxels are grouped into 13 top-level anatomical regions (per the reference atlas), and each group is held out in turn. The model is fit on the remaining voxels and evaluated on the held-out region, cycling through all regions to generate predictions for every voxel. The Pearson correlation between predicted and observed expression defines the gene score, with higher scores indicating that the latent representation captures spatial structure aligned with true gene expression.

Unlike supervised approaches that directly map gene expression to connectivity (discussed in Section 2.1), this method treats gene expression as an independent evaluation target. Because no expression data are used during training, the resulting gene scores reflect how well a model's learned representation implicitly captures biologically meaningful structure. Averaging these scores across genes yields a summary metric for model comparison, used consistently to assess whether the static baseline or the developmental model better reflects transcriptional organization in the mouse brain.

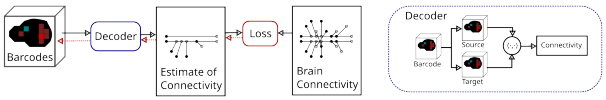

Figure 1: *Overview of the Static Model.* Connectivity is modeled using the top k singular vectors obtained from singular value decomposition (SVD) of the voxel-to-voxel connectivity matrix. These latent variables provide a compact representation that captures the dominant structure of the connectome. While effective as a baseline for reconstruction, this approach does not model biological mechanisms such as spatial growth or local interaction.

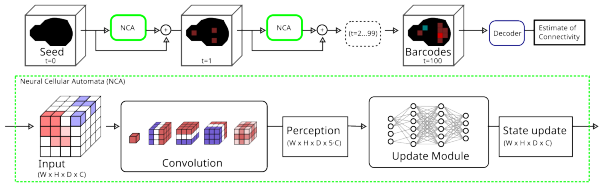

Figure 2: *Overview of the Developmental Model.* A NCA architecture is used to simulate the growth of voxel-level latent representations over time. Each voxel updates its internal state using only local information from neighboring voxels. After a fixed number of steps, the final latent states are used to reconstruct connectivity. This model simulates spatially localized, biologically plausible development.

3.3 Model Architectures

This work compares two modeling approaches for generating voxel-to-voxel connectivity in the mouse brain: a static latent variable model based on singular value decomposition (SVD), and a developmental model implemented as a NCA. Both models produce voxel-wise latent representations ("barcodes"), which are used to reconstruct the observed connectivity matrix. These latent variables are then evaluated against gene expression data using the gene score metric described in Section 3.2.

3.3.1 Static Latent Variable Model (SVD). The static model (Figure 1) follows a latent space modeling framework used in network science, where each node is assigned a vector of latent variables, and connectivity is defined by their dot product [16]. Each latent vector $\mathbf{z}_i \in \mathbb{R}^D$ is composed of two sub-vectors: a source component $\mathbf{z}_i^{\text{src}} \in \mathbb{R}^{D/2}$ and a target component $\mathbf{z}_i^{\text{tgt}} \in \mathbb{R}^{D/2}$, concatenated to represent directional connectivity:

$$\mathbf{z}_i = [\mathbf{z}_i^{\text{src}}; \mathbf{z}_i^{\text{tgt}}]. \tag{1}$$

Predicted connectivity from voxel j to voxel i is computed as the dot product between the source vector of voxel j and the target vector of voxel i:

$$\hat{C}_{ij} = \mathbf{z}_i^{\text{tgt}} \cdot \mathbf{z}_j^{\text{src}}. \tag{2}$$

This formulation allows the model to represent directional connectivity, a defining feature of real neural systems. By separating each voxel's latent representation into source and target components, the model can learn distinct patterns for incoming and outgoing connections.

Latent vectors are learned using a standard singular value decomposition (SVD) solver. As established by the Eckart–Young theorem [10], performing SVD and truncating to the top-k singular vectors yields the optimal rank-k approximation of a matrix under the Frobenius norm. While gradient descent could be used to incorporate prior distributions on the latent variables, empirical tests showed no meaningful effect from applying L1 or L2 regularization in this setting. Model complexity was varied by adjusting the number of latent dimensions (D), enabling a systematic evaluation of how representational capacity impacts both reconstruction performance and alignment with gene expression data (see Section 4.2).

This model serves as a linear baseline, capturing low-dimensional structure in the connectivity matrix. However, it treats each voxel independently, without modeling spatial relationships. The developmental model addresses this limitation by incorporating local interactions between voxels.

3.3.2 Developmental Model (Neural Cellular Automata). The developmental model is implemented as a neural cellular automaton (NCA) [26], drawing inspiration from morphogenetic processes in biological development. Rather than assigning latent variables directly, the model simulates a spatially constrained, iterative process in which voxel states evolve over time through local interactions. After the simulation, each voxel's final state is treated as a latent vector, which is then split into source and target components. Connectivity is predicted by computing dot products between these components, following the same approach as in the static model.

As illustrated in Figure 2, each voxel maintains a state vector that is updated over T developmental steps ($T = 100$) using a shared neural update function. At each step, a voxel observes its local $3 \times 3 \times 3$ neighborhood (including itself), applies a fixed convolutional readout, and passes the result through a two-layer multilayer perceptron (MLP) with ReLU activation to update its own state. The convolution uses a set of five fixed $3 \times 3 \times 3$ kernels—an identity kernel, three Sobel filters (one per spatial axis), and a Laplacian filter—whose outputs are concatenated before being fed into the MLP. The MLP's hidden layer size serves as a complexity knob: larger sizes support more expressive transition dynamics, while smaller sizes enforce stronger inductive constraints. The effect of the MLP size was significant in modeling the developmental process, as described in Section 4.2. The state vector has 32 channels, and unlike the original NCA implementation, no aliveness masking is used.

Each voxel begins from a fixed initial seed state at $t = 0$. Specifically, the state vector for each voxel is a 4-dimensional vector where: the first channel is set to 1.0 if the voxel is part of the brain interior and 0.0 otherwise; the second, third, and fourth channels are set to the x, y, and z coordinates of the voxel within the brain volume, scaled to the range $[-1, 1]$. All other channels are initialized to zero. This seed establishes a morphogen-like gradient that encodes the brain's geometry, while avoiding the center-out bias introduced by seeding from a single voxel.

To train the developmental model, gradients were propagated through the entire rollout sequence using backpropagation through time. Parameter updates were performed using the NAdam optimizer with a learning rate of 6×10^{-4}. Each model was trained for 10,000 steps with a batch size of 1, reflecting the use of the full voxelized brain as a single training instance. Gradient clipping was applied to promote stability, and was essential for preventing gradient explosions during training.

This architecture imposes strong inductive biases reflecting biological principles: the re-use of developmental subroutines to produce reocurring patterns across space. This process produces disambiguating information, analogous to morphogens during biological development, that scaffold the construction of the spatial pattern. Thus, the developmental model incorporates biological constraints, and its representations will be compared with the genetic expression to assess whether it captures key aspects of the developmental process underlying connectivity.

3.4 Randomization Baselines

To ensure that elevated gene scores reflect meaningful biological structure rather than generic spatial or statistical effects, three randomized connectivity baselines were introduced, each preserving different properties of the original connectivity:

(1) **FullRandom**: fully shuffles the connectivity matrix, destroying all spatial and topological structure while preserving the global distribution of connection weights.
(2) **DegreePreserve**: re-wires edges to preserve the in/out degree of each voxel, controlling for effects driven by connection density alone.

The latter baseline isolates a potential confound, connection density, allowing the contribution of region-to-region wiring to be identified more precisely. The results support the central claim that gene expression reflects specific features of structural connectivity. That is, the observed association between gene expression and the model's latent variables cannot be explained by generic spatial structure alone, but instead points to a genetically embedded representation of the brain's wiring architecture.

4 Results

This section evaluates the developmental model's ability to reconstruct mouse brain connectivity and examines whether its learned representations reflect underlying biological processes, as indicated by their correspondence with gene expression. Comparisons are made to a static SVD-based baseline and to randomized control conditions. The results are presented in two parts. First, the developmental model captures a key biological signal: its latent variables show strong alignment with gene expression, suggesting that modeling the developmental process enhances biological fidelity. Second, simpler developmental models yield the highest gene scores, indicating that the underlying biological process may itself be subject to inferential or perceptual constraints.

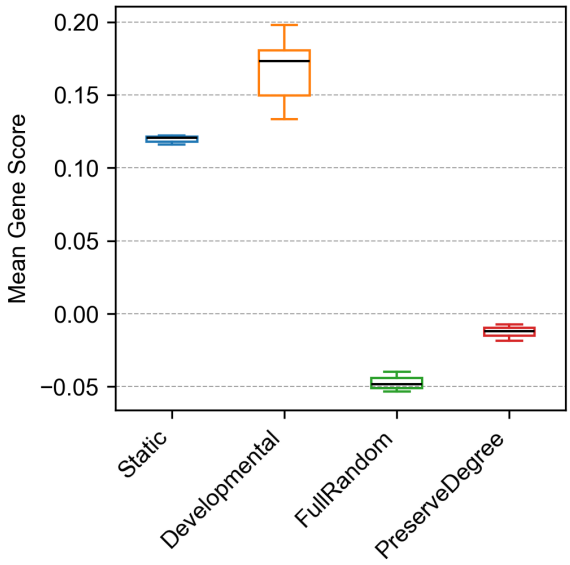

Figure 3: *Gene Score Comparison.* This box plot shows the distribution of gene scores across different model conditions: the developmental model, the static SVD-based model, and two randomized baselines applied to the static model. Each point represents the average gene score from an independent model run. Higher scores indicate stronger alignment between the model's latent representations and empirical gene expression. The developmental model achieves the highest scores, suggesting it most accurately captures biologically relevant developmental structure.

4.1 Predicting Gene Expression from Latent Representations

The central evaluation metric is how well the model's latent variables capture underlying genetic structure. As described in Section 3.2, gene scores measure how accurately voxel-level gene expression can be predicted from the model's learned spatial representations.

As shown in Figure 3, the developmental model significantly outperforms the static model in terms of gene score. The highest-performing developmental model achieves an average gene score of 0.202, compared to 0.120 for the static model. Both models substantially exceed the scores achieved by randomized connectivity baselines, providing computational evidence that gene expression encodes information about the brain's wiring architecture. These results indicate that the developmental model's latent representations also align more closely with underlying genetic structure than the static method.

4.2 Model Complexity and Biological Signal

For both the static and developmental models, a key finding is that *simpler* architectures yield stronger alignment with gene expression when trained to reconstruct connectivity. In the static model, complexity is controlled by the number of latent dimensions in

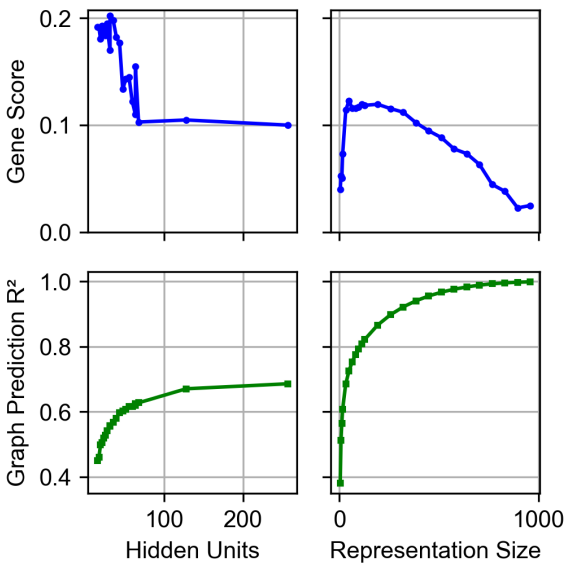

Figure 4: *Tradeoff Between Model Complexity and Biological Alignment. (Left)* As the internal hidden size of the developmental model increases, gene scores decline (upper plot), but connectivity reconstruction improves. Simpler developmental models yield representations that more closely match gene expression, suggesting that the underlying biological process is governed by limited representational complexity. *(Right)* As the number of latent variables per voxel in the static model increases, the gene scores peak at a low level of complexity (upper plot), but the connectivity reconstruction continues to improve (lower plot). As the static model grows in size, it overfits to the connectivity, and its latent variables lose their relevance to genetic expression.

each voxel's barcode. In the developmental model, however, reducing the number of output channels alone was insufficient—strong biological alignment only emerged when the internal computation was also constrained, requiring a small multilayer perceptron in the update rule.

As shown in Figure 4, models with fewer latent variables achieved higher gene scores, despite performing worse at reconstructing the connectivity matrix. Moreover, the developmental model only outperformed the static model in gene score when its hidden layer size was heavily restricted. This tradeoff suggests that simpler models yield more biologically meaningful representations.

These findings align with Occam's Razor, the principle that, among competing explanations, the one with the fewest assumptions is most likely to be correct. They also provide computational support for the view that development operates under informational and energetic constraints. This suggests that the genetic code for wiring is not only efficient but embedded within a tightly bounded developmental program.

5 Discussion: Developmental Programs as Biological Models

The primary empirical finding of this work is that genetic expression profiles are better explained by the developmental model of connectivity than by the static model. This result supports a morphogenetic view of development, in which local interactions give rise to spatial patterns that guide cell differentiation and tissue formation. Since cellular automata have historically been proposed as models of morphogenesis, this work demonstrates that neural cellular automata (NCA) can learn such developmental programs directly from data.

However, several limitations constrain the scope of these conclusions. The model operates on static snapshots of adult brain data, both for connectivity and gene expression. In biological systems, many transcription factors disappear once their developmental role is complete and would therefore be absent from the data used here. Nor does the model capture mechanical processes like cell migration and proliferation, which would better reflect the underlying brain geometry. Additionally, the reliance on voxelized data sacrifices spatial resolution, and the dataset does not distinguish between synaptic and non-synaptic connections. Some of these limitations may be addressed through the use of higher-resolution or temporally resolved data, which is becoming increasingly available through recent advances in large-scale connectomic mapping efforts.

Advances in connectomics are rapidly transforming the ability to study neural structure at scale, creating new opportunities to model the developmental processes that give rise to brain wiring. High-resolution electron microscopy (EM) has enabled synapse-level connectomes in small model organisms, including the complete adult fruit fly brain—with 140,000 neurons and 50 million synapses [9]—and the larval fly brain with over 3,000 neurons [42]. Projects such as MICrONS have extended these methods to mammalian tissue, reconstructing cubic millimeters of mouse cortex at nanometer resolution through automated segmentation and AI-assisted analysis [38]. Even in humans, a petavoxel-scale fragment of brain tissue has been successfully reconstructed [33]. Complementary molecular techniques such as MAPseq [20] and BRICseq [17] use DNA barcoding to multiplex axon-tracing experiments, enabling large-scale connectivity mapping without relying on electron microscopy. Expansion microscopy offers another scalable approach to high-resolution imaging of whole-brain volumes [5]. As datasets continue to increase in resolution and coverage, models that link structural wiring to underlying developmental programs—such as the developmental model of connectivity presented here—offer a framework for making sense of complex brain data and may provide a foundation for leveraging biological organization in artificial intelligence.

6 From Biology to AI: Connectome-Generating AI-Generating Algorithms

The developmental model presented in this paper recreates the mesoscale connectome of the mouse brain, providing a generative mechanism for producing structured connectivity from simple, local rules. The learned representations align with patterns of genetic

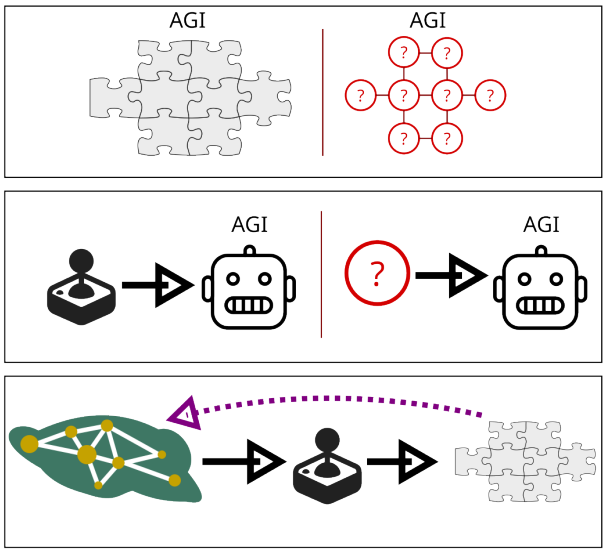

Figure 5: *Three Paradigms for Building AGI. Top:* The *cognitive* approach constructs intelligent systems by assembling cognitive modules (left panel), but suffers from a limited understanding of the brain's modular functional architecture (right panel). *Middle:* The *emergent* approach uses reinforcement learning in task environments to produce intelligent behavior (left panel). But without a complete understanding of the relevant ecological pressures, such task design is difficult (right panel). *Bottom:* The *connectomic* approach grounds architecture search in real brain wiring data (left), using the connectome to shape the design of the task environment (center). A developmental program generates architectures (right) that are trained on this task. If the resulting architecture recapitulates features of the biological connectome—such as spatial layout or structural motifs—it can be linked back to the original neural data (purple dashed line), closing the loop between biological structure and functional learning.

expression, offering evidence that the model captures a link between molecular-level biology and the emergent wiring phenotype.

This connection enables a new strategy for AI design. Because developmental programs encode connectivity in three-dimensional space through an indirect, biologically inspired process, they offer a natural interface between artificial and biological brains. However, while the current model captures structural organization, it does not yet produce functional behavior.

To address this challenge, the proposed approach is to treat the developmental model as a genotype, and evolve it with respect to task performance. As functional models are discovered, those whose generated connectomes also resemble biological wiring can be interpreted as converging on biologically grounded solutions. In this view, the connectome serves as a reference signal for validating evolved architectures, and the developmental model defines the search space in which evolution operates.

Grounding network models in connectomic data offers a potential path toward more brain-like machine architectures—and, ultimately, toward artificial general intelligence (AGI), here defined as an agent with human-level cognitive capabilities [22]. AGI is often regarded as the long-term goal of AI research, and this discussion considers how insights from brain connectivity may inform its development.

This section outlines how developmental models can be used to evolve functional, brain-like networks. The first part reviews existing approaches to AGI and situates this work in relation to cognitive and emergent strategies. The second part introduces a conceptual framework, the Connectome-Generating AI-Generating Algorithm (*CONGA*), which uses developmental programs and biological data to guide the evolution of intelligent systems.

6.1 Approaches to Artificial General Intelligence

This paper introduces a taxonomy of three broad approaches to constructing artificial general intelligence (AGI): cognitive, emergent, and connectomic (illustrated in Figure 6).

Cognitive approaches to AGI begin with theories of mind and attempt to reverse-engineer intelligence by decomposing it into functional modules—such as memory, planning, symbolic reasoning, and attention. Classical frameworks like ACT-R and Soar, as well as recent proposals like OpenCog Hyperon, follow this route by combining learned systems with hand-engineered cognitive functions [15, 24, 31]. While intuitively appealing, these designs rely on a principled taxonomy of mental functions—something cognitive science has yet to deliver. In the absence of a comprehensive model of cognition, modular architectures risk being incomplete or misaligned with the true structure of general intelligence.

Emergent approaches, by contrast, place minimal assumptions on structure and instead rely on scale, data, and environment. Reinforcement learning and self-supervised training have produced strikingly general behaviors in large agents like GPT-4, without requiring cognitive blueprints [3, 34]. AI-generating algorithms (AI-GAs) extend this philosophy, proposing that intelligent systems can be evolved by jointly optimizing architectures, learning rules, and training environments in an open-ended loop [7]. These systems shift the design burden from the agent to the world—but in doing so, they assume the environment itself is rich enough to produce general intelligence, an assumption that may not hold without strong inductive biases.

A **connectomic approach** offers a third alternative. Rather than starting with behavioral modules or designing the perfect environment, it anchors architecture discovery in the structure of real nervous systems. In this view, biological connectomes serve as a guiding prior that narrows the search space and biases the evolution of functional architectures toward those that resemble naturally occurring networks. This forms the basis of the proposed CONGA framework, which incorporates biological structure as an explicit constraint on the evolutionary process.

6.2 Proposal: Biological Structure as a Prior for AI Design

This section introduces a new framework for architecture discovery: CONGA, illustrated in Figure 5 (bottom panel). Like AI-GAs [7], CONGA evolves intelligent agents by meta-optimizing learning

systems within synthetic environments. However, they introduce a key constraint: evolved architectures must resemble biological brains. To achieve this, CONGA combines evolution with development, generating agents whose connectivity emerges from a simulated growth process tuned to match empirical connectomic data. This coupling aligns structural complexity with the gradual refinement observed in natural evolution and development, offering a biologically grounded pathway toward artificial intelligence.

CONGA operates through a nested-loop optimization. In the inner loop, search is conducted over developmental programs—now including neural activations—to evolve agents with high task performance. In the outer loop, the environment is gradually shaped to favor the emergence of agents whose connectomes align with biological data. This structure ensures that the resulting connectivity patterns are driven by task demands, while still converging toward biologically plausible architectures. Because these architectures arise through developmental growth, they are more likely to reflect the structural regularities observed in real nervous systems.

Beyond developmental regularities, optimizing over developmental programs may also produce evolutionary trajectories that parallel the phylogenetic evolution of neural wiring. Brain architectures did not emerge fully formed; they evolved through gradual refinement, elaborating simple circuits into more complex and capable systems [6]. Similarly, CONGA begins with simple, functional developmental programs and incrementally increases architectural complexity, allowing growth processes to scaffold progressively more sophisticated solutions.

As a proposal for future work, the following experiment draws inspiration from an early stage in the evolution of nervous systems: the simple neural architectures of early eumetazoans [6]. These ancestral systems laid the foundation for later brain structures, establishing core serotonergic and dopaminergic pathways that regulate behavioral tradeoffs between short-range exploitation of local resources and long-range exploratory foraging. The proposed experiment will attempt to reproduce this core decision-making circuit through a developmental program, using it as a foundation for evolving more complex navigational architectures. The goal is to identify evolutionary environments under which this circuitry reliably emerges, providing insight into the conditions that may have shaped its origin. If successful, the experiment would not only support the hypothesized link between environment and wiring but also yield a developmental program capable of generating the circuit, enabling a stepwise expansion toward increasingly sophisticated systems. By progressing through increasingly complex tasks and environments, it may be possible to evolve rich decision-making architectures in accordance with Gall's Law: "A complex system that works is invariably found to have evolved from a simple system that worked" [14].

7 Conclusion

This paper introduced a Neural Cellular Automata (NCA) model trained to reconstruct voxel-wise connectivity in the mouse brain. Extending a static baseline that directly learns latent variables to construct the connectivity, the NCA simulates a localized, sequential developmental process to form its representations. This approach mirrors how biological structure emerges. The dataset contains both connectivity and gene expression data on the same voxel grid, enabling a direct biological validation of the learned representations.

Comparison between the final state of the NCA and measured gene expression indicates that the developmental model captures biologically meaningful structure, outperforming a classical linear baseline. This suggests that the NCA, in reproducing the connectome, also reflected aspects of the developmental process that gave rise to it.

Now that the developmental program has been shown to link genetic expression to connective phenotypes, biological connectivity can be used to guide the design of task-performing circuitry by leveraging the search space of developmental programs. A broader framework is proposed for modeling connectomes as the joint product of development and evolution. In this framework, CONGA, evolution serves as a search mechanism that jointly optimizes both the developmental program (which determines network architecture) and the task environment, with the aim of reproducing biological wiring. In doing so, it becomes possible to identify mechanisms that give rise to brain-like structure as a byproduct of functional adaptation.

This approach integrates developmental modeling with evolutionary search, guided by biological data as a structural constraint. As large-scale connectomic datasets continue to emerge, it offers a path toward models that uncover the generative principles underlying brain network connectivity.

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