Ecology & Evolution | May 22, 2026 | 8 min read | By Bryan White

Giving Biobots a Brain: The Next Leap in Synthetic Morphology using Embryonic Frog Cells

Biology * Genetics * Robotics

From Xenobots to Neurobots in Synthetic Morphology

While conventional robotics relies on rigid metals, polymers, and silicon microprocessors, inorganic machines lack the intrinsic capacity of living matter to metabolize nutrients, self-repair after mechanical trauma, or dynamically remodel their physical architecture. Bridging developmental biology, computer science, and bioengineering, the discipline of synthetic morphology constructs autonomous biological machines directly from living cells.[1][7]

This paradigm emerged in 2020 with the first-generation "xenobots" -- millimeter-scale multicellular constructs computationally designed on the Deep Green supercomputer cluster and microsurgically sculpted from embryonic skin and contractile cardiac cells of the African clawed frog, Xenopus laevis.[1][3][8] Subsequent second-generation "biobots" (Xenobots 2.0) and human tracheal cell-derived "Anthrobots" transitioned to bottom-up self-assembly: freed from canonical embryonic signaling gradients, excised epithelial progenitors coalesce into spheres and repurpose mucociliary clearance cilia into thousands of synchronized oars for rapid aqueous locomotion and self-healing.[6][7][10] Yet both generations lacked an internal nervous system, restricting their kinematics to stereotyped loops and spins governed by passive ciliary asymmetry.[2][5]

In spring 2026, a landmark study published in Advanced Science achieved the next major leap in evolution and biohybrid engineering by creating the first "neurobots" -- self-organizing cellular robots integrated with functional internal nervous systems.[5][9][11] By implanting neural precursor clusters into healing Xenopus biobots during a precise morphogenetic window, researchers demonstrated that wild-type amphibian neurons spontaneously wire into a synthetic body plan, innervate peripheral ciliary actuators, fire synchronized electrical bursts, and reorient their transcriptome toward ancient evolutionary strata.[5][9] These findings reshape foundational assumptions across synthetic biology and evolutionary developmental biology.

Embryonic Sourcing and the Stage-9 Morphogenetic Construction Paradigm

Constructing a neurobot requires exploiting a narrow 30-minute window of morphogenesis during host tissue healing.[9] Researchers excise the animal cap -- a sheet of undifferentiated ectodermal cells -- from a Nieuwkoop and Faber stage-9 Xenopus laevis embryo.[9] Upon excision, the flat epithelial sheet curls inward over ~30 minutes, forming a transient open cup before sealing into a closed sphere.[9]

To generate the neural implant without exogenous transgenes, the team leveraged default neural induction: while intact animal cap ectoderm normally differentiates

into epidermis, mechanically dissociating animal caps from ~50 donor embryos into single cells and maintaining physical separation for 3 hours abolishes intercellular bone morphogenetic protein (BMP) signaling, causing the cells to adopt a default neural progenitor fate.[9] These neural-fated cells are reaggregated into dense clusters and microsurgically placed into the open bowl of the healing host cap, which folds over and seals them inside.[5][9]

To verify that observed phenotypes stemmed specifically from neural differentiation rather than added cellular volume, researchers constructed rigorous "sham neurobots" in which dissociated donor cells were reaggregated within 30 minutes -- preventing neural induction and preserving an epidermal fate -- before implantation into stage-9 hosts.[9]

Anatomical Integration, Peripheral Innervation, and Morphological Shifts

Within 48 to 72 hours post-surgery, neurobots consolidate and begin swimming via outer multiciliated cells.[9] Confocal microscopy using an antibody against acetylated -tubulin revealed that implanted neural precursors differentiate into mature neurons with extensive axonal projections and dendritic arbors.[6][9] Immunostaining for synapsin-1 and Microtubule-Associated Protein 2 (MAP2) confirmed dense synapse formation across the internal network.[6]

Crucially, internal axons project outward through the host parenchyma to establish direct peripheral innervation with four outer epithelial cell types:[5]

* Multiciliated Cells (MCCs): The primary ciliary motor actuators driving locomotion.

* Mucus-Secreting Goblet Cells: Regulators of surface fluid viscosity and ciliary hydrodynamics.

* Ionocytes: Epithelial regulators of transmembrane pH and electrochemical ion gradients.

* Small Secretory Cells (SSCs): Serotonergic paracrine cells that modulate ciliary beat frequency.[5]

Active neural integration also remodels macroscopic body geometry. While standard biobots and sham neurobots remain highly spherical (high Roundness Index), mature day-6 true neurobots grow significantly larger in cross-sectional area ($p = 0.0007$) and adopt an elongated, asymmetrical morphology ($p = 0.047$), proving that bidirectional signaling from the developing neural network physically sculpts the host body.[9]

| Morphological Metric | | Standard Biobots | | Sham Neurobots (Control) | | True Neurobots (Neural Implant) | | Statistical Significance |

| Cellular Composition | | Ectodermal cells | | Ectodermal + Non-neural implant | | Ectodermal + Neural precursor cells | | N/A |

| Internal Neural Projections | | Absent | | Absent | | Dense axonal and dendritic networks | | N/A |

| Peripheral Innervation | | None | | None | | Extensive (MCCs, Goblet, Ionocytes) |

| N/A |

| Roundness Index (Shape) | | High (Highly spherical) | | High (Highly spherical) | | Low (Significantly elongated) | | Kruskal-Wallis test, p = 0.047[9] |

| Overall Construct Size | | Baseline Area | | Baseline Area | | Significantly larger area | | Kruskal-Wallis test, p = 0.0007[9] |

Table 1: Morphological and anatomical comparison across standard biobots, sham controls, and innervated neurobots.[9]

Calcium Imaging and Pharmacological Validation of Neural Control

Automated kinematic tracking demonstrated that neurobots maintain significantly higher minimum movement speeds than standard biobots (spending far less time idle) and execute repeatable, structured locomotive motifs.[5][6] To verify electrophysiological activity in vivo, donor neural progenitors were engineered to express the fluorescent calcium indicator GCaMP6s.[6] Live imaging at 5 frames per second over 10-minute windows captured both localized action potential spikes and synchronized, long-range calcium bursts across distant nodes of the internal neural circuit.[2][6][9]

Definitive proof of top-down neural motor governance came from pharmacological challenge with pentylenetetrazole (PTZ), a central nervous system convulsant that antagonizes inhibitory GABAA (neurotransmitter -aminobutyric acid) chloride channels.[6][11] When non-neuronal biobots were exposed to PTZ, direct epithelial toxicity depressed ciliary beating and significantly reduced motility.[5] In contrast, PTZ disinhibited the GABAergic circuitry inside neurobots, triggering hyper-synchronous neural firing whose excitatory motor commands overrode peripheral epithelial toxicity to drive heightened motility and movement complexity.[5]

| Organism Type | | Baseline Motility | | Internal Nervous System | | Expected PTZ Effect (Direct Cellular Toxicity) | | Actual PTZ Movement Response | | Conclusion |

| Standard Biobot | | Continuous, simple | | Absent | | Decreased ciliary beating | | Significantly decreased motility | | Drug exhibits baseline epithelial toxicity. |

| Neurobot | | Continuous, complex | | Present (GABA-A active) | | Decreased ciliary beating | | Heterogeneous; Increased complexity & hypermotility | | Disinhibited neural network overrides peripheral cell toxicity. |

Table 2: Comparative kinematic responses to pentylenetetrazole (PTZ) exposure across biobots and neurobots.[5]

Exploratory Transcriptomics, Visual Cascade Upregulation, and Phylostratigraphy

Comparative RNA sequencing revealed how cells freed from canonical embryogenesis reorganize their gene expression.[5][12] Across 96.06% of expressed loci, the inter-individual Coefficient of Variation in synthetic constructs (CVX mean = 2.6115) vastly exceeded that of age-matched wild-type Xenopus embryos (CVE mean = 1.2537), with neural integration amplifying this variance further.[9][12] This high transcriptional dispersion reflects "exploratory adaptation," wherein cells stochastically sample their genome to stabilize a novel multicellular

morphology.[12]

Remarkably, despite lacking eyes, retinas, or lenses, neurobots spontaneously upregulated not only synaptic and axon-guidance pathways, but also an extensive suite of Xenopus visual-system and photoreceptor genes -- priming molecular machinery for optical perception.[5] Furthermore, phylostratigraphic mapping across the tree of life revealed a striking evolutionary reversion: ~54% of significantly upregulated neurobot genes (941 upregulated versus 279 downregulated ancient loci) belong to the oldest evolutionary strata shared with basal bacteria, early multicellular Metazoa, nerve-net Eumetazoa, and early Bilateria, while modern Xenopus-specific developmental genes were suppressed.[9][12]

| Evolutionary Stratum | | Evolutionary Milestone | | Neurobot Gene Expression Trend (vs. Biobot) | | Phylostratigraphic Enrichment |

| All Living Organisms | | Basal cellular mechanics | | Highly Upregulated | | ~54% of upregulated genes (combined across oldest strata)[9] |

| Metazoa | | First multicellularity | | Significantly Enriched | | Overrepresented among ancient upregulated loci[9] |

| Eumetazoa | | First true tissues/nerve nets | | Significantly Enriched | | Enriched relative to baseline biobots[12] |

| Bilateria | | First centralized nervous cords | | Significantly Enriched | | Enriched across neural-integration loci[12] |

| Xenopus laevis | | Modern, species-specific | | Downregulated / Suppressed | | Depleted relative to wild-type embryonic programs |

Table 3: Phylostratigraphic distribution of differentially expressed genes in neurobots relative to non-neuronal biobots.[9][12]

Teleonomy, Basal Cognition, and Regenerative Medicine

The spontaneous assembly of a functional, behavior-modulating nervous system inside a synthetic body plan never shaped by natural selection proves that multicellular teleonomy and neural circuit wiring are emergent competencies encoded in ancient, conserved genomic toolkits.[5][13] By decoding how implanted neural progenitors autonomously locate peripheral targets and negotiate synaptic control, researchers gain a tractable platform for spinal cord and traumatic brain regeneration, as well as biodegradable patient-derived micro-vehicles capable of targeted drug delivery or clearing arterial lipid plaques.[4][5][11]

Updates... (Nov 21, 2026): Replaced HTTP 403 Medium and magazine links with peer-reviewed Science Robotics (Blackiston et al., 2021) and Advanced Science (Gumuskaya et al., 2023) DOIs, split grouped inline citations, and standardized exact publication dates across all references.

References & Primary Sources

* [1] Blackiston, D., Lederer, E., Kriegman, S., Garnier, S., Bongard, J., & Levin, M. (Mar 17, 2021). A cellular platform for the development of synthetic living machines. Science Robotics, 6(52). -- https://doi.org/10.1126/scirobotics.abf1571

* [2] Quanta Magazine (Mar 31, 2021). Cells Form Into 'Xenobots' on Their Own. -- https://www.quantamagazine.org/cells-form-into-xenobots-on-their-own-20210331/

* [3] The Guardian (Jan 13, 2020). Scientists use stem cells from frogs to build first living robots. -- https://www.theguardian.com/science/2020/jan/13/scientists-use-stem-cells-from-frogs-to-build-first-living-robots

* [4] ScienceDaily (Jan 13, 2020). Living robots built using frog cells. -- https://www.sciencedaily.com/releases/2020/01/200113175653.htm

* [5] Bioengineer.org (Mar 16, 2026). Advancing Autonomous, Self-Organizing Biological Robots Equipped with Nervous Systems. -- https://bioengineer.org/advancing-autonomous-self-organizing-biological-robots-equipped-with-nervous-systems/

* [6] Tufts Now (Mar 16, 2026). Scientists Create Novel Organism with Primitive Nervous System. -- https://now.tufts.edu/2026/03/16/scientists-create-novel-organism-primitive-nervous-system

* [7] University of Vermont (Mar 31, 2021). Scientists Create the Next Generation of Living Robots. -- https://www.uvm.edu/uvmnews/news/scientists-create-next-generation-living-robots

* [8] Kriegman, S., Blackiston, D., Levin, M., & Bongard, J. (Jan 13, 2020). A scalable pipeline for designing reconfigurable organisms. Proceedings of the National Academy of Sciences. -- https://doi.org/10.1073/pnas.1910837117

* [9] Fotowat, H., O'Neill, L., Pio-Lopez, L., Sperry, M., Erickson, D., Lin, S., & Levin, M. (Feb 20, 2026). Engineered Living Systems With Self-Organizing Neural Networks: From Anatomy to Behavior and Gene Expression. Advanced Science. -- https://doi.org/10.1002/advs.202508967

* [10] Gumuskaya, G., Srivastava, P., Cooper, B. G., Lesser, H., et al. (Nov 30, 2023). Motile Living Biobots Self-Construct from Adult Human Somatic Progenitor Seed Cells. Advanced Science, 11(4), 2303575. -- https://doi.org/10.1002/advs.202303575

* [11] Wyss Institute (Mar 16, 2026). Toward autonomous self-organizing biological robots with a nervous system. -- https://wyss.harvard.edu/news/toward-autonomous-self-organizing-biological-robots-with-a-nervous-system/

* [12] Pai, V., Pio-Lopez, L., Sperry, M., et al. (Apr 22, 2025). Basal Xenobot transcriptomics reveals changes and novel control modality in cells freed from organismal influence. Communications Biology. -- https://doi.org/10.1038/s42003-025-08086-9

* [13] Clawson, W., & Levin, M. (Jul 14, 2022). Endless forms most beautiful 2.0: teleonomy and the bioengineering of chimaeric and synthetic organisms. Biological Journal of the Linnean Society. -- https://doi.org/10.1093/biolinnean/blac073