The exploration - exploitation paradigm for the C. elegans brain maturation

(NOT AN ARTIFICIAL NEURAL NETWORK TALK)

Vito Dichio

Cargèse, Thu 24 Oct 2024

ENS | PSL QBio

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Paris Brain Institute ICM

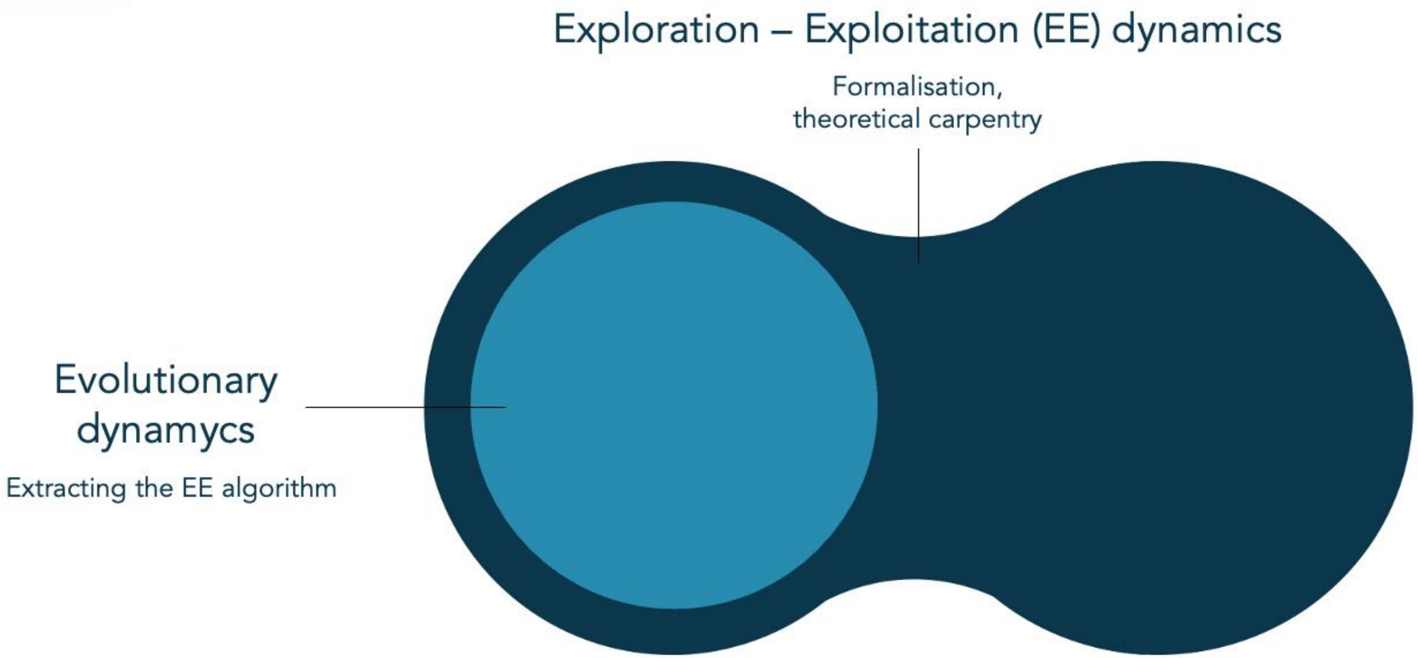
Inria

Sorbonne Université

Fabrizio
De Vico Fallani


Context
Principle
System

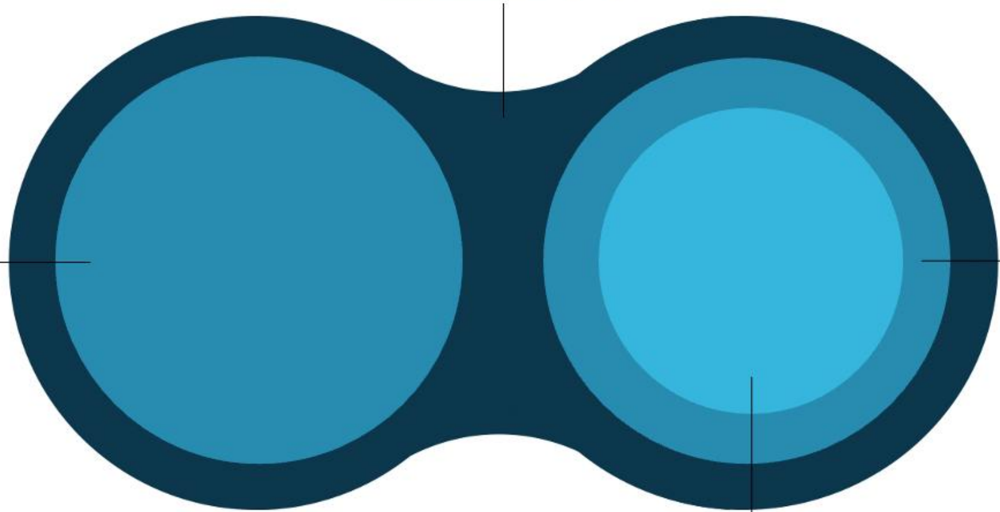
Abstract


Exploration – Exploitation (EE) dynamics
Formalisation,
theoretical carpentry
Evolutionary
dynamycs
Extracting the EE algorithm

Abstract

Exploration – Exploitation (EE) dynamics

Formalisation,
theoretical carpentry



Evolutionary dynamycs

Extracting the EE algorithm

Brain wiring dynamics

Where does the **brain (structural) complexity** come from?

C. elegans

A white-box model of a **whole-brain maturation** validated across development

PART I

EE dynamics

Searching for principles

Achieving a function in spite of / through randomness

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- Stochastic exploration of the configuration space
- State-dependent functional selection (exploitation)

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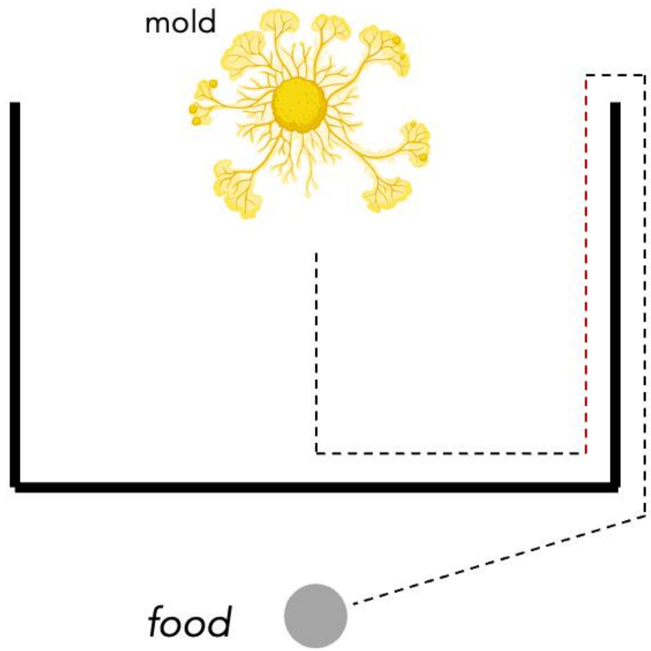
Ex: Navigation in complex environments

CR Reid et al, PNAS 109(43), 2012



Evolution as EE dynamics

Evolutionary dynamics:

- Random genetic mutations
- Natural selection (survival of the *fittest*)

those that are more apt to the environment than the others at a give time

Dichio, Zeng & Aurell, Rep. Prog. Phys. 86(5), 2023 | Manrubia et al, Phys. Life Rev. 38, 2021

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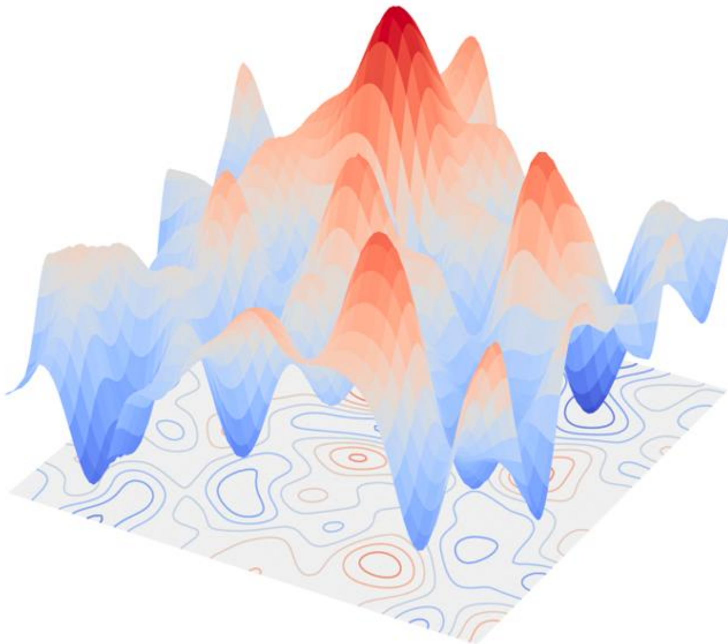
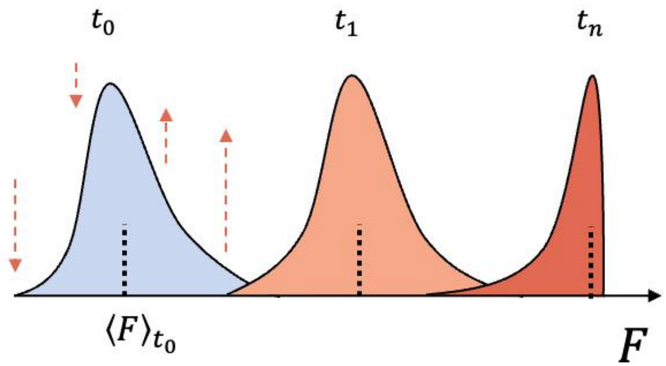
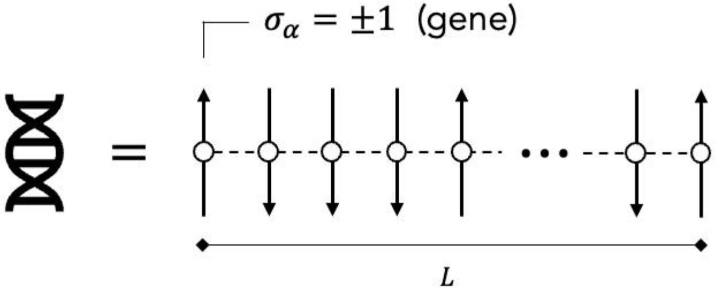




An evolutionary theory

1.



Statistical genetics and evolution of quantitative traits

Richard A. Neher and Boris I. Shraiman
Rev. Mod. Phys. **83**, 1283 – Published 10 November 2011

Dichio, Zeng & Aurell, Rep. Prog. Phys. 86(5), 2023

An evolutionary theory

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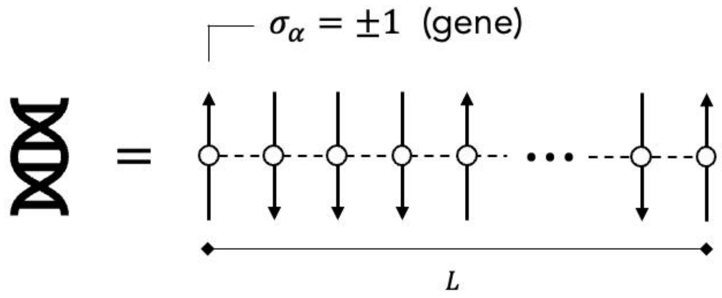
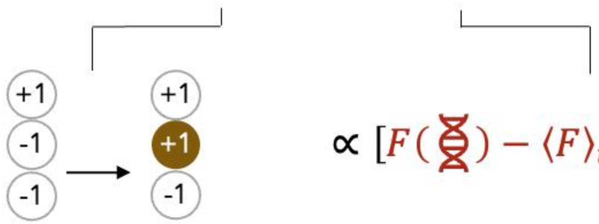


2. $\frac{d}{dt} P(🧬, t) = \textit{mutations} + \textit{selection}$



$\propto [F(🧬) - \langle F \rangle_t]\, P(🧬, t)$

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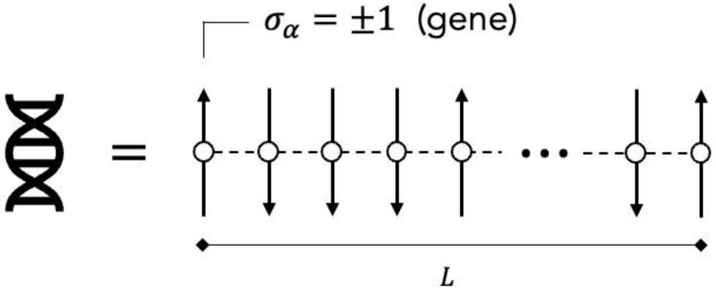
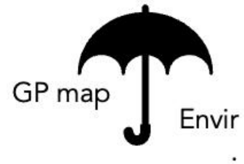
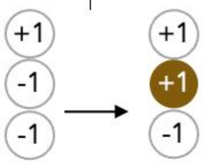


3. What is F?



$$F(🧬) = \sum_{\alpha=1}^{L} h_\alpha \sigma_\alpha + \sum_{\alpha=1}^{L} \sum_{\beta=1}^{L} J_{\alpha\beta} \sigma_\alpha \sigma_\beta$$

2. $$\frac{d}{dt} P(🧬, t) = \mathit{mutations} + \mathit{selection}$$



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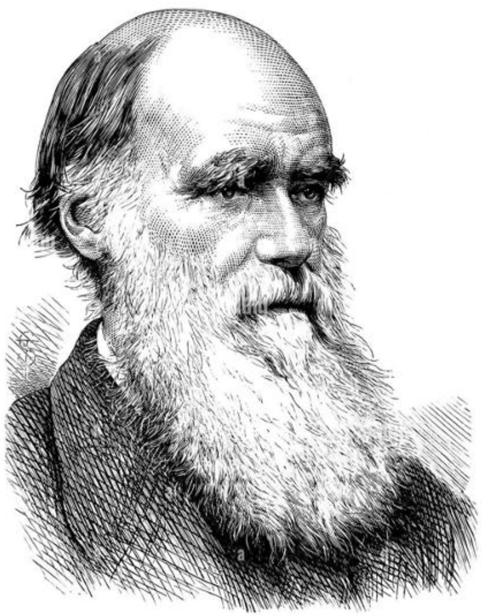
Unveiling the algorithm

Solving an **optimization (EE) problem** for the biological function

$$\max_{x \in \mathcal{X}} F(x)$$

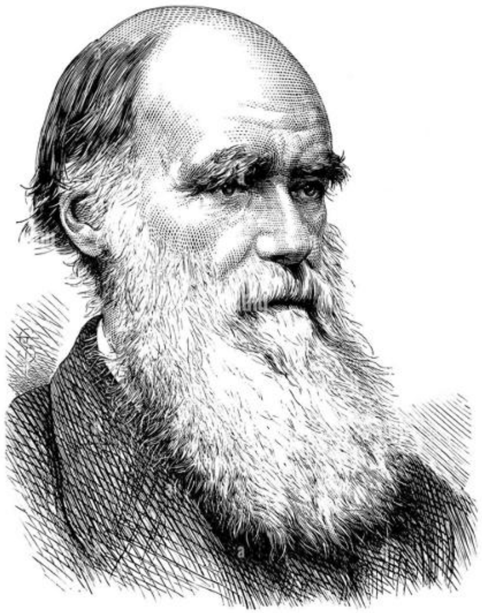
by **stochastic, state-dependent** dynamics.



Unveiling the algorithm

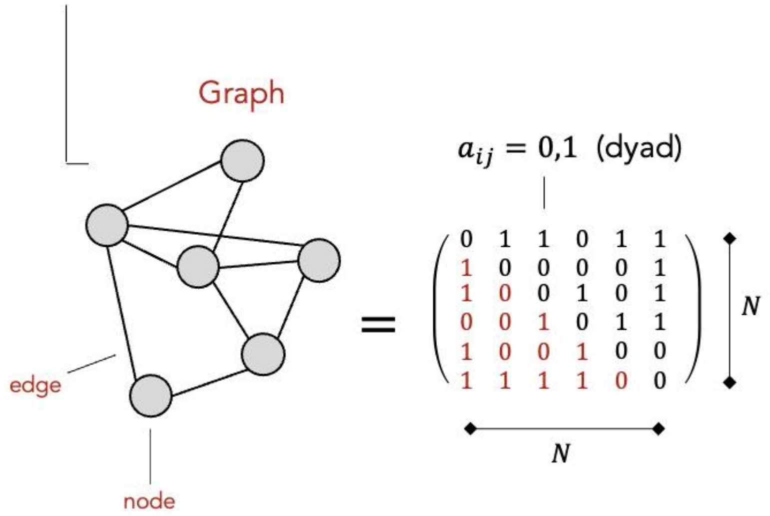
evol. ● ⊂ ● EE

	x	configuration
random genetic mutation	E	random configuration change
fitness	F	biological function
natural selection	E	functional exploitation



The exploration-exploitation graph dynamics

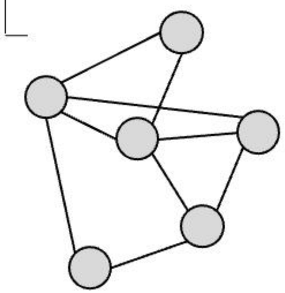
$P(G, t + \Delta t)$



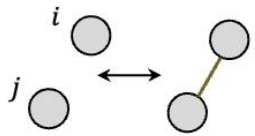
The exploration-exploitation graph dynamics

exploration | exploitation

$$P(G, t + \Delta t) = P(G, t) + \Delta t\, \mu \sum_{i<j} \left[P(M_{ij} G, t) - P(G, t) \right] + \left[\frac{e^{\Delta t\, \varphi\, F(G)}}{\langle e^{\Delta t\, \varphi\, F} \rangle_t} - 1 \right] P(G, t)$$



configuration change



biological function

$F : \mathcal{G} \mapsto \mathbb{R}$

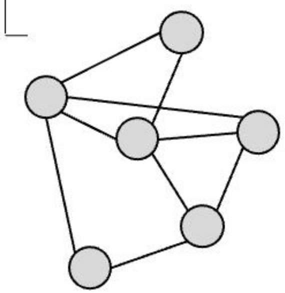
structure

function

The exploration-exploitation graph dynamics

exploration exploitation

$$P(G, t + \Delta t) = P(G,t) + \Delta t\, \mu \sum_{i<j} \left[P\left(M_{ij} G, t\right) - P(G,t) \right] + \left[\frac{e^{\Delta t\, \varphi\, F(G)}}{\langle e^{\Delta t\, \varphi\, F} \rangle_t} - 1 \right] P(G,t)$$



2 parameters (**dynamics**):

μ exploration rate

φ exploitation rate → $\rho = \dfrac{\varphi}{\mu}$ functional pressure

Checkpoint

E E

Exploration – Exploitation

Explore the unknown,
take advantage of what's known
(without gradients!)

Odor navigation
Vergassola et al, Nature 445, 2007

Swarm intelligence (ACO)
Dorigo et al, IEEE CIM 1(4), 2006

for

as generalization of

a MutSel theory of

evolutionary dynamics

Genetic Algorithms

Computer programs that "evolve" in ways that resemble natural selection can solve complex problems even their creators do not fully understand

by John H. Holland

Holland, Sci. Am. 267(1) 1992
Katoch et al, Multimed. Tools Appl. 80, 2021

PART II

Wiring the mind of a worm

The brain wiring problem

Where does the brain (structural) complexity come from? How to wire a brain?

The brain wiring problem

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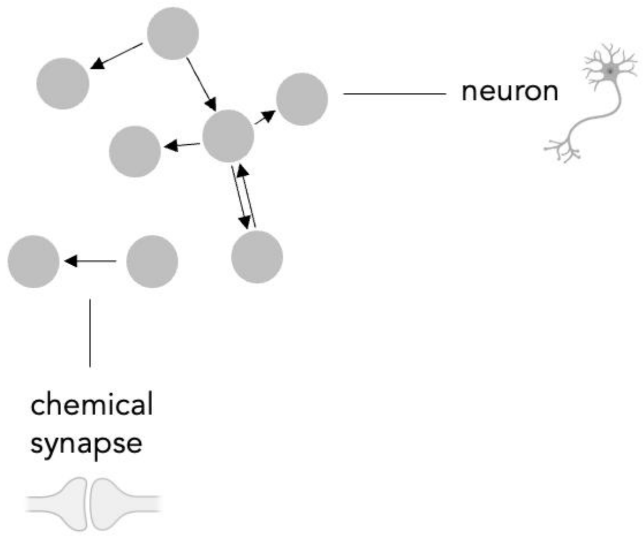

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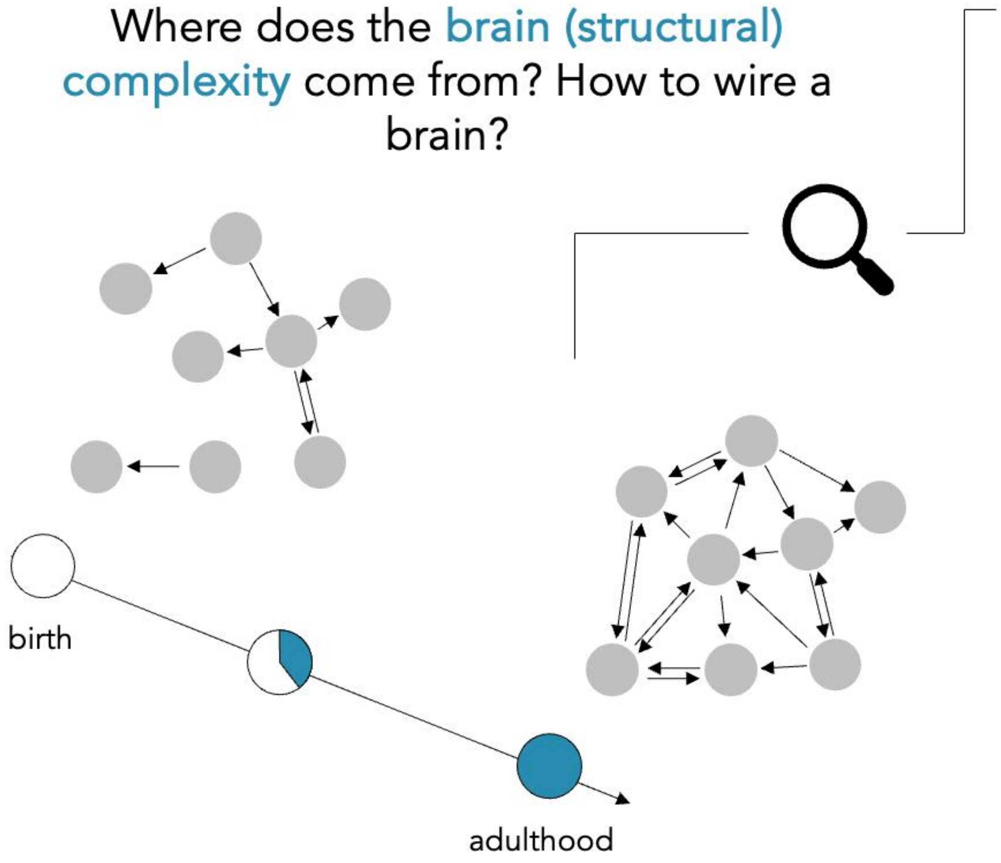

Brain developmental dynamics

- Functionally robust
- Developmental variability
- Non-specific

Bassem & Hiesinger, Cell 163(2), 2015

The brain wiring problem

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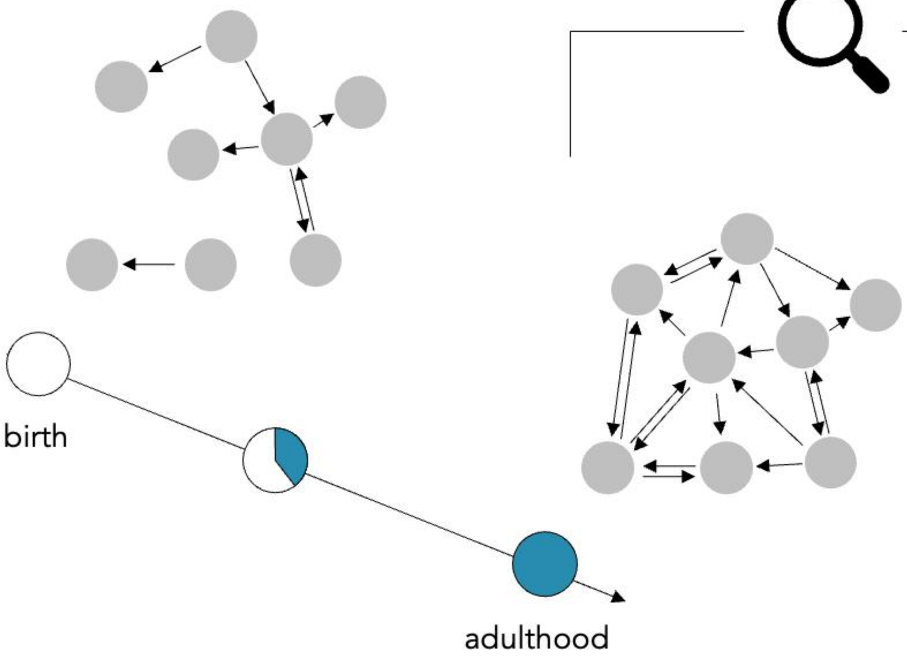

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- Functionally robust
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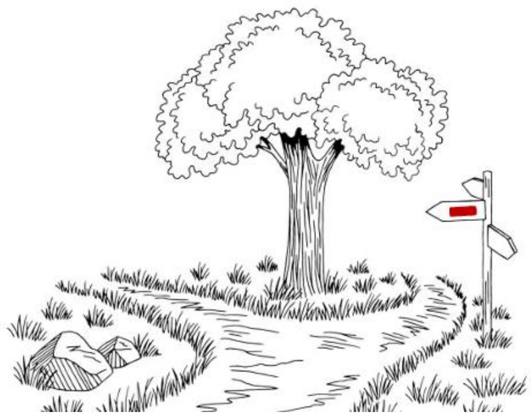
Bassem & Hiesinger, Cell 163(2), 2015

Simple genetically-encoded rules wire complex brains



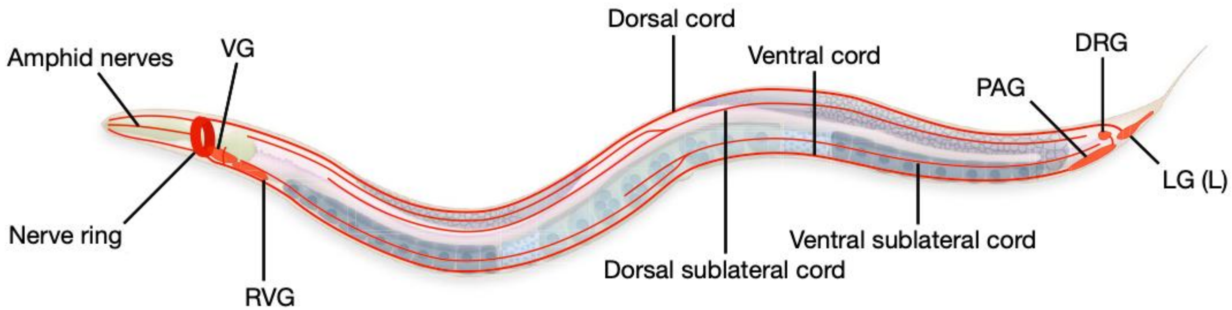
The growing "mind" of a worm

Phil. Trans. R. Soc. Lond. B **314**, 1–340 (1986) [1]
Printed in Great Britain

THE STRUCTURE OF THE NERVOUS SYSTEM OF THE NEMATODE *CAENORHABDITIS ELEGANS*

By J. G. WHITE, E. SOUTHGATE, J. N. THOMSON AND S. BRENNER, F.R.S.
Laboratory of Molecular Biology, Medical Research Council Centre, Hills Road, Cambridge CB2 2QH, U.K.

(*Received 9 August 1984 – Revised 12 November 1984*)



The growing "mind" of a worm

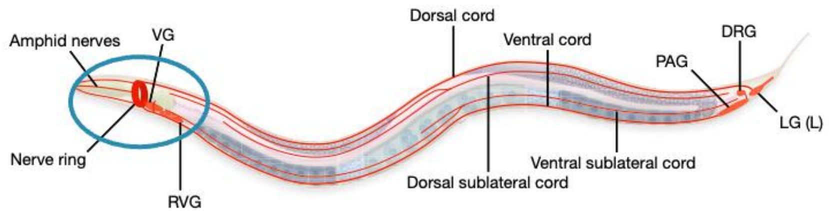
$N \sim 180$
$d \sim 4 - 10\%$

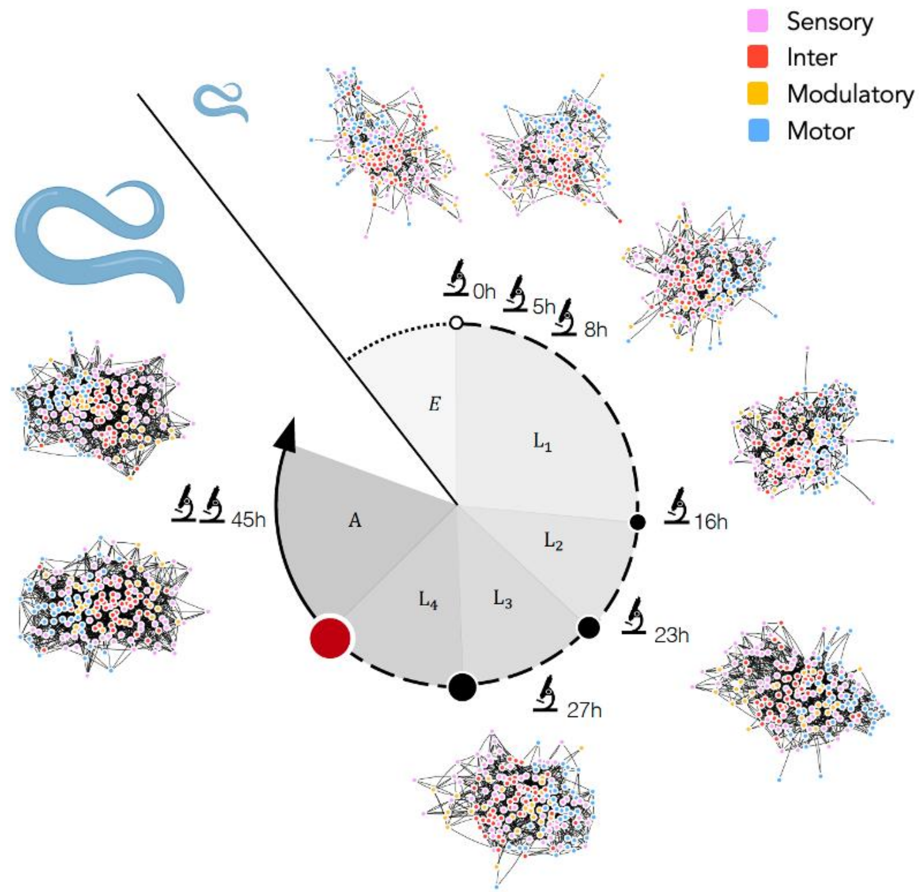
Article

Connectomes across development reveal principles of brain maturation

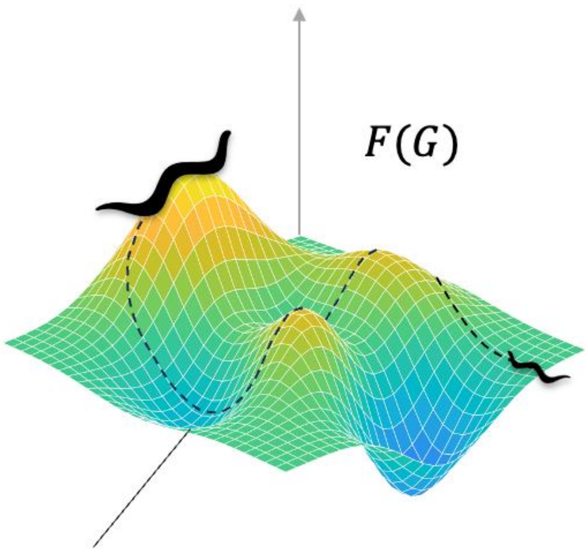
https://doi.org/10.1038/s41586-021-03778-8
Received: 21 May 2020
Accepted: 29 June 2021
Published online: 4 August 2021

Daniel Witvliet[1,2]✉, Ben Mulcahy[1,9], James K. Mitchell[3,4,9], Yaron Meirovitch[4,5], Daniel R. Berger[4], Yuelong Wu[4], Yufang Liu[1], Wan Xian Koh[1], Rajeev Parvathala[5], Douglas Holmyard[1], Richard L. Schalek[4], Nir Shavit[5], Andrew D. Chisholm[6], Jeff W. Lichtman[4,7]✉, Aravinthan D. T. Samuel[3,4]✉ & Mei Zhen[1,2,8]✉



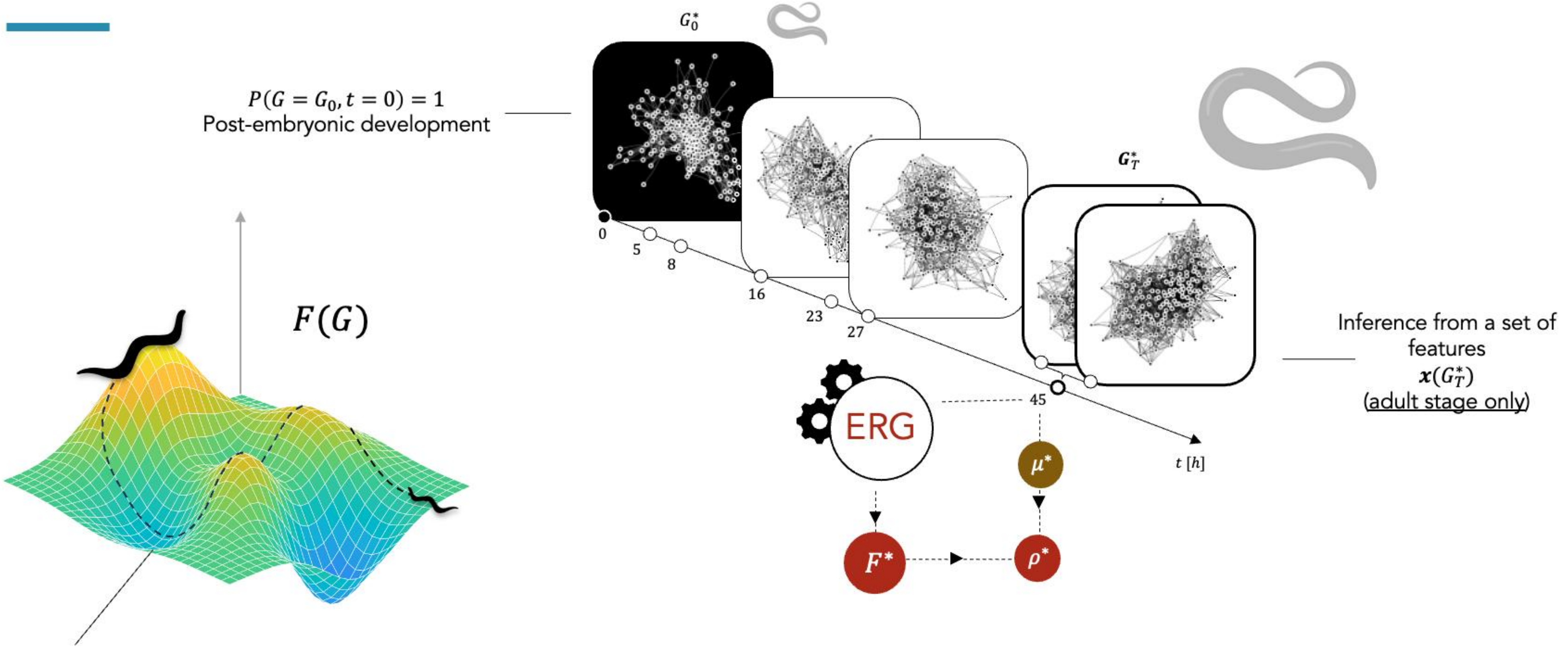


How-to in a nutshell



$$\Delta P_{\Delta t}(G,t) = \Delta t\, \mu^* \sum_{i<j}\left[P\left(M_{ij}G,t\right) - P(G,t)\right] + \left[\frac{e^{\Delta t\, \varphi^*\, F^*(G)}}{\left\langle e^{\Delta t\, \varphi^*\, F^*}\right\rangle_t} - 1\right] P(G,t)$$

How-to in a nutshell



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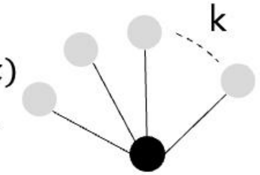
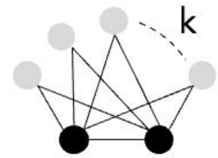
Topography of a functional landscape (4p)

$$F(G) = \boldsymbol{\theta} \cdot \boldsymbol{x}\,(G)$$

$$= \quad \theta_1 \sum_{k,\bullet} w_{\lambda_1}^{(k)}$$



$$+ \quad \theta_2 \sum_{k,\bullet\!-\!\bullet} w_{\lambda_2}^{(k)}$$



geometrically weighted degree

$x_{gwd}(G|\lambda_1)$

Node connectivity

geometrically weighted edgewise shared partner

$x_{gwesp}(G|\lambda_2)$

Relational patterns

Dichio & De Vico Fallani, Rep Prog Phys 86(10), 2023

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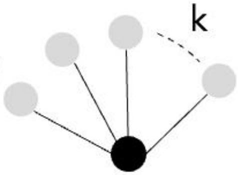

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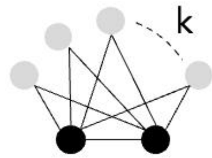

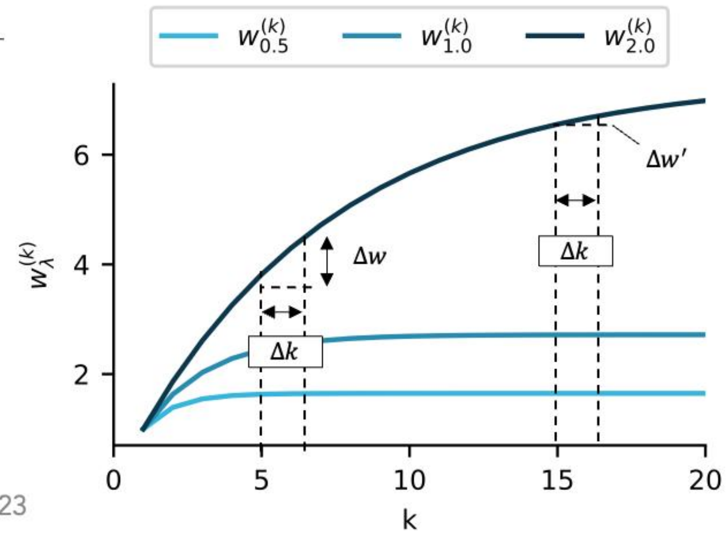

Dichio & De Vico Fallani, Rep Prog Phys 86(10), 2023

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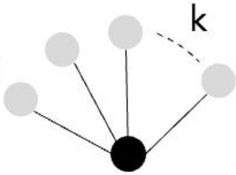

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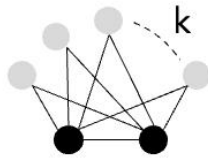
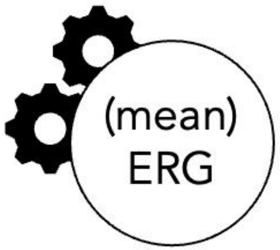


θ_1: $+0.44$; $w_{\lambda_1}^{(k)}$: $+1.94$

θ_2: $+0.578$; $w_{\lambda_2}^{(k)}$: $+1.487$

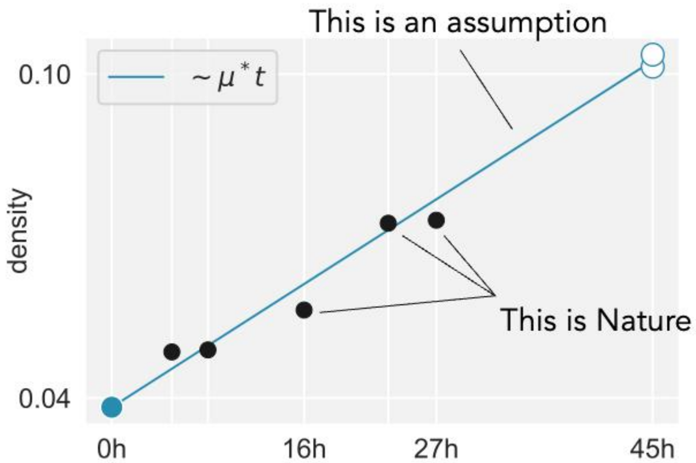


EE dynamics based on this functional landscape favor the emergence of hubs and clusters.

Dichio & De Vico Fallani, Rep Prog Phys 86(10), 2023

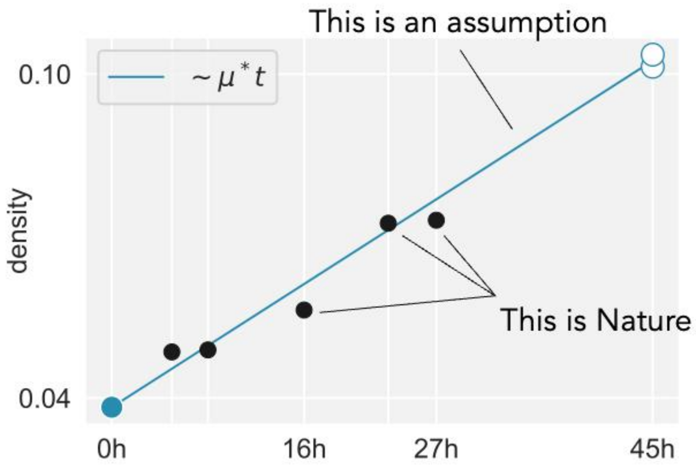
EE parameters (2p)

$1.426 \times 10^{-3}\ h^{-1}$ μ^*

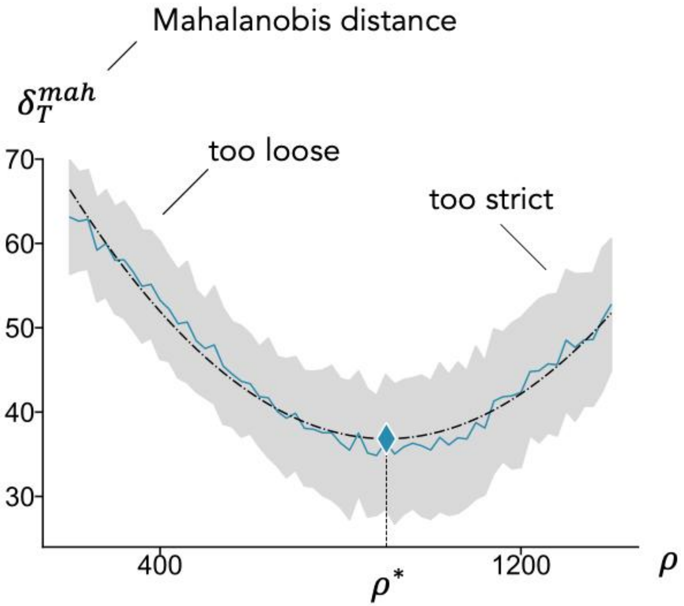


μ exploration rate ρ functional pressure

EE parameters (2p)



$1.426{\times}10^{-3}\ h^{-1}$ — μ^*



$S = 100$ simulations $\forall \rho = 200 + 20\ i.$

ρ^* — $9.017{\times}10^2$

μ exploration rate ρ functional pressure

EE parameters (2p)

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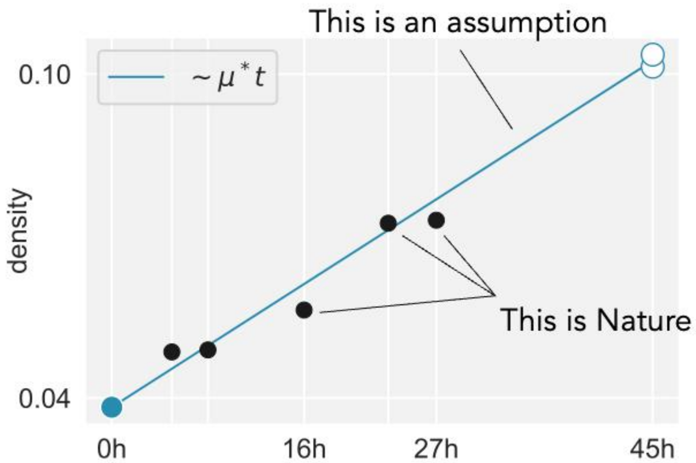

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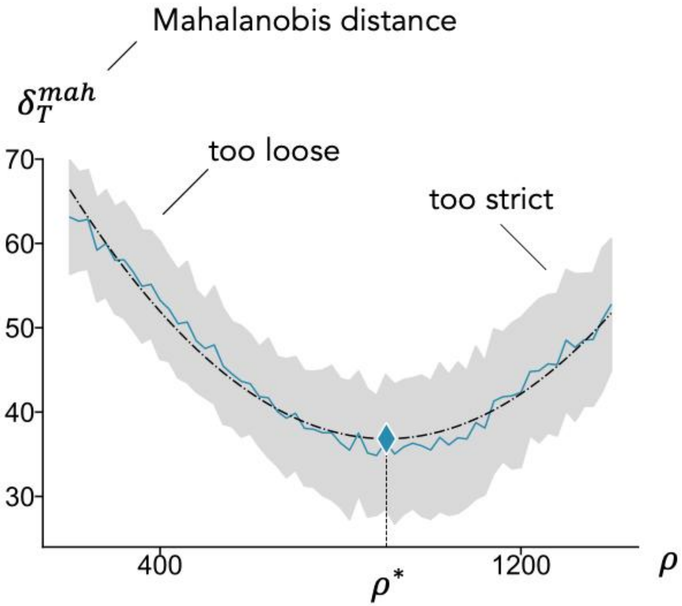
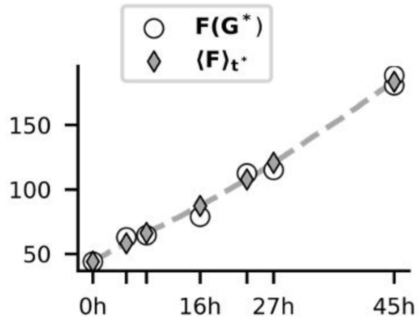


$S = 100$ simulations $\forall \rho = 200 + 20\ i.$

EE parameters are found by evolution, genetically encoded and characteristic of the biological system

Developmental trajectory tracked down

1 | What about F ?



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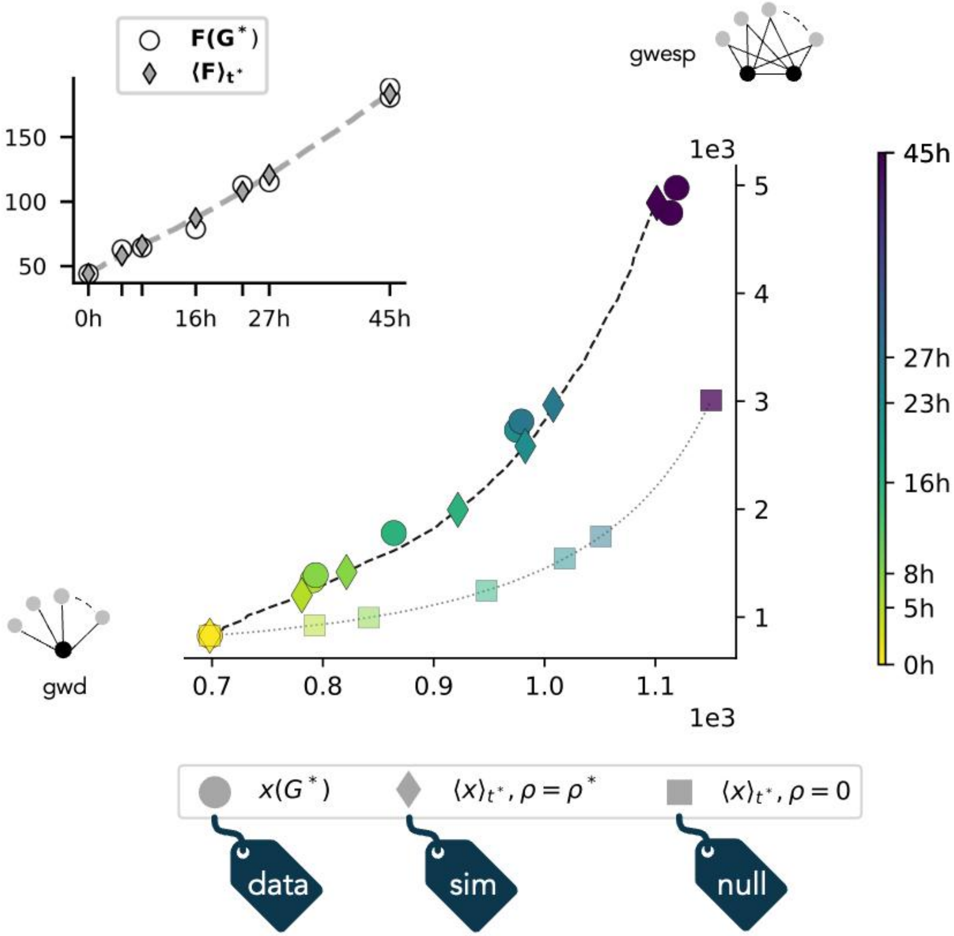

2 | What about $\boldsymbol{x}$?

Developmental trajectory tracked down

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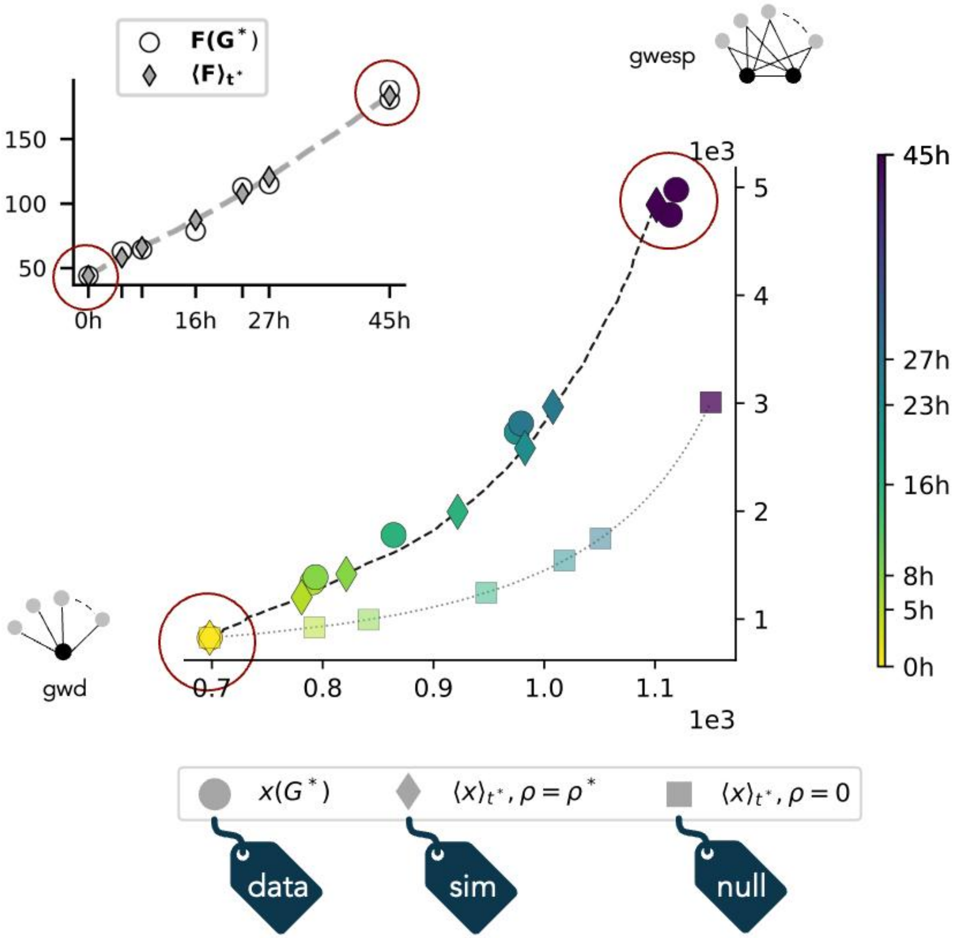

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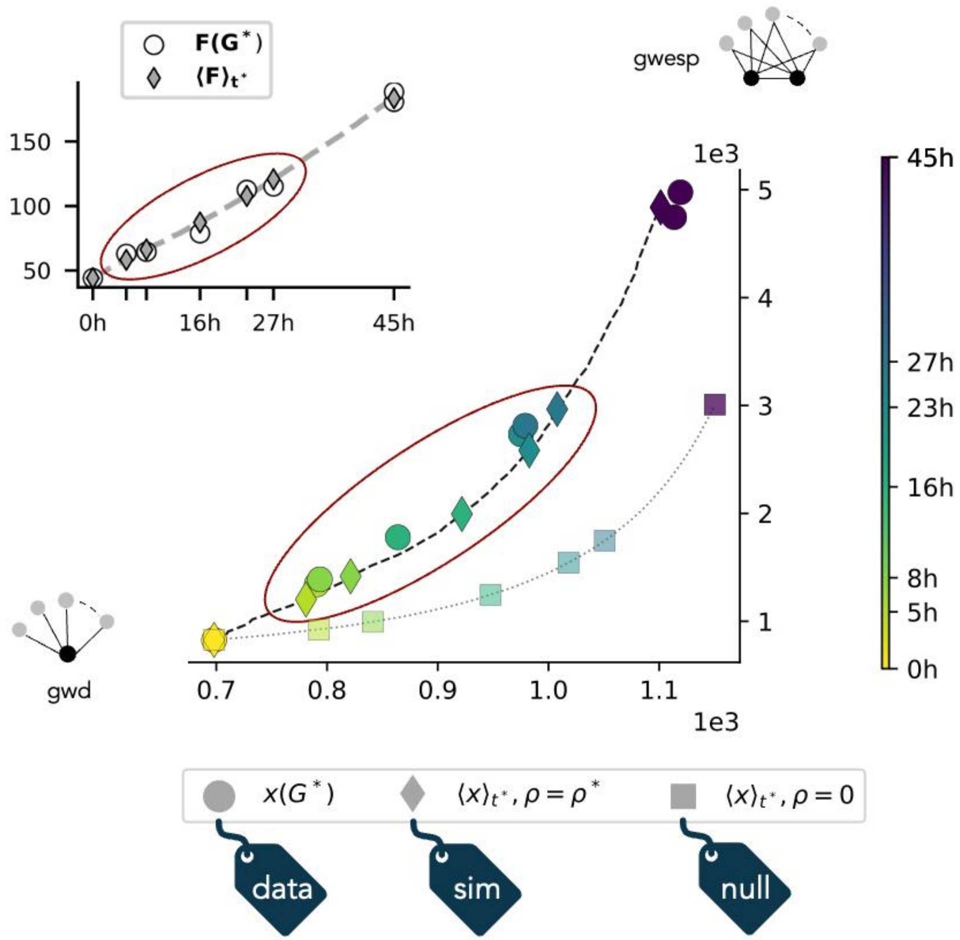
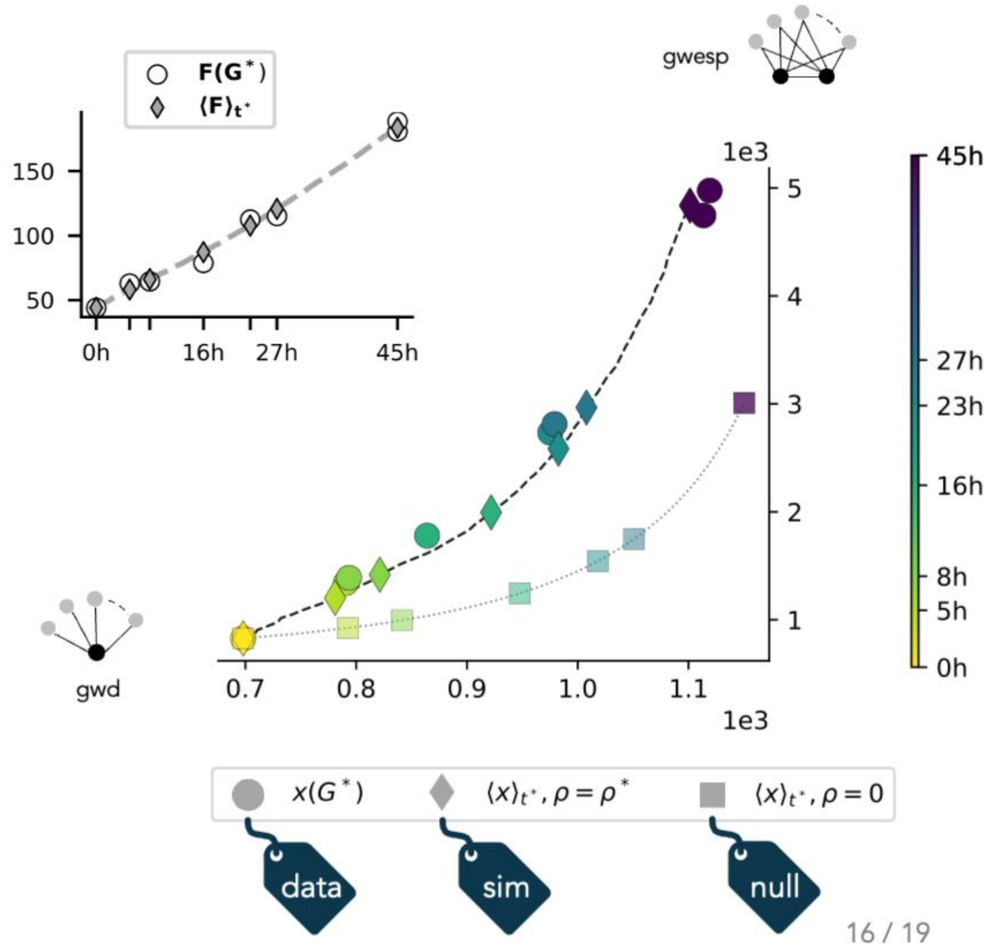


2 | What about $\boldsymbol{x}$?

Developmental trajectory tracked down

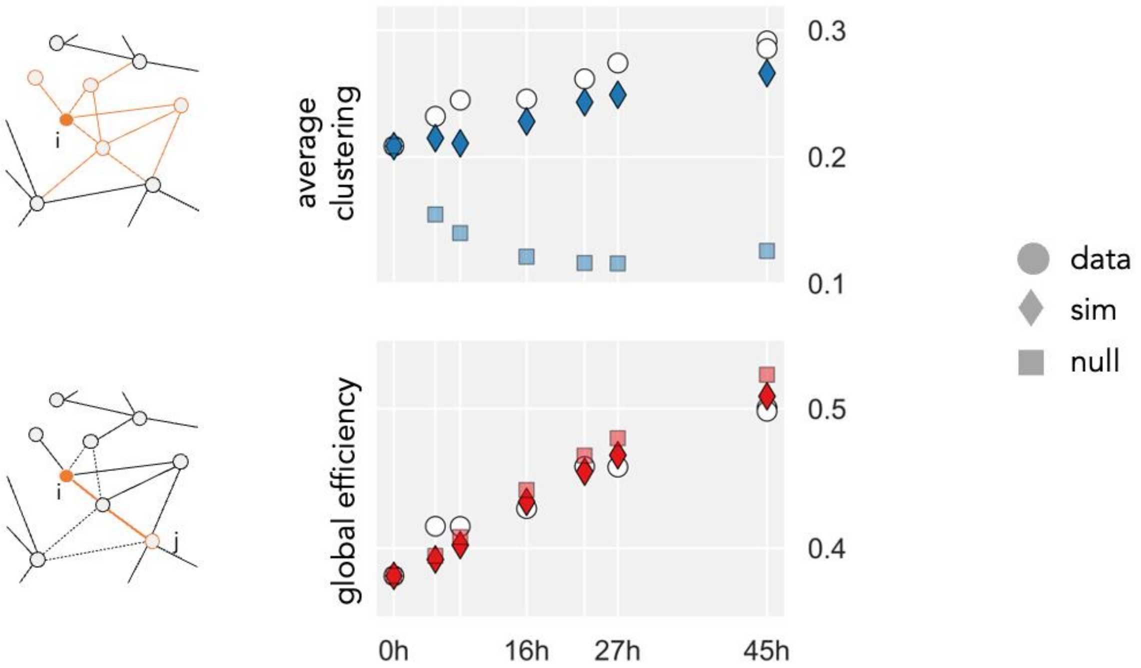
EE dynamics in an adult functional landscape
reproduce
the *C. elegans* brain maturation
at different larval stages

F *x*



Developmental trajectory tracked down

3 | What about $\boldsymbol{y}$?



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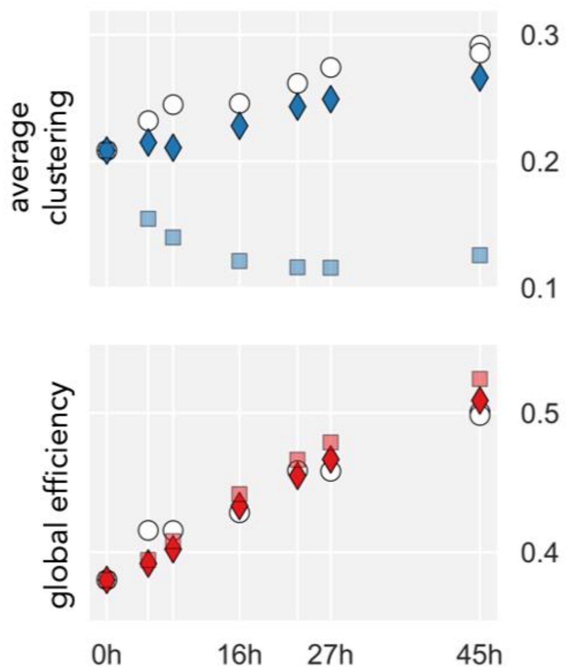

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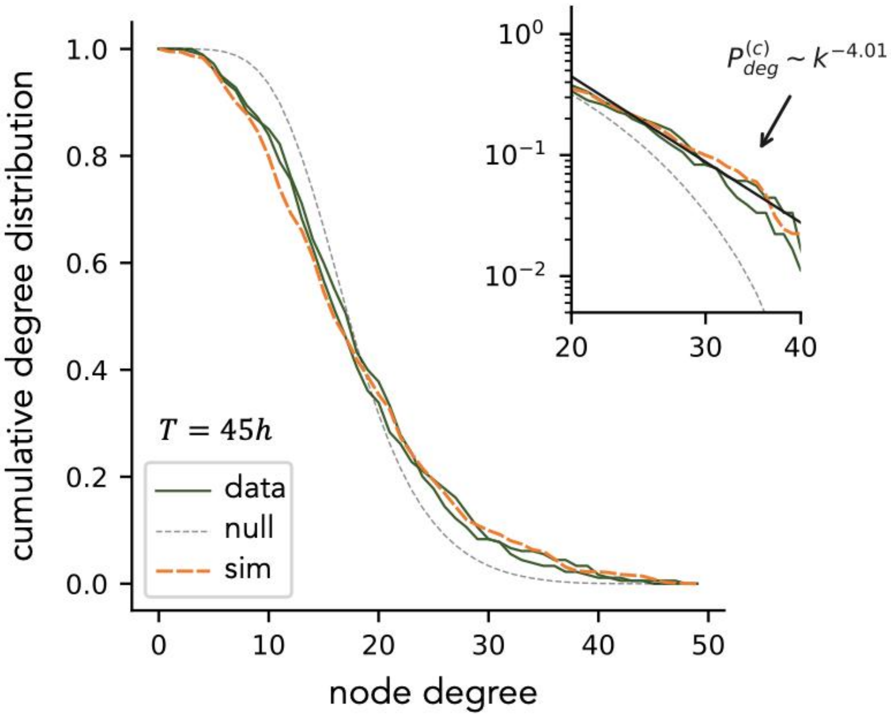
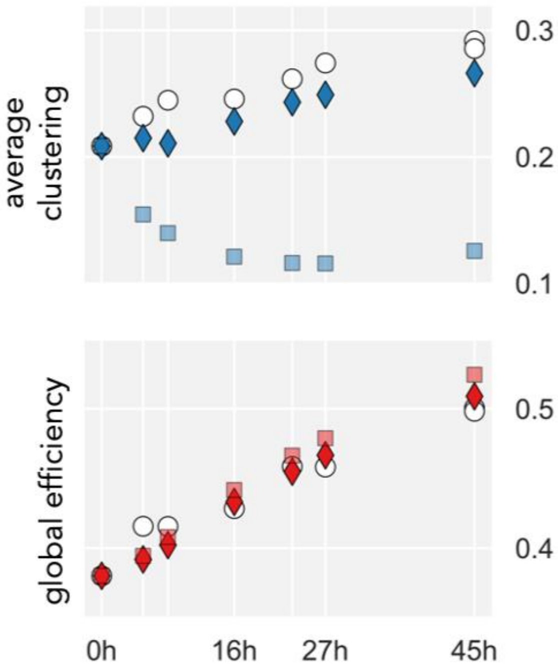
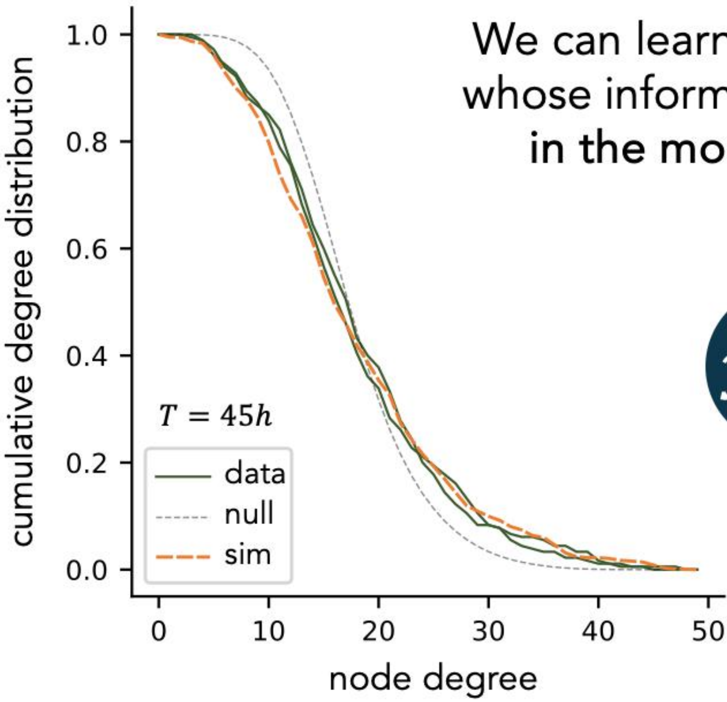


Developmental trajectory tracked down

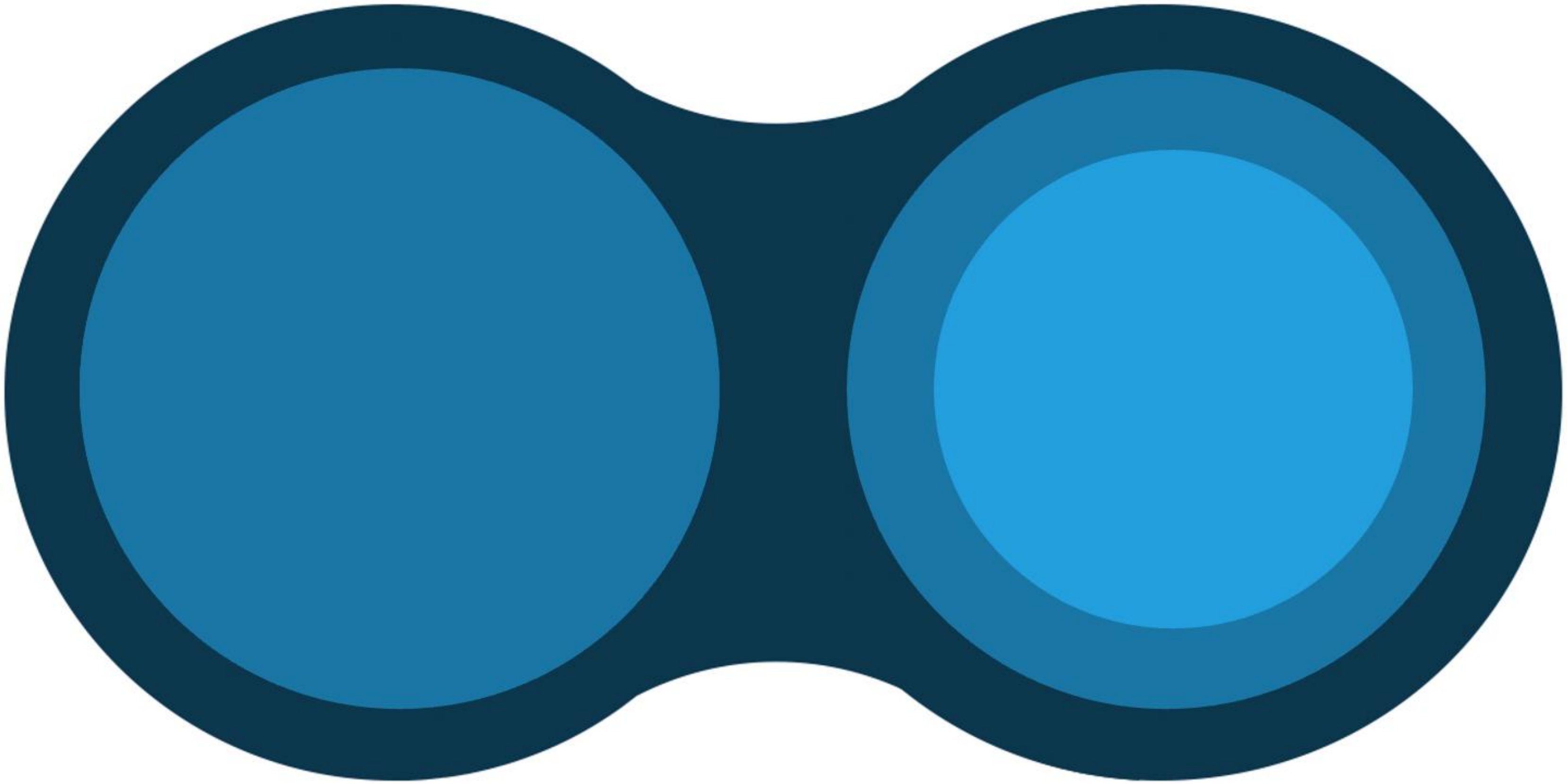
3 | What about $\boldsymbol{y}$?





We can learn those **features** whose information contained **in the model statistics**

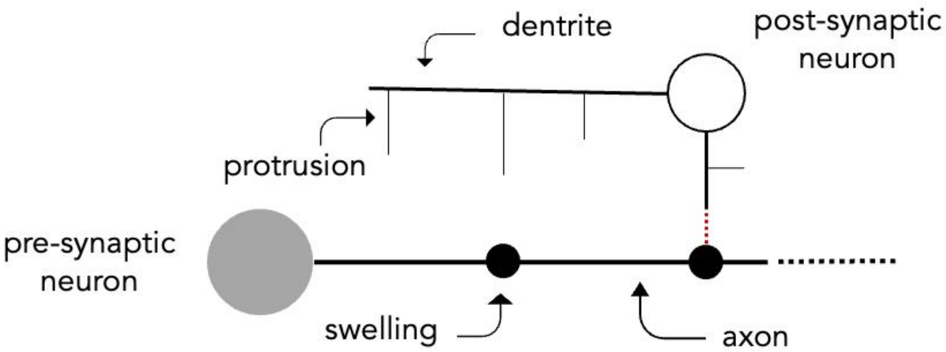
$\boldsymbol{y}(\boldsymbol{x})$

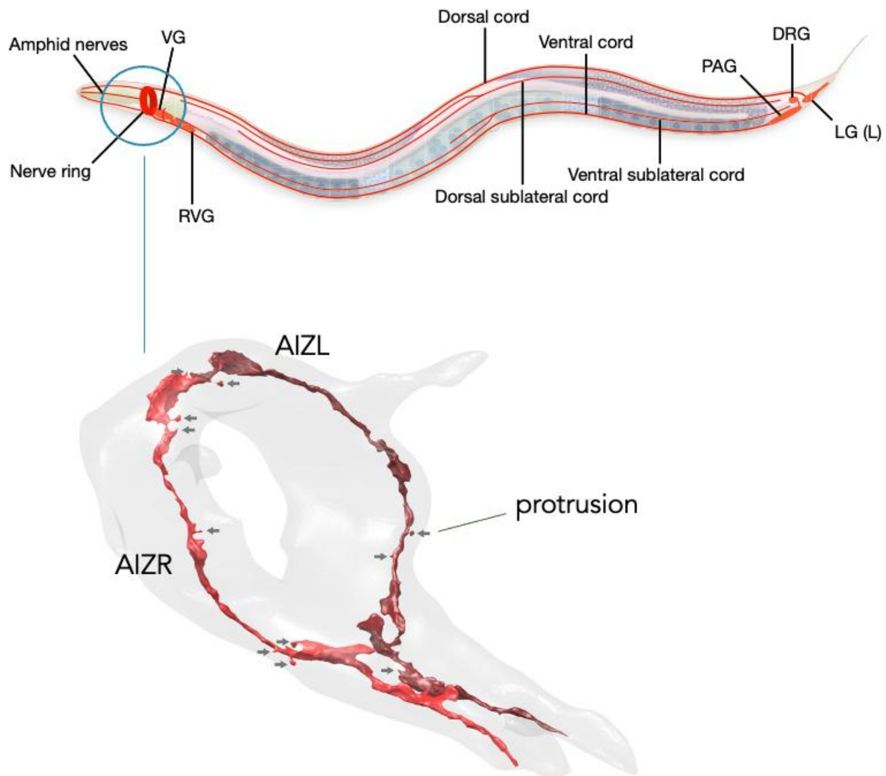


Appendix

Making sense of it

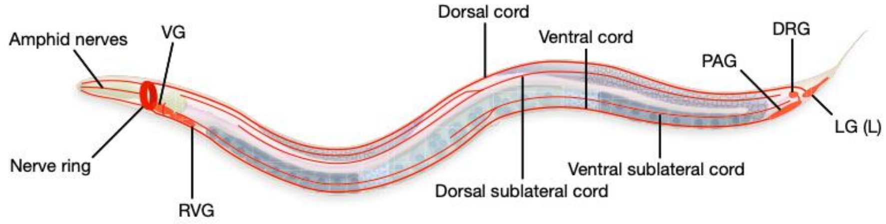
This is what the biologist sees



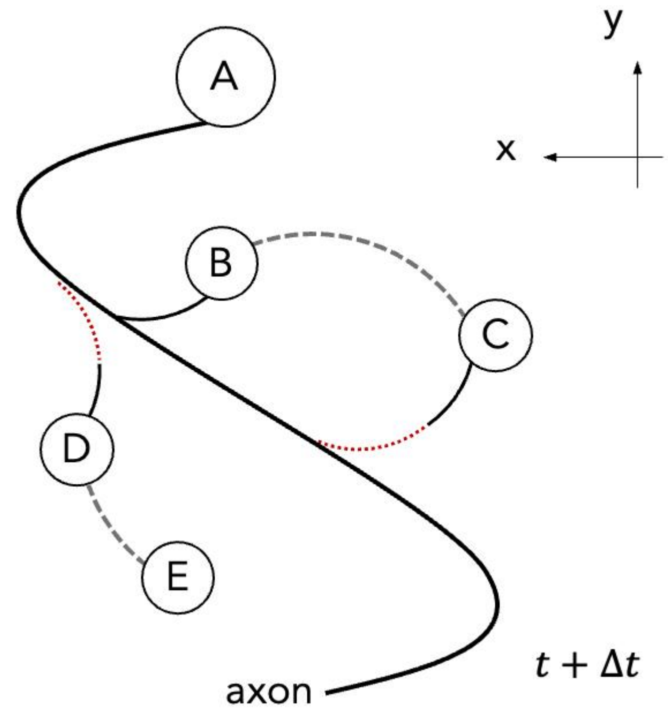


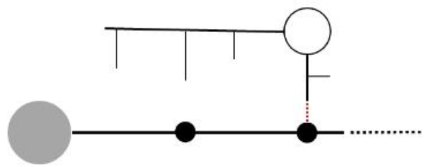
Adult dataset 8, neuron class AIZ / D Witvliet et al, Nature 596(7871), 2021

Making sense of it

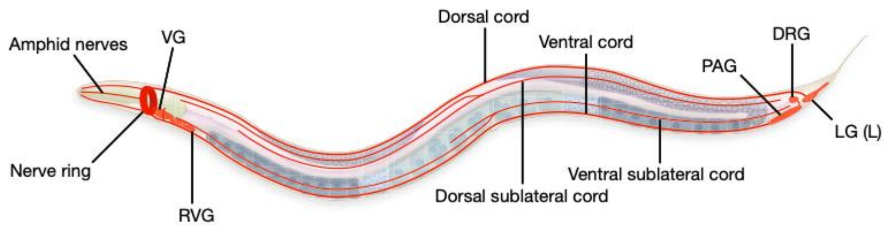


This is an abstraction

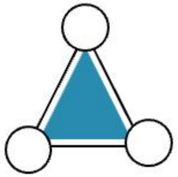


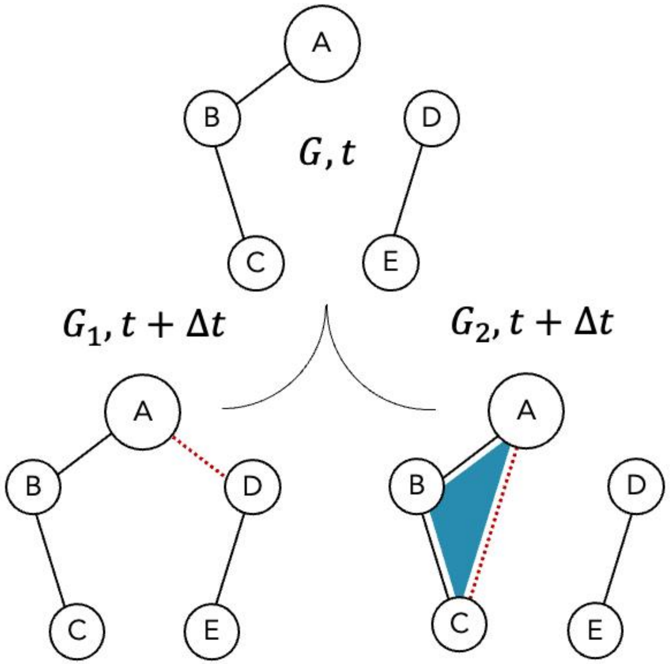


Making sense of it

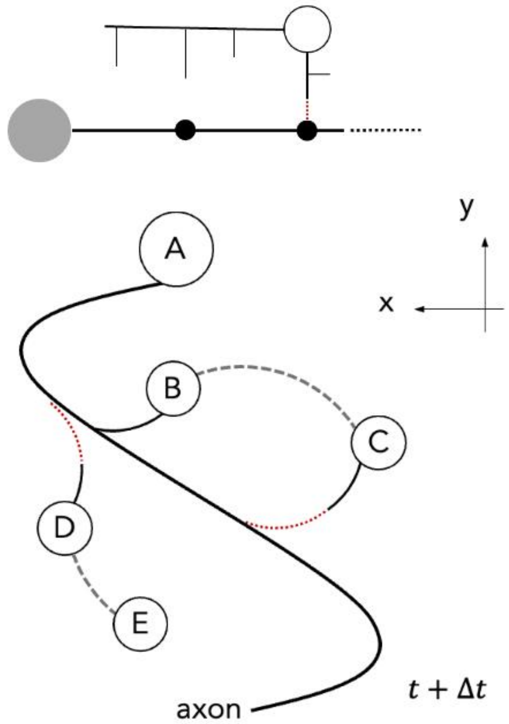


This is a network interpretation

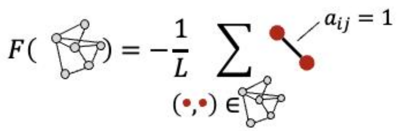
$\mathrm{F(G)} = \sum$ 



$P(G_1, t + \Delta t | G, t) < P(G_2, t + \Delta t | G, t)$

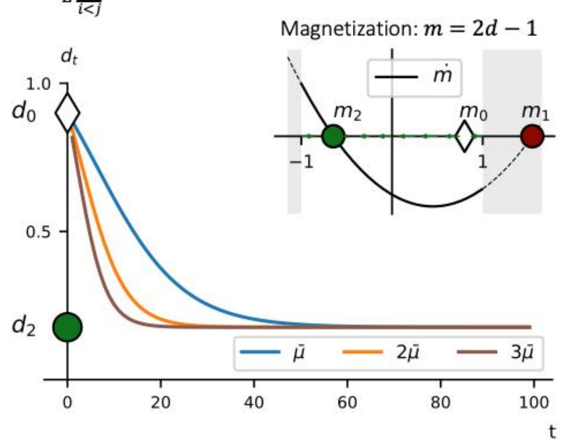


Solve if you can…



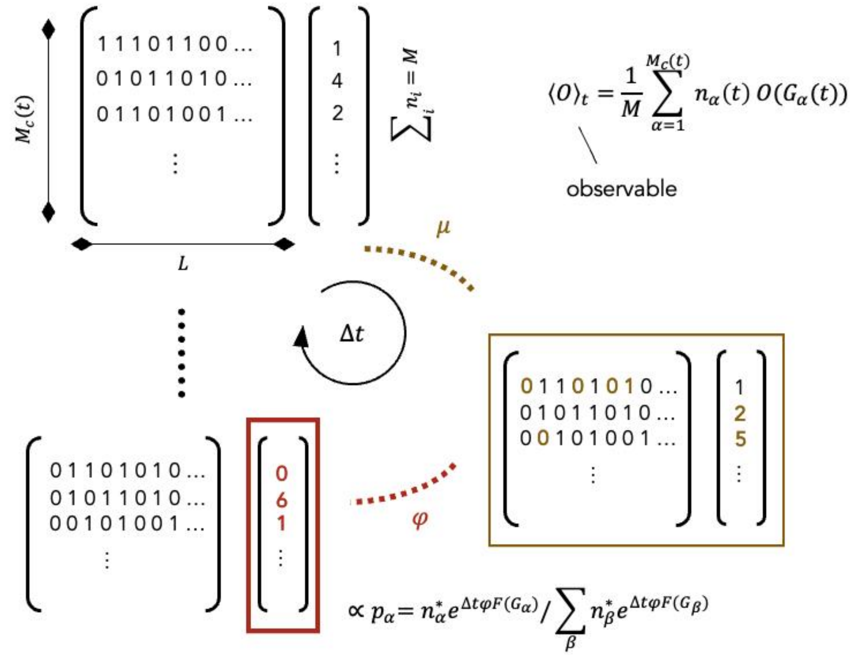
graph density

$d_t = \frac{1}{L}\sum_{i<j}\langle a_{ij}\rangle_t$



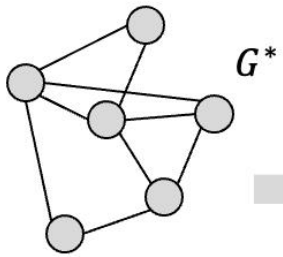
For $\Delta t \varphi F \ll 1$

- Asymptotic state $t \to \infty$ depends on ρ and approaches $\max F$ for $\rho \to \infty$ (perfect exploitation)
- For fixed ρ, the higher μ the faster the approach.



… simulate the rest

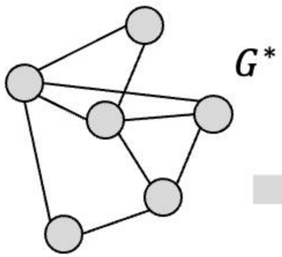
Drawing a landscape

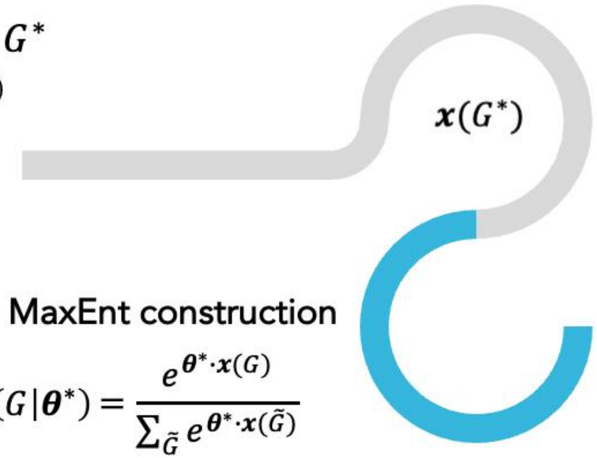


1 | **Model selection** / Which are the relevant features?

$\boldsymbol{x}(G^*) \in \mathbb{R}^r$

Drawing a landscape





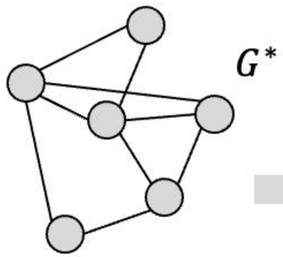
1 | Model selection

2 | MaxEnt construction

$$P_{ERG}(G|\boldsymbol{\theta}^*) = \frac{e^{\boldsymbol{\theta}^* \cdot \boldsymbol{x}(G)}}{\sum_{\tilde{G}} e^{\boldsymbol{\theta}^* \cdot \boldsymbol{x}(\tilde{G})}}$$

Dichio & De Vico Fallani, Rep Prog Phys 86(10), 2023 | Jaynes, Cambridge UPress, 2003 | Cimini et al., Nature Rev Phys 1(1), 2019

Drawing a landscape



$\boldsymbol{x}(G^*)$

1 | **Model selection**

2 | **MaxEnt construction**

$$P_{ERG}(G|\boldsymbol{\theta}^*) = \frac{e^{\boldsymbol{\theta}^* \cdot \boldsymbol{x}(G)}}{\sum_{\tilde{G}} e^{\boldsymbol{\theta}^* \cdot \boldsymbol{x}(\tilde{G})}}$$

Maximum entropy principle

$$\max_P - \sum_G P(G) \log P(G)$$

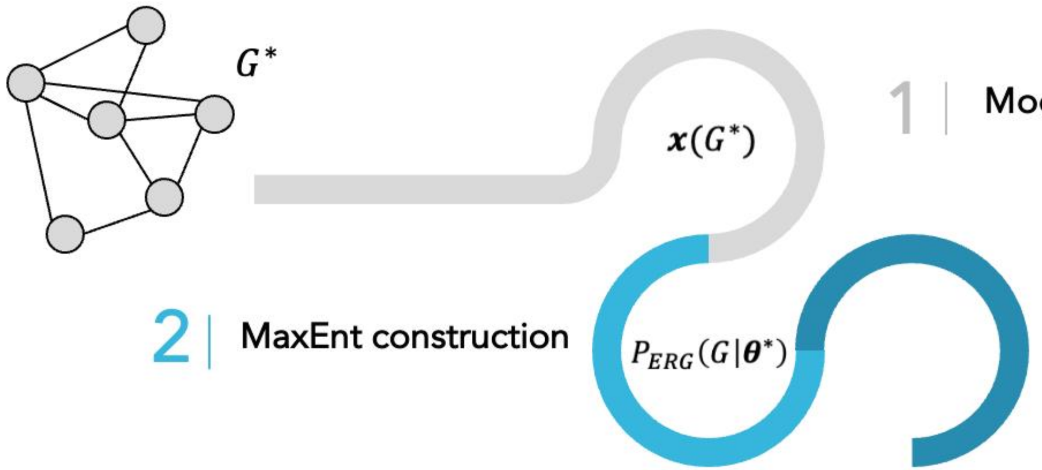
Shannon information entropy

w/

$$\sum_G \boldsymbol{x}(G) P(G) = \boldsymbol{x}(G^*)$$

Dichio & De Vico Fallani, Rep Prog Phys 86(10), 2023 | Jaynes, Cambridge UPress, 2003 | Cimini et al., Nature Rev Phys 1(1), 2019

Drawing a landscape

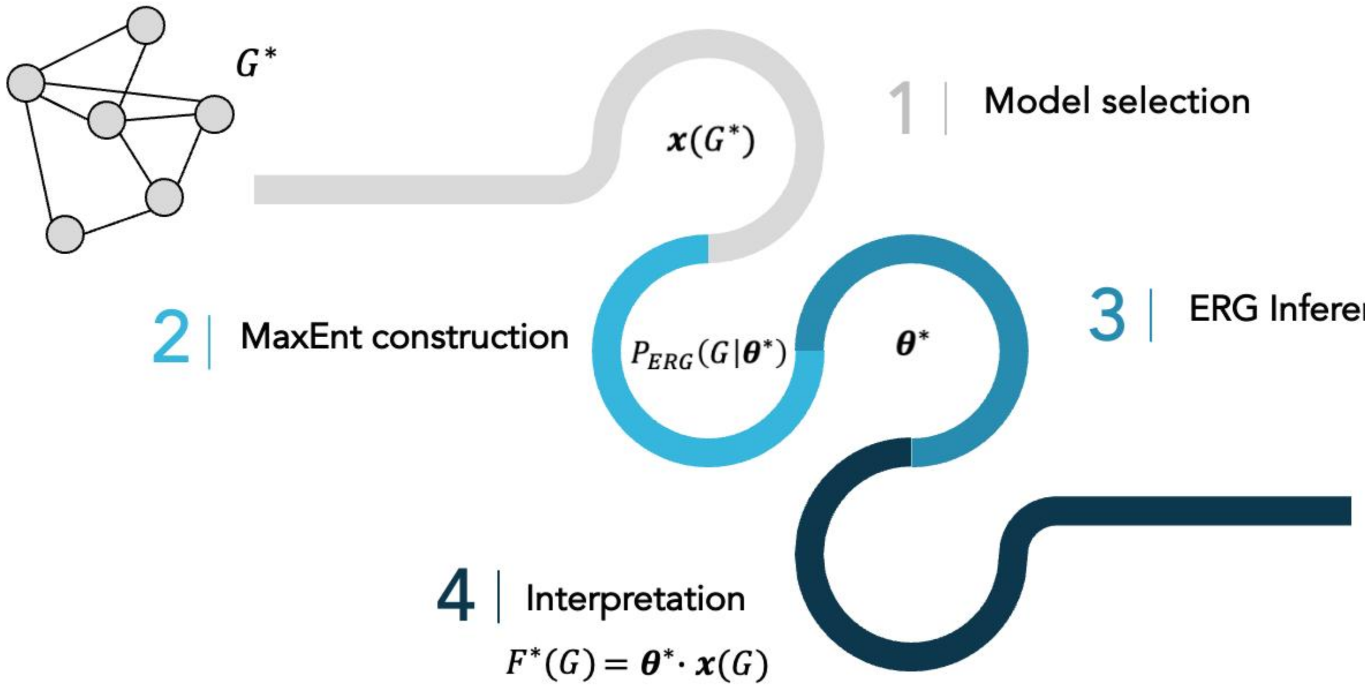


3 | ERG Inference/ MCMC MLE - ergm

$$\boldsymbol{\theta}^* = \underset{\boldsymbol{\theta}}{\operatorname{argmax}} \log P_{ERG}(G^*|\boldsymbol{\theta})$$

Dichio & De Vico Fallani, Rep Prog Phys 86(10), 2023 | Jaynes, Cambridge UPress, 2003 | Cimini et al., Nature Rev Phys 1(1), 2019

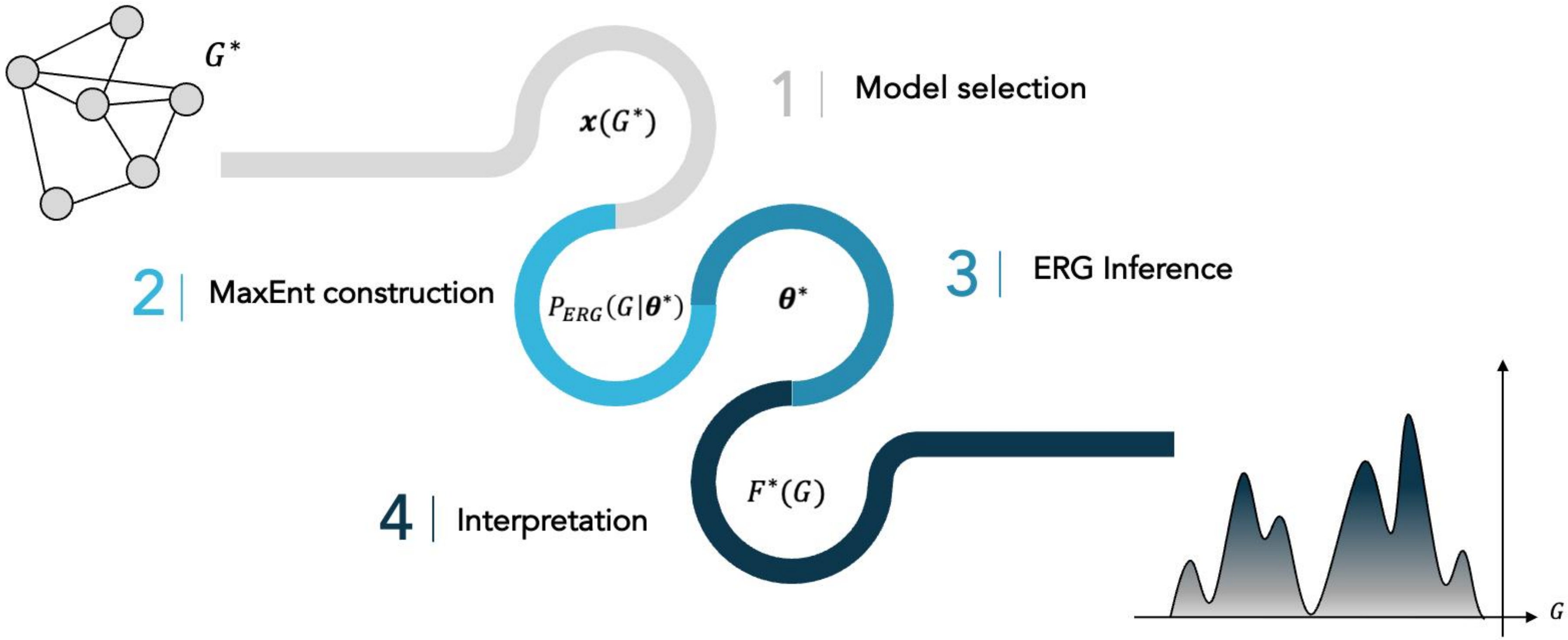
Drawing a landscape



$$F^*(G) = \underbrace{\boldsymbol{\theta}^* \cdot \boldsymbol{x}(G)}_{-\mathcal{H}_{ERG}(G,\boldsymbol{\theta}^*)}$$

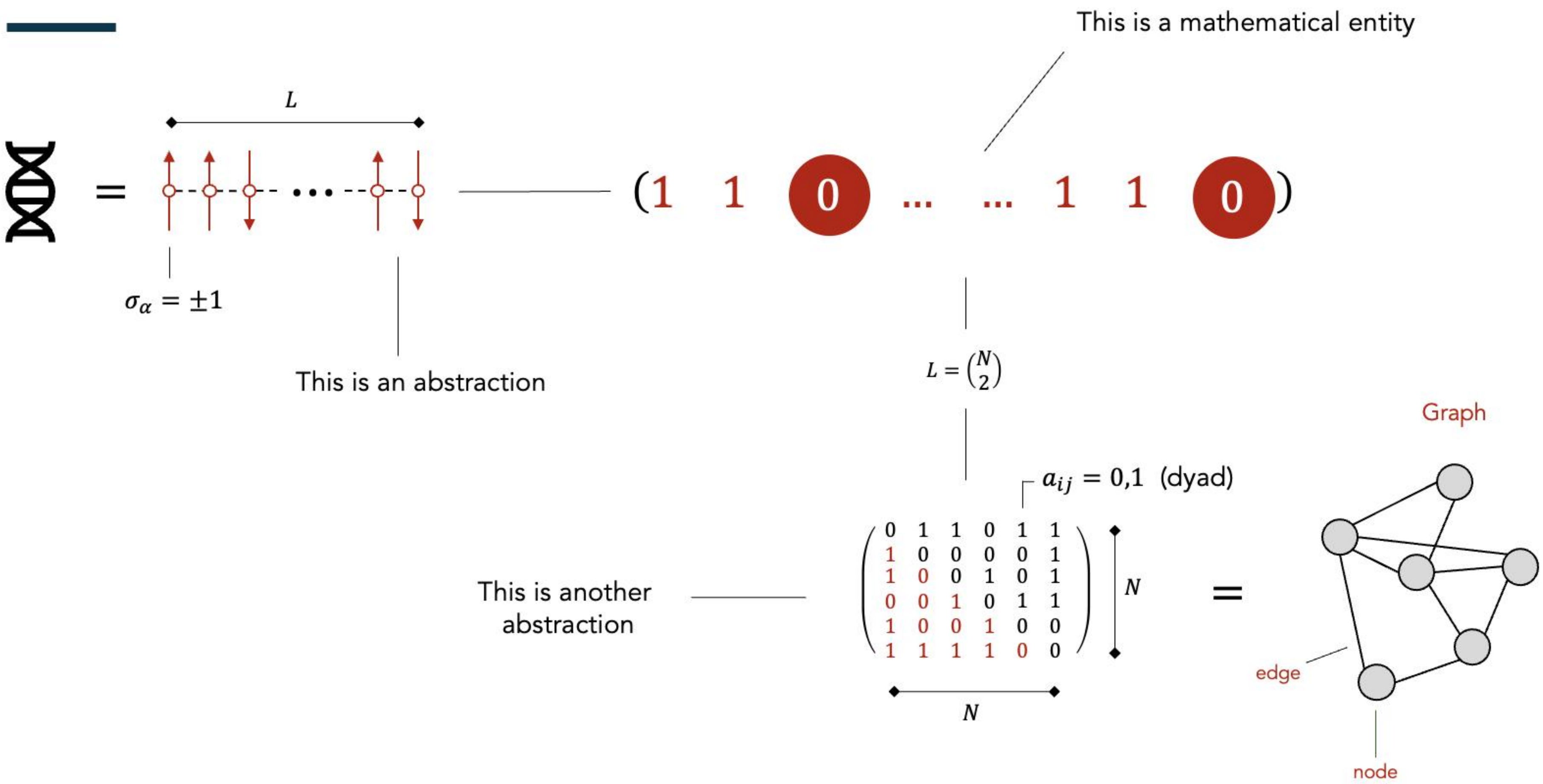
Dichio & De Vico Fallani, Rep Prog Phys 86(10), 2023 | Jaynes, Cambridge UPress, 2003 | Cimini et al., Nature Rev Phys 1(1), 2019

Drawing a landscape



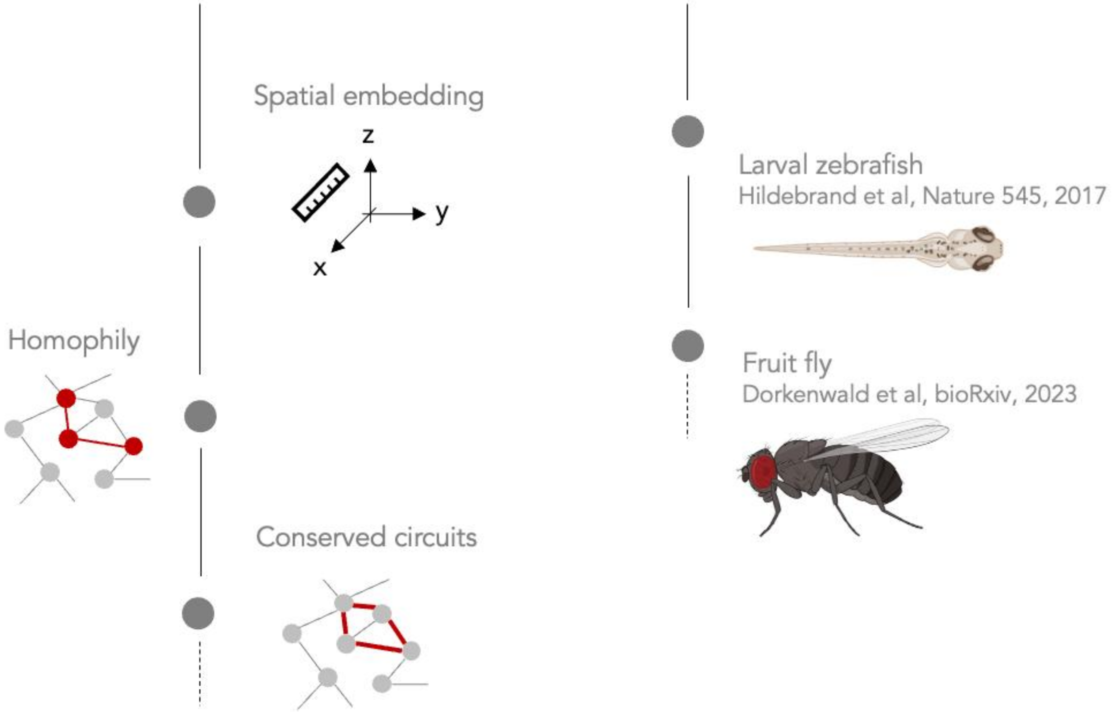
Dichio & De Vico Fallani, Rep Prog Phys 86(10), 2023 | Jaynes, Cambridge UPress, 2003 | Cimini et al., Nature Rev Phys 1(1), 2019

The representation

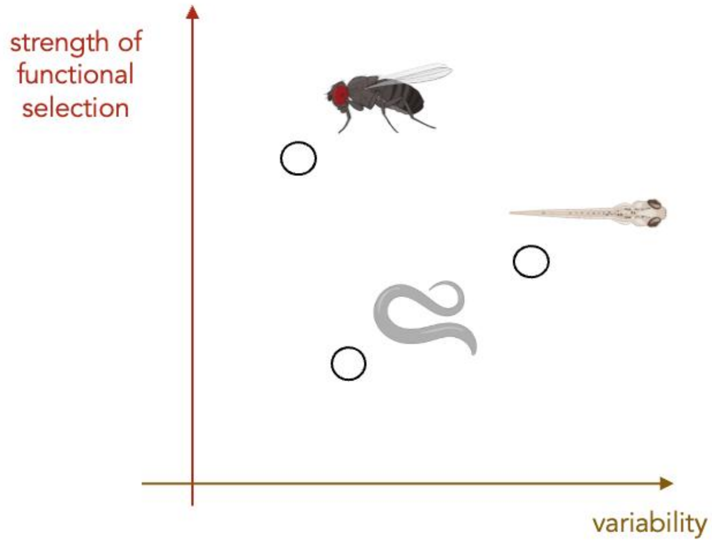


Outlook: simple rules wire complex brains

Detailed EE models of larger brains

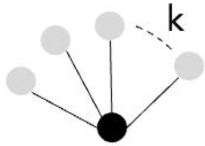


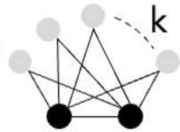
Different details, universal dynamics?



On distance

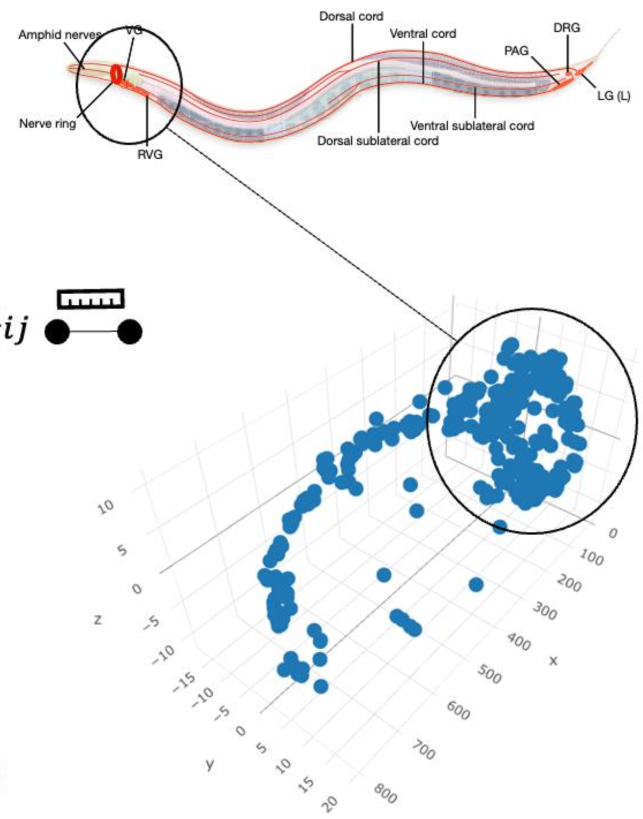
$$F(G) = \theta_1 \sum_{k,\bullet} w_{\lambda_1}^{(k)} \ [\text{k-star}] + \theta_2 \sum_{k,\bullet-\bullet} w_{\lambda_2}^{(k)} \ [\text{k-triangle}] + \theta_3 \sum_{\bullet-\bullet} a_{ij} \ [\text{distance}]$$





θ_1	λ_1	θ_2	λ_2	θ_3
0.44 ± 0.14	1.94 ± 0.32	0.578 ± 0.036	1.486 ± 0.049	-0.065 ± 0.025
(0.45 ± 0.14)	(1.94 ± 0.33)	(0.578 ± 0.037)	(1.487 ± 0.050)	$(/)$

model without distance

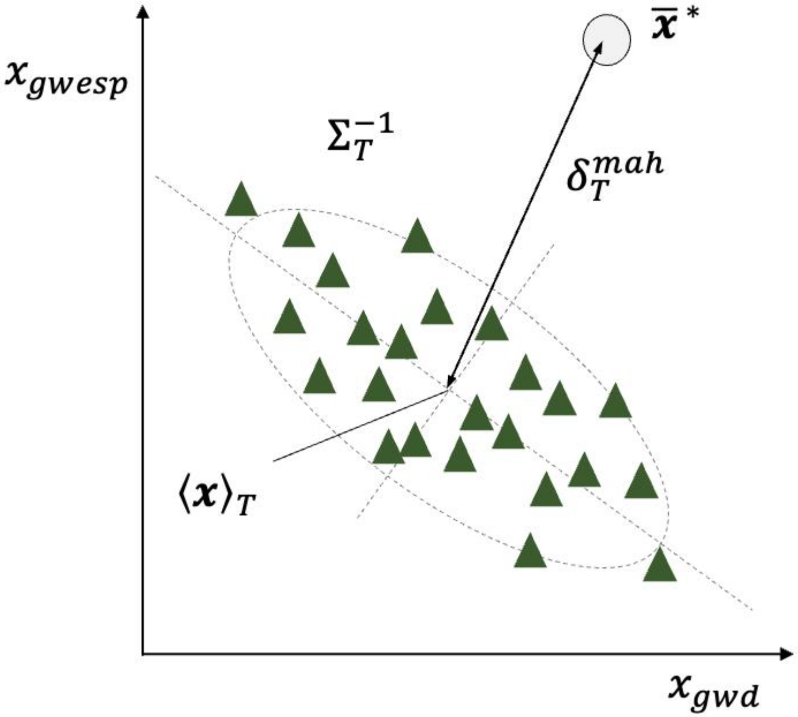


M Skuhersky et al., BMC Bioinformatics 23(1), 2022

cf. V Nicosia et al, PNAS 110(19), 2013 | A Pathak et al, PLoS Comp Biol, 16(1), 2020

Mahalanobis distance

$$\delta_T^{mah} = \sqrt{(\langle \boldsymbol{x} \rangle_T - \overline{\boldsymbol{x}}(\boldsymbol{G}_T^*))^t \Sigma_T^{-1} (\langle \boldsymbol{x} \rangle_T - \overline{\boldsymbol{x}}(\boldsymbol{G}_T^*))}$$



- Accounts for the covariance structure
- Scale-invariant ($\boldsymbol{x} \mapsto A\boldsymbol{x} + \boldsymbol{b}$)