What is biological information?

<u>Course 3:</u> Encoding, Decoding and Representations of Space

Thomas Lecuit

chaire: Dynamiques du vivant

- From letters (chemical species) to « words »: *sequences* and *combinations*
- *Balance between diversity and specificity*
	- Genetic code: deterministic, requires mechanisms for error minimisation (proofreading and « smooth encoding »)
	- Transcriptional code: smooth encoding, but also combinatorial encoding and integration relaxes constraints on 1-to-1 specificity, and increases repertoire of context-dependent regulation.
	- Signalling code: Promiscuous binding and combinatorial encoding increase cellular addressing compared to 1-to-1 L/R signalling. Also allows signal computation.
	- Adhesion code: biased stochastic processes rather than deterministic encoding. Many small contribution rather than few, selective, deterministic molecular codes.

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- From letters (chemical species) to « words »: sequences and combinations
- Balance between diversity and specificity
	- Coding theory provides a framework to understand constraints on code evolution (error load, diversity and cost). Smooth encoding.
	- Combinatorial encoding increases specific « addressing » (cell identity, cell responses)
	- Deterministic use of code: genetic code
	- Stochasticity and Algorithmic encoding: more consistent with self-organisation.
- From « words » to patterns of words (in space and time), ie. « sentences ».

Spatial patterns across scales

Shinji Takada

• Embryo segmentation • Plumage/pigmentation pattern

Interface Focus (2012) 2, 433–450 doi:10.1098/rsfs.2011.0122

Tony Hisgett/Wikipedia

F 5 mm — 10 days

Spatial patterns across scales

• Folding patterns

• Branching patterns

1. Length scales in biological systems

- 2. Positional Information (PI) and Morphogens
- 3. Shannon information theory
- 4. Encoding and Decoding space with PI
- 5. Beyond PI: generalisation

PROGRAM

- hierarchy
- modularity
- heredity (biased initial & boundary conditions) Porodity • heredity (biased initial & boundary conditions)
• deterministic rules b
	- deterministic rules **morphogenesis**

Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, 2021 doi.org/10.1038/s41580-020-00318-6

More viscous

Self-organised spatial patterns More viscous length scale scale

Defining length scales - deterministic models sing langth coolee, detarminietie me inty length scales - deterministic mo \mathbf{e} transforms a homogeneous field of cells into discrete \sim stress. This is a dimensionless. The dimensionless is a dimensionless. The stress is a dimensionless of Ω

 $\bullet~$ Biochemical processes, Diffusion and Morphogen gradients

teristic temporal dynamics, in which, for instance, trigger α instance, trigger α

Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, 2021 doi.org/10.1038/s41580-020-00318-6

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regions of defined length, each with its own morpho-

 $\frac{1}{\text{Total 30:153 (2007)}}$ Thomas Gregor, D. Tank, E. Wieschaus and B. Bialek \mathcal{L}_{max} expressing a Bcd-GFP fusion protein (Gregor et al., 2007); scale bar *Cell* 130:153 (2007)

the concentration-dependent activity of morphogens Defining length scales - deterministic models regions of defined length, each with its own morpho-

• Mechanical processes genetic and differentiation programmes driven by the induction of specific changes in general \bullet . Independent call \bullet

Biochemistry Mechanics Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, 2021 $\frac{\text{Coh}}{\text{det}}$ doi.org/10.1038/s41580-020-00318-6

Etournay R, et al. and Jülicher F, Eaton S. *Elife*. 4:e07090. (2015)

teristic temporal dynamics, in which, for instance, trigger

• Turing chemical instabilities (reaction diffusion)

Local positive feedback - Long range inhibition

11

The length scales of patterns depend on the details of interaction strengths and diffusivities

Economou AD, et al. & JBA. Green Nat Genet. 44(3):348–51 (2012)

Bailles A, Gehrels EW, Lecuit T. *Annu Rev Cell Dev Biol.* 38:321-347 (2022)

• Turing chemical instabilities (reaction diffusion)

Local positive feedback - Long range inhibition

The length scales of patterns depend on the details of interaction strengths and diffusivities

J. Raspopovic et al. and J. Sharpe. *Science* 345, 566 (2014)

Rob Phillips and Christina Hueschen, *The restless cell Continuum theories of living matter.* 2024, Princeton Univ. press.

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A.K Harris, D. Stopak and P. Warner. *J. Embryol exp. Morph.* 1984. 80:1-20

13

Long range inhibition Local positive feedback -

G.F. Oster, J.D. Murray, and A.K. Harris. *J. Embryol. esp. Morph.* 1983. 78:83-125

J.D. Murray, G.F. Oster and A.K. Harris. *J. Math. Biology* 1983. 17:125-129 A. Shyer et al, R. Harland. *Science* 357: 811-815 (2017)

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in which *j*(*s*) is the flux of cells along the ring. For simplicity, we ignore

plate, and *‡* is the stress tensor, for which we use the constitutive relation

here changes in density due to cell product due to cell product due to cell product due to cell death. We use **Patterning regime and contractive contractive contractive contractive contractive contractive contractive contractive** gate relative to the main tendency to spread out. Note that in the main tendency to spread out. Note that in t we refer to the Péclet number as the normalized contractility *'/'*Norm with

Defining **len**gth scales - self-organised instabilities following constitutive relation for the flux *j* $\frac{1}{2}$ + *flv.* (2) $N_{\rm eff}$ is to ϵ other leads to the conditions that leads the formation of aggregations that is not penning wappen scales - sen-organised inst Defining Carloth scales, self-organised instab **Patterning region out of some and contract instability of main text, and contract instability of the main text**

ˆs

Local positive feedback -Long range inhibition the cells characterized by the eective diusion coecient *D*. The second a uniform steady state solution *v* = 0 and *fl* = *fl*0, in which there is no steady

E. Hannezo et al S. Hayashi and J-F. Joanny. *PNAS* 112:8620–8625 (2015)

Example 3 Turing-like mechanical instabilities <mark>article and</mark> here changes in density due to cell proliferation and cell death. We use the an ordinary dierential equation for the velocity *v*, and a partial dierential edback - **for the fluit of the ring. The ring**e instabilities \mathbb{R}^n is the conditions that leads the formalize the formalize the formations that leads the formation of aggre- \bullet - Turing-like mechanical instabiliti patterns. In the first section, we have derived a coupled system consisting of

 p the first section, we have derived a consistency of \mathcal{L}_c and \mathcal{L}_c

we refer to the Péclet number as the normalized contractive interaction $\mathcal{M}^{\mathcal{M}}$

Thomas LECUIT 2024-2025 **and** *the stress* **tensor, for which we use the constitutive relationships the constitutive relations of the constitutive relations of the stress tensor, for which we use the constitutive relations** original theory: J. Bois, F. Jülicher and SW. Grill. PRL. 2011. 106, 028103 Pe:Peclet number (ratio of transport by convection/advection versus diffusion): ζ/ζ_{norm}
Palmouist et al. Cell 185, 1960, 1973, 2022 Palmquist et al., Cell 185, 1960–1973, 2022 average the material of the same contraction of the material of the material. Moreover, we are not include the
Perfected in umber (ratio of transport by convection/advection versus diffusion) : 27 mm simple linear traditionship between active cubit versus diffusion) *.* $\mathcal{G}_{\text{norm}}$ $\mathcal{G}_{\text{norm}}$ Pe:Peclet number (ratio of transport by convection/advection versus diffusion) : عَرَجٌ .
Palmouist et al *Cell* 185-1

cells generate a contraction stress, in other words, the contraction of the stress, they at the stress, they attract each other. stituting $\frac{15}{4}$, we solve for $\frac{1}{4}$, we solve for $\frac{1}{4}$

- 1. Length scales in biological systems
- 2. Positional Information (PI) and Morphogens
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$X\in \mathbb{R}^N$ is the comparison of \mathbb{R}^N in \mathbb{R}^N in \mathbb{R}^N in \mathbb{R}^N is the companion \bullet Theory of transformation from d'Arcy Thompson

- 1. System of coordinates
- 2. Transformation between related species via deformation of the coordinate system.
- 3. Mechanical forces (stress) induce deformations (strain)

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d'Arcy W Thompson, On Growth and Form, 1917 α Arcy w Thompson, *On Growth and Form*, 1917

Evidence that cells « compute » their distance from

It can thus be concluded that a specific concentration of the gradient substance is responsible for the cell forming a rib. The concentration gradient, the existence of which is confirmed by these results, obviously has two functions: (1) to orient the scales by its direction, (2) to supply the cells by its absolute values (or ranges of concentration) with the necessary information about their distance from the segment margins and to induce the corresponding cuticular structures.

Rotation 180° of piece of cuticle leads to deformation of ridge and to reorientation of cuticular patterns

Positional information: an intrinsic coordinate system

d. Theoret. Biol. (1969) 25, 1-47 **Cellular Differentiationt Positional Information and the Spatial Pattern of**

L. WOLPERT

Cellular Differentiationt *Department of Biology as Applied to Medicine,* The Middlesex Hospital Medic<mark>al School, London, England</mark> *J. Theoret. Biol.* (1969) 25, 1-47

The Middlesex Hospital Medical School, London, England

the phenomena are far from clear. This paper is firmly based on the belief

The problem of pattern is considered in terms of how genetic information can be translated in a reliable manner to give specific and different spatial patterns of cellular differentiation. Pattern formation thus differs from method of
molecular differentiation which is mainly concerned with the control of
molecular differentiation which is mainly concerned with the control of molecular differentiation which is mainly concerned with the control of synthesis of specific macromolecules within cells rather than the spatial arrangement of the cells. It is suggested that there may be a universal arrangement of the cells. It is suggested that there may be a universal mechanism whereby the translation of genetic information into spatial patterns of differentiation is achieved. The basis of this is a mechanism whereby the cells in a developing system may have their position specified whereby the cells in a developing system may have their position specified
with respect to one or more points in the system. This specification of position is positional information. Cells which have their positional information specified with respect to the same set of points constitute a information specified with respect to the same set of points constitute a
field. Positional information largely determines with respect to the cells' genome and developmental history the nature of its molecular differengenome and developmental history the nature of its molecular differen-
tiation. The specification of positional information in general precedes and
 $\bigcap_{n\geq 0}$ tiation. The specification of positional information in general precedes and
is independent of molecular differentiation. The concept of positional is independent of indicedual differentiation. The concept of positional information implies a co-ordinate system and polarity is defined as the information implies a co-ordinate system and polarity is defined as the
direction in which positional information is specified or measured. Rules direction in which positional information is specified or measured. Rules be universal rules for genetics, or, of more relevance, for the transcription

It is too often

implicit in embryological thinking that each step in development is a unique or special phenomenon with little general significance. One might, for or special phenomenon with hitle general significance. One implit, for the contract process involving the synthesis of process of \Box a large number of different proteins, the essential feature of each stage being $(i\alpha \mod 1)\alpha$ dependent on the nature of the proteins synthesized (IE. IIId y DE

I would like to suggest that even when parts are removed, or added, and to show size invariance

such a view is quite misleading and that there is good reason for believing that there are a set of general and universal principles involved in the translation of genetic information into pattern and form. patterns of differentiation is achieved. The basis of this is a mechanism

development of the chick limb. It is concluded that these concepts provide

since it would be dependent on the specific properties of a large number of

- An intrinsic coordinate systems specifies positional identity (information)
- Interpret the positional information to produce structures and differentiate
- Uncouples *information* and *interpretation* at cellular and tissue levels:

based on the discovery of scaling property of developmental processes (e.g. Hans Driesch's observation of « regulative » development in sea urchin: cells are not pre-specified, and generate their own coordinate system)

• Mechanisms of positional information are potentially general:

 (ie. may be used in different contexts I would like to suggest that **substanding than the suggest that** within and between organisms)

Lewis Wolpert (1929-2021)

Thomas LECUIT 2024-2025 $\overline{5}$

 $\frac{1}{2}$ This work was first presented at the 3rd Serbelloni Meeting on Theoretical Biology, $\frac{1}{2}$ mechanisms. From an evolutionary point of view development is the process translation of genetic information into pattern and form. While some would

Positional information: an intrinsic coordinate system **D. Busching Street** tional informati

- \bullet The French Flag Problem $\qquad \qquad \blacksquare$
- \bullet Regenerative potential of a tissue with scale invariant **than** pattern t_{in} in realistic \mathbf{D} expected concentration dynamics (see *Methods*). Fig. 1*B* indicates that concentration changes on the length and time scales relevant for development are well described by the diffusion
- Requires (i) a mechanism for \overline{a} specifying polarity; (ii) a **relationships decrease in** vital mechanism for the differential response of the cells, such as thresholds; and (iii) at least one $\begin{array}{|c|c|} \hline \ \hline \ \hline \ \hline \ \hline \ \hline \ \hline \end{array}$ spontaneous self-limiting reaction (Wolpert, 1968). The diffusion of the diffusion of the diffusion of the diffusion of the di (passive diffusion), then it is governed by the Stokes–Einstein dynamics of molecular motion. Although this enhances the

dipteran evolution (17), the eggs of closely related species vary over at least a factor of five in length (Table 2). Despite these

70 5.9 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8 1.4 8

C. vicina (1,420 "m) 4 20.3 % 1.3

Uyghur A. Et al, and J. Briscoe, C. Tabin. response is children. $\frac{12}{120}$ is not Developmental Cell 37, 127–135 ened agonist (SAG) using [i] explants. SAG acts at the level of level of level of level of level of level of level of

T. Gregor, W. Bialek et al, E. Wieschaus. *PNAS*, 51, 18403-18407 (2005).

100µm

Positional information: an intrinsic coordinate system

- The French Flag Problem
- Regenerative potential of a tissue with scale invariant pattern
- Requires (i) a mechanism for specifying polarity; (ii) a mechanism for the differential response of the cells, such as thresholds; and (iii) at least one spontaneous self-limiting reaction (Wolpert, 1968).

• Implications of the universality of positional information

- Same positional information system
- $\bullet\,$ Genotype specifies interpretation

FIG. 5. Some examples to show some possible implications of the universality of positional information. Consider a rectangular field and two different genotypes. Genotype *fr* results in the interpretation of the positional information so that a French Flag is formed (a) while genotype *us* results in the Stars and Stripes (b). If, at an early stage, two pieces are interchanged as in (c), and if positional information in the two fields is the same, then the results shown in (d) and (e) will follow: that is the cells behave according to their genotype and position and are indifferent to the nature of the surrounding tissue. Similarly, if two halves of different genotypes are joined as in (f) a mosaic as in (g) will form (B is blue, W is white, R is red).

Lewis Wolpert, *J. Theoret. Biol.* (1969) 25: 1-47

Positional information: an intrinsic coordinate system

- Clones of cells carry the *Antennapedia* mutation
- Cell identity (namely antenna or leg identity) is changed autonomously: see selector gene.
- There is an *equivalence of different relative positions along limb axis*: positional information
- Invariant property: position along the proximo-distal axis.

Lewis Wolpert, *J. Theoret. Biol.* (1969) 25: 1-47

wild type *Antennapedia*

J. Postlethwait and H. Schneiderman, *Dev. Biol.* (1971) 25:606-640

d to aradiante of nocitional informe Evidence that cells respond to gradients of positional information

- Graft experiments on the cuticle of insects (*Rhodnius*) induce reorientations of hairs in cells at the boundary of the graft
- This is consistent with this orientation being set up by the slope of a gradient of positional information (slope defined by the position of a source)

A GRADIENT OF POSITIONAL INFORMATION IN AN INSECT, *RHODNIUS*

P. A. LAWRENCE, F. H. C. CRICK AND M. MUNRO *Medical Research Council, Laboratory of Molecular Biology, Hills Road, Cambridge, CBz 2QH England*

Fig. 3. Experiment illustrating the dependence of polarity on the direction of gradient α . slope. The operation was performed on the sternite of a 5th-stage larva (left) and the
specific than which conservation was a singlet. Cross sections of the operation landscreen result shown diagrammatically on the right. Cross-sections of the gradient landscapes
are indicated below. Note the regions where the gradient clape is reversed as a result of are marcared below. I vote the regions where the gradient slope is reversed as a result of the anfocal diffusion. Brackets indicate where the oriented tubercies point towards in
terior margin (A) instead of towards the posterior (P). (Compare Figs. 16, 17.) are indicated below. Note the regions where the gradient slope is reversed as a result of

J. Cell Sci. **11**, 815-853 (1972)

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limb elements are produced. Such abnor-
Distal trans rates would be himb elements are produced. Such about that influences by Distal transformation in \hat{f} ϵ the appendage must added the ϵ region, regenerates with multiple distal

 \mathbf{r}_1 and that is identical to that of a preex-
15 and 15 insects: \mathbf{r}_2 and \mathbf{r}_3 is \mathbf{r}_4 their than the A lever. We will can this distalization rule. For simplicity, we adopt a positional value that is more \mathbf{u} me that the new \mathbf{u} isting adjacent cell (as in the case in Fig. $\frac{0.016}{100}$ $\frac{d}{dx}$ and $\frac{d}{dx}$ are $\frac{d}{dx}$ and $\frac{d}{dx}$ are $\frac{d}{dx}$ and $\frac{d}{dx}$ are $\frac{d}{dx}$ and $\frac{d}{dx}$ are $\frac{d}{dx}$ However, if this represents a positional value of $\frac{1}{\pi}$ itional value of $\frac{1}{\pi}$ and $\frac{1}{\pi}$ ition will 8 8 4 positional value which is only one step $\qquad \qquad \qquad \qquad \qquad \qquad$ rather than the A level. We will call this positional value which is only one step
more distal, as shown in Fig. 2a, but this
is not crucial since provimal-distal intervill assume that the new cells adop reus generau
ntercalation In the development of the mature during circum-
the new cells generated during circumto the intercular cells are gooding $\frac{180}{180}$ of the appendage must adopt positional 'B $\frac{1}{2}$ is not crucial since proximal-distal inter-
is not crucial since proximal-distal inter-
 $\frac{3}{8}$ vision for stopping at the distal tip, will $\frac{1}{2}$ \rightarrow | limbs have stage geographical queen granding the control $\frac{1}{2}$ values that are more distal than those of $\frac{u}{na}$ the preexisting cells at the wound edge. $\frac{1}{2}$ and $\frac{1}{2}$ are the wound edge.
We propose that this comes about as a result of a strictly-local interaction as $\frac{n}{1}$ follows: during intercalation, a newly $\frac{1}{w}$ k calculation at the growing tip is more
ting cell.
at the B e calation will fill in any gaps that would be $\frac{a}{b}$ idescens h formed by any less regular process. Re- $\frac{e}{2}$ peated rounds of circumferential interca-
 $\frac{e}{3}$ $\frac{e}{2}$ and $\frac{e}{1}$ of t peated rounds of circumferential interca-
lation with distalization, with some pro-
 $\frac{1}{2}$ ation with distalization, with some provision for stopping at the distal tip, will
vision for stopping at the distal tip, will
example the scheme of th Amphibians: *Notophthalmus viridescens* Fig. 1. Polar coordinates of positional infortween depicted as a flat field and a
assistants as it discrimed as it might be a flat for a flat field and departured and the second and the second
contract discrimed as it might be a flat for a flat for a flat for a flat for a \mathbf{s} in The proximal part of \mathbf{r} $\overline{0}$ and $\overline{1}$ center.
In discussion is $\frac{1}{2}$ unce $\frac{1}{2}$ ^t will a ϵ peated e circle of position
 \ddotsc present at the amputation site and a
present at the amputation site and a ferential intercalation at the growing tip and their positions with respect to the growing tip l cell will normally adopt a posi-
eneration experiments and position tween those of the confronted cells. $\frac{e^{ht}}{dt}$ distal than that of the preexisting cell. Thus the new circle in Fig. 2a is at the B $_{\text{Cockroad}}$ $\frac{1}{2}$ assume that the new cells adopt the lation with distalization, with some pro-
 $\frac{1}{\sqrt{2}}$ the preexisting cells at the wound edge. generated cell will normally adopt a posi-
tional value which is intermediate bedo give an outgrowth which is both circum-
 $\frac{1}{\frac{1}{\alpha}}$ be regarded as two-dimensional epithelial sheets. The limb is a three-dimensional structure with a central core of bone, surrounded by a cylinder of dermis. Nevertheless, our two-dimensional model for pattern regulation is adequate to account for many of the regulative phenomena in amphibian appendages. Experiments on developing limbs have shown that the information for the limitial \mathbf{f} circular disk of mesodermal cells (48- 500 derm is grafted to other regions of the \mathbf{E}^{max} a limb develops (in cooperation with nonlimb epidermis) in which the anteriorthe new cells generated during circumit seems as though positional information values that are more distal than those of limb region or in a hollow cylinder of follows: during intercalation, a newly n in the mature limbs and the mature limbs and the mature limbs and the mature limbs and the mature \sim However, if this represents a positional the distalization rule. For simplicity, we generated cell will normally adopt a posis regeneration experiments and positional lining attion \mathbf{s} at the **D** Cockroach \mathbf{s} ing animals are still comparable to the top still comparable to the still com

a For surgically created symmetrical $\begin{array}{c} 0 \\ \hline 0 \\ 0 \end{array}$ $\begin{array}{c} \end{array}$ saged as comprising several qualita- $\begin{array}{ccc} \end{array}$ ween it and $\begin{array}{ccc} \hline \end{array}$ $\begin{array}{ccc} \hline \end{array}$ saged as comprising several qualita- $\begin{array}{$ s **and predicts that distalization may oc-**
So **model predicts that distalization may oc-**
So **if** it is assumed that the leg field $\frac{a}{r}$ as the set of and the symmetrical partial circum-

the symmetrical partial circum-
 $\frac{a}{c}$ are not shown. (i) Graft homology results into the leg b $\frac{1}{2}$ are not shown. (i) Graft must meet precisional values of $\frac{1}{2}$ lient agree-For the content of distali-

Ferences. However, the extent of distali-
 $\frac{1}{x}$ are not shown. (i) Graft

less file the leg case as in Fig. 7.1.

less file the leg case as in Fig. 7.1.
 $\frac{1}{x}$ and by our $\frac{1}{x}$ $\mathbf g$ referred in the distance compared. w amphibians or cockroaches, the above $\frac{9}{5}$ is $\frac{1}{2}$ ohn's representation of $\frac{1}{2}$ mechanism.
2. An important is that ; cur fr t- terend $\frac{1}{2}$ ferentially and distally complete. $F_{\rm eff}$ (regeneration and distal transformation in the proximal-distal transformation in the proximal-distal $r_{\rm eff}$ s model predicts that distant about hay oc-
 $\frac{3}{10}$ and the symmetrical partial circum-
 $\frac{3}{10}$ and the leg base of the leg base s fields such as "double-half" limbs in $\frac{8}{9}$ $\frac{1}{3}$. s model predicts that distalization may oc-
 $e^{\frac{1}{2}}$ $e^{\frac{1}{2}}$ $e^{\frac{1}{2}}$ For ferences. However, the extent of distali-¹⁰ SEPTEMBER ¹⁹⁷⁶ ⁹⁷⁷ zation will depend on the orderliness and $\limsup_{n \to \infty}$ or $\limsup_{n \to \infty}$

'B

 $p = \frac{1}{2}$ farantially and distally come

 $c = c$

 $\mathbf o$ circumferential intercalation according a complete circle of positional values was present at the amputation site, a new complete circle will be generatedby this .
., \vdash

Fig. 1. Polar coordinates of positional infor-S 0 its position on a radius (A-E) and on a radius (A-E) on a radius (A-E) concertation on a radius (A-E) concerta
 i- $\mathbf f$ **S** d $\mathbf t$ e e $\mathbf h$ t

 $\sum_{n=-\infty}^{\infty}$ istal transformation is also shown by ansformation $(5, 7)$

Pe- and positivated skin (epidermis if the developing limb field and early limb $\frac{let}{dt}$ set of pob. When presumptive lar sequence I I formed by Carlson (57) and Lheureux can frequently reform from the remain-12. C. S. Wu, E. Ambler, R. W. Hayward, D. D. Hoppes, R. P. Hudson, ibid. 105, 1413 (1957); R. **growth** sure (48) . But if only $\lim_{x \to a}$ interval increased by $\lim_{x \to a}$ or regenerated by $\lim_{x \to a}$ regenerated by $\cos i$ _{radia}ted with $\frac{1}{2}$ ch the complete circu-In order to achieve distal outgrowth surfaction asset is excised, a limb bud miments per- $\lim_{t \to 0}$ ions of the limb field, $\frac{1}{2}$ cuff of the field (56). The erary regener \mathbf{r} distal transformation \mathbf{r} t-handed), for $\mathbb{E} \text{ or }$ a complete set of po- \leq s and with va **ge.** the circular sequence $\frac{2}{\alpha}$ umeraries we **is a** cuff on experiments per- $\frac{\alpha}{\beta}$ tion (23, 28). is a set on (57) and Lheureux $\frac{1}{x}$ the shortest I minos, which do not $\frac{1}{3}$ bunt satisfactorily for these results $\frac{1}{2}$ $\frac{1}{18}$ extended the this component as about as $\frac{1}{2}$ limbs, which do not tirdle rudiments, are when amputated. If

Ĩ \mathbf{F} ically contains only a small Fig. $\frac{\text{Sine} \times \text{Sine} \times \text{Sine}}{\text{Sine} \times \text{Sine}}$ (here circumference, then distal $\frac{1}{2}$ and $\frac{1}{2}$ $\mathbb{R}^{1,1,3}$ itional values is pres- ℓex - ℓx ,I ation will occur. How-

 $\frac{1}{2}$ since a c

Fig. 6).

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tations. Sund after 90° shown (26) results

distal

we eegen from weipers ϵ (e) recurring opter- α for these resulting information about their physical positorily for these resulting increased the account satisfactorily for these results tions in the developing cell population. Crickthe shortest intercalation rule c **spatial patterns result from**
 $\frac{1}{x}$ the shortest intercalation rule c **spatial patterns result from** spatial patterns result from cells acquiring information about their physical posi-

Downloaded from Sting us in Ye telly sustinged from はっぽん しょうしょう $\frac{1}{1}$ addition to these results on cock-
Is on cock- ζ ⁻ ts on cockaddition to these results on cock-
es, similar supernumerpy legengind cantesian acoordinate^{251/3}16ffs roaches, similar supernumerary regeneration is on cock-
to be seen the complete circu-
example are produced after contracted and Cantesignacoordinate style **EPOLE PERISTS**
That a leg is in a carte system of that a leg in a cell lag in a leg in a
A leg in a leg $\frac{1}{12}$ are produced after contralateral leg $\frac{1}{2}$ relateral leg that a leg ralateral leg splantation or 180° rotation in ϵ ⁹⁰ by the splantation or 180° rotation in stick (B) $\frac{60}{\pi}$ to the stick of $\frac{67}{\pi}$ 60 120 E 60 transported the strange in the stick of $\sqrt{2}$ with an angular and a radial com-D D ans (30), leg is \sim \sim extending its most computer- \mathbb{E} (31), and spiders (32), and \leftarrow similar si 150 30 C on October 23, 2019 http://science.sciencemag.org/ Downloaded from C $\sum_{\text{and } \text{ceg}}$ $\sum_{\text{after similar}}$ B B perations on the anal cerci $\sum_{n=1}^{\infty}$ after simi- $\frac{3}{34}$. $\frac{180}{180}$ $\frac{1}{180}$ $\frac{2}{180}$ $\frac{3}{180}$ 180 A 180 A $\overline{\text{Down}}$ loaded from $\overline{\text{V}}$ inscienc ϵ . Science. $\overline{\text{O}}$ bttp://science.science.sciencemag.org/ on October 23, 2019 $\overline{0}$ C R lar operations on the anal cerci of crick-ets (33) and earwigs (34). $\frac{a}{\infty}$ rganization of the base of the cockdistal axis of the appendage, with the $\frac{d\theta}{d\theta}$ and the science of the cock- $\frac{3}{5}$ *h* leg. Bohn (35) found the the 210 330 $\frac{d\mathbf{b}}{dt}$, which are produced by a sequence of $\frac{d\mathbf{b}}{dt}$ $\frac{1}{28}$ Id still regenerate after complete $\frac{1}{280}$ that a leg $\begin{array}{c}\n\hline\n\end{array}$ and that a leg $\begin{array}{c}\n\text{S}^{\text{20}} \\
\text{erites}^{\text{28}} \\
\text{20}\n\end{array}$ 310 310 $\frac{6}{9}$ al of the entire leg including its most omplete reomplete re- $\frac{a}{B}$ and the complete re-
 $\frac{b}{B}$ imal segment, the coxa. $\frac{b}{B}$ ing its most l from E -and praeit, the coxa. r_{90} virpat-
cumfe of the entire definition on a cross section of the entire contract of the entire contract of the entire c 90 \overline{C} 120 $\sum_{n=1}^{\infty}$ different amounts of ti \sum_{150}^{120} \sum_{30}^{60} 60 Den Tyled from the sciencemag.org/ on October 23, 2019 60 C $rac{d}{d}$ and $rac{d}{d}$ extimple. $rac{d}{d}$ iso $rac{30}{d}$. δ ₁₅₀ posterior to the base of $\frac{1}{100}$ by extirpation of the coxa, he 30 30 150 A $\frac{q_{\text{total}}}{q_{\text{total}}}$ anterior $\frac{q_{\text{total}}}{q_{\text{total}}}$ anterior $\frac{q_{\text{total}}}{q_{\text{total}}}$ and $\frac{d}{dx}$ anterior $\frac{d}{dx}$ and $\frac{d}{dx}$ and $\frac{d}{dx}$ and $\frac{d}{dx}$ and $\frac{d}{dx}$ on October 23, 2019 http://science.sciencemag.org/ Downloaded from $\overline{\omega}$ position to the proximal 180 of 0 180 0 $\frac{1}{\text{d}}$ that a leg can be proximal $\frac{1}{330}$ be pr₂₁₀ 330.
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le or LIM; see Fig. 7a). The screen or LIM; see Fig. 7a). The scale is screen of the scale is sterior $\frac{d}{dx}$ and $\frac{d}{dx}$ $\frac{d}{dx$ $\frac{1}{\sqrt{2}}$, $\frac{1}{\sqrt{2}}$, $\frac{1}{\sqrt{2}}$, $\frac{1}{\sqrt{2}}$ and $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ called the scheme $\frac{1}{\pi}$ $\frac{1}{\pi}$ mem-
envisories
dom the
ent by
h Bohn ne segment are separated $\begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}$ meming, the discontinuity in position \mathcal{B}_1 and \mathcal{B}_2 $S = \begin{bmatrix} \text{mean} & \text{p} \\ \text{linear} & \text{p} \end{bmatrix}$ some pro- $\frac{3}{2}$ $\frac{1}{2}$ in the next anterior systems can be understood in the systems can be understood in the understood in terms of strictly leftness \sim $\frac{1}{2}$ centres $\frac{1}{2}$ o $\frac{1}{2}$ nous zone, $\sqrt[4]{\frac{1}{\text{max}} \cdot \frac{1}{\text{max}} \cdot$ $\frac{1}{2}$ d the sclerite-inducing membrane or $\frac{1}{2}$ is a B com $\mathbf{r} \in \frac{1}{6}$. D at the position position position \mathbf{p} are \mathbf{p} and \mathbf{p} are \mathbf{p} $\int_{0}^{\frac{\pi}{2}} \frac{d\theta}{\theta}$ is egment by $\int_{0}^{\frac{\pi}{2}} \frac{1}{2}$ $\int_{0}^{\frac{\pi}{2}} \frac{1}{2}$ Ing memorane or $\frac{9}{8}$ iegment by $\frac{7}{8}$ $\frac{6}{8}$ g W? Equivalent and the science-inducing membrane of $\frac{9}{8}$ egment by since a confrontation between it and $\frac{9}{8}$ mon between it and $\frac{9}{8}$ which Bohn $\frac{8}{8}$ $\frac{6}{8}$: ral qualitascheme a confidentially between a direction of the $\frac{3}{8}$ which Bohn \overline{a} y and distally complete.
 $\frac{1}{5}$ and distally complete.
 $\frac{1}{5}$ and distally complete. embrane or \overrightarrow{B} es.

ween it and \overrightarrow{B} \overrightarrow{C} llent agree-

ation of the \overrightarrow{B} \overrightarrow{C} ade by our $\int_S \frac{\varphi}{\rho}$ embrane or $\frac{\pi}{2}$ \int_S^{π} es. g rerentially and distally complete.

a For surgically created symmetrical $\begin{bmatrix} 5 \\ 0 \\ 0 \end{bmatrix}$ and $\begin{bmatrix} 1 \\ 2 \\ 3 \end{bmatrix}$ are it and $\begin{$ October 23, 2019 ween it and saged as comprising several qualita- \ddot{Q} ween it and $\frac{24}{9}$ v distinct transverse zones. $\frac{9}{9}$ ation of the ation of the $\frac{5}{9}$ and by our density of the leg field $\frac{1}{\sqrt{2}}$ of the show $\frac{1}{\sqrt{2}}$ ohn's results are in excellent agree- $\frac{1}{\sqrt{2}}$ g was thus g was thus **ns or cockroaches, the above** $\frac{3}{8}$ y $\frac{3}{10}$ and $\frac{3}{10}$ the predictions made by our $\frac{3}{8}$ ral qualitahe leg field $\frac{d}{d}$ in Fig. 7a. at distant at our and that the leg field $\frac{10}{N}$ es. $\frac{10}{N}$ es. $\frac{10}{N}$ es. $\frac{10}{N}$ es. tial routes (the "shortest intercalation $\frac{1}{2}$ lent agree-
 $\frac{1}{2}$ ade by our $\frac{1}{2}$ occupy the metrical partial circum-
 $\frac{\tilde{\varphi}}{\tilde{\varphi}}$ are not shown. (i) Graft he leg base as in Fig. 7a. $\frac{\tilde{\varphi}}{\tilde{\varphi}}$ llent agree- $\frac{\tilde{\varphi}}{\tilde{\varphi}}$ er, the extent of distali-
 $\frac{Q}{Q}$ are not shown. (i) Graft combinations proximal positional values of $\frac{Q}{Q}$ ade by our $\frac{Q}{Q}$ cocupy the ade by our \leq \leq $\begin{array}{ccc} \mathbf{e} & \mathbf{\varpi} & \mathbf{e} & \math$ \sim from the distal cut surface and from the graft and from the graft and the graft and the simulated parts fail region of the SIM. Within the SIM. Within this most provided parts fail region of the SIM. Within this most α ssumed to occupy the α is a the theory

Graded substances during early development

• 1901: Thomas Hunt Morgan postulated that gradients of "formative stuff" underlie regeneration events We might make an appeal to the hypothesis of formative stuffs, and assume that there are certain

substances present in the head, and others in the tail, of such a sort that they determine the kind of differentiation of the new part; but this view meets also with serious objections. In the first place, it gives only the appearance of an explanation because it assumes both that such stuffs are present, and that they can produce the kind of result that is to be explained. Until such substances have been found and until it can be shown that this kind of action is possible, the stuff-hypothesis adds nothing to the facts themselves, and may withdraw attention from the real solution of the problem.

 \bullet 1901: Theodor Boveri proposed that gradients of substances pattern the embryo along the animal vegetal axis (working on sea urchins)

• 1905: Edwin Conklin

are not directly visible. Recent experimental work on some of BIOLOGICAL BULLETIN these forms confirms and extends these conclusions and proves

March, 1905. Vol. VIII. NO. 4

MAGAN-FORMING SUBSTANCES IN THE EGGS OF to enter into specific parts of the embryon of the embryon.

EDWIN G CONKLIN.

Where the interview of α **Recent experimental work on some of** α these forms confirms and extends these conclusions and proves that even in the egg before cleavage begins different substances may be present which are destined in the course of development **the embryo. the embryo. enter into specific parts of the embryo.**

egg. Here the different substances of the egg are strikingly dis- \mathbf{s} imilar; they are localized in their definitive positions at a remarkably early period, and they may be traced with ease and certainty
1.0005 g. Here the different substances of the egg are strikingly di

These facts point to the conclusion that the complex organization of an egg, such as that of an ascidian, has not arisen through the "reflection of adult characters upon the egg," but rather that this organization is primary. Furthermore they seem to indicate that evolution has taken place, not through modifications of adult structure, but through changes in germinal organization; modifications of this organization, however produced, are probably the real causes of evolution.

Cynthia (Slyela) partita

Thomas LECUIT 2024-2025 \overline{A} Pand \overline{B} **Phiysa, Planorbis and Limnnwa (Conklin, 1902, I903). In none of lation and the later stages until they give rise to specific organs a considerable body of experimental work on the development of the ovum; fragments of eggs or isolated blastomeres in many**

Discovery of gradients of morphogens - case study: Bicoid

The bicoid Protein Determines Position in the Drosophila Embryo in a Concentration-Dependent Manner

• Increasing the gene copy number of *Bicoid* increases the length **Summary** scale of the Bicoid **The bicoid (bcd) protein in a Drosophila embryo is de-rived from an anteriorly localized mRNA and comes to gradient distribution whether the levels of bcd protein are directly related**

Cell, Vol. 54, 95-104, July 1, 1988, Copyright © 1988 by Cell Press

- **e** And modifies the embryo pattern and **the bcd protein gradient, and correlated the gradient with the fate map of the respective embryos. Increases** morphology consistent with Bicoid specifying the anterior (head) **half of the embryo.** $\mathsf{region.} \qquad \qquad \blacksquare$ **terior shift of anterior anlagen in the embryo. The bcd Introduction**
- **•** Bicoid is required for the head region $\begin{array}{|c|c|}\hline \text{the } & \text{the} \end{array}$ termined by a small number of maternal effect genes. By

howald, 1987). Several lines of evidence suggest that it is in the suggest that it is in the suggest that it is the bcd gene product that determines anterior pattern.

 $1\leq l\leq n$ and $1\leq l\leq n$ mented head anlagen (parasegments 1-5) is much en-

trations detected in control embryos are not reached at the

W. Driever and C. Nüsslein-Volhard Cell 54, 95-104 (1988) for survival it is not necessary to achieve wild-type levels in $\mathcal{L}_{\mathcal{A}}$ at the anterior tip. As long as a certain range of bcd con-

Discovery of gradients of morphogens - case study: Bicoid (see Section E in the Supporting Material). This value was supported Material). This value was supported was the Support of the Supp an independent assessment of the cytoplasmic modern containing the contact of the contact of the contact mobili $\mathcal{L}_{\mathcal{D}}$. The contribution $\mathcal{L}_{\mathcal{D}}$ higher than that of the \mathcal{L} is important of the \mathcal{L} tadients of morphogens - case s \overline{a} . Crauk, O., and N. Dostatning. 2005. Bicoid determines sharp and precise sharp and pre target general expression in the Drosophila embryo. Curr 1888–1898. earlier. In a search in a dition on the concerns only provide a search of the search of the search o snapshot of \overline{a}

 \overline{D} \overline{D} \overline{D} \overline{D} \overline{D} \overline{D} \overline{D}

 -1530

 $t = \frac{t}{D}$ Measures of Bcd diffusivity: Using FCS, in the range of D~7µm²/s being the photometric during the photographs of P photographs step, $\frac{1}{2}$ \sim $\frac{1}{\pi}$ \sim $\frac{1}{\pi}$ and $\frac{1}{\pi}$ is the scale of the $\frac{1}{\pi}$ \sim $\frac{1}{\pi}$ 4. Bergmann, S., O. Sandler, ., N. Barkai. 2007. Pre-steady-state decod- $5.$ COPP / μ m, μ $\frac{3}{2}$
I leing ECS in the range of D_{∞} 7um²/s $\frac{1}{2}$ begins the range of D. $\frac{1}{2}$ melanogaster D. me

 $S_{\rm eff}$ in the Supporting Material). For all the Supporting Materials \sim

(), and do not rule out that do not rule out that diffusion $\mathcal{O}_\mathcal{A}$ and $\mathcal{O}_\mathcal{A}$ and diffusion $\mathcal{O}_\mathcal{A}$

3. Houchmandzadeh, B., E. Wieschaus, and S. Leibler. 2005. Precise

 \mathbf{F} and \mathbf{F} are all \mathbf{F} and \mathbf{F} and \mathbf{F} are all \mathbf{F} and \mathbf{F} and \mathbf{F} are all \mathbf{F} and $\$ $\begin{bmatrix} \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} \end{bmatrix}$ $\begin{bmatrix} \frac{1}{2} & \frac{1}{2} \\ \frac{1}{2} & \frac{1}{2} \end{bmatrix}$ This value is large enough to explain the ctable octablishment of the Red aradient $\begin{bmatrix} 1 & 1 & 1 & 1 \\ 0 & 0.1 & 0.2 & 0.3 & 0.4 & 0.5 \\ 0.1 & 0.2 & 0.3 & 0.4 & 0.5 \end{bmatrix}$ $\lim_{x \to 0.5} \frac{1}{x}$ as $\lim_{x \to 0.5} \frac{1}{x}$ simply by diffusion before the onset of $\frac{1}{2}$ and $\frac{1}{2}$ cygotic transcription. /s, and given the stable establishment of the Bcd gradient simply by unlusion before the onse /s, and given the ϵ y gode dansemption.

$$
\lambda \sim 125 \ \mu \text{m} \qquad \tau \sim \lambda^2/D \sim 40 \text{ min}
$$

141–152 (2007) A. Abu-Arish, et al, N. Dostatni and C. Fradin. Biophysical Journal 99(4) L33–L35, 2010 $14. B + 1.6 B + 1.8$ (4) L_{JJ}-L_{JJ}, 2010

Cdl 1262 defines sharper and sharper domains of expression. One of the transtriptional architectures that has been studied in most detail in most detail is related in most detail in mos to the activation of the transcription \mathcal{L} defines sharper and sharper domains of expression. One of the transcriptional architectures that has been studied in most detail is related Discovery of gradients of morphogens - case study: Bicoid

- binding to six sites of different strengths that lie upstream from the upstre Hunchback promoter, as seen in Figure 19.32. The resulting pattern axis of the developing embryo. Activation by Bicoid is realized by binding to six sites of different strengths that lie upstream from the upstrea • Bcd is a concentration dependent transcriptional activator
- Concentration threshold for gene activation

Thomas LECUIT 2024-2025 G. Struhl, K. Struhl and P. MacDonald *Cell* 57, 1259-1273 (1989) R. Phillips, J. Kondev, J. Thériot & H. Garcia. Physical Biology of the Cell (Garland Science) 2012

is expressed in an exponential profile along the anterior–posterior

scription factor Bicoid. As shown in Figures 19.2 and 19.32(A), Bicoid

Discovery of gradients of morphogens - case study: Bicoid \mathcal{Q} across embryos embry bryo is *c* = 4.8 ± 0.6 molecules/mm³ or 690 total molecules 10dens - case study: Bicold concentration thus amounts to changes of !70 molecules. Discovery of gradients of morphogens If the noise is large, so that there is considerable scatter in the relationship between Bcd and Hb measured for individual cells, then the sharp Hb Hayward, 2006; Holloway et al., 2006). In contrast, our $rac{1}{2}$ results and $rac{1}{2}$ defined $rac{1}{2}$ \cdots believe bility. \cdots Since Bcd is a transcription factor, what matters is the concentration in the nuclei of the forming cells. A variety of experiments on Bcd (Ma et al., 1996; Burz et al., 1998; orphogens - **1** pression are very different. At right, we con-

How precise is Bicoid/Hunchback system? bryos. The results, shown in Figure 5B, are consistent with Berg and Purcell (1977) emphasized, in the context of $t_{\rm t}$ measurements is set not by the total number of available $t_{\rm t}$ spatial profile of Bicoid concentration (Houchmandzadehorum) et al., 2002). To answer the second question we need to \mathbf{m} means that the solution and information with \mathbf{m} is Dicoluzi iurichidack sy trations of transcription factors are fixed, the resulting levels of gene expression will fluctuate (Elowitz et al., 2002; Raser and O'Shea, 2004), and there are physical limits to how much this noise can be reduced (Bialek and Setayeshgar, 2005, 2006). If the noise is low, such that a scatter plot of Hb expression versus Bcd concentration is relatively tight, then the qualitative picture of a sharp Hb expression boundary is perturbed only slightly.

• Precision: **constant lines in the constant lines on average and not along individual rows in individual rows in individual rows in individual rows in** \mathbf{r}

 $\mathcal{F}_{\mathcal{F}}$ and direct expression switches from direct experiments on simplex systems we know that, even when the concentration on simplex systems we know that, even when the concentration of $\mathcal{F}_{\mathcal{F}}$

anterior half of the embryo, with variability gradually rising ior spatial discrimination or adjacent nuclei *in* at their target locations. Consider a receptor of linear size *a* • Expectations for spatial discrimination of adjacent nuclei *in vivo:* • Expectations for spatial discrimination of adiacent r tions which differ by a fraction tal discrimination of adjacent r of the Bcd protein with the green fluorescent protein, GFP (Gr*in vivo:* $\overline{}$ means that they acquire positional information with an $\bullet\,$ Expectations for spatial disc. $M_{\rm eff}$ and $M_{\rm eff}$ concentration by immunostation by immunostation by immunosity immunosity immunosity immunosity in

steps of pattern formation.

 $\frac{\Delta c(x)}{c(x)} = \frac{1}{c(x)} \left| \frac{d c(x)}{dx} \right| \Delta x = \frac{\Delta x}{\lambda} \sim 0.1.$ $\Delta x \sim 100 \mu m$ Measurement point (70 molecules a |
|
| *dc*ð*x*Þ *dx* $\frac{\Delta c(x)}{c(x)} = \frac{1}{c(x)} \left| \frac{dc(x)}{dx} \right| \Delta x = \frac{\Delta x}{\lambda} \sim 0.1.$ $\Delta x \sim 100 \mu m$ $\frac{c(x)}{c(x)} - \frac{c(x)}{dx} \frac{dx}{dx} = \frac{c}{\lambda} \approx 0.1.$ $\lambda \sim 100 \mu m$

 Δx ₂₀₀₁ $\Delta x \sim 8 \mu m$ Measurement precision [Bcd] ~10% λ and λ \sim 100 μ m (70 molecules at 50% embryo length) $\Delta x \sim 8$ µm. Distinct fates in negative measurement precision [Bcd] \sim 10%

 $\sum_{n=1}^{\infty}$ or $\sum_{n=1}^{\infty}$ in δc 1 \pm 20 \pm 1.20 \pm . Dery α runder \overline{c} $\overline{\sqrt{D}acT}$, \overline{c} communion row prediction may reflect a reflect a regular system of additional signaling systems of additional signaling systems of additional systems of additi ⁴*DT* ^p and hence an area *^A* ! ⁴p*DT*. But at cycle 14 $_{\sf parm \; atoms}$ $\;\;\bullet\;$ Physical limit: Berg & Pur $\displaystyle{\frac{\delta c}{c}}\sim\frac{1}{\sqrt{DacT}},\,$ $7{\sim}20$ min for 10% precision (D~7µm²/s) To distinguish individual nuclei from their neighbors \bullet Physical limit: Berg & Pu require each nucleus to ''measure'' the Bcd concentration 154 Cell *130*, 153–164, July 13, 2007 ª2007 Elsevier Inc. (Houchmandzadeh et al., 2002). Neighboring nuclei, at locations *x* and *x* +D*x*, thus experience Bcd concentra- $\bullet\,$ Physical limit: Berg & Purcell

by measuring the (fractional) standard deviation of con-

Data: Does Hb read Bcd with such precision?
 No within 10% are cision of the model to which the molecule to wh $\text{Yes, within 10\% precision.}$
Yes, within 10% precision. T_{S} and T_{S} and T_{S} defines a map $\frac{1}{\sigma}$ defines a map $\frac{1}{\sigma}$ defines a map $\frac{1}{2}$ ² ^{6.15} $t \in S$, within $t \cup S$ is determined in part by S *^c*ð*x*^Þ ⁼ ¹ *c*ð*x*Þ ! *dx* ! ^l ! ⁰:1: (1) Yes, within 10% precision. require each nucleus to ''measure'' the Bcd concentration • Data: Does Hb read Bcd with such precision?

Bcd-mRNA serves as a source for new protein synthesis,

$\mathsf{ty} \colon$ \bullet Reproducibility:

• The reproducibility of the Bcd gradient profile from embryo to **e** embryo and from one cycle of nuclear division to the next within $\frac{1}{\text{Bicod}^2}$ and $\frac{1}{\text{Bicod}^2}$ and $\frac{2}{\text{Bicod}^2}$ and $\frac{3}{\text{Bicod}^2}$ and $\frac{4}{\text{Bicod}^2}$ one embryo is at the 10% level. that we (and the embryo!) can ''read'' the position by measionity of the bcd gradient prome from embry stained embryos) are completely consistent. \mathbb{R} the same effect of the non- \mathbb{S} increproducibility of the same as \mathbb{S} $\begin{bmatrix} \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \end{bmatrix}$ • The reproducibility of the Bcd aradient profile from emb can promote the effective noise in Equation that is a set of the equal below that is in Equal below that in Equal S rom one cycle of nuclear division to the ne: $\begin{array}{|c|c|c|c|c|c|c|c|c|} \hline \quad & \frac{1}{2} & & \frac{1}{2} & \frac{1$ experiments of the reproductionity of the 1992; Pedone et al., 1996; Winston et al., 1999) suggest one embryo is at the TV The difficulty of achieving precise and reproducibly func- \bullet The reproducibility of the Be the absolute concentration of the relevant molecules: for embryo and from one cycle vidual molecular events must set a limit to precision (Berg and Purcell Purcell Purcell, 1978. In an analysis

Converting the measured rms
in concentration profile into concentration profile into individual in concentration profile into 64, 2007 ms of spatial coordinate and mechanisms that mechanis (positional error) concentration and thus compare fluorescence levels of in the *Drosophila* embryo. $\begin{pmatrix} 1 \\ 2 \end{pmatrix}$ Experiment should be proportional to the protection of the measured rms
Converting the measured rms
in aggregativity with the μ ositional error μ the same moiety under the same optical conditions (see Converting the measured ring $t_{\rm rms}$ of enatial coordinate \sim 1-2 Converting the measured rms $\frac{1}{2}$ in concentration profile into In Figure 2011 and Discourse the Section of the Section terms of the second section to the \sim

 σ $\boldsymbol{x}) = \delta \boldsymbol{c}$ \boldsymbol{x} |
|
|
| *dc*!ð*x*Þ *dx* |
|
|
|
| $\frac{1}{2}$ correcting for measurement noise $\frac{1}{2}$ rdinate \sim 1-2% of embryo length after \sim 0.00 $\frac{131}{100}$ $\frac{111}{100}$ $\frac{111}{100}$ $\frac{111}{100}$ $\sigma(X) = oC(X) \frac{1}{|X|}$. $\leq 0.04 \frac{1}{|X|}$ made to activate \mathcal{B} . Bicoid diffuses slowly diffuses s dec_{ay} *C_{reep}* ration is the correlation in the correlation in the correlation in the correlation in the set of the correlation in the correlation of the correlation in the correlation of the correlation of the correlat

$\bullet\,$ Bcd may be noisy and the system compensates via averaging or through properties of network. j and input j direction between Bcdds relation between \mathcal{L} compensates via averaging or through absolute concentration measurements on many embryos, twork. \blacksquare The answer to the first depends on the first depends o sv and the system \blacksquare et al., 2002). To answer the second question we need to we measure this using the Bcd-GFP fusion constructs [this issue of *Cell*]). To answer the third question we char-0.1) requires *T* ! 7000 s or nearly two hours. This is almost the entire time and the properties

• Bcd may be precise and downstream steps • Physical l maintain or increase this precision up to **concentration** of increase this precision up to physical limits. with side ' ! 8:5 mm, so the area *A* contains ϵ and downsucalli steps function ϵ \bullet Data: Do \mathbf{y} $B = \frac{1}{2}$ tise and downstream step:
. $\overline{\text{c}}$ ico and downstroam stone and domination in stops is bryos. Finally, to answer the fourth question we make $\mathop{\mathsf{case}}\nolimits$ consequents on many $\mathop{\mathsf{co}}\nolimits$ \overline{a} \bullet bcd may denote Bcd concentrations over this long time, especially given thannam c priyon in

trations of the results are fixed, the results in gene expression will fix and $\frac{13.366 \text{ nuclei in } 9 \text{ embryos}}{13.366 \text{ nuclei}}$ 13,366 nuclei in 9 embryos

expression boundary will exist only on average and not along individual rows in individual embryos.

T. Gregor et al and W. Bialek. Cell 130, 153-164, 2007 ms of spati et al., 2002). To answer the second question we need to answer the second α $\mathbf{1}$. \mathbf{C} ₁

DE FRANCE Thomas LECUIT 2024-2025 (C) Scatter plot of Hb versus Bcd concentration from a total of 13,366 concentration from a total of 13,366 co

Discovery of gradients of morphogens - in growing tissues

Diffusible morphogens and spatial patterning in growing tissues

Discovery of gradients of morphogens - in growing tissues **A B**

Diffusible morphogens and spatial patterning in growing tissues

- Opposing gradients generate patterns
- \bullet Temporal integration and network properties are required for spatial patterning

Reviewed in: J. Briscoe and S. Small. Development (2015) 142, 3996-4009 doi:10.1242/dev.129452 Reviewed in: J. Briscoe and S. Small. *Development* (2015) 142, 3996-4009 doi:10.1242/dev.129452

Boundary (1995)
Boundary (1995)
Boundary (1995)

Need for a quantitative theory of positional information extracted. \mathcal{A} and any level of \mathcal{A} integration, the theory preserved will be the theory preserved will be the theory preserved will be the three states \mathcal{A} \mathcal{E} chemical paleogenetics have been faced at the presentation of the presen neeting by two disapproving two disapproving sciences of the original science of the organism of the organism evolution and the one hand, and some pure (very pure some pure α

• The concept of Information is generally qualitative (causal power) The concept of Information is generally qualitative (causal power) amative (cadour pov

information of the genes or a transcript thereof. The genes themselves are the information of the genes or a transcript thereof. The genes themselves are the primary semantides (linear "sense-carrying" units). Messenger-RNA mole cules are secondary semantides. Polypeptides, at least most of them, are tertiary semantides. (1) Semantophoretic molecules or semantides-molecules that carry the

greater, the greater the greater the greater the elements at the elements at the smaller smaller α

 $T_{\rm eff}$ mechanism showled, however, not be applied exclusive \sim The type of molecules that have been called informational macromolecules (68) or semantides (75) (DNA, RNA, proteins) has a unique role in determining the properties of living \mathbf{m} at the matter in each of time perspective that differ by the magnitude of time \mathbf{m}

 \overline{P} required the processes are the short-timed. The short-time short-time

underganismal) biochemists on the other hand. Some of the other hand. Some of the biochemists on the biochemists of the bioch

 \overline{C} and \overline{C} in the put \overline{C} of \overline{C} absonce in the absolute by end absonce in the absolute \overline{C} absonce in the absonce in the absonce in th E. Zuckerkandl and L. Pauling *J. Theoret. Biol.* (1965) 8, 357-366

E. Zuckerkandl and L. Pauling (1966) $\frac{\text{doi.org}}{10.1016/B978-1-4832-2734-4.50017-6}$

\bullet Vot positional information calls for a que • Yet positional information calls for a *quantitative measure of information*

- This requires a quantitative theory of inf \bullet This requires a quantitative theory of information in order to:
- $f_{\rm c}$ define how much information is eng – define *how much* information is encoded, transmitted and decoded?

 $m = 100$ denotes into a generation $m = 1$ – understand how information may be reliably transmitted in the face of internal and external noise. Products of catabolism are not included in this classification. During the

- 1. Length scales in biological systems
- 2. Positional Information (PI) and Morphogens

3. Shannon information theory

- 4. Encoding and Decoding space with PI
- 5. Beyond PI: generalisation

Towards a theory of information

- Harry Nyquist *Transmission of Intelligence* 1924
- Bell labs and telecommunication in US

BELL SYSTEM TECHNICAL JOURNAL

Certain Factors Affecting Telegraph Speed¹

By H. NYQUIST

SYNOPSIS: This paper considers two fundamental factors entering into the maximum speed of transmission of intelligence by telegraph. These factors are signal shaping and choice of codes. The first is concerned with the best wave shape to be impressed on the transmitting medium so as to permit of greater speed without undue interference either in the circuit under consideration or in those adjacent, while the latter deals with the choice of codes which will permit of transmitting a maximum amount of intelligence with a given number of signal elements.

Thomas LECUIT 2024-2025

THEORETICAL POSSIBILITIES USING CODES WITH DIFFERENT NUMBERS OF CURRENT VALUES

The speed at which intelligence can be transmitted over a telegraph circuit with a given line speed, *i.e.*, a given rate of sending of signal elements, may be determined approximately by the following formula. the derivation of which is given in Appendix B.

 $W = K \log m$

Where W is the speed of transmission of intelligence, m is the number of current values.

 \overline{K} is a constant. (ie. the number of current values sent/unit of time) and.

- The number of current values is the number of characters in the code that are used, ie. the number of letters in the alphabet, or 0/1 in binary signal.
- The larger number of values to choose from, the fewer need to be sent to convey a given intelligence, because the larger the density of intelligence in each value.

Towards a theory of information

- Ralph Hartley *Transmission of information* 1928
- Constructs a quantity to measure the information transmitted which is independent of psychological considerations (meaning).
- Information is a measure of uncertainty about an outcome.
- The Hartley function quantifies the information gained when a sample is picked randomly from a finite set, considering that all outcomes have same probability of occurence.

BELL SYSTEM TECHNICAL JOURNAL Transmission of Information¹

By R. V. L. HARTLEY

SYNOPSIS: A quantitative measure of "information" is developed which is based on physical as contrasted with psychological considerations. How the rate of transmission of this information over a system is limited by the distortion resulting from storage of energy is discussed from the transient viewpoint. The relation between the transient and steady state viewpoints is reviewed. It is shown that when the storage of energy is used to restrict the steady state transmission to a limited range of frequencies the amount of information that can be transmitted is proportional to the product of of information that can be transmitted is proportional to the product of illustrations of the application of this principle to practical systems are included. In the case of picture transmission and television the spacial variation of intensity is analyzed by a steady state method analogous to that commonly used for variations with time.

Thomas LECUIT 2024-2025

Ralph Hartley (1888-1970)

Towards a theory of information

- Ralph Hartley 1928
- The Hartley function *H* quantifies the information gained when a sample is picked randomly from a finite set, considering that all outcomes have same probability of occurence.

n selections among *s* symbols

The number of distinguishable sequences is *sn.*

This measure of information would increase exponentially with sequence length.

Need of measure of transmitted information which is *proportional* to sequence length.

$$
\left|\frac{\partial}{\partial x}\right|
$$

$$
H = n \log s
$$

$$
= \log s^{n}.
$$

$$
H(A) := \log_b(|A|).
$$

For a particular system let the amount of information associated with n selections be

where K is a constant which depends on the number s of symbols

available at each selection. Take any two systems for which s has

the values s_1 and s_2 and let the corresponding constants be K_1 and K_2 .

$$
H = Kn, \tag{4}
$$

$$
H = K_1 n_1 = K_2 n_2,
$$

 $s_1^{n_1} = s_2^{n_2}$

$$
\frac{K_1}{\log s_1} = \frac{K_2}{\log s_2}
$$

This relation will hold for all values of s only if K is connected with s by the relation K

$$
f = K_0 \log s,\tag{8}
$$

where K_0 is the same for all systems. Since K_0 is arbitrary, we may omit it if we make the logarithmic base arbitrary. The particular base selected fixes the size of the unit of information. Putting this value of K in (4) ,

$$
H = n \log s \tag{9}
$$

$$
= \log s^n. \tag{10}
$$

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Mathematical theory of Information and Communication

- Claude Shannon 1948
- Extends and generalises the work of Hartley:
	- semantic is not relevant
	- probabilistic nature of information
	- considers non uniform frequency of « events » and statistics of the message

Claude Shannon (1916-2001)

Thomas LECUIT 2024-2025

The Bell System Technical Journal *Vol. XXVII J Illy, 1948 No.3* **A Mathematical Theory of Communication** By c. E. SHANNON **INTRODUCTION**

THE recent development of various methods of modulation such as PCM and PPM which exchange bandwidth for signal-to-noise ratio has intensified the interest in a general theory of communication. A basis for such a theory is contained in the important papers of Nyquist¹ and Hartley² on this subject. In the present paper we will extend the theory to include a number of new factors, in particular the effect of noise in the channel, and the savings possible due to the statistical structure of the original message and due to the nature of the final destination of the information.

The fundamental problem of communication is that of reproducing at one point either exactly or approximately a message selected at another point. Frequently the messages have *meaning;* that is they refer to or are correlated according to some system with certain physical or conceptual entities. These semantic aspects of communication are irrelevant to the engineering problem. The significant aspect is that the actual message is one *selected from a set* of possible messages. The system must be designed to operate for each possible selection, not just the one which will actually be chosen since this is unknown at the time of design.

If the number of messages in the set is finite then this number or any monotonic function of this number can be regarded as a measure of the information produced when one message is chosen from the set, all choices being equally likely. As was pointed out by Hartley the most natural choice is the logarithmic function. Although this definition must be generalized considerably when we consider the influence of the statistics of the message and when we have a continuous range of messages, we will in all cases use an essentially logarithmic measure.

The logarithmic measure is more convenient for various reasons:

1. It is practically more useful. Parameters of engineering importance

¹ Nyquist, H., ''Certain Factors Affecting Telegraph Speed,*'' Bell System Technical Jour-*
ual, April 1924, p. 324; ''Certain Topics in Telegraph Transmission Theory,'' *A. I. B. E.*
Trans., v. 47, April 1928, p. 617.

2 Hartley, R. V. L., "Transmission of Information,*" Belt System Technical Journal*, July
1928, p. 535.

379

Theory of Information and Communication

« The fundamental problem of communication is that of reproducing at one point either exactly or approximately a message selected at another point. » ✐ 125.9

\bullet Biology \bullet Biology chemoattractants and chemorepellents \leftarrow INFORMATION ∩'∩ **SOURCE TRANSMITTER** RECEIVER DESTINATION \langle M M CheR chemoreceptor INPUT OUTPUT $CheA$ M $SIGNAL \rightarrow$ RECEIVED sensor SIGNAL kinase CheW MESSAGE MESSAGE CheB-P two-component system motif P CheY-P *En*coding *De*coding response Che^y regulator P CheB integral

• Basic architecture of a communication system

NOISE SOURCE

CYTOPLASM PERIPLASM

inner membrane

outer membrane

sensor module

INPUT

Concentration

transduction module

> actuator module

> > **OUTPUT**

rotation frequency

Clockwise

 $\frac{1}{\sqrt{1-\frac{1}{2}}\log(1-\frac{1}{2\pi})}$ are involved the base of intervention units of information will be called natural units of information will be c

and the counts of information will be called natural units of information will be called natural units. In t Change **be from the base of the base of the base of the base of the base** *a***. The base** *a***.** By a communication system we will mean a system of the type indicated schematically in Fig. 1. It is the type in Fig. 1. It is the type in the type in Fig. 1. It is the type in Fig. 1. It is the type in Fig. 1. It is the t

R. Phillips, The Molecular Switch: signaling and allostery. Princeton Univ. Press. 2020 T indiction only, T ress. ω so ω

flagellum

CheZ

flagellar motor

feedback module

Theory of Information and Communication

« The fundamental problem of communication is that of reproducing at one point either exactly or approximately a message selected at another point. » to the activation of the transcription factor Hunchback by the tran- $\mathop{\rm there}\nolimits$ is and 19.2 and 19.2 and 19.2 and 19.2 and 19.2 and 19.32(A), Bicoid. Bicoid

scriptional architectures that has been studied in most detail is related

Physical Biology of the Cell (Garland Science) 2012 R. Phillips, J. Kondev, J. Thériot & H. Garcia.

Theory of Information and Communication We have represented a discrete information source as a Markoff process. Can we define a quantity which will measure, in some sense, how much information is "produced" by such a produced by such a produced by such a *j* after *N* symbols, approach the equilibrium values as *N* ∞. y UI IIIUIIIIat Γ how we fluid we stion ond Γ Theory of Information and Communication The entropy in the case of two possibilities with probabilities *p* and *q* 1 *p*, namely d Communication with probabilities with probabilities with probabilities p *H K* ∑ *pi* log *pi*

• Consider a set of discrete events i with probability of occurence p_i . 1. *H* should be continuous in the *pi*. α is the much is involved in the selection of the event of the event of the event of the oriogeness α μ , and the properties μ is required to μ , it is properties: μ , it is the following properties: 3. If a choice be broken down into two successive choices, the original *H* should be the weighted sum der a set of discrete events *i* with probability of occurence p_i . $H = -(p)q$ der a set or discrete events ι with probability or occurence p_i .

information is produced?

• What is a **measure** H of how much « choice » is involve<u>y</u> in the • vinat is a measure *H* of now much « choice » is involveg in the set of the selection of the event or of how uncertain one is of the outcome? If a choice be be broken down into two successive. i **measure** H of how much « choice » is involved in the $\begin{array}{c} \text{if } n \text{ is a constant, } n \text{ is a constant,$ a band *W* and duration *T* correspond to points in a space of 2*TW* dimensions.

Expected properties:

that duration.

H continuous in *pi*

onic function of If $p_i = 1/n$ then *H* is a monotonic function of *n* as there is more uncertainty when there $\frac{1/6}{2}$ $\frac{1}{3}$ $\frac{1}{3}$ $\frac{1}{6}$ $\frac{1}{1/3}$ $\frac{1}{1/6}$ are more possible events are more possible events $H(\frac{1}{2}, \frac{1}{3}, \frac{1}{6}) = H(\frac{1}{2}, \frac{1}{2}) + \frac{1}{2}H(\frac{2}{3}, \frac{1}{3}).$

$$
\frac{1/2}{1/3}
$$
\n
$$
\frac{1}{2}
$$
\n
$$
\frac{1}{2}
$$
\n
$$
\frac{2}{3}
$$
\n
$$
\frac{1}{2}
$$
\n
$$
\frac{1}{2
$$

²*^H* ²

will measure, in some sense, how much information is "produced" by such a produced μ

$$
H = -\sum p_i \log p_i
$$

- size or uncertainty or information. T 16 The coefficient ¹ ² is because this second choice only occurs half the time. play a central role in information theory as measures of information, choice and uncertainty. The form of *H* • *H* is a measure of choice or uncertainty or information. The more 20. ENTROPY OF A CONTINUOUS DISTRIBUTION ingredients we need to make a mathematically precise version of $\frac{1}{2}$ uncertainty or information. The more $\vert\vert$
	- \bullet *H* has the form of entropy (ie. $S = k_B \log W$). the foundation of entropy (i. S_1 *p* I_1 *p* I_2 *p* I_3 *p* I_4 *p* I_5 *p* I_6 *p* I_7 *p* I_8 *p* I_7 *p* I_8 *p* I_9 *p* I_9
- *H* is a number, with unit bit (binary integer) with log_2 base.
Fig. 7—Entropy in the case of two possibilities with probabilities p and $(1-p)$. tive information (20–22).
- Can be extended to continuous distributions with $H=0$ when one is certain of outcome (all probability density distribution $p(x)$: $H = -\int_{-\infty}^{\infty} p(x) \log p(x) dx$.
 F H bas a maximum when all name orual ∞ *probability density distribution* $p(x)$ *:* $H = -\int^{\infty} p(x) \log p(x) dx$. Downloaded from https://www.pnas.org/
Downloaded from IP address 124.8.21

 T_L E G E
RANCE Thomas LECUIT 2024-2025 Or $S[P_x(x)] = -\int$ \sum_{x}^{n} **F** *N* \sum_{x}^{n} **F** *H* \sum_{x}^{n} *S* in \sum_{x}^{n} *S* $\sum_{x}^{n} P_{x}(x) = -\int dx P_{x}(x) \log_{2} [P_{x}(x)]$, There is maximum uncertainty of $\sum_{x}^{n} P_{x}(x)$ Z Or $S[P_x(x)] = -\int dx P_x(x) \log_2[P_x(x)]$

*H p*log *p q*log*q*

much smaller than the entropy $S_{\mathcal{A}}$, we define

- $H=0$ when one is certain of outcome (all p_i are zero but one, and the last one =1) \mathbf{F} and define any probability distribution, we can define an entropy \mathbf{F}
	- are certain of the outcome does *H* vanish. Otherwise *H* is positive. *p_i* are zero but one, and the last one = 1)
• H has a maximum when all *p_i* are equal. $\mathrm{g}_{2}[P_{x}(x)] ,$ There is maximum uncertainty \mathcal{L} is the formulation probability of observing a cell at \mathcal{L}

$$
40\,
$$

Theory of Information and Communication

- A device with two stable positions, such as a relay can store one bit of information.
- *N* such devices can store *N* bits, since the total number of **E F** possible states is 2N.
- It takes 1 bit of information to discriminate between 2 states
- N bits are needed to discriminate with zero error between 2^N states, or Log₂N bits to discriminate between N states.
- Example: chain of letters and space (27 options). If letters were equiprobable, the entropy of 1 letter would be $Log₂27~4.75$. The transmission of each letter requires 4-5 bits.
- Shannon entropy can be interpreted as the number of Yes/No questions required to fully resolve the uncertainty about a state (discriminate between N possible states).

60 nuclei

bors that share a boundary (j, 1:6 in this case).

 $\bullet\,$ Consider two variables $x,\,y$ of a system occurring at probability $p(x)$ and $p(y)$: *i j* (x, y) of a syst $\bullet\,$ Consider two variables $x,\,y$ of a system occurring at probability $p(x)$ and $p(y)$: according to the probability of getting that particular *x*. That is

We define the *conditional entropy* of *y*, *Hx y* as the average of the entropy of *y* for each value of *x*, weighted

Let *p i j* be the probability of the joint occurrence of *i* for the first and *j* for the second. The entropy of the • For the joint event, with probability $p(x, y)$, the Shannon entropy is: The end your event, were probability $p(x, y)$ and onarmore of $x \in \mathcal{Y}$ or α *y r*obability $p(x, y)$, *i j* **p** For the joint event with probability $p(x, y)$ the Shannon entrepy is: \bullet For the joint event, with probability $p(x,y)$, the Shannon entropy is:

pi ∑

$$
H(x, y) = -\sum_{i,j} p(i,j) \log p(i,j)
$$

- Furthermore $H(x, y) \le H(x) + H(y)$, with equality if *x*, *y* are independent $p(x)$, with equality if x , *i j y* are indepe $H(x) + H(y)$, with equality if *x*, *y* are independer
- $H_x(y)$, measures how unce
p exerces of the entrepy of what ϵ *i j j* probability of getting that particular x : • Conditional entropy, $H_x(y)$, measures how uncertain we are of y on average when we know x.
defined as the average of the entropy of y for each value of x weighted according to the \sim conditional entropy, $H_X(y)$, meas defined as the average of the entropy of y for each value of x, weighted according to the
probability of sotting that particular \ldots *H x y H x Hx y* $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ according to the probability of getting that particular *x*:

$$
H_x(y) = -\sum_{i,j} p(i,j) \log p_i(j).
$$

• From this we deduce that:
$$
H(x,y) = H(x) + H_x(y).
$$

 \bullet The knowledge of x increases knowledge of y , unless they are independent variables: $H(y) \geq H_x(y)$. $\frac{1}{2}$ and $\frac{1}{2}$ *p* in parameter $\frac{1}{2}$ *p*₂ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\mathbf{S} = \mathbf{S} \mathbf{S}$ and $\mathbf{S} = \mathbf{S} \mathbf{S}$ and $\mathbf{S} = \mathbf{S} \mathbf{S}$ and particular independent. For any particular $\mathbf{S} = \mathbf{S} \mathbf{S}$

- Consider two variables *x, y* of a system occurring at probability *p(x)* and *p(y)*
- *x, y* are not independent variables: a change to *x* leads to change to *y* with certain probability. In other words, *x* and *y* can be said to « share information ».
- Quantifying the degree of shared information would allow to infer *y* when we know *x* or vice versa.
- Definition of mutual information, as a function of entropy:

 $I(x,y) = H(x) + H(y) - H(x,y)$ or equivalently: $I(x, y) = H(x) - H_y(x) = H(y) - H_x(y)$

• It captures the non-linear dependence between variables (generalizes linear regression)

Information across a noisy channel If the capacity of this channel is less than the equivocation the right-hand side will be greater than zero and and the channel left in state . Thus and range over the possible states, *i* over the possible transmitted

- \bullet If a noisy channel is fed by a source there are two statistical processes at work: the source and the noise. The source are two statistical processes at work: the source and the noise. *P* if a noisy channel is led by a source there
	- $\bullet\,$ We conciser the entropy $H\!(x)$ at the source (input), the entropy of $\qquad \qquad \vert\qquad \vert$ the output of the channel, $H(y)$. In the noiseless case $H(y) = H(x)$. and *q* 1 *p* that it is right. These errors can be corrected if their position is known. Thus the
	- conditional entropies $H_x(y)$ and $H_y(x)$, the entropy of the output $\overline{S_{\text{source}}^{\text{NUSE}}}$ when the input is known and conversely. • The joint entropy of input and output is $H(x,y)$. There are two conditional entropy of input and output is $H(x,y)$. There are two

 $P(x,y) = H(x) + H_x(y) = H(y) + H_y(x).$

• We want to estimate the rate of information in this noisy channel. We have no knowledge of when some information is lost.

The rate of transmission *R* can be written in two other forms due to the identities noted above. We have The effective rate of transmission of information R: 19

$$
R = H(x) - Hy(x)
$$

= H(y) - H_x(y)
= H(x) + H(y) - H(x,y).

time and other variables as in black and white television — here the message may be thought of as a *ie*. the amount of information sent less the uncertainty of what was sent where *x* is the input and *y* the output and *y* the maximization is over all sources which might be used as input to use of a inpu

a decimal digit is about 3¹

dimensional "sound transmission or if the system is intended to see several individual channels individual channels in *ie*. the amount of information received less the part due to noise

on \log the initial ortropy. This is in a same \log $(y)-H(x,y).$ ie. the sum of the two information less the joint entropy. This is in a sense ϵ common to the two (mutual information) the number of bits per second common to the two (mutual information)

Capacity of noisy channel:

\n
$$
C = \text{Max}(H(x) - H_y(x)) = \text{Max } I(x, y)
$$

COLLÈGE

- Positional information calls for a *quantitative measure of information: —* we now have this
- This requires a quantitative theory of information in order to:
	- define *how much* information is encoded, transmitted and decoded? — understand how information may be reliably transmitted in the face of internal and external noise.

Mutual information as Positional Information rositional information. \mathbf{g} is corresponding and entropies \mathbf{g} itional Information the entropy so \ldots . The reduction of α by reading out level around the mean at each position, estimated by \mathbf{r} Mutual information as Positional Information more concentrated than the nearly uniform distribution PxðxÞ. ingredients we need to make a mathematically precise version of \mathbf{x}/\mathbf{I} al Informations Polandistributions Polandistributions Polandistributions Polandistributions Polandistributions $\prod_{i=1}^n f_i$ and $\prod_{i=1}^n f_i$ and $\prod_{i=1}^n f_i$ al Information we need to make a mathematically precise version of \mathbb{R}^n the qualitative statement that "the expression level g of a gene

- \bullet When we measure g, then there is still some uncertainty in x , but this is reduced significantly. The conditional probability $P(x/g)$ has a narrower $\frac{x}{\sqrt{L}}$ distribution but reflects also the effect of noise. t_i , dien diele is suit some ditertative in t_i α significatitiy. The conditional probability $r(xg)$ has a f when is annorm $r_{x(x)} = r_{i}E_{i}$
Vhen we measure g, then there is still some uncertainty in x, but this is in information is IðgÞ ≡S½PxðxÞ\$− S½PðxjgÞ\$ =log2ðL=ΔxÞbits. Nowhen we measure g , then there is still some uncertainty in x, but this is
educed significantly. The conditional probability $P(x/g)$ has a narrower difference of entropies, independent of the choice (22). is still some uncertainty in $x_{\rm c}$ but this is is still some uncertainty in x , but this is \int
- $B_{1,2}$ $\begin{array}{cccc} 8 & 1.2 & 1.2 \end{array}$ $\begin{array}{cccc} 1.2 & 1.2 \end{array}$ For $P_x(x) = I/I$, $S[P_x(x)] = \log_2(I)$ setels in a 38- to 48- to 48- to 48- to 48- to 48- to 48-min time interval after the \sim $S[P(x|a)] = \int dx P(x|a)$ For $P_x(x) = 1/L$, $S[P_x(x)] = log_2(L)$
 \therefore ing the corresponding entrepiece $S[P(x)] = \int dx P(x)dx$ $\mathbf{B}_{1,2}$ as position, the nearly uniform $\mathbf{B}_{1,2}$ as $\mathbf{B}_{1,2}$ as $\mathbf{B}_{1,2}$ as $\mathbf{B}_{x}(x)$ and $\mathbf{B}_{x}(x)$ are $\mathbf{B}_{x}(x)$ and $\mathbf{B}_{x}(x)$ are $\mathbf{B}_{x}(x)$ and $\mathbf{B}_{x}(x)$ are $\mathbf{B}_{x}(x)$ and $\mathbf{B}_{x}($ $S[P(x|g)] = - \int dx P(x|g) \log_2|x|$
For $P_x(x) = 1/L$, $S[P_x(x)] = \log_2(L)$ If the corresponding entropies: $S[P_r(x)] = -\int dx P_r(x) \log x$ gain information in the contract of the contra Effects also the effect of noise.
 $\int dx P(x) \log [P(x)]$
 $\left[P(x) \right]$ • We define the corresponding entropies: $S[P_x(x)]=$ z
Z dx $P_x(x) \log_2 [P_x(x)]$ $,$ $\qquad \qquad$ $\frac{1}{x^2}$ $S \begin{array}{c} S \ \hline \end{array}$ ice address 139.124.8219 on September 23, 2024 from IP address 139.12 Before measuring g^* :
 $P_x(x)$ $\{[P_x(x)]\}$ Z $dx P(x|g)log_2[P(x|g)]$. $P(x|g^*)$ $\sigma_x(x^*)$ is st Π address 139.124.822.812.912.81

Therefore $S[P(x/g)]$ is smaller than $S[P_x(x)]$. percious of $w(y)$ is singlet than of $x(x)$. Therefore $S[P(r/a)]$ is smaller than $S[P(r)]$ " pression of $\mathcal{L}^{(v)}$ g drawn from the $\mathcal{L}^{(v)}$. Therefore *S*[*P*(*x/g*)] is smaller than *S*[*P_x*(*x*)]. $\sum_{i=1}^n$ from $D[i]$ $\chi(v)$. $\mathbf{F}_{\mathbf{r}}$ if we measure \mathbf{r} from \mathbf{r} to \mathbf{r} along the length of length of length of length of length of maller than $S[P_x(x)]$.

• The reduction in entropy when we measure g compared to before measuring is the measure of information that g provides about x, $\sum_{\substack{0.2 \text{ prime} \\ 0 \leq x \leq x}} \frac{1}{\left|f(x) - 1\right|}$ $\sum_{\substack{0 \leq x \leq 18 \text{ bits} \\ 0 \leq x \leq x}} \frac{1}{\left|f(x) - 1\right|}$ measured in bits. $I(g) = S\left[P(x|g)\right]$. $\mathbb{E}^{\mathbb{I}}[x]$ and $\mathbb{E}^{\mathbb{I}}[x]$ and $\mathbb{E}^{\mathbb{I}}[x]$ are \mathbb{I} are position in entropy when we measure g compared \mathbf{S} = \mathbf{S} = \mathbf{S} = \mathbf{S} = \mathbf{S} action in entropy when we measure green parea to be he reduction in entropy when we measure g compared to before
Peasuring is the measure of information that g provides about x S_{in} formation that g provides about x. formation that g provides about x,
 $\mathcal{L}[\mathcal{D}(t,\cdot)]$ we measure g compared to before \mathcal{L}

 $I_{g\to x} = \int dg \int dx P(g,x) \log_2 \left| \frac{I(g,x)}{P(g)P(x)} \right|$ \int drawn from the distribution $\left[\frac{q}{\delta} \frac{\delta}{\delta} \right]$ \int $\mathcal{L}(\mathbf{r})$ $=\int dg \int dx P(g,x) \log_2 \left| \frac{P(g,x)}{P(g)P(x)} \right|$ $\int dg \int dx P(g,x) \log_2$ $\left[$ $P(g,x)\right]$ $P_g(g)P_x(x)$ $I_{g\to x} = \int dg \int dx P(g,x) \log_2 \left[\frac{P(g,x)}{P(g \cap P(x))} \right]$ \int information that the position of the ex- $\begin{bmatrix} P(\sigma x) \end{bmatrix}$ 16302 μ $dx P(\sigma x) \log_{10} \left| \frac{1}{\sigma} \sqrt{S(0,1)} \right|$

 \blacksquare provides about \blacksquare and in bits. As an example, if \blacksquare observe the expression level \bullet . Thus us, symmetric that the cell is located in a small region of size $\mathcal{L}_\mathcal{A}$ the mutual information is S≫P for the component of the this expression level provides about position is the next position is then $I = I$ $\frac{1}{2}$ nformation is the positional information $\iota_{g\to\lambda}$ \mathbf{r} inequality $=$ $I_{x\rightarrow g}$ and is th e mutual i<mark>r</mark> $oformati$ ymmetric $\textstyle \int_{g \to x}$ $=$ $\textstyle \int_{x \to g}$ and is the mutual informatior Dubuis, J. O., Tkacik, G., Wieschaus, E. F., G The mutual information is the positional information $I_{g\to x} = \int dx P_x(x) (S[P_g(g)] - S)$ • This is symmetric $\textstyle \int_{g \to x} = \textstyle \int_{x \to g} \textstyle$ and is the mutual information between g and x the oriental information is not one and the state of information is not one among many equal to be equally good many equal to be equally good in the state of $dx P_x(x) (S[P_g(g)] - S[P(g|x)])$

Positional $\frac{1}{2}$ information, in $\overline{1}$ DIIS. \overline{Y} ₁NAS . ϵ and ϵ and we have realistical information in hits $PNAS$ 110 16 \mathcal{S} the symmetry information that the expression level provides \mathcal{S} μ information that the position of the extension of the extension of the extension of the ex $p_{\text{adual, }3}$, D., That, O., Westmas, E. 1., Oregot, 1. and Black, W.
46 Positional information, in bits. *PNAS* 110, 16301-16308 (2013) Positional information, in bits. *PNAS* 110, 16301-16308 (2013)

 $\ddot{\cdot}$

 \mathbf{v} \cdot)] \mathbf{x}

 $\overline{}$

 \times

 $\ddot{\mathbf{v}}$

Mutual information as Positional Information $\overline{}$

- Mutual information linking position *x* and morphogen concentration *g*, is the proper formalisation of PI
- Definition: $PI = I(g; x) = H(g) + H(x) H(g, x) = H(g) H_x(g)$

PI is the sum of the two information (entropy) less the joint entropy.

PI is in a sense the number of bits common to the two informations

Ex: If information associated with Bcd concentration along the anteroposterior axis, and information about the position are independent, then *I*(*Bcd; x*)= 0 and there is indeed no PI.

- PI and channel concepts do not depend on the underlying mechanisms, but only on statistical dependence between x and g
- Determines how much a change in concentration *g* can be used to interpret as a change in position *x.*
- PI can be used for any combination of input concentrations

G. Tkacik and T. Gregor. *Development* (2021) 148, dev176065. doi:10.1242/dev.176065

- 1. Length scales in biological systems
- 2. Positional Information (PI) and Morphogens
- 3. Shannon information theory

4. Encoding and Decoding space with PI

5. Beyond PI: generalisation

Mutual information as Positional Information Positional Information

Concentration • Positional information can be recoded and yield a new representation (Maternal gradients -> Gap genes -> Pair rule genes)

Concentration

Fig. 1. A framework for positional information. In the pattern conception, $\frac{1}{2}$ are provided by concentration fields of patterning chemicals, depicted by concentration fields of patterns of patterns of patterns of pa G. Tkacik and T. Gregor. *Development* (2021) 148, dev176065. doi:10.1242/dev.176065

Mutual information as Positional Information around the concept of a noisy information channel (Shannon, 1948). Mutual information as Positional Information It encodes different positions $\mathcal{L}_\mathbf{z}$ into concentrations $\mathcal{L}_\mathbf{z}$ into concentration levels g, $\mathcal{L}_\mathbf{z}$ patterning, but it cannot explain how and where these limits arise. A 'channel' here represents an evolved biochemical reaction network. It encodes different positions x into concentration levels g, pattern in patterning, but it cannot explain how and where the set of the whole the set of the set of the set o celled, but annotice distinguished from the best estimated that the best estimated the cells

- How many bits of information are required to discriminate every cell/nuclear position? \mathbf{r}_i is described by P(g) as described by P(g)x). Neither the concept of \mathbf{r}_i $\overline{\text{max}}$ or information are required to discriminate every cell/nuclear position? $Log_2 60 = 5.9$ bits needed to determine with zero error all cell position \mathbb{R}^n cannot answer local questions or make testable t probabilistically, as described by P(g|x). Neither the concept of PI \bullet frow many pits on in $S_{\rm p}$ cannot answer local questions or make testable testable testable testable testable testable testable testable mation are required to discriminate every cell/nuclear positio by means of a decoding mechanism. Although many such iminate every cell/nuclear position iminate every cell/nuclear position? o determine with zero error all cell position
- What is the amount of PI associated with Bcd and the downstream gap gene network? Biological mechanisms inside the channel are de facto treated as a $\frac{1}{2}$ black box. In associated with bcd and the downstream $\frac{1}{2}$ • What is the amount of PI associated with Bcd and the downstream gap gene network? black box. Information theory then introduces a general and unique

 $m_{\tilde{c}}$

In a continuous form:
$$
I(\mathbf{g}; x) = \langle \int dg P(\mathbf{g}|x) \log_2 \frac{P(\mathbf{g}|x)}{P_g(\mathbf{g})} \rangle_x
$$

\n $H(g) - H_x(g)$
\n $\begin{array}{c}\nH(g) - H_x(g) \\
\hline\n\end{array}$ \n
\n $\begin{array}{c}\n\text{H(s, Kr, Gt, Kni)} \\
\hline\n\end{array}$ \n
\n $\begin{array}{c}\n\text{Hb, Kr, Gt, Kni} \\
\hline\n\end{array}$ \n
\n $\begin{array}{c}\n\text{Before measuring g:\ng (Hb, Kr, Gt, Kni)\n\end{array}$

average of the distribution of \Box positions \mathcal{L} is representations that a particular that a particular probability that a particular \mathcal{L} $P_{g}(\boldsymbol{g}) = \langle P(\boldsymbol{g}|x)\rangle_{x}$ $\sum_{i=1}^{n}$ $\sum_{j=1}^{n}$ is mathematically derived from P(g) by Eq. 1. This is the average of the distribution of morphogen $\left\| \int_{\left[\frac{R(X|g)}{R(X;X)}\right]}^{\left[\frac{R(X|g)}{R(X;X)}\right]}$

This is the average of the distribution of morphogen $\begin{bmatrix} \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix} & \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix} & \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix} & \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix} & \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix} & \begin{bmatrix} 1 & 1$ concentrations across all position $\hbox{probability that a particular combination of} \begin{equation} \left\{ \begin{array}{cc} \mathbf{S} & \mathbf{S} \rightarrow \mathbf{S} \end{array} \right\} \end{equation}$ concentrations, g, can be seen anywhere in the embryo. positions is the average of the distribution of morphoger concentrations across an positions x, it represents
probability that a particular combination of $\frac{1}{\sqrt{2}}$ probability that a particular combination of $\bigcup_{\sigma_x(x)}$ This is the average of the distribution of morphogen concentrations across all positions x; it represents the

 $\mathcal{C}^{\text{max}}_{\text{max}}$ from morphogen concentration measurements $\mathcal{C}^{\text{max}}_{\text{max}}$

On the right-hand side, we have the a priori distribution of Ω encode positional inform

ode positional:

gið

dg gi PðgjxÞ. Yet there is no fundamental reason to focus

 \mathbf{r} et al., 2013a,b; Gregor et al., 2014; Tkačik et al., 2015). Here, we stress

Mutual information as Positional Information Shannon's original formulation of information theory revolved A 'channel' here represents an evolved biochemical reaction network. lutual informatio s P ϵ is a ϵ lie f

 $\bullet\,$ How many bits of information are required to discriminate every cell/nuclear position? |
|
e $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ tion are required to discriminate every co $t_{\rm tot}$ and required to discriminate every σ I
I required to discriminate every cell/nuclear position? $\frac{1}{2}$

 $\rm Log_2$ 60 = 5.9 bits needed to determine with zero error all cell position (60 cells) no.
Its nooded to determine with zero error all coll position (60 co $Log₂60 = 5.9$ bits needed to determine with zero error all cell position (60 ce deg
digines
digines ϵ caca to actumne with $\cos 60 = 5.9$ bits needed to determine with z Log₂60 = 5.9 bits needed to determine with zer σ -dust settles, our experimental or measuremental or measurement errors are σ Log260 = 5.9 bits needed to determine with zero error all cell position (60 cells) below the observed noise levels (28). Note that measurement

- $\bullet\,$ How much information is actually used to determine with precision cell fate in the embryo? determ [−] ^S½PðgjxÞ\$\$ extually used to determine with procisithis actually used to determine with precisiv This emphasizes that the amount of information that can be a set in the amount of information that can be a set in the can be a set of information that can be a set of information that can be a set of information that can • How much information is actually used to determine with precision actually used to determine with precision ρ is actually used to determine with pred tion is actually used to determine with precision cell fate in the embryo? on centrate in the embryor.
- Some cells are determined with precision: position of the cephalic furrow has 1% accuracy. measure of how well information can be sent through such noisy All the terms in Eq. 11 are experimentally accessible. • Some cells are determined with precision: position of the cephali below the productive position of the depthen pression levels and determines Some cells are determined • Some cells are determined with precision: position of the cephalic ϵ rmined with precision: position of the cephalic pression procioiom pockton of the copi ic furrow ha Finally, as has been addressed in other contexts (Materials and
- What is the amount of PI conveyed by the gap gene network? channels, the mutual information I(g|x) (Cover and Thomas, 2006): Eq. 11 tells us the precision with which expression levels enit is the amount of PI conveyed by the gap gene network*:*
. or noise in expression levels at a fixed position, which is mea- \bullet vinat is the amount \overline{f} DI convoyed by the gap gene network? biological si pression levels at the same sent of DI conserved beeth contexts (Gaussian, dependent of of PI conveyed by the gap gene network? samples we collect is sufficient to get a reliable estimate of Ig→^x ; currement of information, where $\frac{1}{2}$ invited us to the $\frac{1}{2}$ C rk ℓ

Z

accuracy to characterize the noise in the system. This allows us

 \mathbf{q}

Estimating the mutual information that one gene expression level provides about position requires, from Eq. 6, that we obtain

str, in WT. g1 g2

immunofluorescent staining, we can measure g vs. x along the anterior/posterior axis of single Drosophila embryos, and by making such measurements on multiple embryos, as shown in

- And expression data for all 4 gap genes *g* at all positions: $= 2.26 \pm 0.04$ bits
 $= 1.95 \pm 0.07$ bits $I = 1.84 \pm 0.05$ bits $I(\mathbf{g};x) = \langle$ ð • Based on: $I(\mathbf{g};x) = \langle \mid dg P(\mathbf{g}|x) \mid \rangle$ $\begin{bmatrix} 0 \\ \frac{1}{2}y & 1 \end{bmatrix}$ PgðgÞ ix: Ö $t = 0.0$ estimate, or infer, its position. Early demonstrations of quantitative limits to this process (Gregor et al., 2007) were followed by the development of a rigorous mathematical framework $\begin{matrix} \begin{matrix} \cdots \end{matrix} \end{matrix}$ $\sum_{i=1}^{n}$ celling position, at $\int_{a}^{b} I_{n} p(x) dx$ \bullet Dased OII. $I(g; x) = \langle \mid dg \, P \rangle$ really should write σxðxÞ. Checking our intuition, we see that this R_{nos} is so all α is smaller when the variability in expression data for all 4 gap genes **g** at an positions: $I_{g_{\text{cm}} \to x} = 2.26 \pm 0.04 \text{ bits}$ $F = 0.0$ is proportional to the reproductional to the proportional to the proportional to the proportional to the profiles and is proportional to the proportional to the proportional to the proportional to the proportiona inversely proportional to the derivative of the mean profile. (B) Positional error based on the expression of Hb alone (red; mean ± SEM from bootstrapping) compared with the mean profile (gray). (C) Positional error based $\overline{\mathsf{B}}$ is information from all the net position $\overline{\mathsf{B}}$ $\mathbf f$ • Based on: $I(\boldsymbol{\alpha} \cdot \mathbf{x}) = \langle \n\begin{bmatrix} d\boldsymbol{\alpha} & P(\boldsymbol{\alpha}|\mathbf{x}) \end{bmatrix} \rangle$ \mathcal{L} sabbel of $\mathcal{L}(\mathcal{S}, \mathcal{N}) = \bigcup_{i} \mathcal{U}(\mathcal{S}^{\mathcal{N}})$ however, once we have control over the potential systematic systematic systematic systematic systematic systema
The potential systematic systematic systematic systematic systematic systematic systematic systematic systemat errors, the statistical errors in our measurements are very small. $\rule{1em}{0.15mm}$ and expression data for all 4 ga $I_{\text{g}_{\text{Hb}} \to x} = 2.26 \pm 0.04 \text{ bits}$ h_{reco} over h_{reco} over the potential systematic control over Pused on. $I(g; x) = \langle \mid dg \ P(g|x) \mid$ \overline{A} the position of a cell along the middle 80% of the middle 80% of the Δ posterior and cap control and can repeat the gap genes of the gap gen $k_{\text{SHB}\to x} = 2.26 \pm 0.04 \text{ bits}$ $\mathbf t$ • Based on: $I(\boldsymbol{\varphi} \cdot \mathbf{x}) = \ell \cdot d\boldsymbol{\varphi} P(\boldsymbol{\varphi})$ $\begin{pmatrix} \mathbf{e} & \mathbf{$ conveyed not by the expression level of one general convex but by the expression level of one general convex but by the expression level of one general convex but by the expression level of one general convex but by the ex componed expression data for all Λ $\frac{m_1}{m_1}$ and expression data for all 4 $I_{g_{\text{Hb}} \to x} = 2.26 \pm 0.04$ bits $C = 0.0$ $C = 0.9$ $C = 0.0$ $C = 0.0$ Analysis of the data in \mathbb{R}^n shows that the expression level \mathbb{R}^n shows that the expression level \mathbb{R}^n of Hb provides IgHb→^x = 2:26 ±0:04 bits of information about the position of a cell along the middle 80% of the anterior/ p axis. We can repeat this analysis for the gap generator p k p genes k at an positions. and we find IgKr→^x = 1:95 ± 0:07 bits, IgGt→^x =1:84 ± 0:05 bits, and **B C** *I(Kr; hb) = 3.4 I(Kr, hb; x) = 3.5* $C = 0.0$ $C = 0.9$ $C = 0.0$ $C = 0.0$ $C = 0.0$ $|C = 0.9$ $|C = 0.0$ $|C = 0.0$
- g1 g2 g4 g3 ðxÞ \$ n considering all 4 gap genes: $\begin{bmatrix} 0 & 0 \\ 0 & 1 \end{bmatrix}$ M hich is r exterior) Similarly, Particular generalizations.

Posterior and the gap generalizations of the gap generalization of t $c_0 = 1.95 \pm 0.07$ bits, $I_{g_{\text{Gt}} \to x} = 1.84 \pm 0.05$ bits, p is representing an independent of the probability that a particular particular p -0.5 combination of concentrations, g, can be seen any -0.5 concentrations, 0.5 \$ \blacksquare ports our approximations and gives us confidence that the mea $s_{\rm th}$ and $s_{\rm th}$ and $s_{\rm th}$ are entirely and $s_{\rm th}$ \mathbb{G} tich is more than if they were simplified to \mathbb{G} and we find \mathbf{I} = 1:95 \mathbf{I} bits, \mathbf{I} bits, and \mathbf{I} When considering all 4 gap genes: $\overline{}$ In all cases, the expression of a single gene carries much more than one bit of information; indeed, it carries more nearly two $I_{g_{\text{Kr}} \to x} = 1.95 \pm 0.07$ bits, $I_{g_{\text{Gt}} \to x} = 1.84 \pm 0.05$ bits, $\frac{1}{2}$ Which is more than if they were simpl $\frac{1}{8}$ than one bit of information; indeed, it carries more nearly two characterized by domains of expression, with boundaries, and the sharpness of the boundary of the boundary of the boundary of the boundary of PHYSICS $\frac{1}{\sqrt{2}}$ G^{t} is which is more than if they were simple g_{t} on f^{t} is the primary only the f^{t} morphogen [e.g., Bicoid in the Drosophila embryo (23–25)] When considering all 4 gap genes: could arise entirely from communication between neighboring cells, in a Turing-like mechanism (26, 27). In these different $\frac{1}{2}$ \mathbb{I} and \mathbb{I} and \mathbb{I} and \mathbb{I} are \mathbb{I} and \mathbb{I} and than one bit of information; indeed, it can be a set of \mathbb{Z} of \mathbb{Z} in the nearly two more near \mathbb{Z} bits. The conventional view of the gap general view of $\overline{}$ domains of $\overline{}$ the sharpness of the boundary often is taken as a measure of $\begin{array}{ccccccccc}\n-0.5 & 0 & 0.5 & 1 & 1.5 \\
\hline\n-0.5 & 0 & 0.5 & 1 & 1.5\n\end{array}$ 0.5 $\begin{array}{ccccccccc}\n0.5 & 1 & 0 & h b \\
\hline\n-0.5 & 0 & 0.5 & 1\n\end{array}$
	- embry 1983.
• Can information increase? Bcd vs Gap genes. \$ $\frac{3.8}{-0.5}$ 0 0.5 1 1.5 cm s 1 0 hb $\bullet\,$ Can information increase? Bcd vs Gap genes. h domains with infinitely sharp boundaries, the ex-
- our can now be made precise. $\frac{N_{\text{U}_i}(X)f_i,\,C_{ij}(X)}{N_{\text{U}_i}(X)}$ at al C_0 and $N_{\text{U}_i}(X)$ and N_{\text $m_{\rm{max}}$ can then deliver then deliver then deliver the probability of finding and α $\frac{1}{2}$ considering Bcd dynamics cleus to know its position with an extensive with an extensive with an extensive with an extensive with $\frac{1}{2}$ bar $\frac{1$ \mathbf{t} sharpness of the boundary of the bou precise of the patterns of the patterns of expression. The patterns of the provide nearly two bits $\frac{1}{2}$ ros in instantancous promo_r no $h(x) = h(x)$ and available bits tells us about of available bits tells us about $\mathcal{C}(1)$ $\bullet\,$ Yes if instantaneous profile, α about position. Our result that gap generation. Our result that gap generation α o if considering Bcd dynamics. expression levels are sufficiently reproducible from embryo to • Yes if instantaneous profile, No if considering Bcd dynamics.

the efficiency of staining, which means we can avoid previously

patterning, but it cannot explain how and where these limits arise.

 \mathbb{Z} connected to information-theoretic concepts (Dubuis et al., 2013b; et a $\overline{}$

 $\begin{array}{c} 0.5 \\ h b \end{array}$

 $\frac{1}{\sqrt{1}}$

x

Decoding positional information from concentrations auon fioni concentrations might be able to extract from g, denoted here as implied position, x*. Decoding positional information $\boldsymbol{\nu}$ m concentrations solely on average server and variability in the variability in the profiles of profiles in the profiles of pro

• Bayes' theorem:

$$
P(x^*|\mathbf{g}) = \frac{1}{Z}P(\mathbf{g}|x^*)P_x(x^*).
$$

by means of a decoding means of a decoding means of a decoding mechanism. Although many such a decoding α

Posterior Measuremen<mark>ts Prior</mark> \sim concentrations) Posterior (Decoded position based on measured

locations (Decoded) to be decoded (A priori position of \mathbb{R}^n , which is because to be decoded in the material position of \mathbb{R}^n . position based contracts in the unit of the unit o
Provided contracts in the unit of the u Prior nuclei to be decoded)

for a particular g, the posterior may be sharply localized around a

ⁱ ^ðxÞ ¼ ^Ð

dg ðgi % giÞ

[mathematically given by ^s²

the maximum likelihood estimate [assuming a uniform prior Px(x*)],

G. Tkacik and T. Gregor. *Development* (2021) 148, dev176065. G_1 the mean profile with G_2 is C_3 and C_4 are spaced are spaced are spaced are spaced at (2.52) . Nuclei are spaced at (2.52) $u_{\text{S_{11}}}$ </sub> across x, as shown by the unit by the bottom; $P_{\text{S}}(x)$, at $\frac{101!10.1242}{\text{GeV}}$. 1/6065

Decoding positional information from concentrations

• Decoding positional information with an increased number of gap genes positional information with an increased number of gap genes $t_{\rm eff}$ focus on measuring mea

mechanisms and their biological implementations are possible,

$$
P(x^*|\mathbf{g}) = \frac{1}{Z} P(\mathbf{g}|x^*) P_x(x^*).
$$

 $\bullet\,$ The complete set of all 4 gap genes provides a uniform precise positional information with a high precision within 1% of embryo length

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Petkova, M.D., Tkačik,G., Bialek,W., Wieschaus, E.F. and Gregor,T. *Cell* 176, 844-855 (2019) After measuring g*: Petkova, M.D., Tkačik, G., Bialek, W., Wieschaus, E.F. and Gregor, T. Cell 176, 844-855 (2019)

necessary for a probabilistic approach. P(g|x) keeps all the information

Decoding positional information from concentrations

- Is this positional information actually used in the embryo?
- Comparaison of inferred position based on gap genes PI and actual position of downstream pair rule genes.

g1 g2 g4 g3

Decoding positional information from concentrations

- Is this positional information actually used in the embryo?
- Perturbations of maternal inputs to gap genes, expecting that the same decoding strategy is used as in controls: implied positions are shifted in specific domains.
- Comparaison of implied position based on gap genes PI and actual position of downstream pair rule genes.

Petkova, M.D., Tkačik,G., Bialek,W., Wieschaus, E.F. and Gregor,T. Optimal decoding of cellular identities in a genetic network. Cell 176, $844-855(2019)$

Mutual information as Positional Information relates morphogen input to the positional identity of neural progenitors. Analysis of the mutual information as Positional Information. Analysis of the mutual provided provided progenitors. Analysis o Neither the Shh nor the BMP signaling gradient throughout the DV axis. By contrast, the joint the

transcriptional network that provides a mechanistic basis for the observed cell fate decisions α S^a and dynamics of pattern formation and dynamics of pattern formation. Together, our data links S^a errors in response to the joint input of α reverse-engineered and α reverse-engineered and α transcriptional network that provides a mechanistic basis for the observed cell fate decisions RESEARCH ARTICLE Research article Developmental Biology | Physics of Living Systems • Morphogens in growing tissuespositional error (7, 10) resulting from the com- \mathbf{b} ined interpretation of both signals was \mathbf{c}

or
I receptor promiscuity as a strategy for The integration of Shh and hedgehog (Shh) and bone morphogenetic proattui att and TODUST in during morphogenesis anga af u accurate and robust inference of position $\mathbb{R}^{\mathbb{N}}$ and Shh signaling profiles in the growing mouse Cellular compartmentalisation and

observed responses indicates that the underlying interpretation strategy minimizes patterning

Krishnan S Iyer¹, Chaitra Prabhakara², Satyajit Mayor^{2*}, Madan Rao^{1*}
Entis de la propone de la p

¹Simons Center for the Study of Living Machines, National Center for Biological Simons Center for the Study of Eiving Machines, National Center for Biological
Sciences - TIFR, Bangalore, India; ²National Center for Biological Sciences - TIFR, Bangalore, India A

Iyer et al. and M. Rao eLife 2023;12:e79257. DOI: https://doi.org/10.7554/eLife.79257 $\frac{1}{2}$ or absolute distance to the source distance dista j \mathbf{B}

Decoding of position in the developing neural tube from antiparallel morphogen gradients t decouping of position in the various \mathbf{w} t therefore α is bring about fidelity in morphogenetic decoding α tors, cells achieve a more accurate and robust inference. We explore these ideas in the patterning

Marcin Zagorski,¹ Yoji Tabata,² Nathalie Brandenberg,² Matthias P. Lutolf,² Gašper Tkačik,¹ Tobias Bollenbach,^{1,3}* James Briscoe,^{4*} Anna Kicheva^{1,4*} marcin Zagorski, Yoji Tabata, Nathanae Brandenberg, Matthias P. Luton, ence in the high dimensional space in the highest parameters provided a measure for robustness and reduced a measure for robustness and α

Like many developing tissues, the vertebrate neural tube is patterned by antiparallel morphogen gradients. To understand how these inputs are interpreted, we measured morphogen signaling and target gene expression in mouse embryos and chick ex vivo assays. From these data, we derived and validated a characteristic decoding map that relates morphogen input to the positional identity of neural progenitors. Analysis of the observed responses indicates that the underlying interpretation strategy minimizes patterning errors in response to the joint input of noisy opposing gradients. We reverse-engineered a errors in response to the joint input or noisy opposing gradients, we reverse-engineered a
transcriptional network that provides a mechanistic basis for the observed cell fate decisions and accounts for the precision and dynamics of pattern formation. Together, our data link opposing gradient dynamics in a growing tissue to precise pattern formation.

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Zagorski et al., *Science* 356, 1379-1383 (2017)

Use of Shannon information theory beyond positional information Position along the AP axis (a.u.)

• Could also apply to mechanical input or output (mechanochemical patterning): eg. Mechanogens

Lower degradation $c(x)$ Columnar Higher degradation Squamous- $\rightarrow x$ Crossover: x_c

Mechano-induction:

K. Dasbiswas, E. Alster & S. A. Safran (2016) *Scientific Reports* | 6:27692

K. Dasbiswas, E. Hannezo and Nir S. Gov **source, here confned to the** *x***=0 plane.** Te difusion and the degradation (or capture) of these molecules by the cells computed to result in a steady-state gradient of both the mechanogeneity and the mechanogenei \mathcal{L}

 \bullet Morphogen (cell fate) and mechanogen (motility driven un-jamming) a decimal digit is about 3¹ \bullet Morphogen (cell fate) and mechanogen are involved the base *e* is sometimes useful. The resulting units of information will be called natural units. \mathcal{S} communication system we will mean a system of the type indicated schematically in \mathcal{S} in Fig. 1. It is the type in \mathcal{S} in Fig. 1. It is the type in \mathcal{S} in \mathcal{S} in \mathcal{S} in \mathcal{S} is the ty

D. Pinheiro, et al, E. Hannezo & CP. Heisenberg solid, black line: L⁰ ¼ 25 (part squamous and part columnar); dashed line is for L⁰ ¼ 15 (all squamous). (B) Mechanoinduction: Mechanogen concentration *Nature Physics* 18, 1482–1493 (2022) and cell radius profiles are shown for the intrinsic cell contractility, $L^2(\omega)$ V D D , f innero, et al, E. Hannezo α Cf. Heisenberg

See also: Yang et al, and A. Shyer and A. Rodrigues. Science 382: eadg5579 columnar crossover is later is later is concentration is for units at concentration is for units and other para $\frac{1}{2}$ μ channel. In the channel channel. In this operation consists merely μ .

 DE FRANCE Thomas LECUIT 2024-2025

Diffusion *D* ר c Concentration Information theory and self-organisation

- \bullet What about other situation where there is no clear input? e.g self organisation ation
- **Modules of Programmed Self-organized** b • Constituents of a system interact with each other to create system-wide spatiotemporal patterns.

• Precision

τ = λ² /*D* Timescale

- No input and initial conditions are difficult to define: components, interactions, noise, boundary conditions
- Self-organised systems exhibit 1) **spontaneous patterns** from homogeneous **nature structural & molecular biology mammalian pseudo-embryos** initial state and 2) reproducibility **Article** https://doi.org/10.1038/s41594-024-01251-4

τ = η/*E*

Timescale

CDX2

BRA

 Δ ^m/^m/^m protein concentrations by a signalling via p

 2^2

Precise and scalable self-organization in mammalian pseudo-embryos & Thomas Gregor 1,2

how precise and reproducible patterns of gene expression emerge in three-dimensional in vitro model for early mammalian development. Our study reveals intrinsic reproducibility in the self-organization of gastruloids, encompassing growth dynamics and gene expression patterns. We observe a remarkable degree of control over gene expression along the main body axis, with pattern boundaries positioned with single-cell precision. Furthermore, as gastruloids grow, both their physical proportions and gene expression patterns scale proportionally with system size. Notably, these properties emerge spontaneously in self-organizing cell aggregates, distin<mark>c</mark>t from many in vivo systems constrained by fxed boundary conditions. from many in vivo systems constrained by fxed boundary conditions. Our fndings shed light on the intricacies of developmental precision, Our fndings shed light on the intricacies of developmental precision, reproducibility and size scaling within a mammalian system, suggesting that mammals. Here we investigate this phenomenon using gastruloids, a Gene expression is inherently noisy, posing a challenge to understanding these phenomena might constitute fundamental features of multicellularity.

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JCE Thomas LECUIT 2024-2025

> gene expression domains and other phenomena, reflecting the intri-In contrast to organisms with well-defined developmental boundaries, such as flies, frogs or worms, mammalian development relies on self-organization and continuous growth. λ ments of reproducibility, precision and scaling in mammalian systems have been limited, prompting inquiries into whether the precision

 n of the cellular and tissue level processes driving shape changes. These shape changes. These shape changes. These shape changes are shaped changes. The contract of the contract of the contract of the contract of t

M. Merle et al. and T. Gregor. Nature Structural & Molecular Biology, 31, 896-902 (2024)

60

Pz (*z*) = ¹

P*N*

P*Z*

where *P*(*z, i*) is the joint distribution of cell fates and indices,

to naturalistic sources of noise and variability (Fig. 1*A*). A typical An information theoretic mathematical formulation for 1) spontaneous patterning features, but are not always identical. We can think of these reproducibility distribution \bullet π **distribution that the extra patterns are the entropy of the entropy of** ontropies for reproducibility and patterning ${\sf y}$ lation for 1) spontaneous patterning and 2) ϵ ϵ <u>ucell fat</u>es in the entire development of the energy μ reproducibility **Figure 1999** Two entropies for reproducibility and patterning • An information theoretic mathematical formulation for 1) spontaneous patterning and 2) $u - t$ $\frac{1}{2}$ tion theoreuc mathematical for replicates while creating diversity of cell types is general. Thus, in *P*(*z, i*) = *Pi*(*zi*)*P*index(*i*) and the fact that the indices are by definition uniformly distributed, *P*index(*i*) = 1*/N*, this simplifies *^S*pat ⁼ *^S*[*Pz* (*z*)] = P*^Z ^z*=¹ *Pz* (*z*)log2 *Pz* (*z*)*.* **[3]** theoretic measure of self-organization performance in embryonic mation theoretic mathematical fo developmental processes in the language of stochastic dynamical \cdots

of a developmental process, such as a collection of embryos α

content.

where α is zero or vanishingly small cannot reasonably small cannot reasonably self-

zi=¹ *P*(E*z*)(*zi, z*) (Fig. 1*A*), where (*zi, z*)

$$
U = S_{\text{pat}} - S_{\text{rep}}.
$$

 \Box represents represent the diversity of realized cells of realized cells of realized cells • internation: positional information (local) and correlational ation (non-local statistical structure) Downloaded from https://www.pnas.org by "IST AUSTRIA - LIBRARY, INSTITUTE OF SCIENCE & TECHNOLOGY" on June 3, 2024 from IP address 81.223.14.210. versa (Fig. 1*A*). However, reproducibility entropy can also be $t_{\rm{max}}$ is often referred to a define $t_{\rm{max}}$

$$
U = \text{PI} + \text{CI}.
$$

utility of *U* = log2 *Z* bits is in the top right corner. This optimum

This approach has previously been applied to formalize the

- Hypothesis: self-organization in developmental systems is a simultaneous maximization of reproducibility and of cell type diversity (ie. utility U is maximised) of our careful definitions; on the other, however, its biological definitions; on the other, its biological definition, α nization in develonmenta values of utility close to their maximal bound, the only way r cell Taken together, our framework identifies three entropies to mechanical and chemical degrees of freedom (16, 17). retame ie a eimultanaoue i treat is a since it integral part of the problem, since it is integral part of the problem, since it is in pos constraints and trade-offs on signaling mechanisms which needs on signalize mechanisms which needs on signalize v U is maximised) achieve fi focus on self-organization of intrinsically stochastic systems and Download
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Ca
- Self-Organized Patterning as a Stochastic Dynamical System

x*ⁱ* as dynamical variables and allowing for couplings between

 $\bullet\,$ Exploring how parameters affect patterning and reproducibility entropies and utility.

the one hand, this result is a mathematical necessity by virtue

• The utility function can be used as an optimization criterion to select model parameters. patterns *g*E(*t*). (*D*) Each cell autonomously interprets the patterning concentrations at readout time *T* to decide its fate *zi*. (*E*) Fate decisions of all cells yield the

Ex: Lateral inhibition

. Hypothesis: self-organization in developmental systems is a simultaneous maximization of reproducibility and of cell type diversity (ie. utility U is maximised) pothesis. Sen organization in aevelopi $r_{\rm c}$ because by plane. Ci quantifies the amount of nonlocal state $\frac{1}{2}$ mtal systems is a simultaneous maximiz tital systems is a simulations maximiz u tility U is maximised) \mathbf{b} bifurcation motifs that comprise that computes \mathbf{b} . We build \mathbf{c}

intracellular gene regulatory networks and dynamical systems

 \bullet A possible general trend:

breaking has already occurred.

- The systems first break symmetry, giving statistical structure (proportion of cell fates) without spatial pattern (CI) and the states with out spatial pattern (CI) and the states with \sim and positions. This decomposition suggests that, interestingly, a e systems inst break symmetry, giving statistic \mathbf{u}_1 is the final outcome. It is the final outcome. In the future, it is in the future, it structure (proportion of cell fates)
- The systems later acquires spatial organisation and reproducibility (PI). (Fig. 7). For instance, intestinal organoids first break symmetry utility of discretized cell fate patterns. Our approach allows us

D. Brückner a d G. Tkacik. *PNAS* 121, e2322326121

- 1. *Shannon information theory* provides a powerful framework to:
	- *Quantify* biological information encoded in a chemical system
	- Assess information transmission in a noisy channel, such as in any input/output system in biology.

2. *Mutual information* provides a measurement of positional information through the statistical structure of correlations between concentrations of molecules and spatial coordinates.

3. In self-organised systems, exploration of other means to quantify total information: eg. positional and correlational information.

4. Need to consider other parametrizations of space (than spatial coordinates): polarity, nematic order etc.

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Book recommendations as a background

