What Bodies Think About:

Bioelectric Computation Beyond the Nervous System as Inspiration for New Machine Learning Platforms

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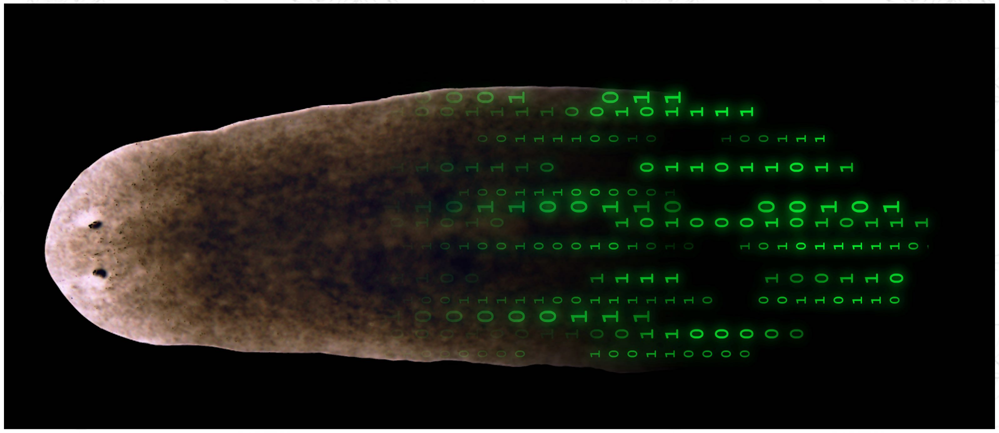

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Integrated
Cellular
Systems

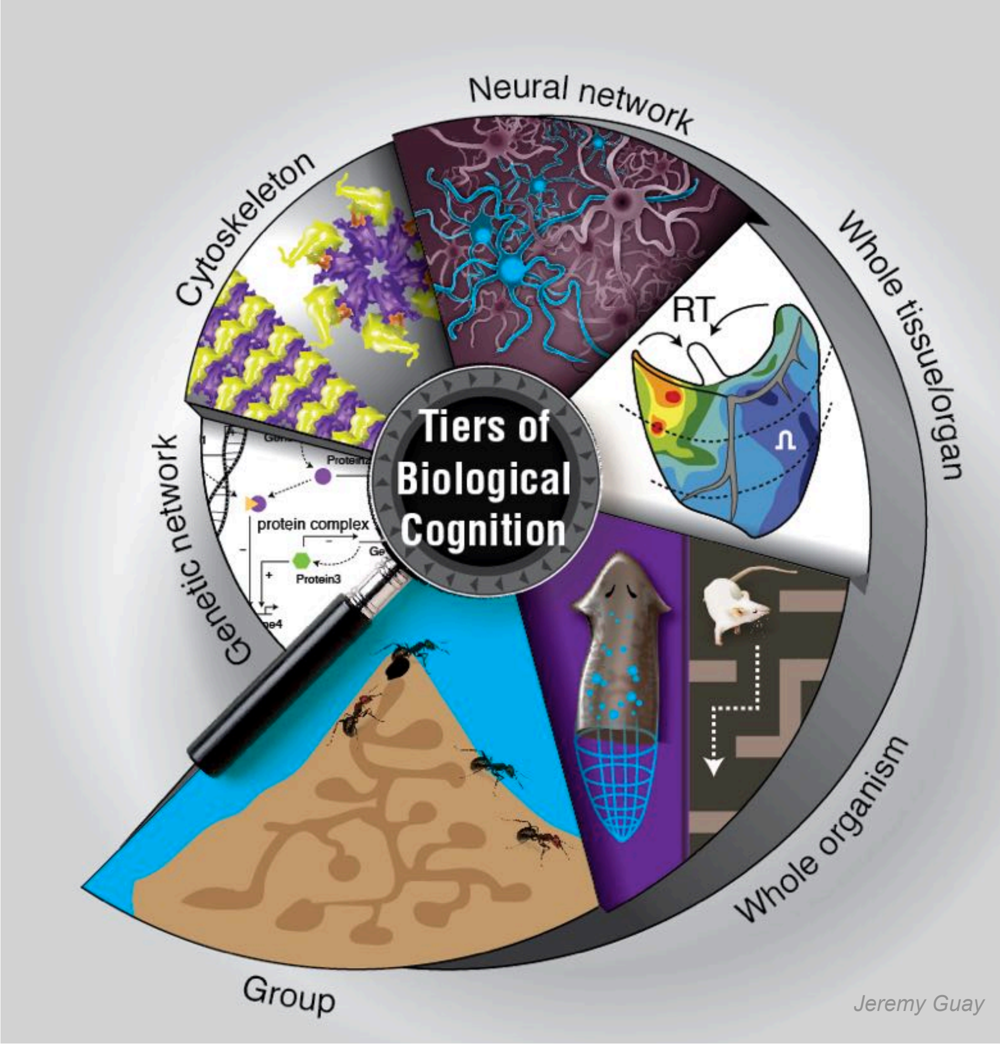
Main Message:

- Biology has been computing, at all scales, long before brains evolved

- Somatic decision-making and memory are mediated by ancient, pre-neural bioelectric networks across all cells

- Exploiting non-neural cognition is an exciting, untapped frontier for development of robust new AI platforms

- We are looking for experts in ML to collaborate with us to take bioelectrics beyond regenerative medicine



Outline

- Brain-body plasticity: processing info across brain and body
- Somatic cognition in the body: decision-making during self-editing of anatomy
- Bioelectric mechanisms of non-neural pattern control
- The future: regenerative medicine, synthetic living machines, novel AI architectures

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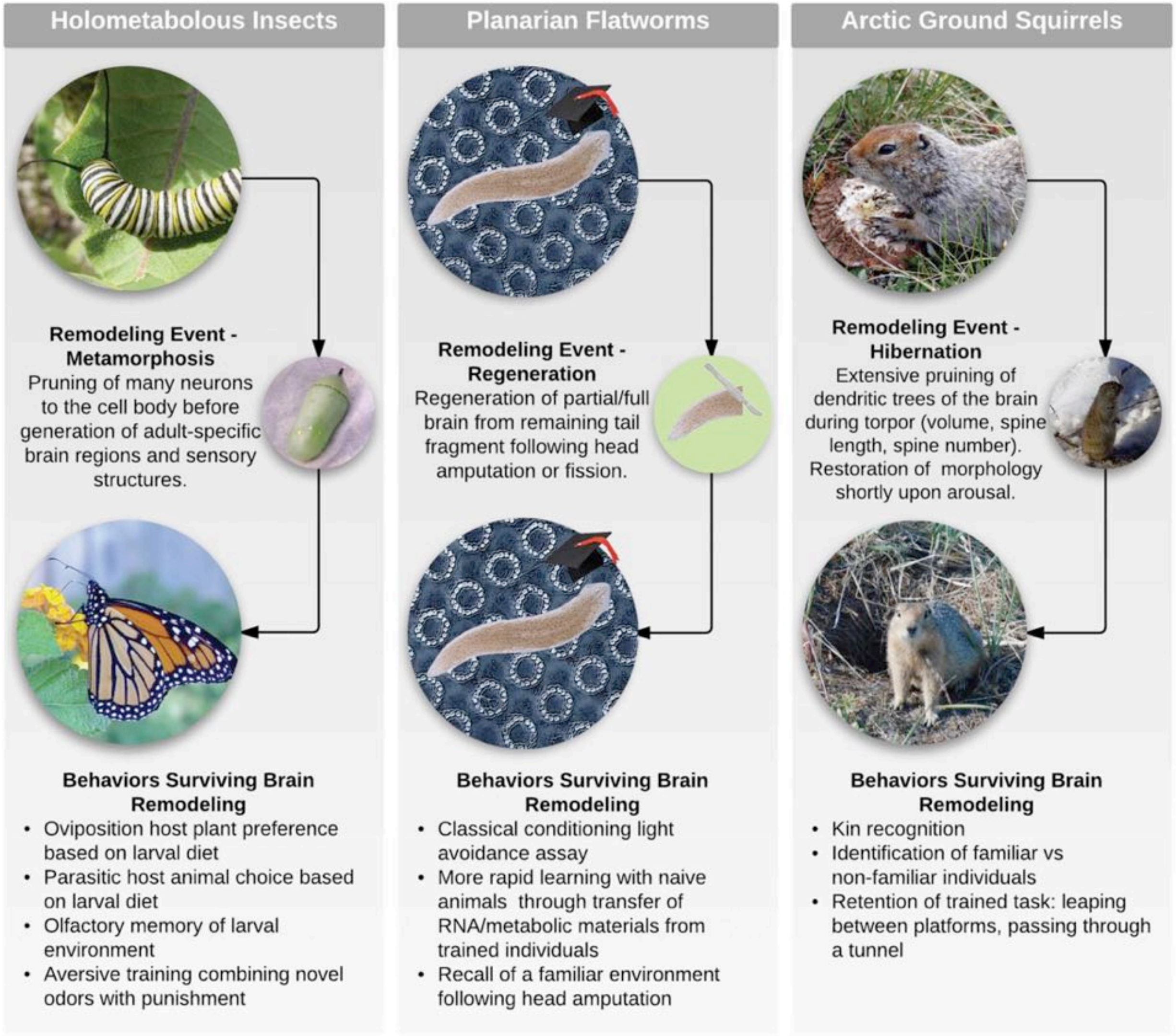
Behavioral Programs Adapt to Hardware Change

crawls, chews plants

brain is liquefied, rebuilt

flies, drinks nectar

The butterfly has the caterpillar's memories despite radical brain reconstruction



Holometabolous Insects

Remodeling Event - Metamorphosis
Pruning of many neurons to the cell body before generation of adult-specific brain regions and sensory structures.

Behaviors Surviving Brain Remodeling

- Oviposition host plant preference based on larval diet
- Parasitic host animal choice based on larval diet
- Olfactory memory of larval environment
- Aversive training combining novel odors with punishment

Planarian Flatworms

Remodeling Event - Regeneration
Regeneration of partial/full brain from remaining tail fragment following head amputation or fission.

Behaviors Surviving Brain Remodeling

- Classical conditioning light avoidance assay
- More rapid learning with naive animals through transfer of RNA/metabolic materials from trained individuals
- Recall of a familiar environment following head amputation

Arctic Ground Squirrels

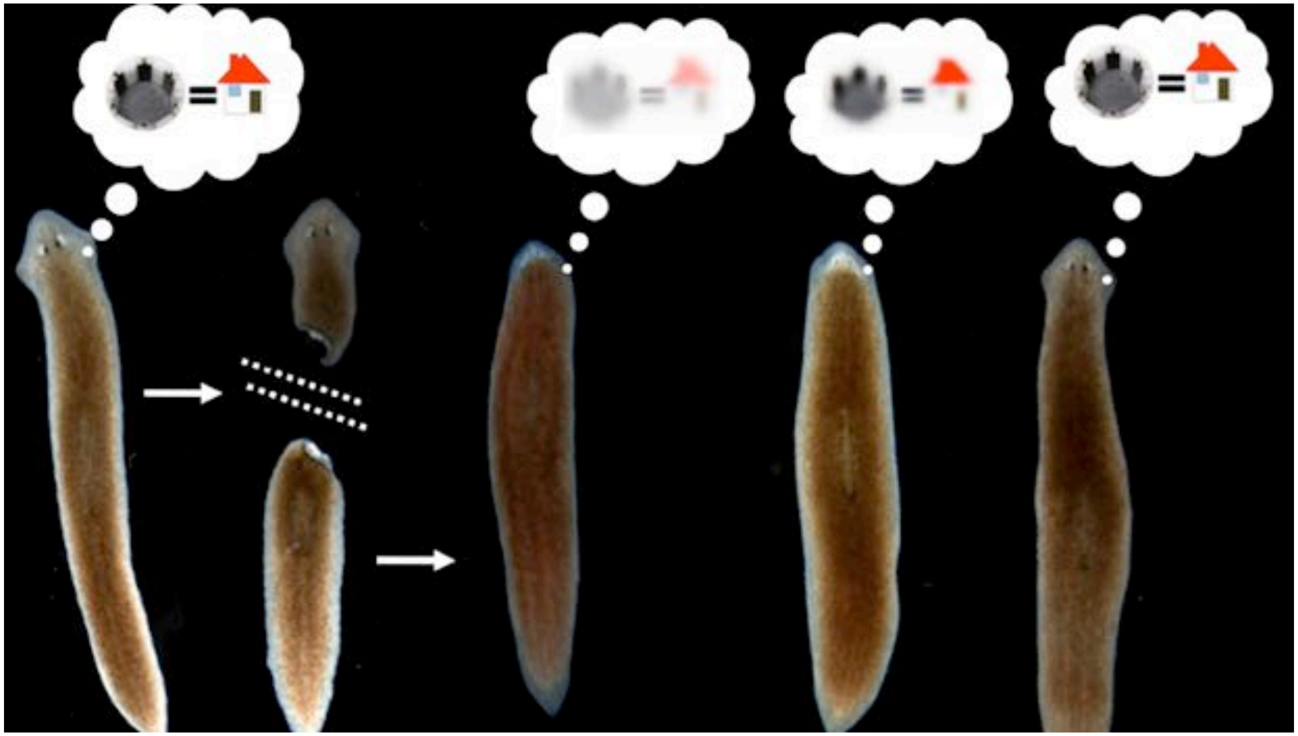
Remodeling Event - Hibernation
Extensive pruining of dendritic trees of the brain during torpor (volume, spine length, spine number). Restoration of morphology shortly upon arousal.

Behaviors Surviving Brain Remodeling

- Kin recognition
- Identification of familiar vs non-familiar individuals
- Retention of trained task: leaping between platforms, passing through a tunnel

Planarian Memories Survive Brain Regeneration

Memory stored outside the head, imprinted on regenerated brain

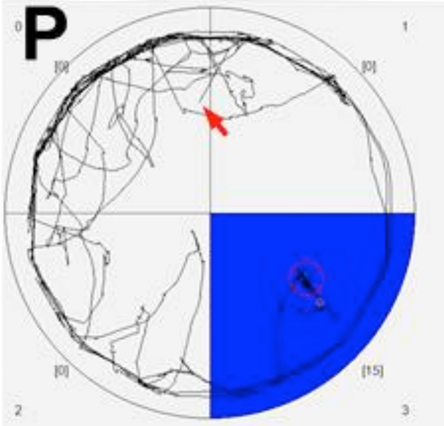


training -> memory

decapitation

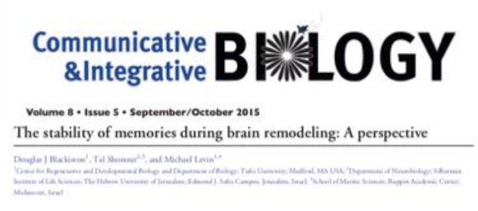
head regeneration

memory testing



Capturing the Public Interest


When I read that researchers trained flatworms, decapitated them, and discovered that after their heads grew back the worms had retained their training...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The stability of memories during brain remodeling: A perspective

Douglas J Blackiston[1], Tal Shomrat[2,3], and Michael Levin[1,*]


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RESEARCH ARTICLE

An automated training paradigm reveals long-term memory in planarians and its persistence through head regeneration

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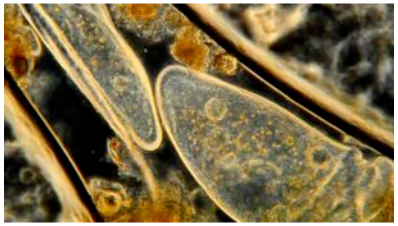
Wiener's Levels of Cognition



- Behavior
  - Active
    - Purposeful
      - Feed-back (teleological)
        - Predictive (extrapolative)
          - 1st, 2nd, etc. oder of prediction, self-reference
        - Non-predictive (non-extrapolative)
      - No feedback (non-teleological)
    - Non-purposeful (random)
  - Non-active (passive)

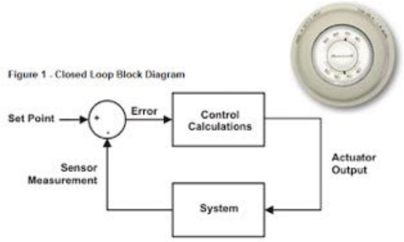


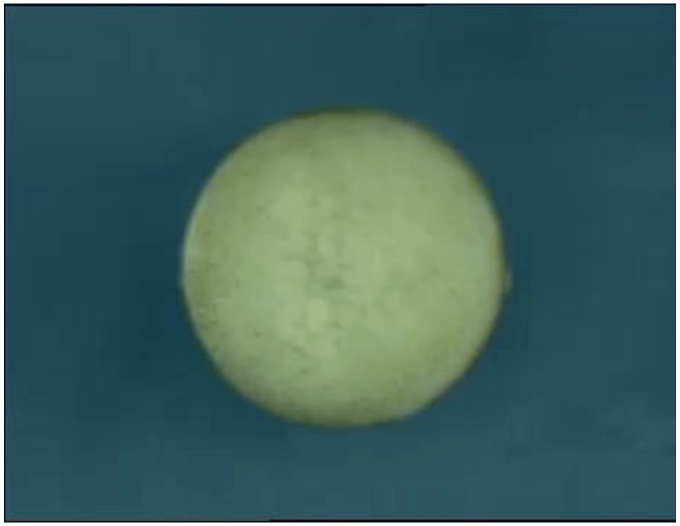
Figure 1 . Closed Loop Block Diagram

Unicellular organisms robustly achieve physiology, patterning, and behavior goals

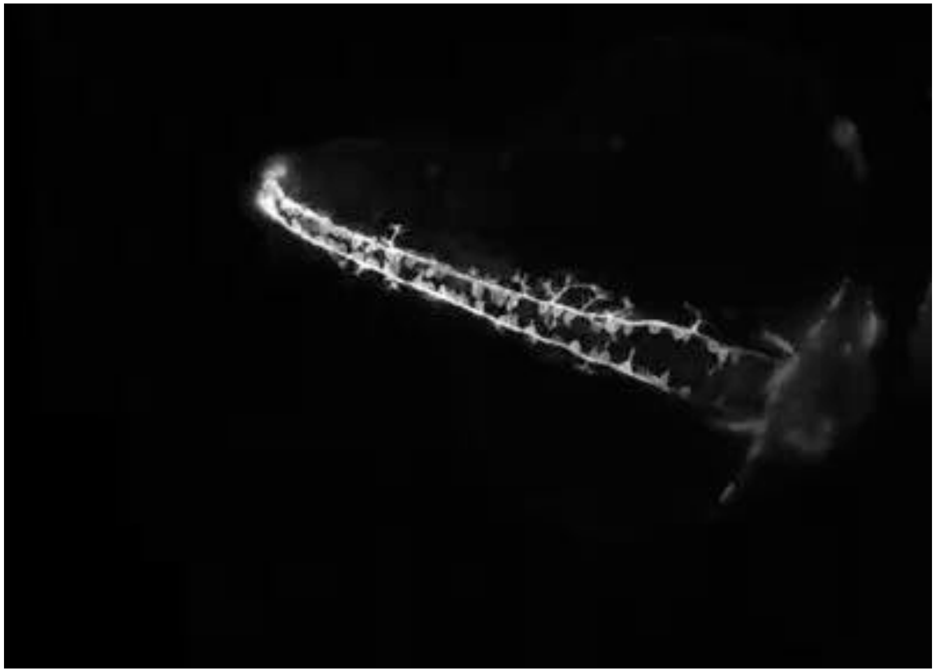
1 cell
no "brain"

Lacrymaria

Cells did not lose their smarts when joining up to form multicellular creatures; they broadened their (computational) horizons - increased the boundary of the "self" - the borders of what they measure/control



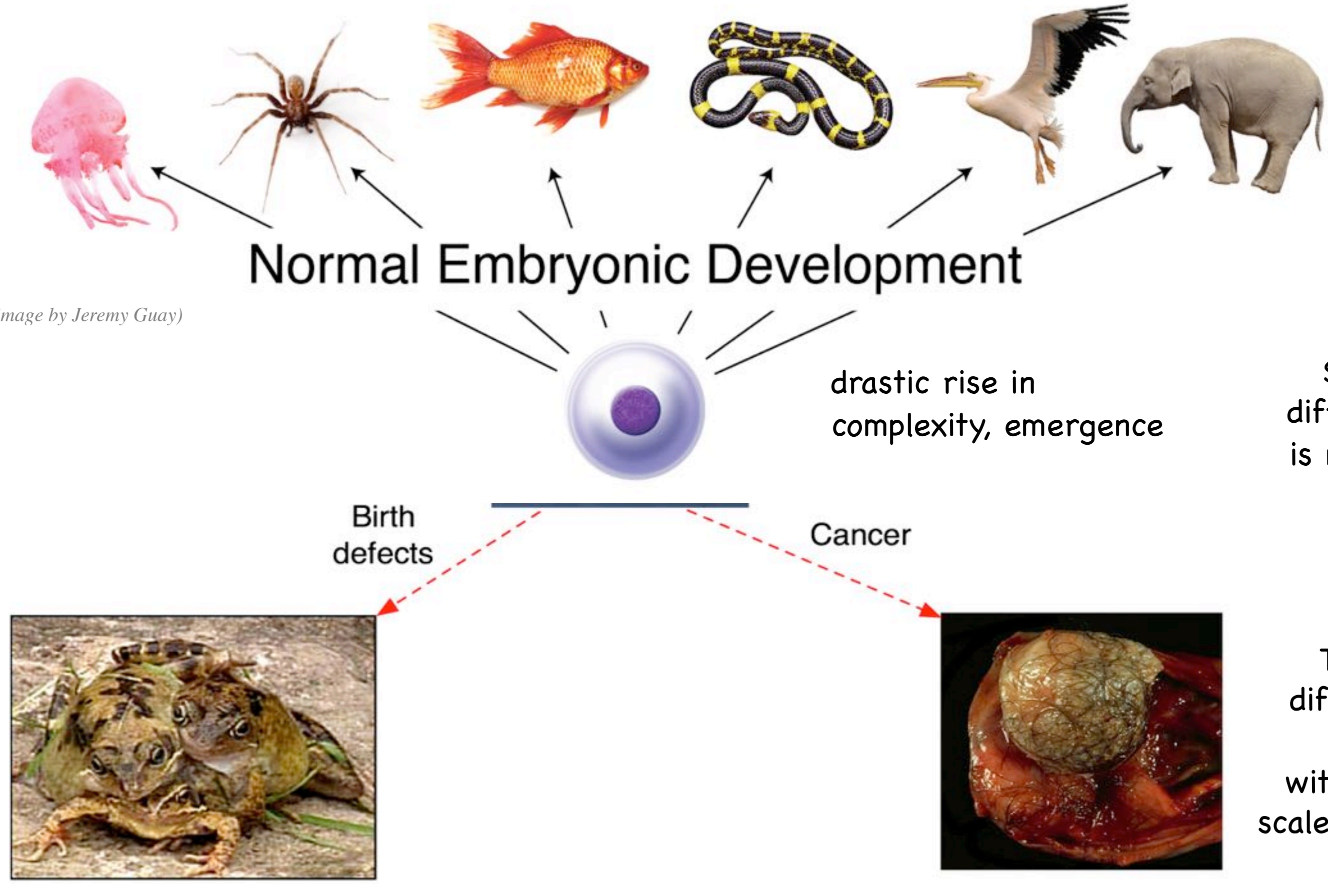
frog embryo developing



Nervous system developing

Elizabeth Haynes & Jiaye He

Embryogenesis: reliable self-assembly



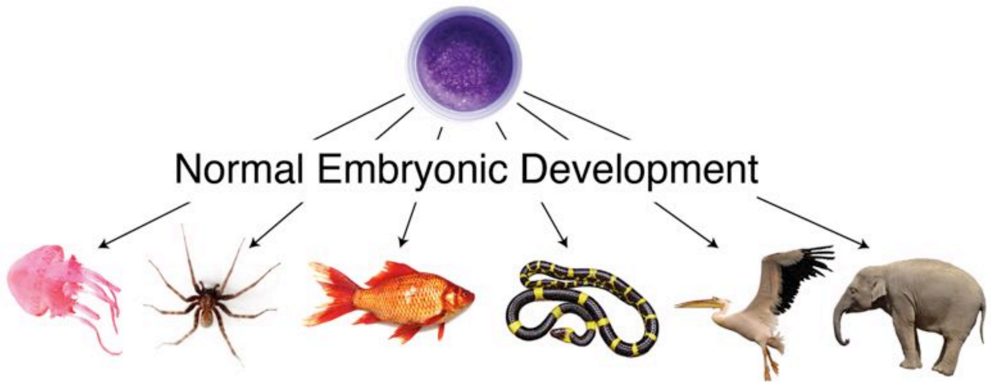
(image by Jeremy Guay)

drastic rise in
complexity, emergence

Stem cell
differentiation
is not enough

Teratoma:
differentiated
tissues
without large-
scale organization

Development: initial generation of form



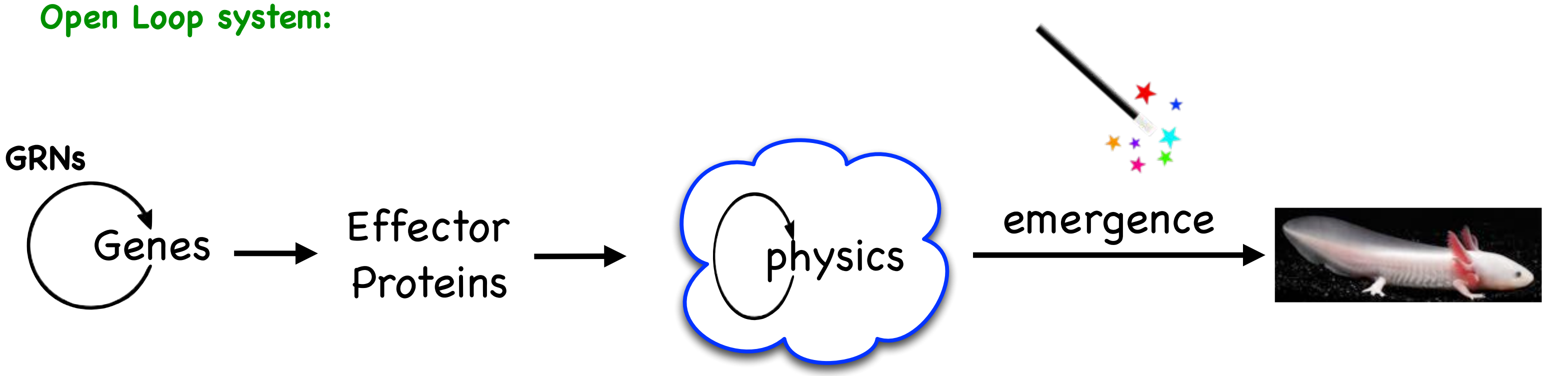
(image by
Jeremy Guay)

Tissues/organs emerge from
- cell differentiation
- cell proliferation
- cell migration
- apoptosis

under progressive unrolling of genome

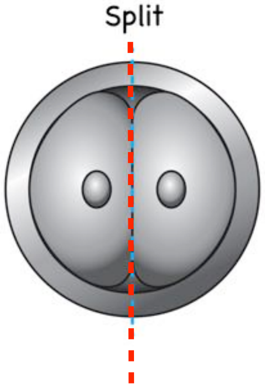
The current paradigm:

Open Loop system:

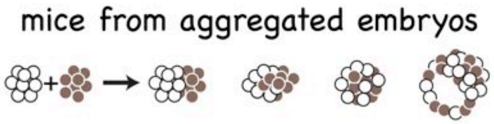

GRNs

Genes → Effector Proteins → physics —emergence→

Embryogenesis is reliable, but not all hardwired -
- regulation after drastic perturbation



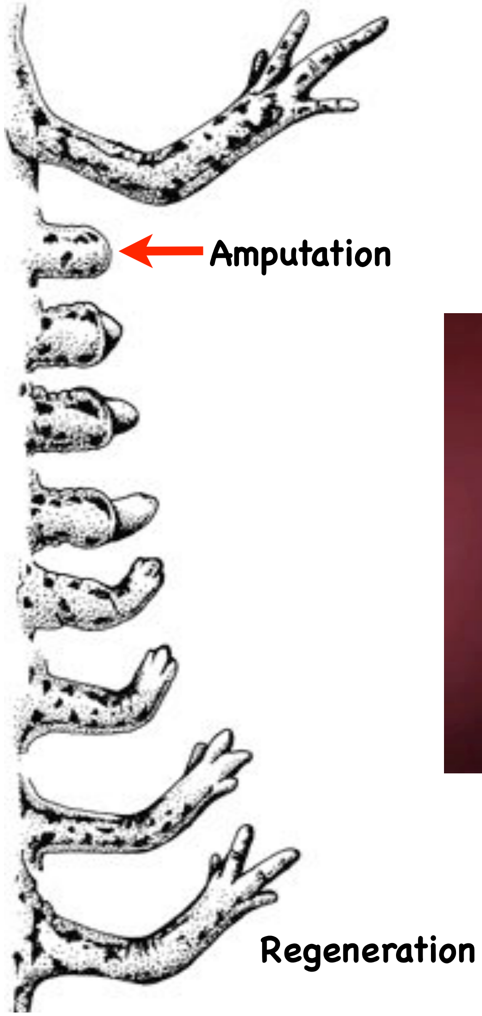
Splitting an embryo in half
makes 2 normal embryos

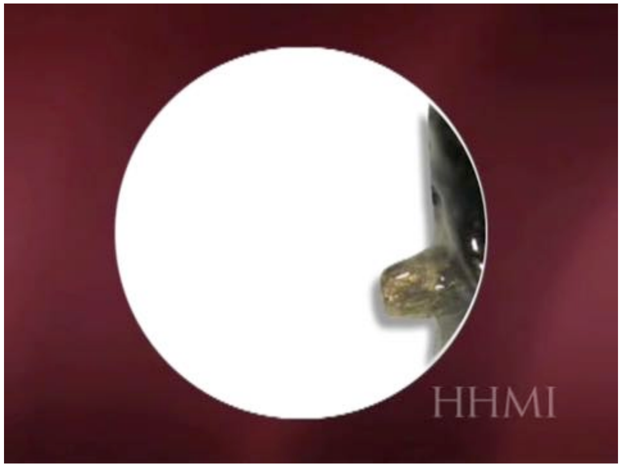


(image by Jeremy Guay)

Combining 2 embryos
gives 1 normal organism

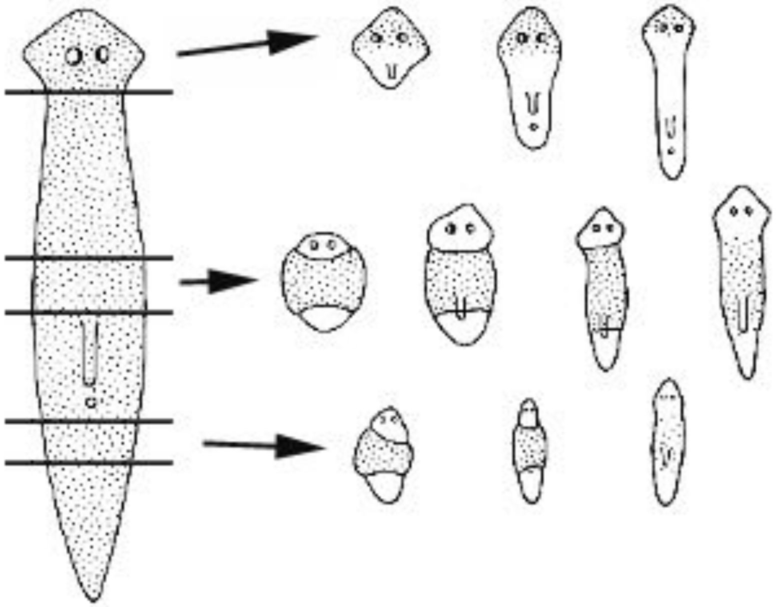
Regeneration: rebuild the target morphology after unpredictable deformations, then stop

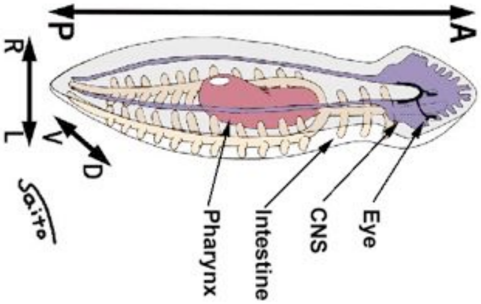


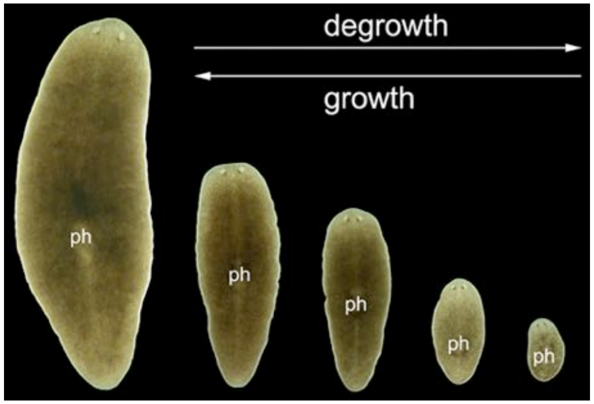


Axolotl - a complex vertebrate that regenerates limbs, eyes, jaws, portions of the brain, heart, and tail, including spinal cord, muscle, and other tissues.

Planarian Regeneration: restoring global order







Precise allometric rescaling,
immortality!

Regeneration is not just for "lower" animals

The human liver is highly regenerative

Every year, deer regenerate meters of bone, innervation, and skin

Price and Allen, 2004

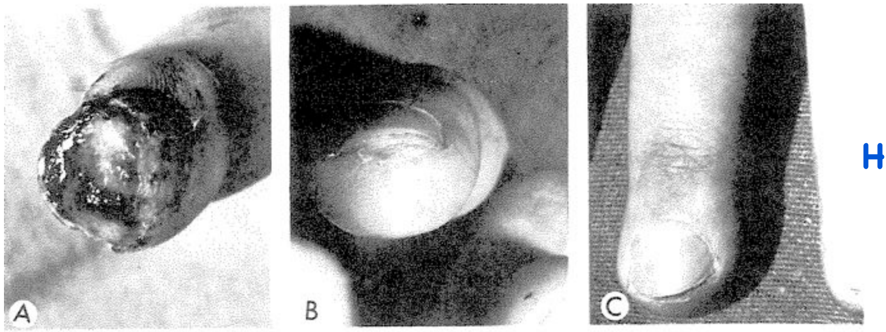
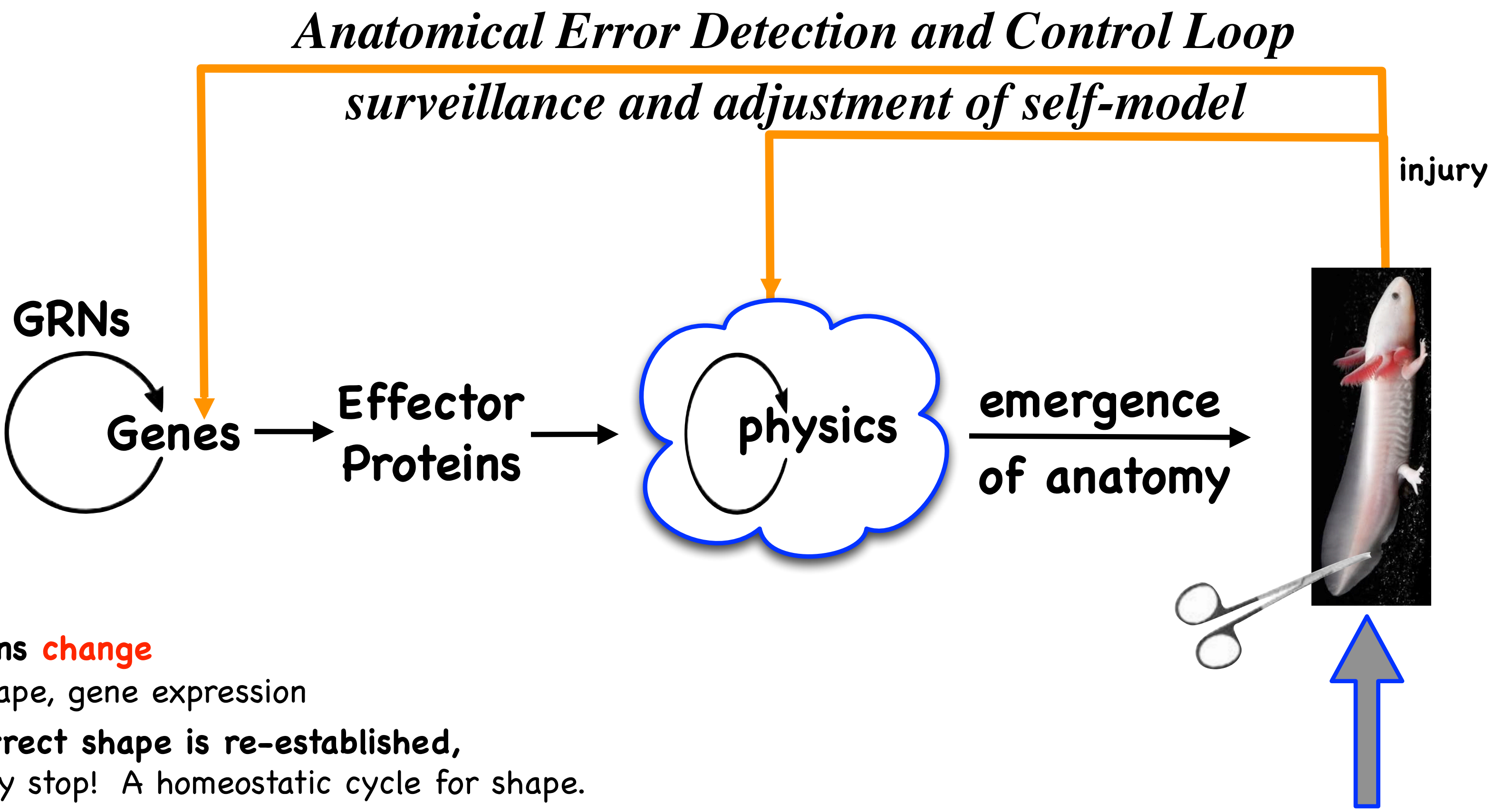


Fig. 2. (A) Amputation of finger tip in 5-yr-old girl. (B), (C) Twelve weeks after accident.

Human children below 7-11 years old regenerate fingertips

Closed Loop Pattern Homeostasis



Anatomical Error Detection and Control Loop

surveillance and adjustment of self-model

injury

GRNs

Genes

Effector Proteins

physics

emergence of anatomy

Unpredictable

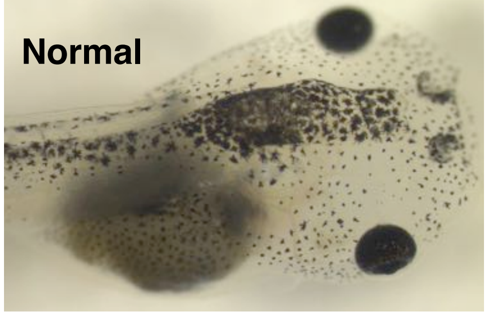
environmental

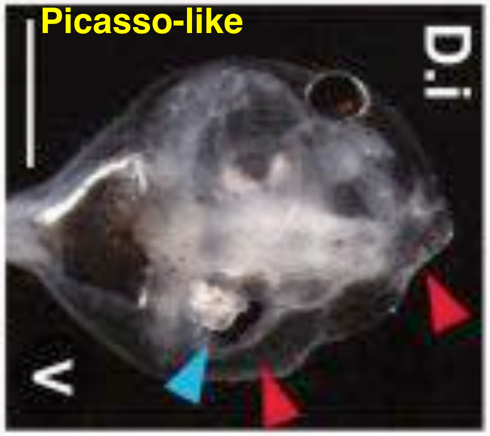
perturbations

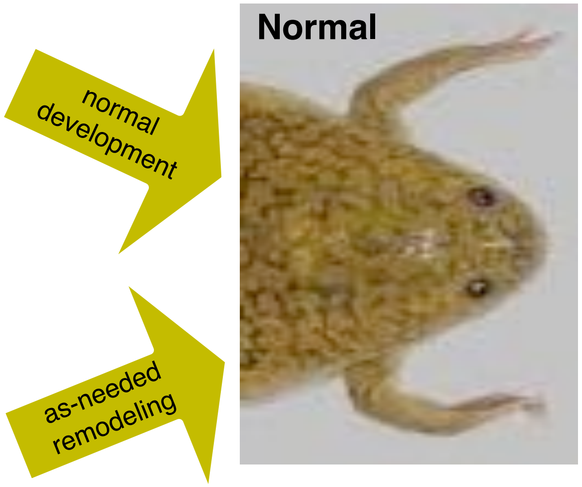
Tissues/organs change
position, shape, gene expression
until the correct shape is re-established,
and then they stop! A homeostatic cycle for shape.

Our strategy:
- target the homeostatic setpoint (pattern memory)
- rewrite it, let cells build to spec

Remodeling until a "correct frog face" is made








Dany Adams


Laura Vandenberg

Change bioelectric prepattern

↓

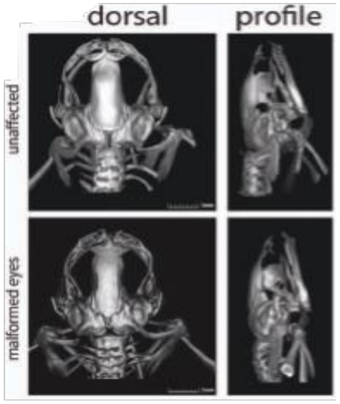
Craniofacial mispatterning

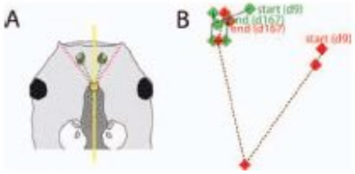
↓

Metamorphosis

↓

Morphometric analysis and modeling reveals: faces fix themselves!!



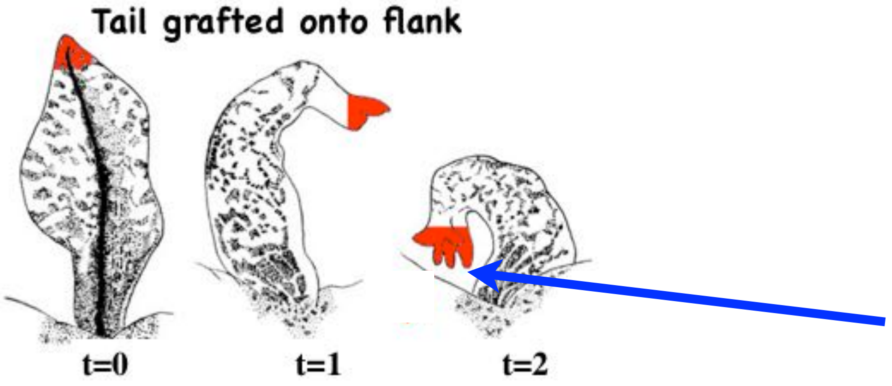


Cannot just follow a hardwired set of movements.

How does it know when it's "right"?

Anatomical surveillance and remodeling toward globally-correct structure:

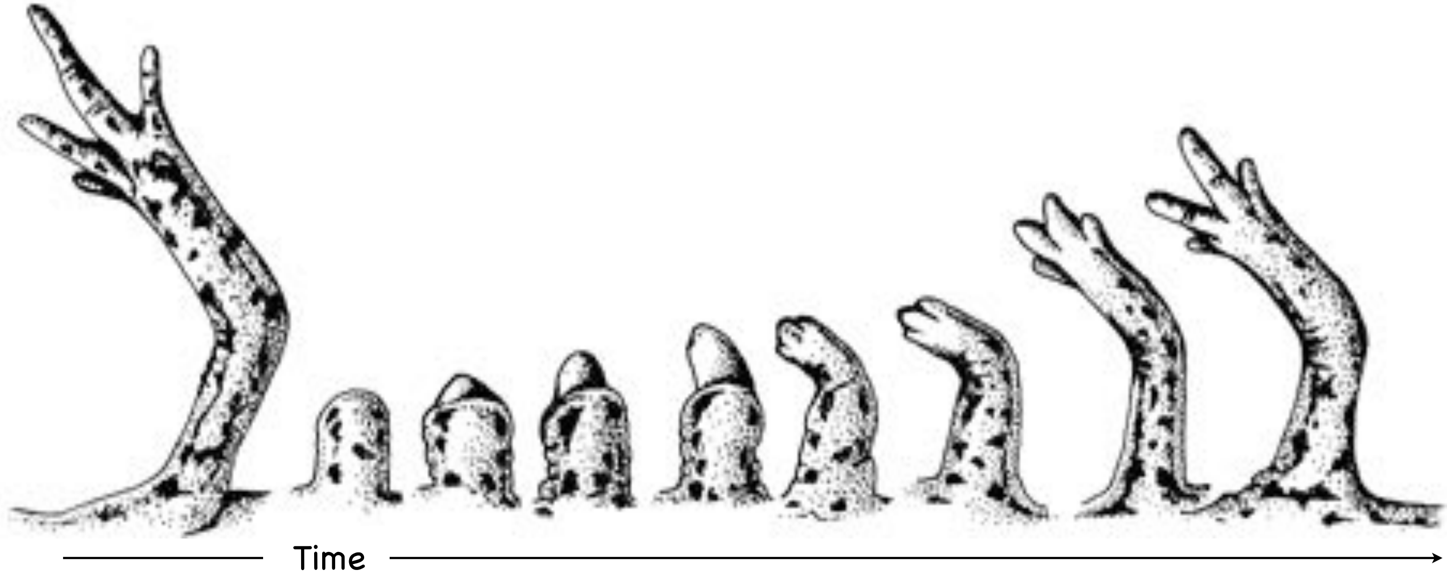
A tail grafted onto the side of
a salamander remodels into a limb.



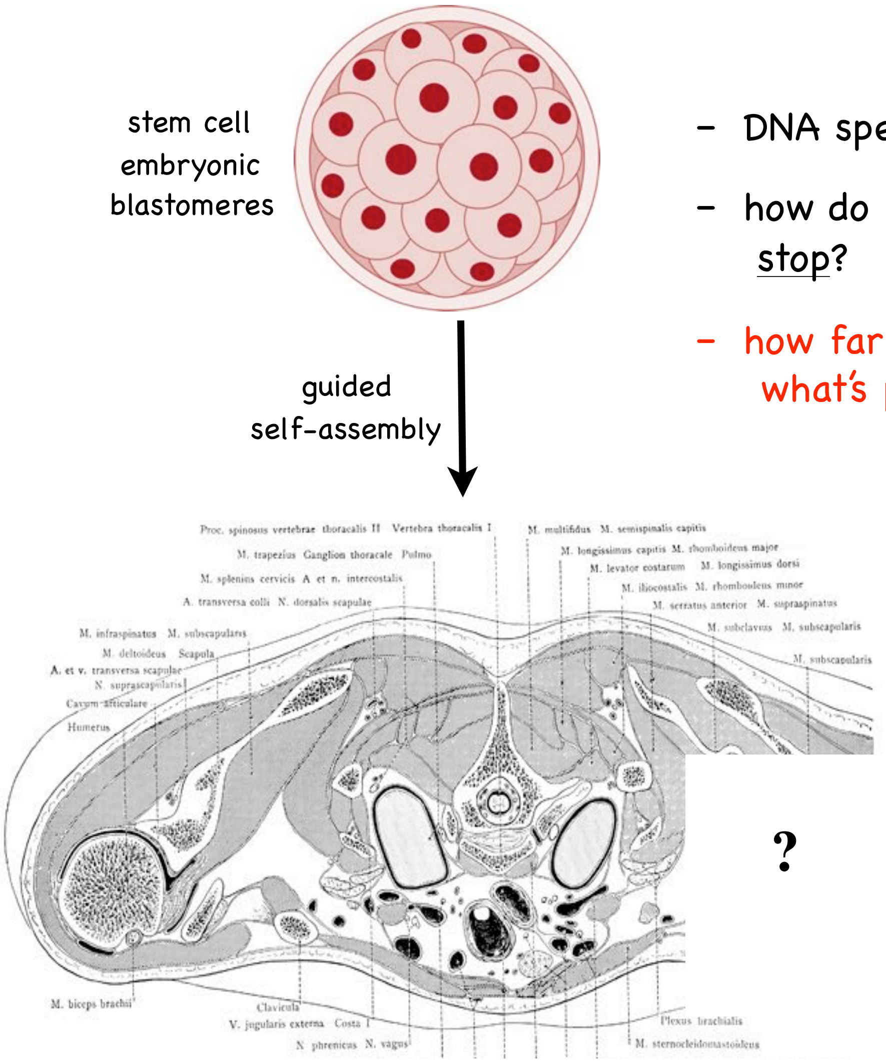
**not just local
environment
matters**

Fundamentally, regeneration is a computational problem:

What shape do I need to have? (remembers goal)
What shape do I have now? (ascertains current state)
How do I get from here to there? (plans)
When should I stop growing? (makes decision)



What determines patterning?

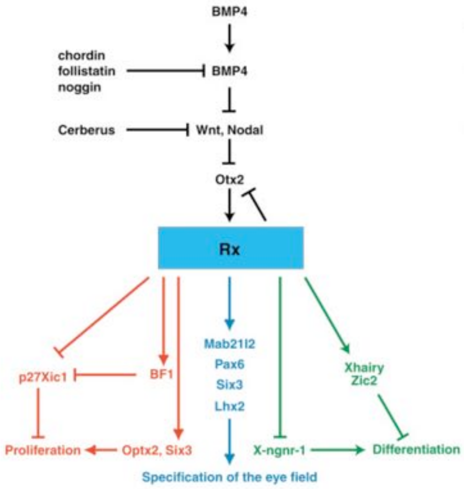


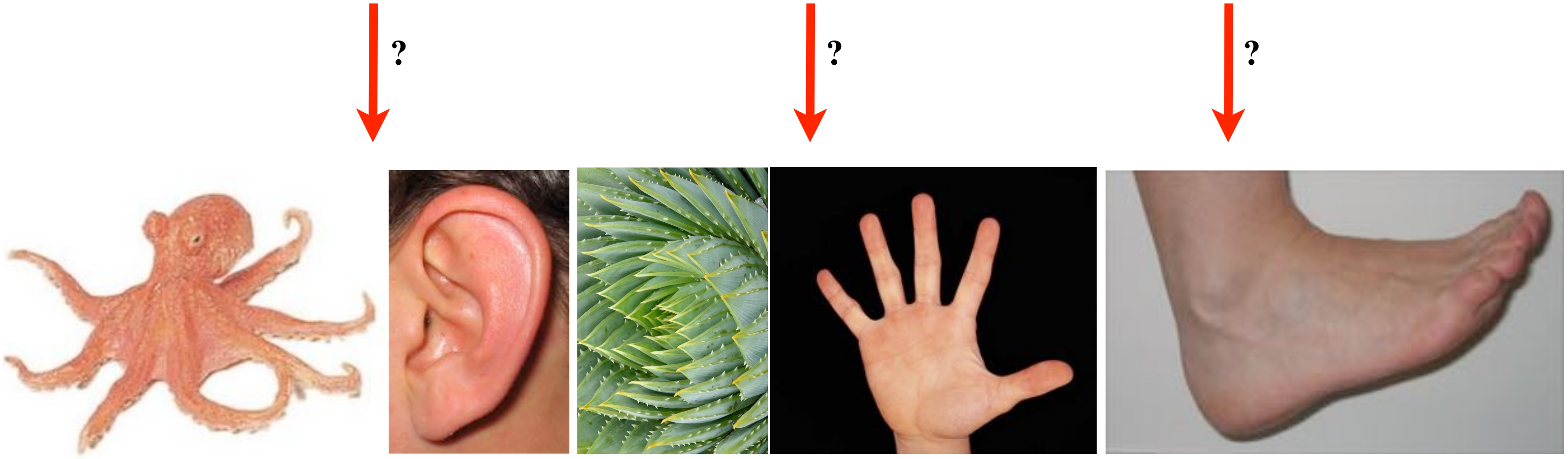
- DNA specifies proteins; whence Anatomy?
- how do cell groups know what to make and when to stop?
- how far can we push shape change? Engineers ask: what's possible to build?

How to repair (edit) it?

Knowledge gap:

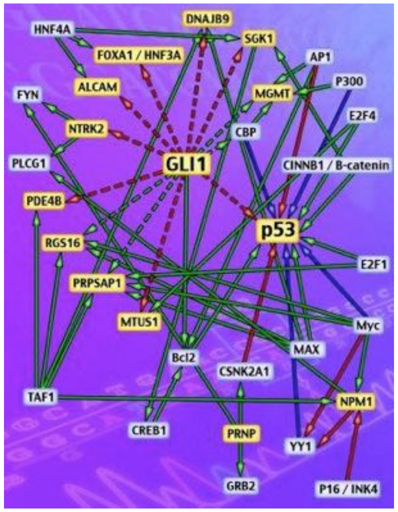
We cannot
read a genome
and predict
anatomy!





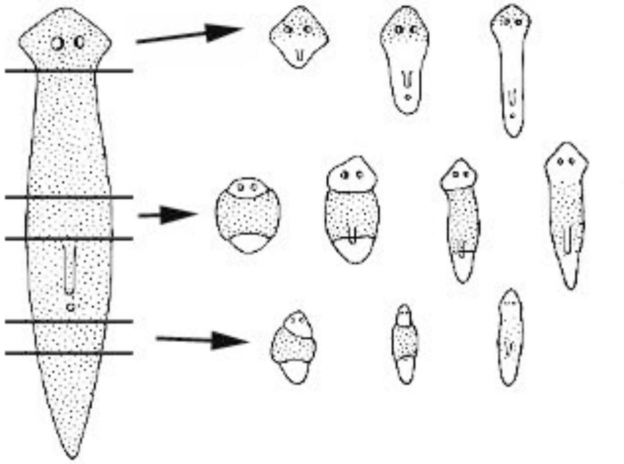
Knowledge gap:

We want to fix a birth defect
or induce shape change
for regenerative repair.

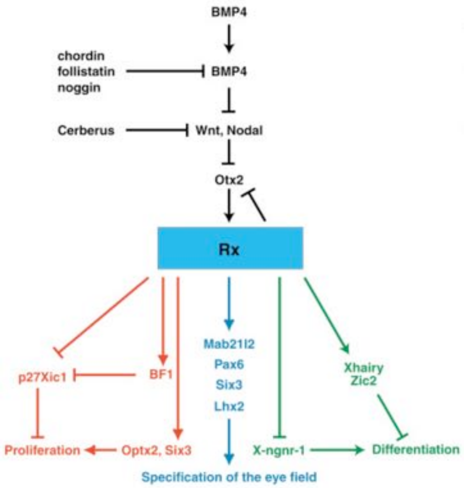


What to manipulate in this
network, to get the shape
change we want?!?

Knowledge gap:



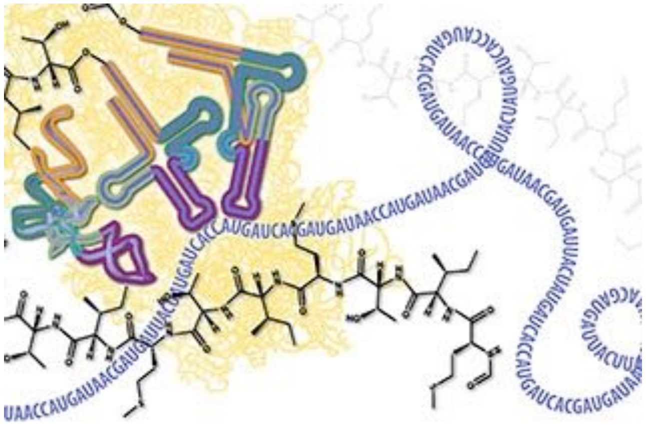
You want to implement this remarkable ability in your robot:



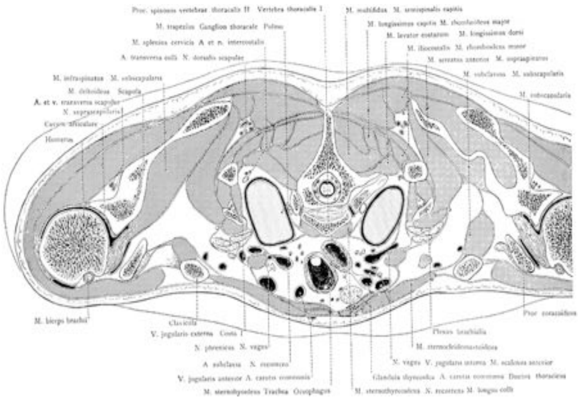
What aspects of this network are actually responsible for the shape-regulating property we want to copy in the robot?

The State of the Art

We are very good at manipulating molecules and cells necessary for complex pattern control

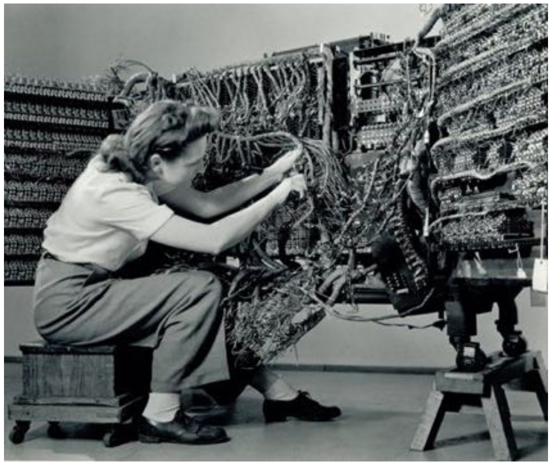


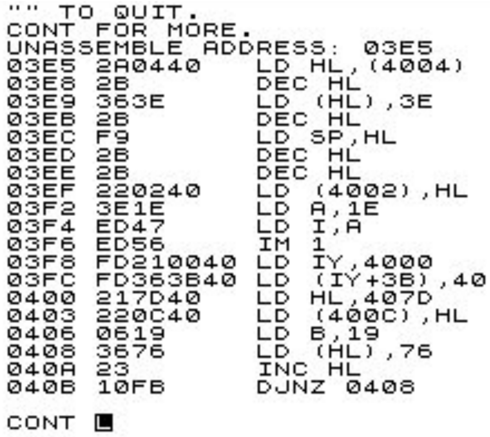
We are a long way from understanding algorithms sufficient for control of large-scale form and function



can we move biology beyond machine code to address anatomical decision-making?

Key insights that allowed computer science to drive a revolution in information technology





```
"" TO QUIT.
CONT FOR MORE.
UNASSEMBLE ADDRESS: 03E5
03E5 2A0440   LD HL,(4004)
03E8 2B       DEC HL
03E9 363E     LD (HL),3E
03EB 2B       DEC HL
03EC F9       LD SP,HL
03ED 2B       DEC HL
03EE 2B       DEC HL
03EF 220240   LD (4002),HL
03F2 3E1E     LD A,1E
03F4 ED47     LD I,A
03F6 ED56     IM 1
03F8 FD210040 LD IY,4000
03FC FD363B40 LD (IY+3B),40
0400 217D40   LD HL,407D
0403 220C40   LD (400C),HL
0406 0619     LD B,19
0408 3676     LD (HL),76
040A 23       INC HL
040B 10FB     DJNZ 0408

CONT ■
```

```
Kruskal($N, E, cost$) :
    sort edges in $E$ by increasing $cost$
    **while** $|T| < |N| - 1$:
        let $(u, v)$ be the next edge in $E$
        **if** $u$ and $v$ are on different components:
            join the components of $u$ and $v$
            $T = T \cup \{(u, v)\}$
    **return** $T$
```

Progress

biology
today

- Focus on information and control algorithms, not hardware
- Hardware-software distinction (device-independence)

Cognitive-like properties of pattern homeostasis

- Goal-directed behavior toward specific anatomical outcomes
- Flexibility (robustness) under variable conditions
- Global integration of cell functions into complex large-scale outcomes

if anatomical editing is a kind of memory process,
the engram should be re-writable

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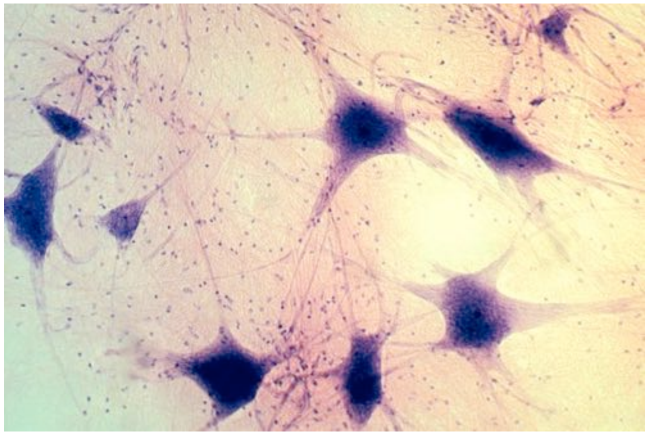
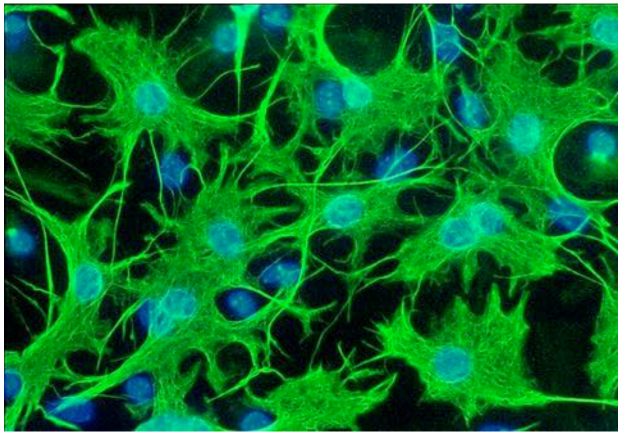
- The future: regenerative medicine, synthetic living machines, novel AI architectures

Like the brain, somatic tissues form bioelectric networks that make decisions (about anatomy). We can target this system for control of large-scale pattern editing.

Brains did not Invent their Tricks de Novo



nerve circuits that
compute, expect, learn, infer, make
decisions, remember patterns



electrically-communicating
non-neural cell groups
(gap junctions = synapses)

1. Our unicellular ancestors already had synaptic machinery, ion channels, neurotransmitters

2. Neural computation evolved by speed-optimizing ancient computational functions of somatic cells

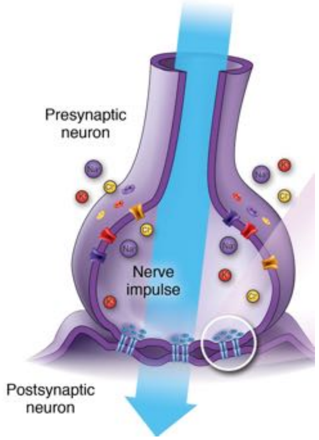
Hardware

gene products -> electric circuits

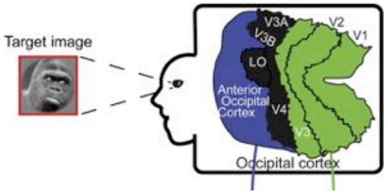
Software

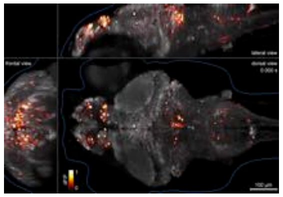
electrical dynamics -> memory

ion
channels,
electrical
synapses



neural





http://www.nature.com/nmeth/journal/v10/n5/full/nmeth.2434.html

Hardware

gene products -> electric circuits

Software

electrical dynamics -> memory

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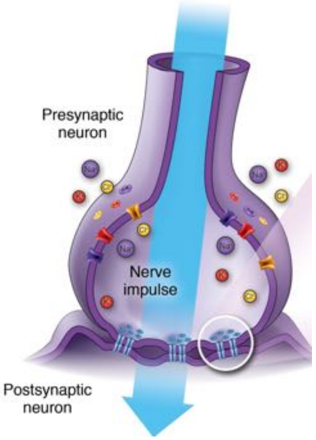
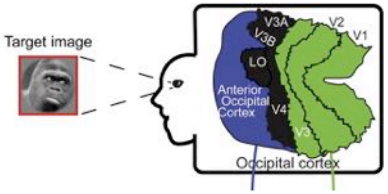
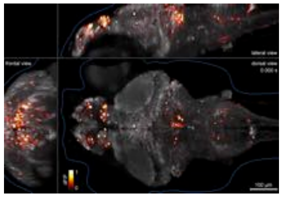


neural





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ion
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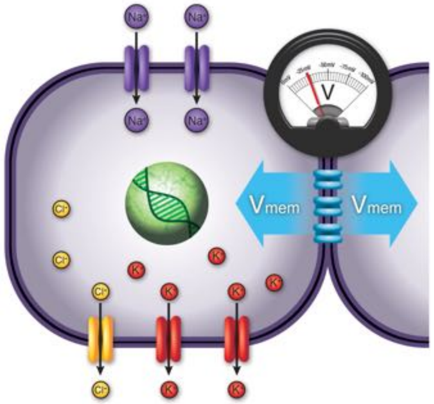
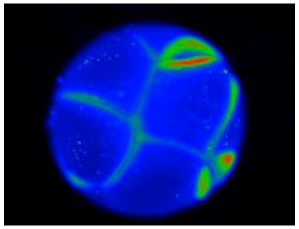
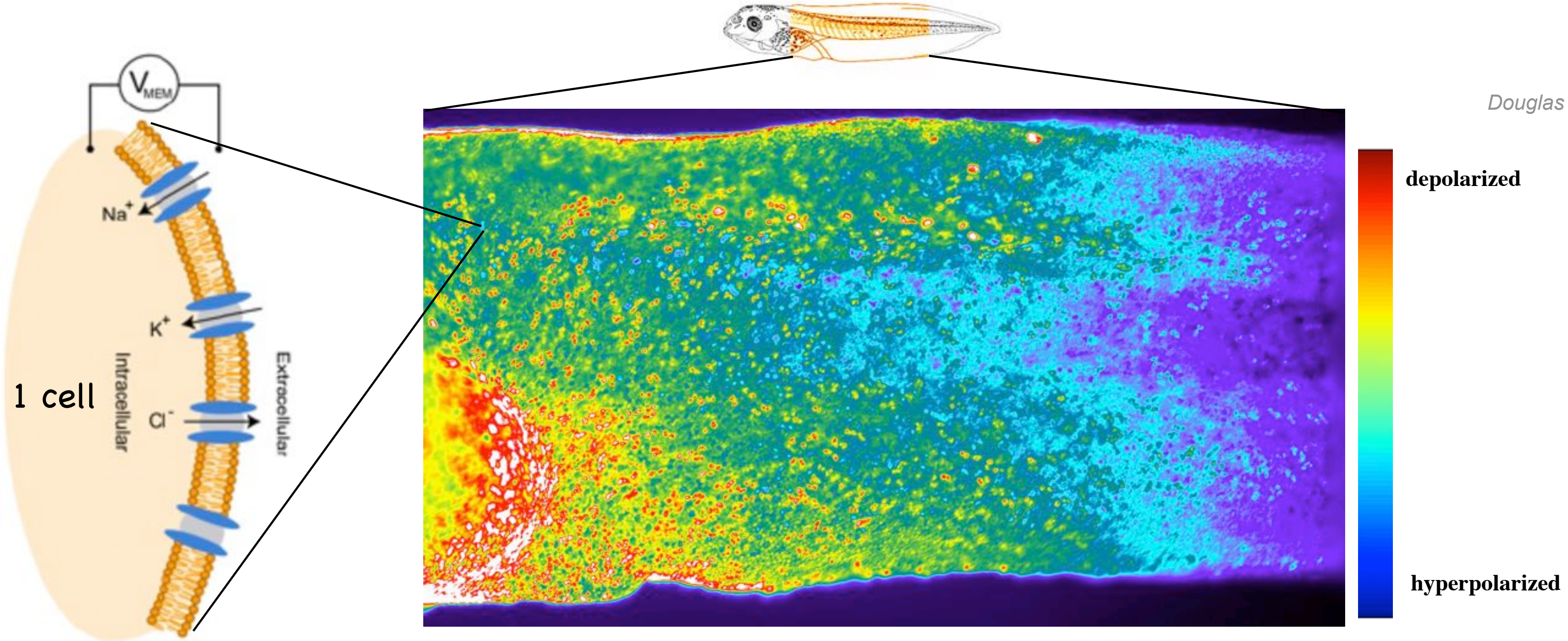


developmental

TBD



V_{mem} pattern = spatial difference of cells' resting potential across a tissue



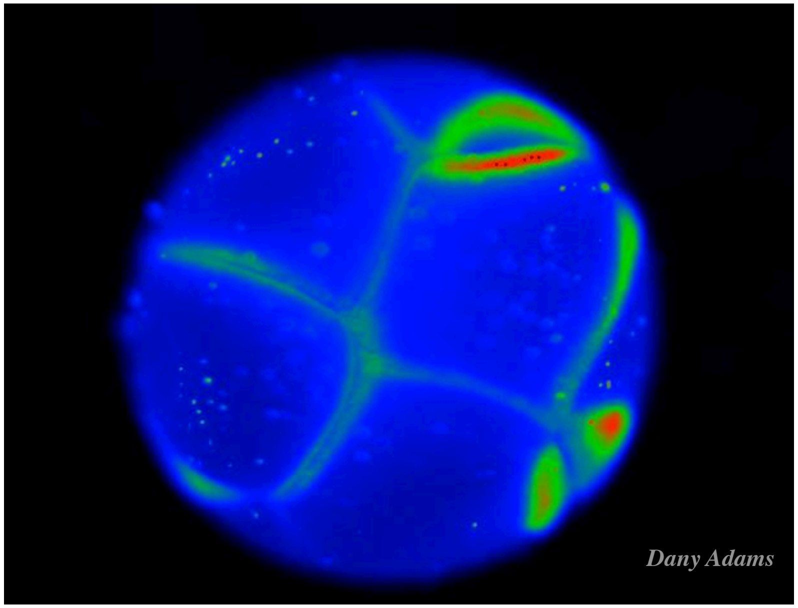
Douglas Blackiston

voltage dye reveals distribution of V_{mem} across intact Xenopus embryo flank (A-P gradient)

Bioelectrical signal = a change (in time) of spatial distribution of resting potentials in vivo

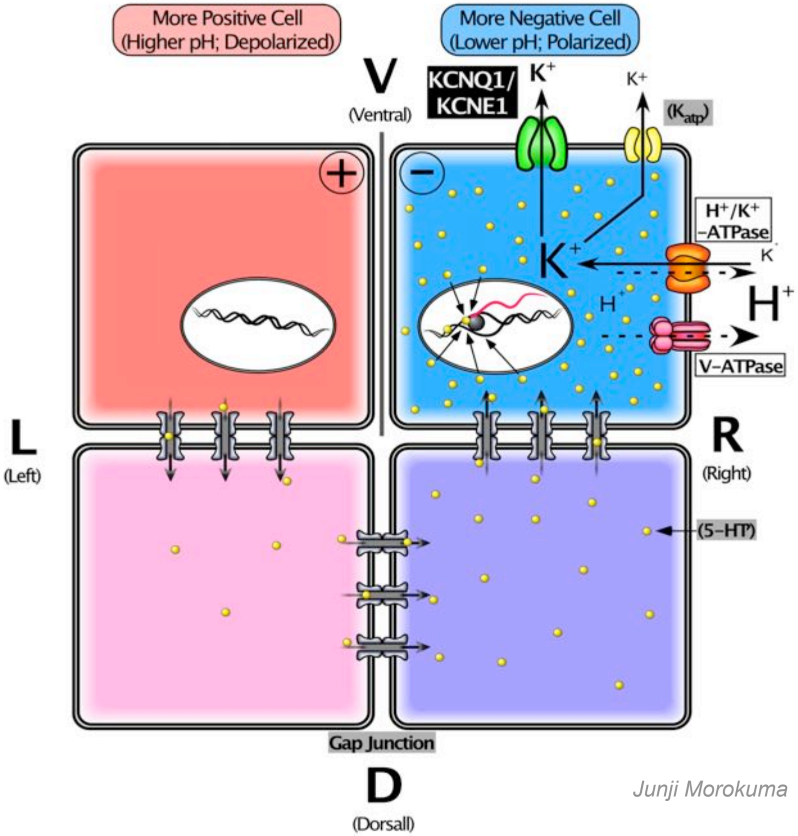
How we detect and model bioelectric signals:

Characterization of endogenous voltage gradients - direct measurement and correlation with morphogenetic events



Voltage reporting fluorescent dye
in time-lapse during Xenopus development

Quantitative computer simulation: synthesize biophysical and genetic data into predictive, quantitative, often non-linear models

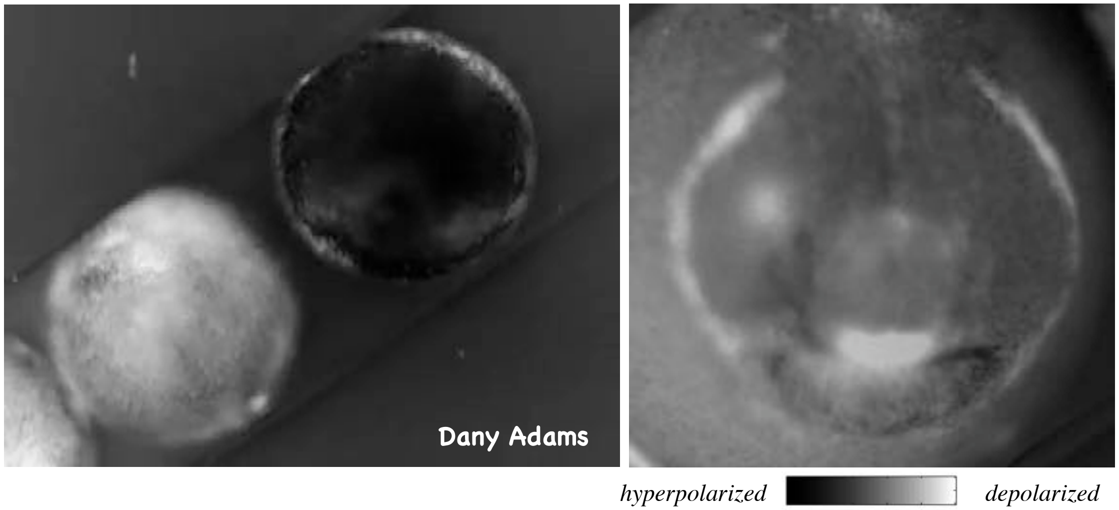


Junji Morokuma

Eavesdropping on Computation during Patterning

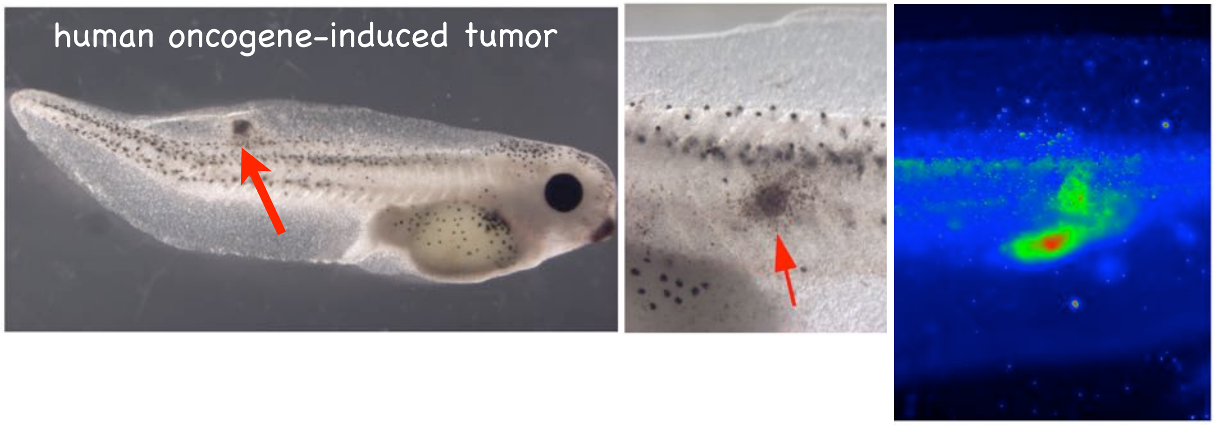
Normal

craniofacial
development
"electric face"
prepattern



Pathological

Bioelectric
signature of
cancer:
defection to
a unicellular
boundary of
self

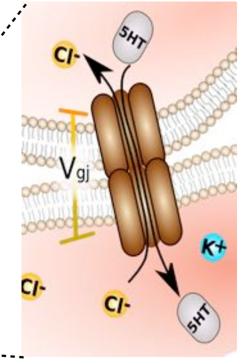


Manipulating Non-neural Bioelectric Networks

Tools we developed

NO applied electric fields -
molecular physiology only

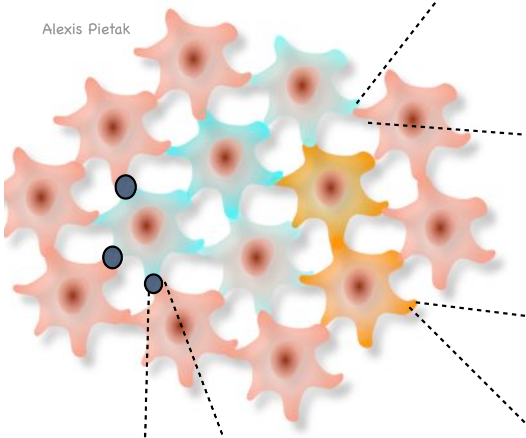
Gap Junction
(electrical synapse)



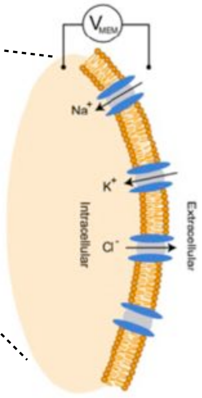
- Dominant negative Connexin proteins
- GJC drug blockers
- Cx mutants with altered gating or permeability

Synaptic plasticity

Non-neural cell network

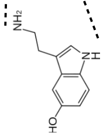


Ion channels
(setting V_{mem})



- Dominant ion channel over-expression (depolarizing or hyperpolarizing, light-gated, drug-gated)
- Drug blockers of native channel
- Drug openers of native channel

Intrinsic plasticity



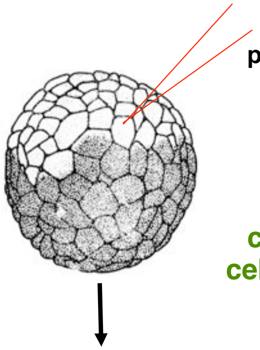
Network Activity

- Transporter or receptor mutant overexpression
- Drug agonists or antagonists of receptors or transporters
- Photo-uncaging of neurotransmitter

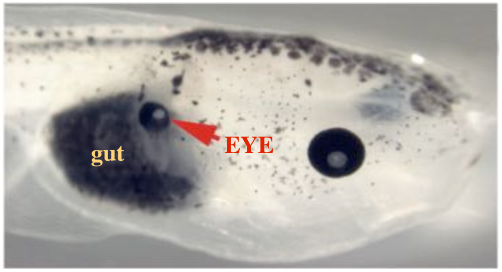
Manipulation of V_{mem} enables organ-level reprogramming

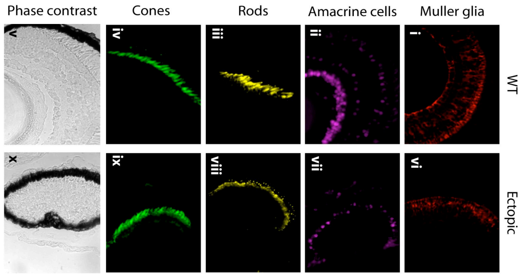
– gut endoderm into complete eye

Kv1.5 channel mRNA targeted to ventral or posterior regions



can reprogram many cell types into complete ectopic eye!

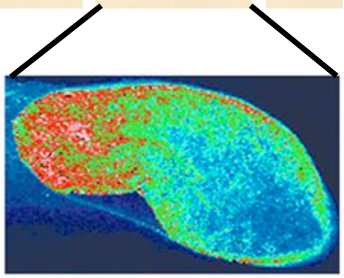




– cells -> make 2nd head

Head and tail amputation

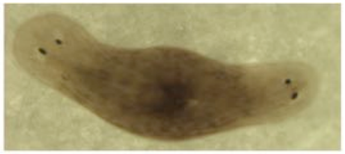
endogenous body-wide voltage gradient



use drugs and RNAi to change V_{mem} pattern across fragment

1st 3 hours

bi-axial 2 head worm

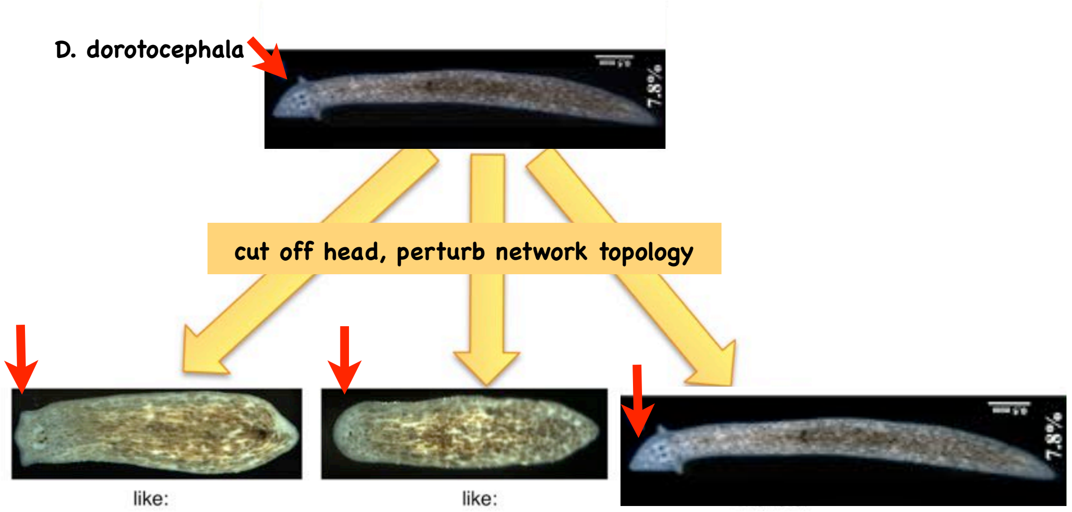


bi-axial no head worm

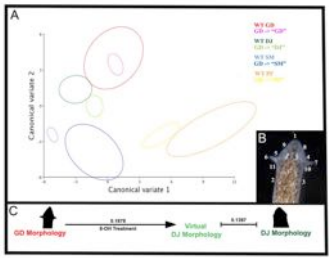
?

Bioelectric circuit editing over-rides default genome-specified target morphology and switches among species

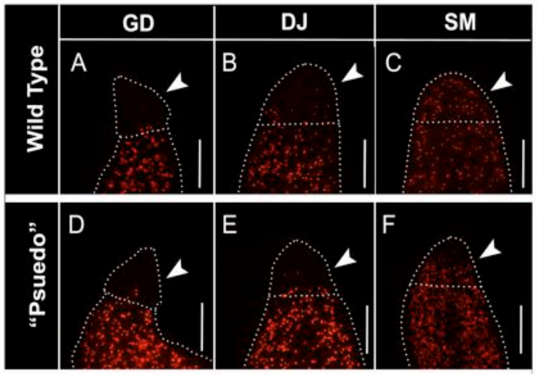
Tweaking of bioelectric network connectivity causes regeneration of head shapes appropriate to other species! (150 m.y. distant)
(also includes brain shape and stem cell distribution pattern)

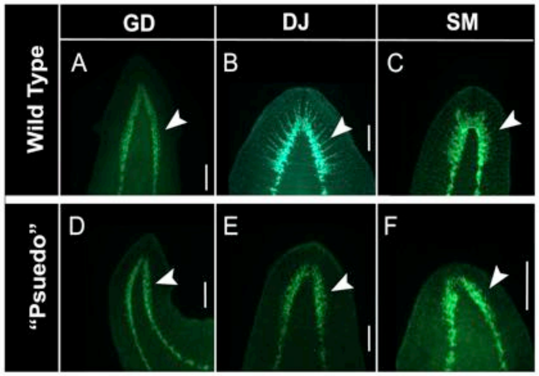


quantitative morphometrics



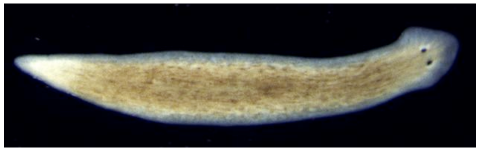
brain shape and
stem cell patterns
change also!



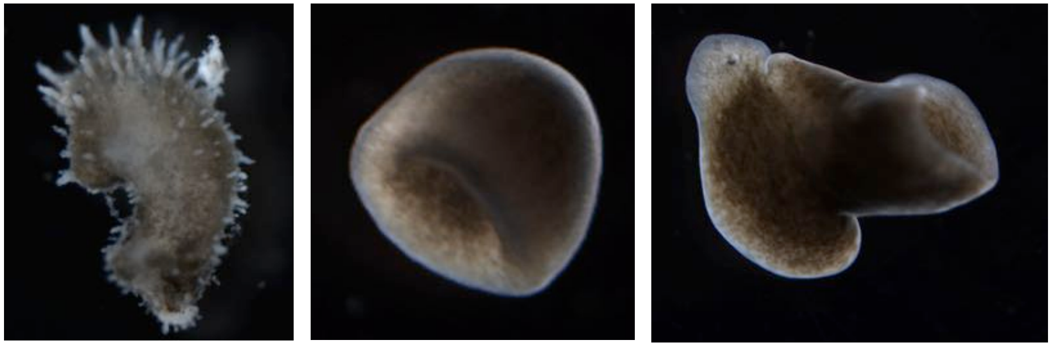


Drastic body-plan editing: flatworms, with a normal planarian genome, don't have to be flat!

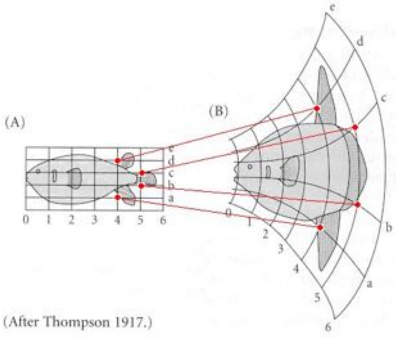
Normal



Bioelectric Circuit Altered After Bisection



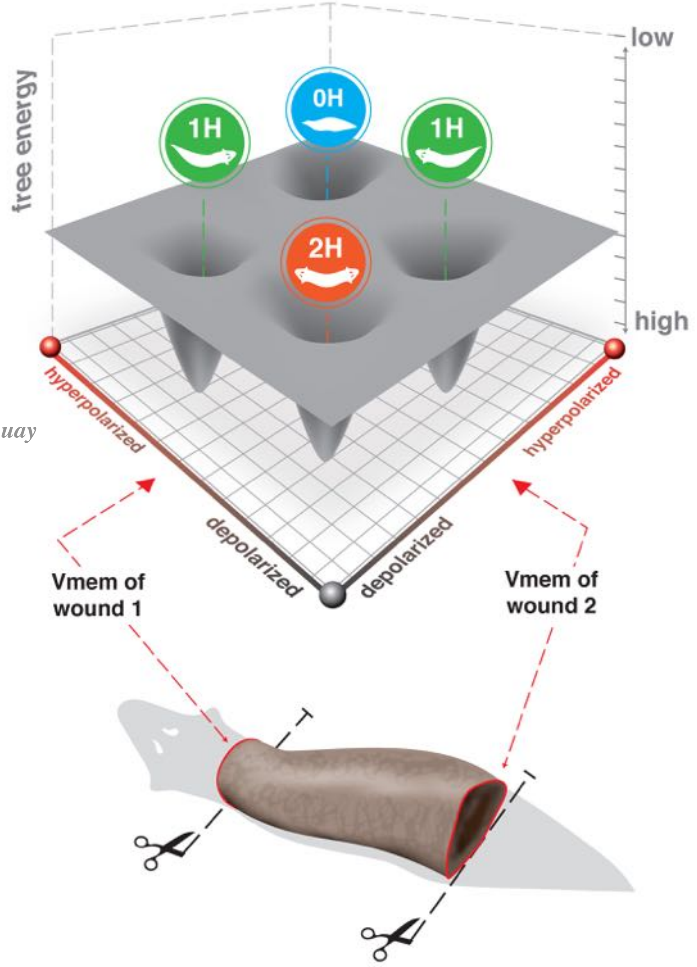
Fallon Durant



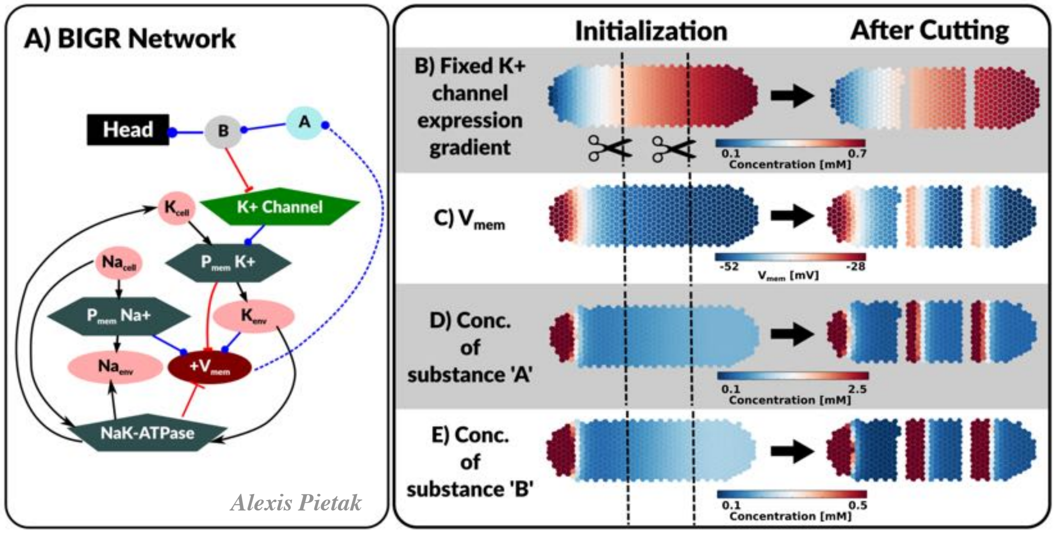
(After Thompson 1917.)

We can reach regions of the morphospace not explored by evolution, by changing electric circuits' dynamics in vivo

Global Pattern Control by Bioelectric Circuits



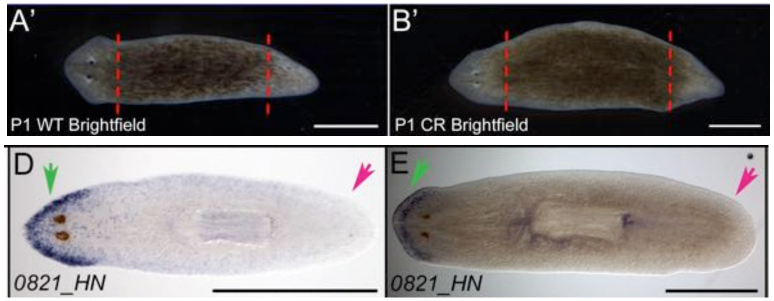
Jeremy Guay



Alexis Pietak

If information is in the dynamics of the electrical "software", we ought to be able to re-write goal states without editing the genomic hardware

Can Pattern Memory be Re-written??



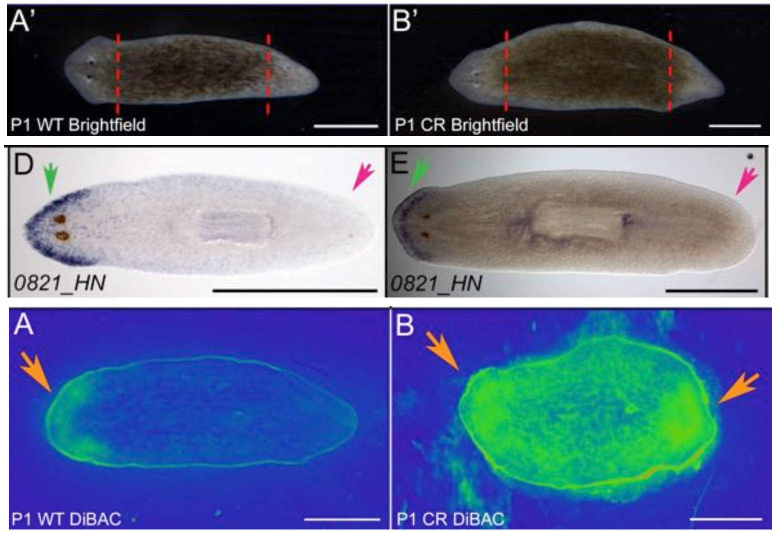
normal anatomy

normal molecular histology

middle-third regenerates:

distinct anatomical outcomes despite identical, wt genomic sequence

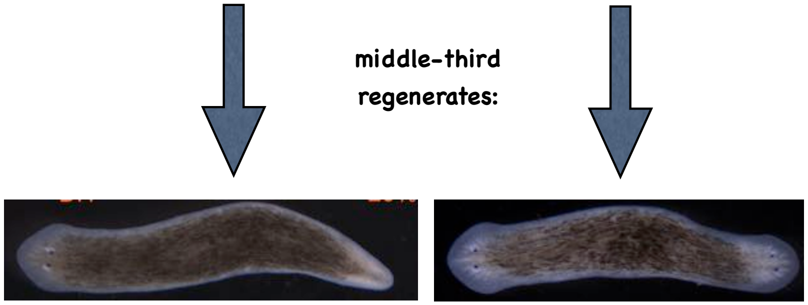
Revising the Patterning Engram



normal anatomy

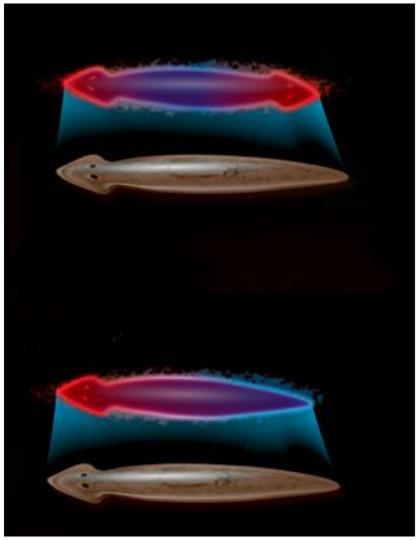
normal molecular
histology

edited bioelectric
pattern



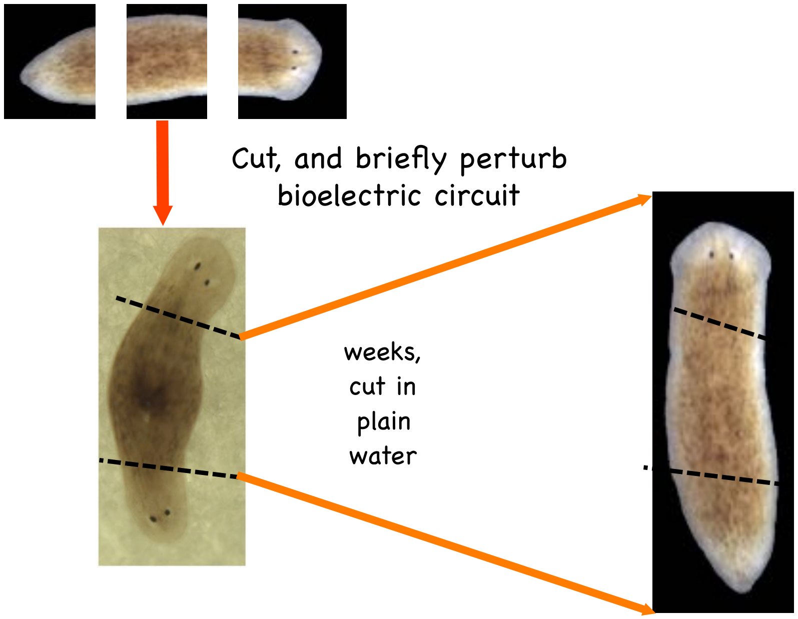
middle-third
regenerates:

The Same Body can Store different
Electrical Pattern Memories



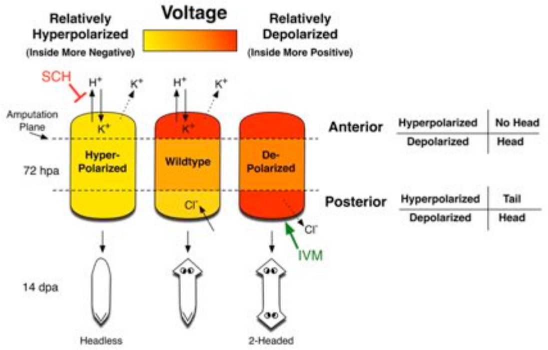
The bioelectric pattern doesn't indicate what the anatomy is now,
it encodes the pattern that will guide anatomy **if** it is cut at a future time

Long term: an organism's genome sets its long-term anatomy, doesn't it?



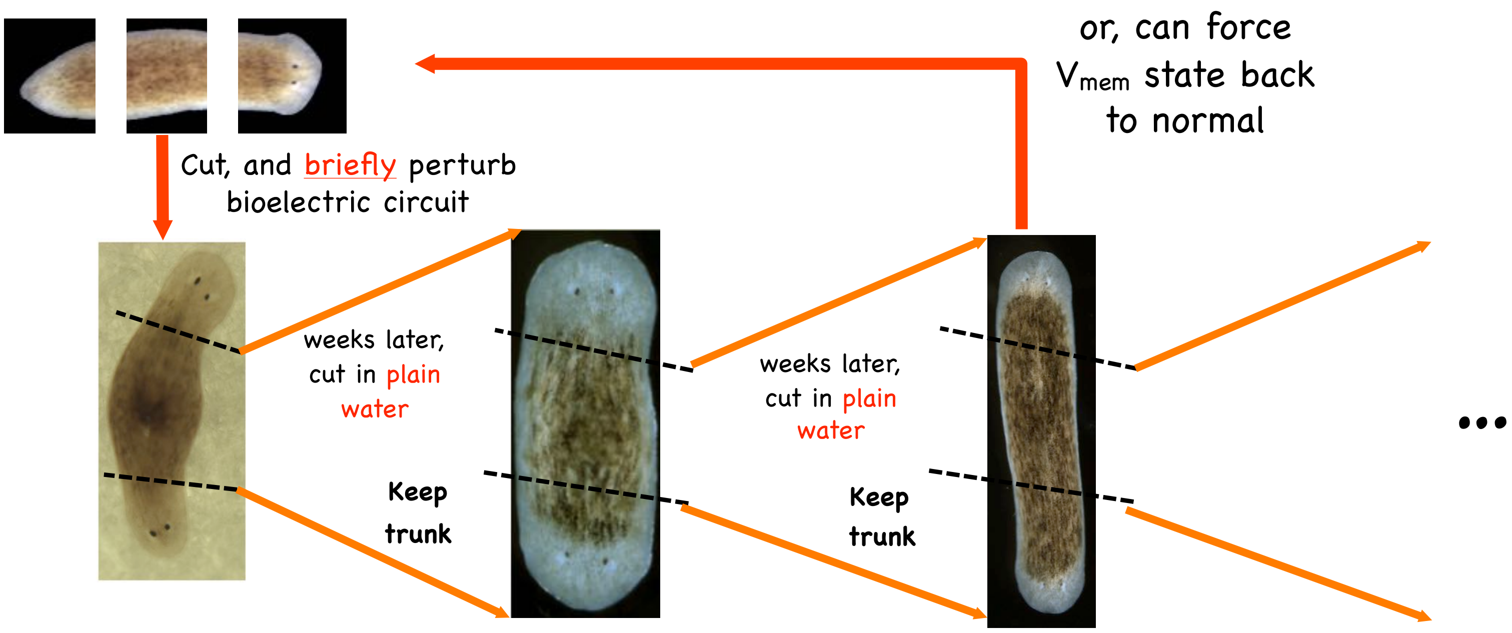
Cut, and briefly perturb bioelectric circuit

weeks,
cut in
plain
water



surely a normal worm must result once ectopic heads are removed in plain water (no more reagents), since genome is wild-type...

Transient re-writing of bioelectric circuit state permanently changes target morphology without genomic editing



or, can force V_{mem} state back to normal

Cut, and briefly perturb bioelectric circuit

weeks later, cut in plain water

Keep trunk

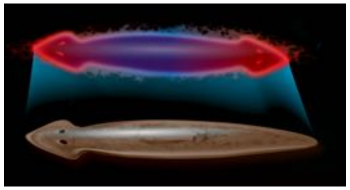
weeks later, cut in plain water

Keep trunk

...

Basic properties of memory

- Long-term stability
- Lability (rewritable)
- Latency (conditional recall)
- Discrete possible outcomes (1H v. 2H)

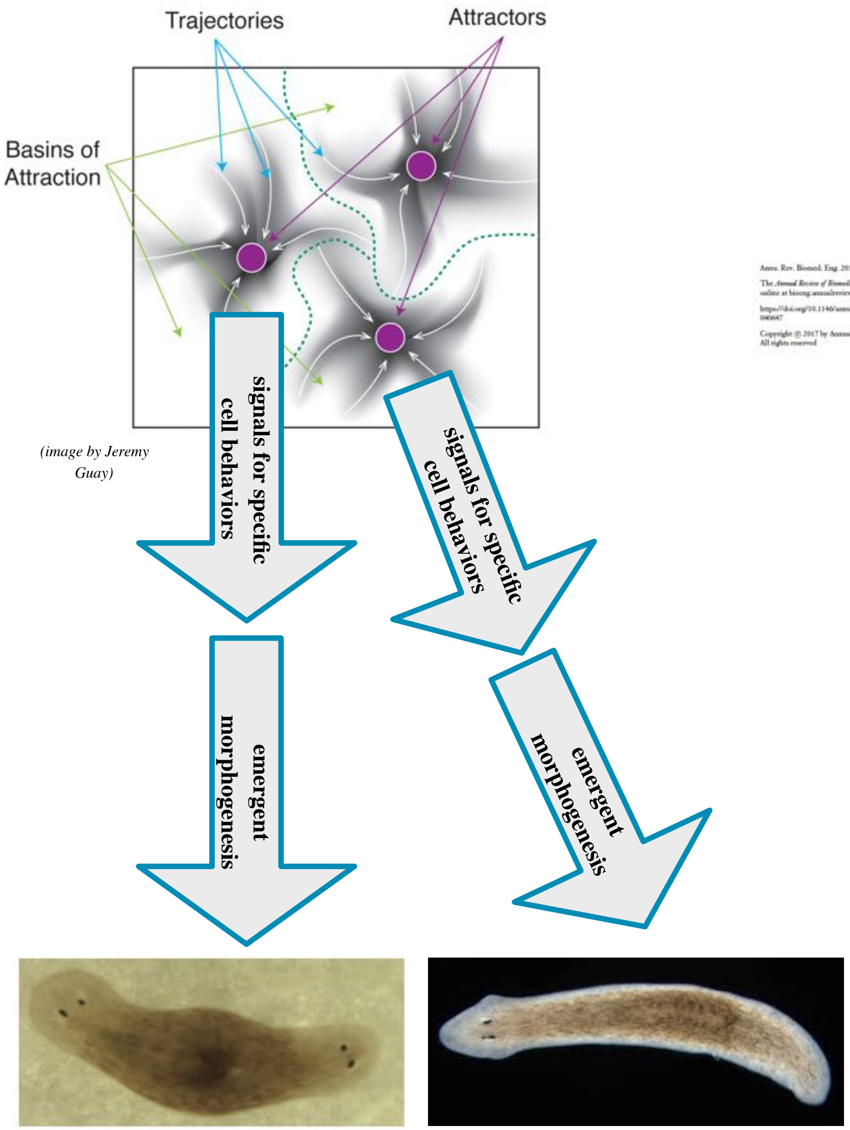


- Non-neural bioelectric info-processing in all cells enables large-scale anatomical decision-making

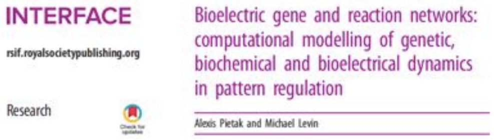
- Not micromanagement of cell fates but high-level goal (pattern memory) re-specification

- Neural Net-like dynamics may allow non-neural tissues to maintain internal models of complex geometrical goal states

- We're extending connectionist models to pattern control



(image by Jeremy Guay)


INTERFACE
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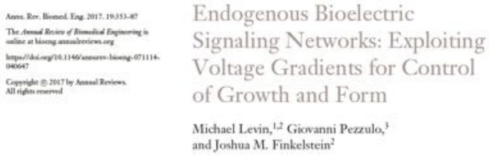
Research

Bioelectric gene and reaction networks: computational modelling of genetic, biochemical and bioelectrical dynamics in pattern regulation

Alexis Pietak and Michael Levin


Annu. Rev. Biomed. Eng. 2017. 19:353–87

The *Annual Review of Biomedical Engineering* is online at bioeng.annualreviews.org

https://doi.org/10.1146/annurev-bioeng-071114-040647

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Endogenous Bioelectric Signaling Networks: Exploiting Voltage Gradients for Control of Growth and Form

Michael Levin,[1,2] Giovanni Pezzulo,[3] and Joshua M. Finkelstein[2]


INTERFACE
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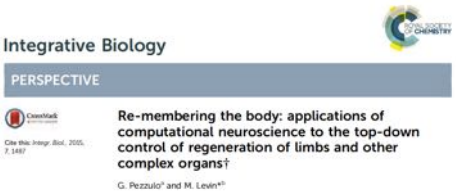
Research

Knowing one's place: a free-energy approach to pattern regulation

Karl Friston[1], Michael Levin[2], Biswa Sengupta[1] and Giovanni Pezzulo[3]

[1]The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, Queen Square, London, UK
[2]Biology Department, Center for Regenerative and Developmental Biology, Tufts University, Medford, USA
[3]Institute of Cognitive Sciences and Technologies, National Research Council, Rome, Italy


Integrative Biology

PERSPECTIVE

Cite this: Integr. Biol., 2015, 7, 1487

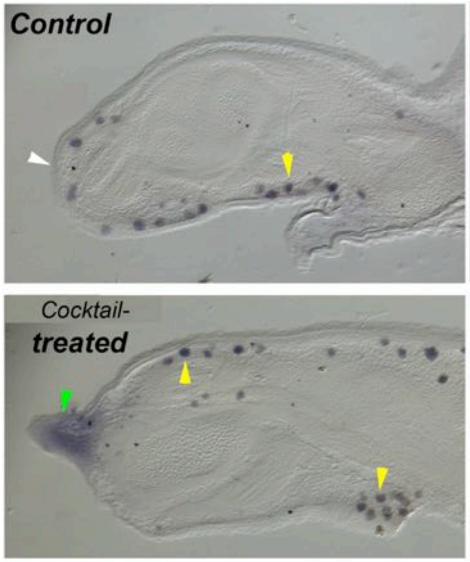
Re-membering the body: applications of computational neuroscience to the top-down control of regeneration of limbs and other complex organs†

G. Pezzulo[a] and M. Levin*[b]

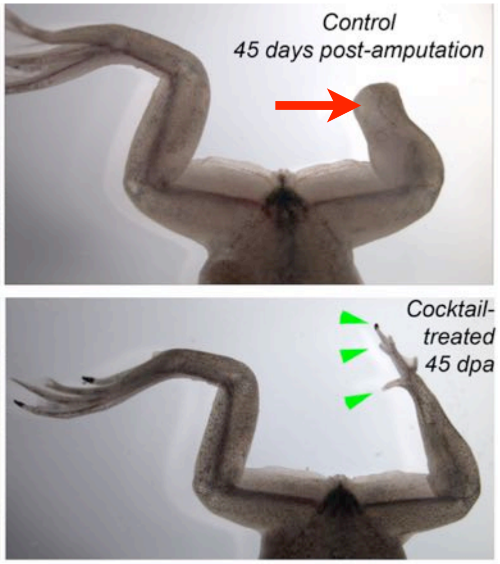
Exploiting bioelectric signals to trigger anatomical subroutines:

Mainstream approach: micromanage cell fates

Cognitive approach: re-write target state, let cells pursue the goal



MSX1 marker - blastema induced



Outgrowth with distal patterning induced (and still growing)

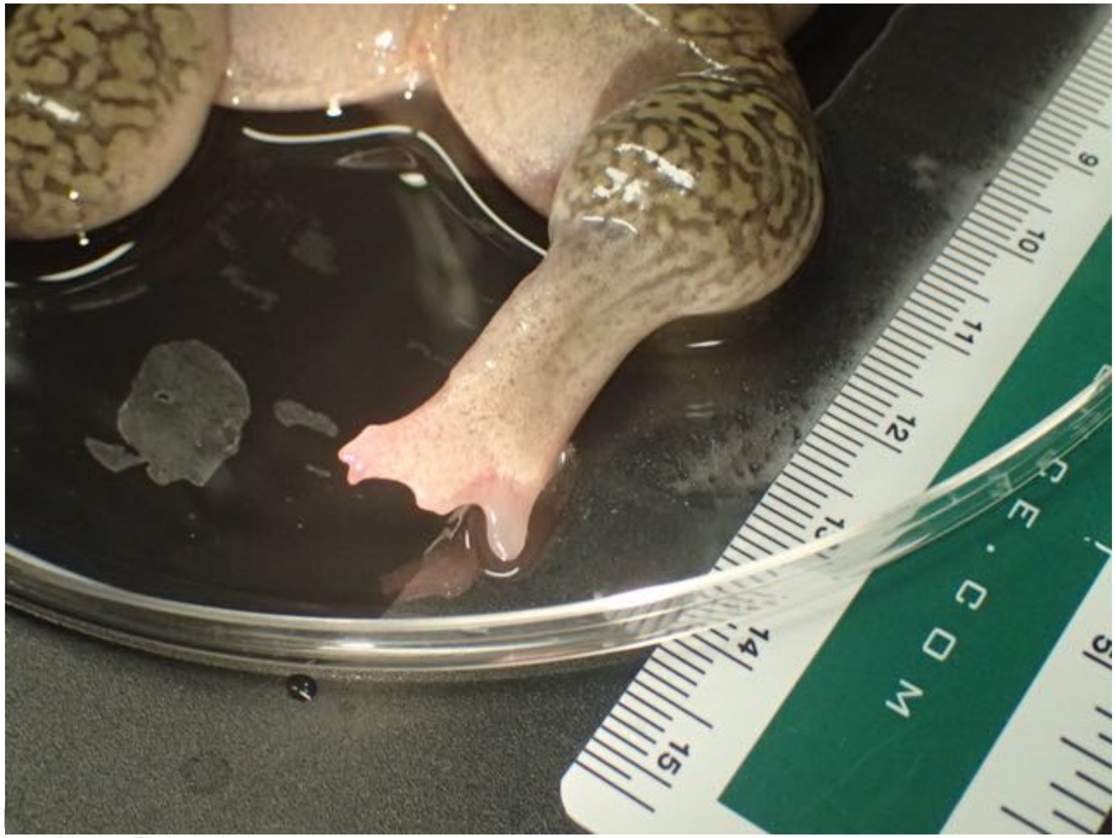
The regenerated leg has both sensation and mobility:

AiSun Tseng

Electroceutical cocktail + regenerative sleeve for 24 hours => 9 months of regeneration

Control

Regenerative sleeve + cocktail



Cell Reports

Brief Local Application of Wearable Bioreactor Induces Long-Term Regenerative Response in Adult *Xenopus* Hindlimb

Celia Herrera-Rincon

Next: mammalian applications

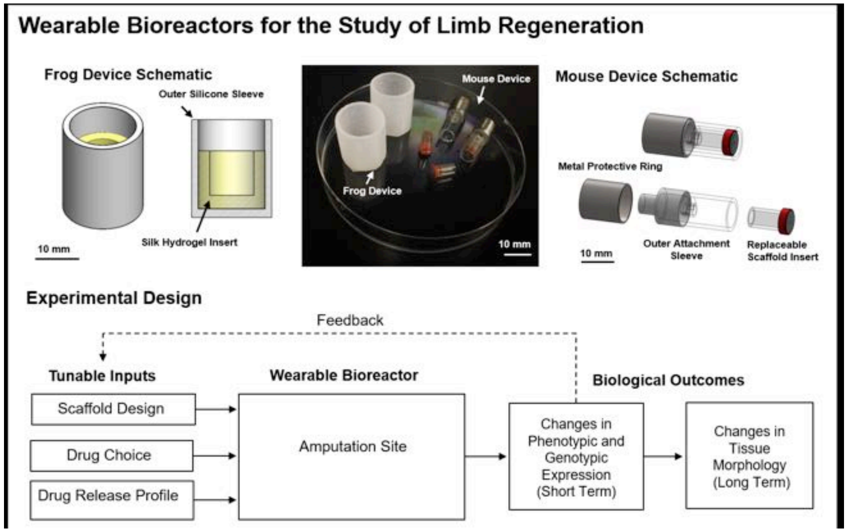
- Wearable bioreactors to deliver bioelectric state in vivo: a path to mammalian limb regeneration:

PLOS | ONE

RESEARCH ARTICLE

A Tunable Silk Hydrogel Device for Studying Limb Regeneration in Adult *Xenopus Laevis*

Anne Golding[1], Justin A. Guay[2¤], Celia Herrera-Rincon[2¤], Michael Levin[2], David L. Kaplan[3]*

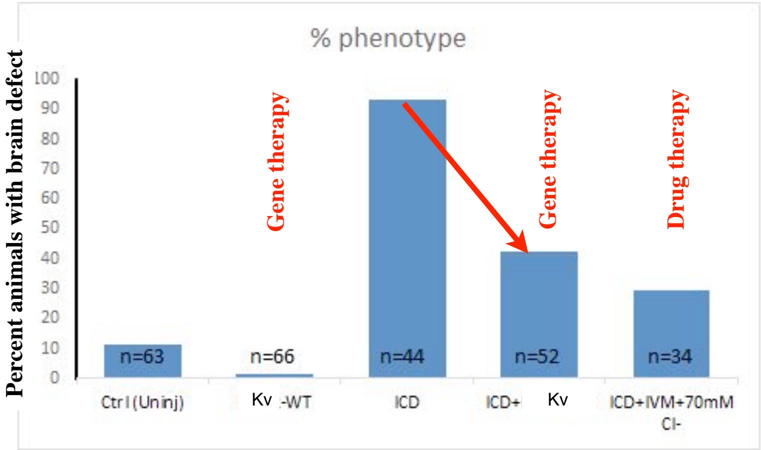


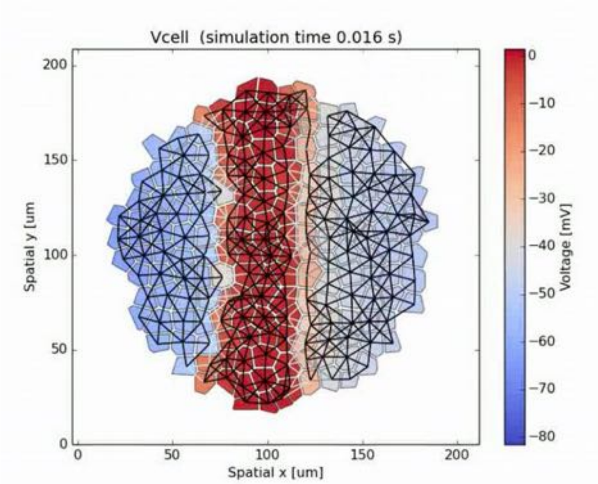
Annie Golding, David Kaplan's lab, Tufts BME

Ion channel modulators

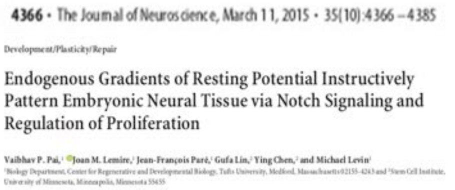
Jay Dubb

Bioelectric patterns over-ride genomic defects in vertebrate brain patterning





Alexis Pietak



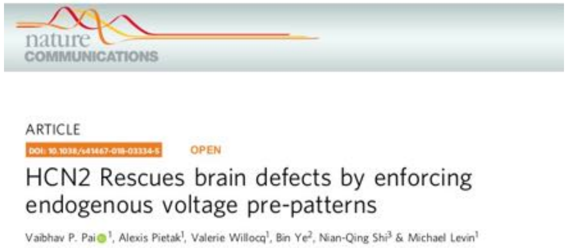
4366 • The Journal of Neuroscience, March 11, 2015 • 35(10):4366–4385

Development/Plasticity/Repair

Endogenous Gradients of Resting Potential Instructively Pattern Embryonic Neural Tissue via Notch Signaling and Regulation of Proliferation

Vaibhav P. Pai,[1] Joan M. Lemire,[1] Jean-François Paré,[1] Gufa Lin,[2] Ying Chen,[2] and Michael Levin[1]

[1]Biology Department, Center for Regenerative and Developmental Biology, Tufts University, Medford, Massachusetts 02155-4243 and [2]Stem Cell Institute, University of Minnesota, Minneapolis, Minnesota 55455



nature COMMUNICATIONS

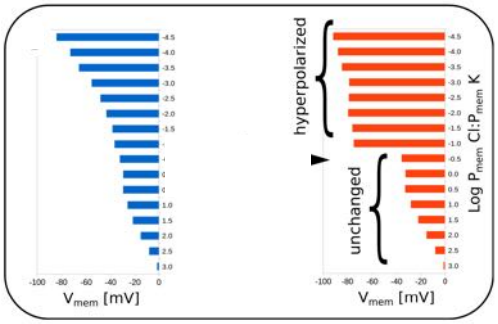
ARTICLE

DOI: 10.1038/s41467-018-03334-5

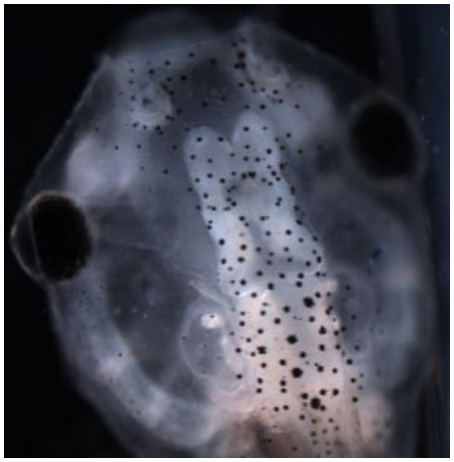
OPEN

HCN2 Rescues brain defects by enforcing endogenous voltage pre-patterns

Vaibhav P. Pai[1], Alexis Pietak[1], Valerie Willocq[1], Bin Ye[2], Nian-Qing Shi[3] & Michael Levin[1]

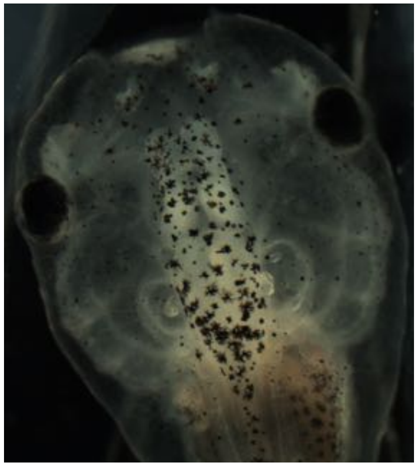


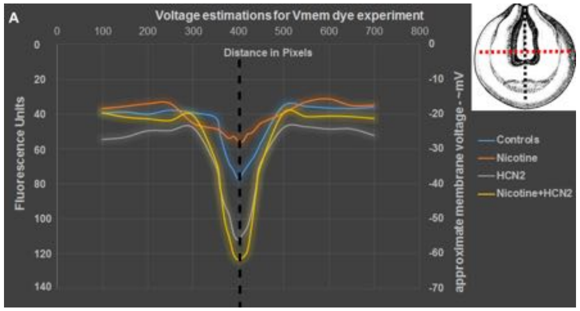
Normal tadpole brain



Truncated, misshapen brain resulting from dominant *Notch* mutation

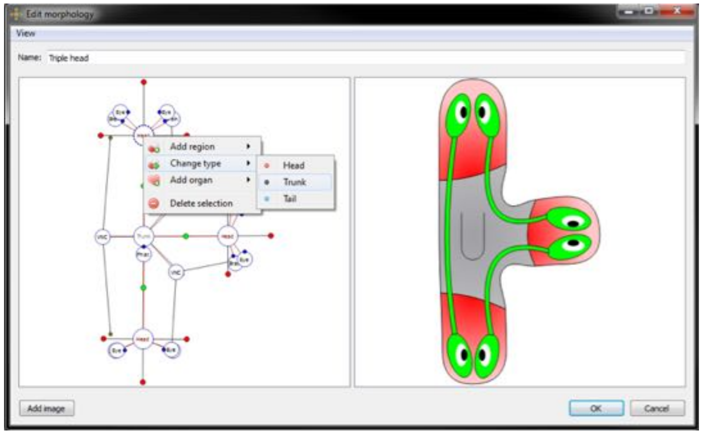
Normal tadpole brain resulting from hyperpolarization despite *Notch* mutation





Evolution learned to exploit computational properties of electric circuits for large-scale anatomical homeostasis.

Cracking the bioelectric code => reprogramming biological software



Name: Triple head

Impacts on

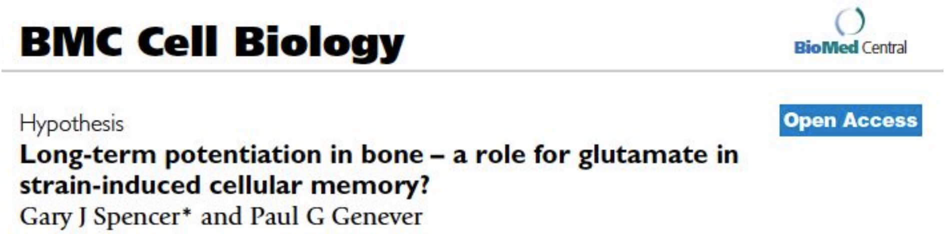
- Cellular biophysics
- Regenerative medicine
- Cognitive neuroscience
- Primitive cognition
- Synthetic bioengineering
- Morphological computation
- Soft-body robotics

Outline

- Brain-body plasticity: seeing from a tail
- Somatic cognition in the body: decision-making during self-editing of anatomy
- Bioelectric mechanisms of non-neural pattern control
- The future: regenerative medicine, synthetic living machines, novel AI architectures

Could a highly-robust (non-brittle) ML roadmap be based on non-neural architectures? Seeking collaborators!

Somatic Cells: bone, heart, pancreas



BMC Cell Biology

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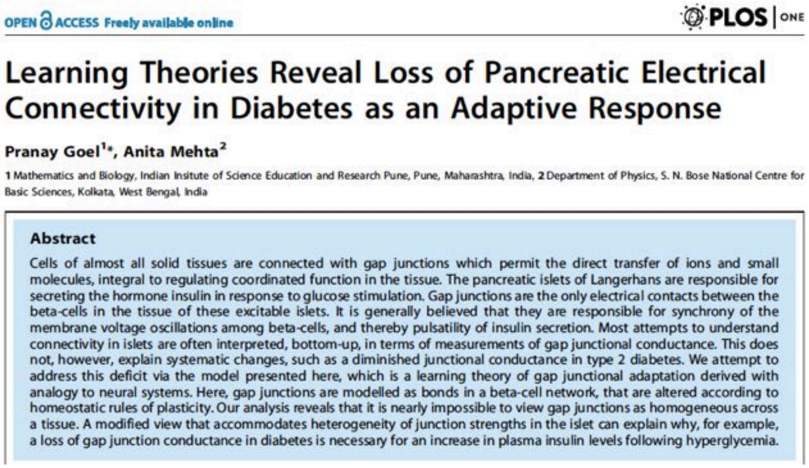
Hypothesis

Long-term potentiation in bone – a role for glutamate in strain-induced cellular memory?

Gary J Spencer* and Paul G Genever



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PLOS | ONE

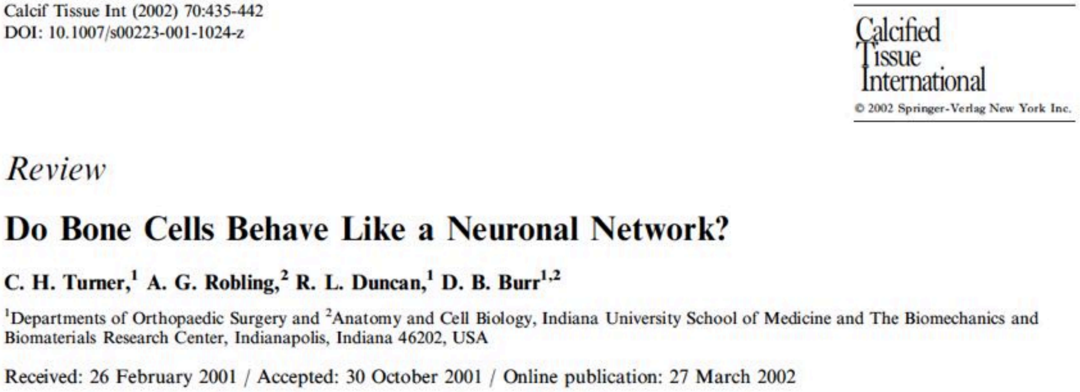
Learning Theories Reveal Loss of Pancreatic Electrical Connectivity in Diabetes as an Adaptive Response

Pranay Goel[1]*, Anita Mehta[2]

1 Mathematics and Biology, Indian Insitute of Science Education and Research Pune, Pune, Maharashtra, India, 2 Department of Physics, S. N. Bose National Centre for Basic Sciences, Kolkata, West Bengal, India

Abstract

Cells of almost all solid tissues are connected with gap junctions which permit the direct transfer of ions and small molecules, integral to regulating coordinated function in the tissue. The pancreatic islets of Langerhans are responsible for secreting the hormone insulin in response to glucose stimulation. Gap junctions are the only electrical contacts between the beta-cells in the tissue of these excitable islets. It is generally believed that they are responsible for synchrony of the membrane voltage oscillations among beta-cells, and thereby pulsatility of insulin secretion. Most attempts to understand connectivity in islets are often interpreted, bottom-up, in terms of measurements of gap junctional conductance. This does not, however, explain systematic changes, such as a diminished junctional conductance in type 2 diabetes. We attempt to address this deficit via the model presented here, which is a learning theory of gap junctional adaptation derived with analogy to neural systems. Here, gap junctions are modelled as bonds in a beta-cell network, that are altered according to homeostatic rules of plasticity. Our analysis reveals that it is nearly impossible to view gap junctions as homogeneous across a tissue. A modified view that accommodates heterogeneity of junction strengths in the islet can explain why, for example, a loss of gap junction conductance in diabetes is necessary for an increase in plasma insulin levels following hyperglycemia.



Calcif Tissue Int (2002) 70:435-442
DOI: 10.1007/s00223-001-1024-z

Calcified
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International

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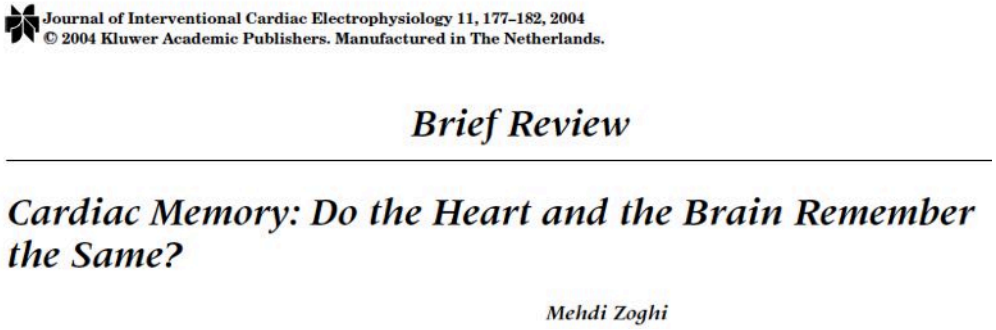
Review

Do Bone Cells Behave Like a Neuronal Network?

C. H. Turner,[1] A. G. Robling,[2] R. L. Duncan,[1] D. B. Burr[1,2]

[1]Departments of Orthopaedic Surgery and [2]Anatomy and Cell Biology, Indiana University School of Medicine and The Biomechanics and Biomaterials Research Center, Indianapolis, Indiana 46202, USA

Received: 26 February 2001 / Accepted: 30 October 2001 / Online publication: 27 March 2002



Journal of Interventional Cardiac Electrophysiology 11, 177–182, 2004
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Brief Review

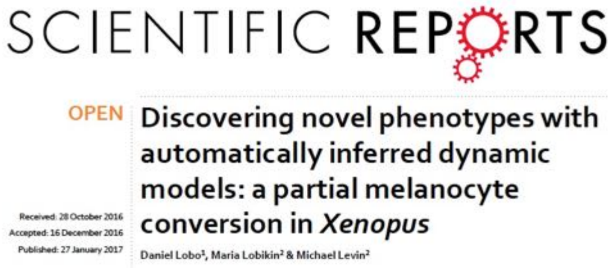
Cardiac Memory: Do the Heart and the Brain Remember the Same?

Mehdi Zoghi

Machine Learning Platform
for model discovery and intervention prediction

Micah Brodsky (Tufts University/MIT):

- Brodsky, M., Pietak, A., and Levin, M., (2017): "GABEE - Genetic Algorithm for Bio-Electric Exploration"

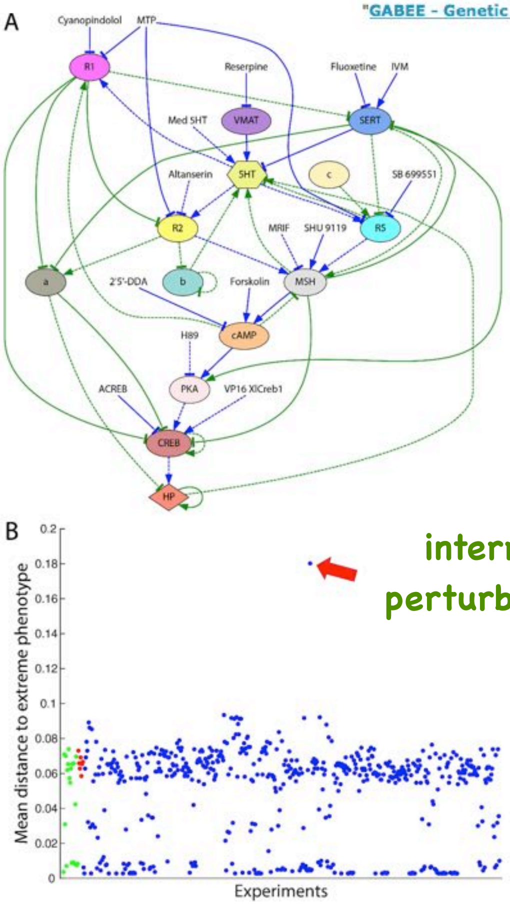

SCIENTIFIC REPORTS

OPEN

Discovering novel phenotypes with automatically inferred dynamic models: a partial melanocyte conversion in *Xenopus*

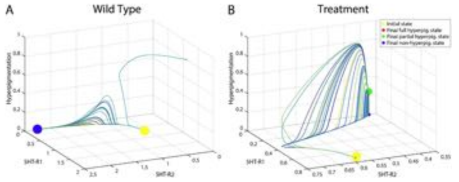
Received: 28 October 2016
Accepted: 16 December 2016
Published: 27 January 2017

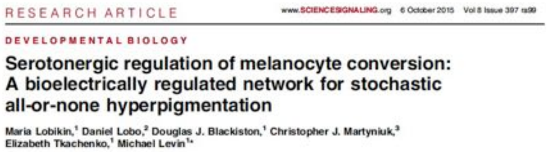
Daniel Lobo[1], Maria Lobikin[2] & Michael Levin[2]



use genetic algorithm to identify a network model that fits functional dataset

interrogate that model to identify a set of perturbations that give rise to desired outcome (iterative simulation)




RESEARCH ARTICLE

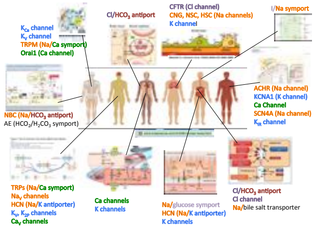
www.SCIENCESIGNALING.org 6 October 2015 Vol 8 Issue 397 ra99

DEVELOPMENTAL BIOLOGY

Serotonergic regulation of melanocyte conversion: A bioelectrically regulated network for stochastic all-or-none hyperpigmentation

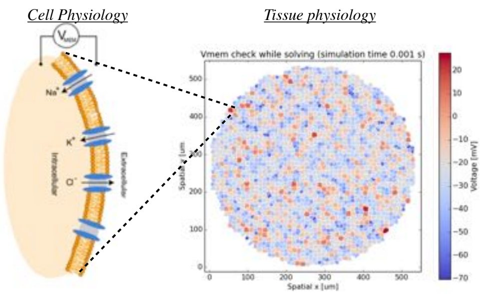
Maria Lobikin,[1] Daniel Lobo,[2] Douglas J. Blackiston,[1] Christopher J. Martyniuk,[3] Elizabeth Tkachenko,[1] Michael Levin[1*]

Morphoceuticals: ion channel drugs that allow rewriting of bioelectric patterns

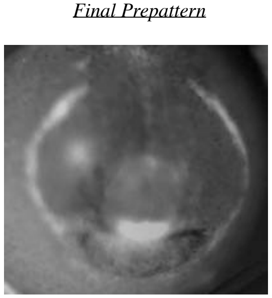


ion channel expression data

what V_{mem} pattern/state is desired?



modeling by
Alexis Pietak



spatialized Goldman equation

design cocktail of channel openers/blockers

SIGMA-ALDRICH

global or meso-local application

Thank you to:

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Kelly Tseng, **Celia H-Rincon** - bioelectricity of limb regeneration
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Douglas Blackiston - brain plasticity
Juanita Mathews - information processing in somatic cell networks
Vaibhav Pai - voltage gradients and eye/brain induction
Daniel Lobo - symbolic modeling of regeneration
Douglas Moore - mathematical analysis of information processing

Students:
Brook Chernet – V_{mem} and oncogene-mediated tumor formation
Maria Lobikin - V_{mem} as a regulator of metastasis
Fallon Durant - V_{mem} and pattern memory in planarian regeneration
Maya Emmons-Bell - bioelectric control of planarian head shape
+ many undergraduate students working in our lab over the years

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Rakela Lubonja, Jayati Mandal - lab management
Erin Switzer - animal husbandry
Cuong Nguyen - opto-electrical engineering
Junji Morokuma - planarian molecular biology
Joan Lemire, Jean-Francois Pare - molecular biology
Joshua Finkelstein, Bill Baga - administrative support

Collaborators: Allen Center members +
Alexis Pietak - computational modeling of bioelectrics
Dany Adams - V-ATPase in asymmetry & regeneration, craniofacial patterning
David Kaplan - V_{mem} and human MSC differentiation, regenerative sleeves
Fiorenzo Omenetto - optical approaches to bioelectric modulation
Giovanni Pezzulo, Francisco Vico - cognitive science models of pattern regulation
Vitaly Volpert, Chris Fields - mathematical models of pattern regulation
Paul C. W. Davies, S. I. Walker, Karl Friston - top-down causation models
Don Ingber, V. J. Koomson, J. H. Dungan - bioengineering
John Y. Lin, Thomas Knopfel, Ed Boyden - optogenetic control of V_{mem}
Fabrizio Falchi, Hava Siegelmann - computational analysis
Jack Tuszynski - biophysics/chemistry modeling

Model systems: tadpoles, planaria, zebrafish, chick embryos, computers

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Openings for post-docs and visiting scientists!

1) robotic bodies for biological systems
2) basal cognition - memory and learning in cells
3) connectionist models of tissue decision-making
4) new AI platforms based on non-neural architectures
5) machine learning for patterning model inference
6) CS applications in bioelectrics, regenerative medicine
   in birth defects, regeneration, tumor reprogramming

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