What is biological information?

<u>Course 4:</u> Encoding, Decoding and Representations of *Time*

Thomas Lecuit

chaire: Dynamiques du vivant

- 1. Length scales are defined in chemical and mechanical systems in a variety of ways (deterministic and self-organised models).
- 2. *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.

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

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

- From letters (chemical species) to « words »: sequences and combinations Balance between diversity and specificity
- From « words » to patterns of words (in space and time): « sentences ».
	- *Static* chemical representation (combinatorial): « music chord ».
	- *Dynamic* chemical representation: « melody »

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Lamarck - *Time* is an *inherent property* of the living

PHILOSOPHIE ZOOLOGIQUE.

SECONDE PARTIE.

Considérations sur les Causes physiques de la $\mathcal{V}ie$, les conditions qu'elle exige pour exister, la force excitatrice de ses mouvemens, les facultés qu'elle donne aux corps qui la possèdent, et les résultats de son existence dans ces corps.

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JB de Lamarck (1744-1829) \mathcal{L} differences \mathcal{L} existent \mathcal{L} is the less corps in \mathcal{L}

378 COMPARAISON DES CORPS

 g_{trans} faut met Dynamics en parallèle les caractères estentiels estentiels estentiels estentiels estentiels estentiel
Dynamics

Caractères des Corps inorganiques mis en parallèle avec ceux des Corps vivans.

Tout corps , au contraire , qui possède la vie , rout corps, au contraire, qui posseue la vie,
se trouve continuellement, ou temporairement, animé par une *force particulière* qui excite sans cesse des mouvemens dans ses parties intérieures , qui produit, sans interruption, des changemens d'état dans ces parties, mais qui y donne
mens d'état dans ces parties, mais qui y donne. lieu à des réparations , des renouvellemens, des développemens , et à quantité de phénomènes qui sont exclusivement propres aux corps vivans; en sorte que, chez lui, les mouvemens excien sorte que, chez tur, les mouvemens exci-
tés dans ses parties intérieures altèrent et détruisent, mais réparent et renouvellent, ce qui étend la durée de l'existence de l'individu, tant que l'équilibre entre ces deux effets opposés, et qui ont chacun leur cause, n'est pas trop fortement détruit; et animalie peut offrir une masse dividue communement, ou temporarrement mus par une *jorce particuliere* qui excite soit est. dividualisé dans ses parties interieures alterent et sou voltait et son volume ; et son volume ; et son volume véritablementhomogène ,

Transformism HISTOIRE NATURELLE STORAT STANG STILLWIGHTER SO ... Brien partie an an aun $\frac{1}{1}$ ANIMAUX SANS VERTÈBRES. DES

7.º La nature, dans toutes ses opérations, ne pouvant procéder que graduellement, n'a pu produire tous les animaux à-la-fois : elle n'a d'abord formé que les plus simples ; et passant de ceux-ci jusques aux plus composés, elle a établi successivement en eux différens systèmes d'organes particuliers, les a multipliés, en a augmenté de plus en plus l'énergie, et, les cumulant dans les plus parfaits, elle a fait exister tous les animaux connus avec l'organisation et les facultés que nous leur observons. Or, elle n'a rien fait absolument, ou elle a fait ainsi.

Lamarck - *Time* is an *inherent property* of the living

- Time is *constructed from within* cells and organisms: *How*?
- Time is *relative*: use of different time scales to organise cells and developing embryos
- Temporal information is encoded and decoded

https://www.thisiscolossal.com/2017/02/mechanical-crustaceans-with-clockwork-insides-illustrated-by-steeven-salvat/

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• Time scales in biology:

— Phenomenology of time and features: nested time scales (from molecules to evolution).

• How is time encoded?

• How is temporal information decoded?

- Signalling information: information encoded in dynamics.
- Mechanical temporal information in morphogenesis.
- Segmentation clock: decoding time to encode space

Phenomenology of time in Biology

- Life manifests over many time scales: (11 to 14 order of magnitude in a given organism)
- Molecular scale: 1- few ms
- Cellular scale: few minutes to hours
- Tissue scale: few 10s of min or hours
- Organismal scale: 1 day to years
- Evolutionary time:
	- —Species radiation can be « fast »
	- —Some species remain the same over longer time than major geological time.

Weizmann Institute of Science, Rehovot 7610001, Israel California Institute of Technology, Pasadena, CA 91125, USA Phenomenology of time in Biology

- Time scales are connected:
- Cellular time scales emerge from molecular time scales.
- Example: molecular oscillator such as cell cycle lasts 10 minutes to 24 hours

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 $-1530-$

Phenomenology of time in Biology — Molecular cycle/oscillations

• ATP synthase Period T=10ms ~300 ATP per s

Phenomenology of time in Biology – Cell division cycle

Phenomenology of time in Biology — Heart beat cycle

 $\mathsf{a} \mathsf{I} \mathsf{e}$ in this direction would be a • Heart beat Period $T \sim 1$ s in human ranging from 0.04s in Etruscan shrew to 10s in submerged blue whale

iwa a 4500 km journey to a few sites 1km² each. .
Aruba d Ecuador <u>I</u>
A E mil 4.5 million km² migrate in 2 months • Few hundred millions monarch butterflies, distributed in 4.5 million km² migrate in 2 months

D. eresimus

Australia generations/years bac nerations/years back to the original spots. $f(x)$ spow. trunk in Michoaca´ n, Mexico. Photo credit: Thomas \bullet They then migrate back, step by step, in 3-5 generations/years back to the original spots.

Mexico [25,102]. Reproduced from Reppert *et al.* [3]. (E) Journey north. Eastern migrants remain at the overwintering sites in Mexico until spring, when these Period T=3-5 years

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SM. Reppert and JC. De Roode *Current Biology* 28, R1009–R1022 (2018) σ the overwintering sites in central sites in σ

Sample sites: Blue dots, Pacific Islands; red dots,

Phenomenology of time in Biology — cicada emergence cycles

Magicicada septendecim

Period T=13 or 17 years

https://www.sciencenews.org/article/mystery-synchrony https://www.inaturalist.org/guide_taxa/370386

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13-17 year broods geographical mapping (non overlapping)

[https://yardandgarden.extension.iastate.edu/article/2024/05/2024](https://yardandgarden.extension.iastate.edu/article/2024/05/2024-periodical-cicada-emergence-what-should-you-expect) [periodical-cicada-emergence-what-should-you-expect](https://yardandgarden.extension.iastate.edu/article/2024/05/2024-periodical-cicada-emergence-what-should-you-expect)

<https://cicadas.uconn.edu/broods/>

Embryonic development entails temporal control

Andante con moto (2° mvt)

Orderly temporal succession of cellular processes during embryonic development

Zebrafish embryonic development Sea Urchin early cell division

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- Time scales in biology:
	- Phenomenology of time and features: nested time scales (from molecules to evolution).

• How is time encoded: defining time scales locally and globally.

- How is temporal information decoded?
	- Signalling information: information encoded in dynamics.
	- Mechanical temporal information in morphogenesis.
	- Segmentation clock: decoding time to encode space

Linear time: accumulation Cyclic time

• Biochemical processes: diffusion, reaction waves \mathbf{r} temporal dynamics, in the instance, the instance, the instance, trigger instance, trigger instance, the instance, biochemical processes: diffusion, reaction waves θ diffusion reaction waves \ldots amasion, to action waves extracellular side, stochastic opening of the voltage-sensitive so-stochastic op dium channels occurs more frequently. Channel opening allows so- $\mathbb{F}_{p,q}$ equations can be viewed as a simple and general model of $\mathbb{F}_{p,q}$ \bullet Biochemical processes: diffusion,

interactions22 (BOX 2). Excitable systems manifest charac-

Huxley model of action potentials (Hodgkin and Huxley, 1952), the \mathcal{H}

parameter i de la parameter d
La parameter de la parameter d

transforms a homogeneous field of cells into discrete

side of the membrane becomes less negative with respect to the

switches, and oscillations over $\mathcal{L}_{\mathcal{S}}$ and oscillations over large distances. Before distances. Before

Martin Behrndt,1,2* Guillaume Salbreux,3* Pedro Campinho,2 Robert Hauschild,² Felix Oswald,¹

kinase (MAPK) pathway components traf2/nika

 \bullet Mechanical processes - ex: active viscoelastic flow As another example, Turing instabilities control pal- $\mathcal N$

the local concentration depends on the production–

Tuning time scales *globally*

- RESEARCH | RESEARCH ARTICLE • Developmental tempo and protein stability
- Specification of motoneurons in the vertebrate neural tube depends on a Gene Regulatory Network (GRN) and growth factor signalling (Shh morphogen gradient)
- In Mouse and Human the tempo is different by a factor of ~2.5 fold (3-4 days vs 2 weeks)
- This can be recapitulated in vitro

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RESEARCH | RESEARCH ARTICLE

 $F = 1.5 \text{ F} \cdot \frac{64 \text{ F}}{1.5 \text{ F}} \cdot \frac{1.766 \text{ F}}{1.5 \$ Rayon et al. and J. Briscoe, *Science* 369, eaba7667 (2020) Matsuda et al and M. Ebisuya, *Science* 369, eaba7668 (2020)

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- \bullet Developmental tempo and protein stability
- The 2.5 fold difference in tempo is:
- *Not due to a difference sensitivity* to Shh signalling $\sum\limits_{n=1}^{\infty}\sum\limits_{n=1}^{\infty}$ (Similar Shh signalling dynamics is associated with different $\sum\limits_{n=1}^{\infty}\sum\limits_{n=1}^{\infty}$ transcriptional regulation of target genes) half-life in mouse (orange) and human (blue) neural $\frac{1}{2}$ when annotone
- Not associated with a difference in specie's sequence of $\frac{1}{2}$ target genes (eg. replacing Olig2 gene from human to mouse in ES cells does not change the tempo). \mathcal{L} beducies of 1.5 times the international range of the 25th and 75th a proteome in mouse (orange) and human (blue) neural
- \bullet Indicates, species specific cellular environment.
- mRNA stability (half life is not different)
- Protein stability (half life) shows a ~2.5 fold difference α corresponds with α overlap between the distributions α 35th to the 75th percentile of the 75th percentile of the 75th percentile of the range of the range of the 75th percentile of the
- Computational modelling indicates higher constraints in protein stability to account for 2.5 fold change in tempo compared with other parameters. The Nkx2. the computational model of the neural tube \mathbb{R}^n $\begin{array}{ccc} \text{S} & \text{$ G Gramscors Paxe G
- A general cellular property:
- An exogenous protein (mKate2) has different half life. erent half-life. Relevant b
- Cell cycle duration show similar tempo difference $\mathfrak A$ time factor of $\mathfrak A$. The reduced $\mathfrak A$

(light blue). Boxplots indicate the 25th to the 75th

 α rate is an effective mechanism to regard mechanism to regard mechanism to regmatsuda et al α is nonelinear relationship between α Matsuda et al and M. Ebisuya, *Science* 369, eaba7668 (2020) fluorescence in inhibited cells. FACS analysis $\mathrm{SO}(2)$ Rayon et al. and J. Briscoe, *Science* 369, eaba7667 (2020)

Transcription rate Trans
fold change in total

fold change in manage fold change fold

Mouse EpiLCs Presomitic Λ A Λ 25b mesoderm **Humar** iPS cells Presomitic **XXX** 5 h Mouse or human Human *NCRM1* (no reporter) 3° *E14* (no reporter) b contract the contract of the e f 0 3 6 9 12 15 18 0 0.2 0.4 0.6 0.8 1.0 Time (h) Normalized fuorescence intensity (AU) Human 0123 0 \overline{Q} \overline{a} \mathbf{d} \overline{a} Mouse Human $\mathcal{M}(\mathcal{M})$ Mouse Human \circ \overline{A} $^{\circ}$ period (h) Mouse Human **2** Mouse 3 M
H Mouse
. . **COM** Mouse \sim Human co-culture e El \mathcal{L} 40 \sim Hessen 0.7354 HES7-Achilles **Fig. 1 | Cell-autonomous differences in developmental rate between** differentiation of the second mouse and human points $\sum_{i=1}^{\infty}$ of $\sum_{i=1}^{\infty}$ $\sum_{i=1}^{\infty}$ $\sum_{i=1}^{\infty}$ developmental pace of mouse cells is reflected in the reduced induction time of HES7-Achilles oscillations in PSC-derived mouse and human PSM cells. Data are mean ± s.d. *n* = 25. Unpaired two-sided *t*-test: *P* = 7.33 × 10[−]41. **f**, Left, experimental strategy for the co-culture of CAS-M2B-mCherry; Hestiga for \mathbb{R}^n human or CAG-NLS-BFP; Hestiman or Substitution or Substitution or Substitution or Substitution or Su \bullet $\,$ Developmental rate and Metabolism **Mouse Human** Mouse Human Mouse Human Mouse Human Mouse Human $\overline{2}$ 0.2 -10 \overline{a} 15 \geq 0.0 \sim $\overline{10}$ fluores Aouse Cell volume (f) Mass-specific OCR 2019 \mathbf{X} Σ^2 $\frac{1}{\sqrt{2}}$ $\frac{1}{\sqrt{1-\frac{1}{2}}}$ 012345 6 0 123456 2 4 6 $8 - 8 -$ Mouse * * * Mass-specifc glucose consumption (×10–10 μmol pg–1) 0 1 2 **Mouse** Human * * * * * Mass-specific lactate secreted (×10–9 μmol pg–1) $\frac{1}{2}$ $\frac{1}{\sqrt{2}}$ $\begin{array}{ccccccc}\n0 & 1 & 2 & 3 & 4 & 5 & 6\n\end{array}$ Mouse Human 0 < 0.0001 1 $\frac{9}{10}$ 30 ٢ C **MAAA** 2.5 h ت
س 0 0.2 0.4 0.6 red
L $\overline{}$ $(0, 0)$ 01234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 6 0234 \mathcal{T} \sqrt{t} 1
18 $\overline{}$ (×10–10 μmol pg–1) e
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ma 0 10 20 30 50 60 0.0002 Mass-specific MitoTrackerGreen (MFI pg–1 0.0017) $\frac{1}{2}$ 20 $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ g h i j চ 요. 90 ይ' $\breve{\mathrm{e}}$ 1000 ss-snecific lacta Presomitic mesoderm $\frac{1}{\sqrt{2}}$ e \mathbb{R} is constant. Mouse or *E14* (no reporter) 0123 1 20 12 15 18 MSGN1[–] Ω 10 20 40 Cell cycle duration (h) \mathbf{a} Mouse \Box $\overline{}$ co-culture \sim $\sqrt{2}$ Human \Box 5 $\ddot{ }$ ë $\tilde{\pi}$ $\overline{\mathbf{x}}$ Hessel Human He $\frac{d}{2}$ \bar{P} \bar{P} \bar{P} ਸ਼ੁਰਾਰ ਕੀਤੀ ਹੈ। ਇਸ ਪ੍ਰਾਚ ਕੀਤੀ ਹੈ। ਸ਼ੁਰੂ ਹੋ ਕੀਤੀ ਸਾਹਿਬ ਕੀਤੀ ਹੈ। ਸ਼ੁਰੂ ਹੋ ਕੀਤੀ ਸਾਹਿਬ ਸਿੰਘ ਸੀ ਕੀਤੀ ਹੈ। ਸ਼ੁਰੂ ਹੋ ਕ
ਸ਼ੁਰੂ ਹੋ ਕੀਤੀ ਹੈ। ਸ਼ੁਰੂ ਹੋ ਕੀਤੀ ਸਿੰਘ ਸੀ ਕੀਤੀ ਹੈ। ਸ਼ੁਰੂ ਹੋ ਕੀਤੀ ਸਿੰਘ ਸੀ ਸਿੰਘ ਸੀ ਸਿੰਘ ਸੀ ਸਿੰਘ ਸੀ ਸਿੰਘ ਸੀ ਸਿੰਘ ਸ e \sim \sim 0.0001 \Box Time (h) Mouse Human 0 1 2 3 4 5 6 Segmentation clock period (h) **Fig. 1 | Cell-autonomous differences in developmental rate between differentiating mouse and human PSM cells. a**, Schematic illustrating the differentiation of mouse and human PSCs towards PSM fate. The accelerated particles provided by the accelerated particles of the accelerated particles in the accelerated particles of the accelerated particles in the accele developmental pace of mouse cells is reflected induction time reduced in the reduced induction time α and short oscillatory period relative to human cells. EpiLCs, epiblast-like cells; $\frac{1}{2}$ cells. **b**, $\frac{1}{2}$ **b**, $\frac{1}{2}$ **c** $\$ \sim $\frac{8}{\Omega_{\text{eq}}}$ 0.0002 of cells expressing MSGN1-Venus was assessed by flow cytometry. *n* = 5 independent experiments. **c**, Cell cycle duration for PSC-derived mouse and human **PSM cells. Data are mean the s.d.** *n* **= 33 (novel)**, *n* = 33 (novel), *n* = 26 (novel). Unpaired are designed and the s. two-sided **to-test:** *P* + **P** + 2.88×2.88×10−15. **defined** profiles for profi PSC-derived mouse and human PSM cells over the course of 18 h. Data are mean ± s.e.m. *n* = 5 independent experiments. AU, arbitrary units. **e**, Period

4,000

Time (h)

<u>D</u>

U I 2 3 4 3 0

Time (h)

2,500

<0.0001

d

 \sum_{1}^{n} or \sum_{1}^{n} or \sum_{1}^{n} entropy of \sum_{1}^{n} ratio of \sum_{1}^{n} ratio of \sum_{1}^{n}

of 1 \pm 100 (Fig. 1f), the segmentation clock period remained unchanged uncha (2.29 ± 0.57 h versus 2.19 ± 0.46 h, *P* = 0.73) (Fig. 1g, Extended Data Fig. 1d,f,h,I and Supplementary Video 3). This was also true for indi-

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Mouse Human

-
- \bullet Segmentation in vertebrates depends on sequential formation of somites based on the oscillatory dynamics of a molecular clock. \overline{z}
- \bullet This process can be recapitulated in vitro.
- \bullet In humans, the clock period is 2x longer than in the mouse. Ω ر
. k
. is
.
- The cell cycle is also longer.
- \bullet Metabolic rate density is higher in faster developing embryos. 5 7
- Metabolic activity (eg. glucose 3 consumption rate) normalised to unit 2 mass is greater in the mouse. 0 The density of mitochondria is also higher. co
ise rc
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sl \mathbf{p} $\mathbf{$ differentiation model model with $\frac{d}{dx}$ and $\frac{d}{dx}$ and $\frac{d}{dx}$ is $\frac{d}{dx}$ and $\frac{d}{dx}$ if $\frac{d}{dx}$ is $\frac{d}{dx}$ if $\frac{d}{dx}$ if $\frac{d}{dx}$ is $\frac{d}{dx}$ if $\frac{d}{dx}$ if $\frac{d}{dx}$ is $\frac{d}{dx}$ if $\frac{d}{dx}$ if $\frac{$

and short oscillatory period relative to human cells. Epidemic to human cells. Epidemic cells, epidemic cells; epidemic cells; epidemic cells; epidemic cells, epidemic cells, epidemic cells; epidemic cells; epidemic cells;

Time (h)

 \bullet Developmental rate and Metabolism

12.02 ± 0.3, *P* = 0.4634) (Extended Data Fig. 7a).

/NADH ratio measurements included both mito-

chondrial and cytoplasmic NAD(H) pools. We generated a human PSC line carrying the fluorescent sensor Peredox, which exhibits

versus 1.12 ± 0.05, *P* = 0.038) (Extended Data Fig.7b) in PSM cells treated

- The Electron Transport Chain (ETC) but not ATP synthase affects the period of the segmentation clock.
- Role of NAD+/NADH rather than ATP.
- Protein translation sets the segmentation clock period.

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• The ETC and NAD+/NADH ratio affects protein translation.

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- Developmental rate and Metabolism
- tissue specific developmental rate • Hypothesis: Tissue specific regulation of Electron Transport Chain and NAD+/NADH ratio could allow
- Mitochondria metabolism also affects the tempo of neuronal development Iwata et al., *Science* 379, 553 (2023)

M. Diaz-Cuadros. Current Opinion in Genetics & Development 86:102178 (2024)

Tuning time scales *globally*

- Metabolic scaling: Kleiber law
- Sublinear scaling of metabolic power across many adult organisms
- It is not yet clear whether this also extends to embryonic development

$\overline{}$ Tuning time scales globally d*t B* = Σc *N*c *B*c + *E*^c d*N*^c d*t*

tion energy, and *k* is Boltzmann's constant.

many different biological reactions. So the contract of the contract of the contract of the contract of the co

 t_{tot} and t_{tot} and t_{tot} The t_{t} Theorem approximate t_{t} (1000/°K)

 $Temperature^{-1}(1000\textdegree K)$ Ten

 $\begin{array}{cccc} -64 & 3.0 & 3.4 & 3.8 & 3.6 \\ 3.0 & 3.4 & 3.8 & 3.0 & 3.4 \end{array}$ Tem

. How to relate whole organism metabolic rate to biochemical reaction within cells? many different biological reactions. So to biochemical reaction within cells? te whole organism metabolic rate to biochemical reaction within cells? value of approximately –7.40 K. choosing *T0* to be the freezing point of water pends on three major variables: *Ri* ! (concenrganism metabolic rate to biochemical reaction within cells? s supply of s substrates and removal of products, s tion rates are reduced by the increasing influfow to relate whole organism metabolic ra \bullet How to relate whole organism metabolic rate to bio production *vs* maintenance. Recently, Guiot et al. (2003) *<i>t* \mathbf{M} • How to relate whole organism metabolic rate to bioche humans. They showed they showed that the growth curve derived from the g al reaction within cells? of the mass and temperature dependences and the relatively

 $B = \sum_{i}$ $R_i\,$, where R_i is the rate of energy consumption per chemical r $\,$ associated with metabolism value of analysis consumption par organism metabolic rate $\,B = \sum R_i\,$, where R_i is the rate of energy consumption per chemical reaction i \int production via the individual reactions (*i*) that e rate of energy consumption per chemic with metabolism $\frac{3}{2}$ eaction i netic energy of the system). The first two systems of the system \mathcal{L}_1 $t = \sum R_i$, where R_i is the rate of energy consumption per chemical reaction i dence. Because of allometric constraints on perthermaphiles, specialized organisms that $p = \sum_{i=1}^{n} p_i$ is that p_i is that organism metabolic rate $B = \sum_i R_i$, where R_i is the rate of energy consumption per chemical reaction i

tion rates are reduced by the increase are reduced by the interperature incremental control of the interperature influe-
Temperature influe-
 $\frac{3.8}{2}$ Temperature interperature interperature interperature interperature i

 $1 (1000)^{\circ}$ K)

range that organisms commonly operate within under natural conditions. Near 0°C, ence of catabolism. We do not consider hy-È G E

Thomas LECUIT 2024-2025 Gillooly, J. F., Brown, J. H., West, G. B., Savage, V. M. and Charnov, E. L. (2001). Science 293, 2248-2251. interaction of basic metabolic properties at cellular and whole-

 $\frac{1}{3.4}$ $\frac{1}{3.8}$ $\frac{-6 + \frac{1}{3.4}}{3.4}$ $\frac{1}{3.8}$
 $\frac{1}{3.8}$

Temperature⁻¹ (1000/°K)

 3.8 Temperature⁻¹ (1000/°K)

metabolic reactions. Because these activations. Because these activations. Because these activations are activ

average of approximately 0.6 eV (*5*, *6*), the

perature, *Tc* (often 20°C).

isms: aerobic microbes, plants, multicellular

netic energy of the system). The first two systems $\mathcal{L}_{\mathcal{A}}$

 $\ln \frac{1}{\ln \$

 Γ (1000/°K)

 p_{00} theory of the set of the set of the use fractal-like frac

dependence in terms of degrees Celsius by

Thomas LECUIT 2024-2025 Gillooly, J. F., Brow

\bullet A new definition of biological rat. *Temperature and universal biological clocks* $\mathbf{g}_{\mathbf{g}}$ • A new definition of biological rates and times.

such rates are predicted to scale as: predicted to scale as: predicted to scale as: predicted to scale as: pre

e–E/kT, which controls the temperature dependence of

temperature scaling law for *all* rates and times connected

closely fit a single universal curve (Fig. α). Only α activation energy for rate limiting chemical reactions: $E \sim 10^{-19}$ J interaction of basic metabolic properties at cellular and wholesuch rates are predicted to scale as: average activation energy for rate limiting chemical reactions: E ~ 10⁻¹⁹J

> **biological rates** $R \propto M_b^{-1/4} e^{-E/kT}$ and all times to $M_{\rm b}^{\rm 1/4}e^{\rm E/kT}$ biochemical reaction rates; here, *E* is a chemical activation biological rates $R \propto M_b^{-1/4} e^{-E/KT}$ energy biological times $t \propto M_b^{-1/4} e^{L/KT}$

applied to growth of solid tumors in \mathbf{c} humans. They showed that the growth curve derived from I_m and the same « clock » adjusted for mass (internal constraint orgy denvery) and temperature (external constraint) humans. They showed that the growth curve derived from $\mathcal{F}_{\mathcal{F}}$ gave very good fits, even though the parameters the parameters the • All animals run the same « clock » adjusted for mass (internal constraint on energy delivery) and temperature (external constraint) $\frac{1}{2}$ constraint. • All animals run the same « clock » adjusted for mass (internal constraint

t ! *M*^b

The critical points here are the separable multiplicative nature nature separable multiplicative nature nature

R ! *M*^b

1/4*e*E/kT ·. (9)

–1/4*e*–E/kT ·, (8)

amphibians, aquatic insects and zooplankton) confirm these

3.0 3.4 3.8

Temperature–1 (1000/°K)

- Time scales in biology:
	- Phenomenology of time and features: nested time scales (from molecules to evolution).
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Temporal information in biological signalling

• Encoding and decoding different temporal patterns of cellular signalling

The topology of signalling networks endow cells with capacity to compute various features of temporal information coming from the cell environment.

—*Duration* of signalling instead of level: persistence detectors (coherent FFL), adaptation (incoherent FFL) —*Frequency* of pulsatile or oscillatory signalling —*Number* of pulses

—*Phase difference* between oscillatory signals

Temporal information in biological signalling rion in piological signa \ldots \mathcal{S} \mathcal{S} of \mathbf{C} but did not completely abolish its expression (Supplementary) abolish its expression (Supplementary) Ind and consistent with observa-visual consistent with $\mathsf{Ind$ $t_{\rm f}$ tions in mouse embryos containing an un-inducible allele of P \mathbf{F} . Consistent with the model state model, probability \mathbf{F} tion in biological signa commonde greative compare \blacksquare ofcPTC1 but did not completely abolish its expression (Supplementary) its expression (Supplementary) is expressed abolish its expression (Supplementary) is expressed abolish its expression (Supplementary) is express $F_{\rm I}$ and data not shown in the shown $F_{\rm I}$ tions in mouse embryos containing an un-inducible allele of Ptc110,

 $t \rightarrow t$ or the induction of signal transmusical trans *duration o*f sidnalling throi mediate region neural plate explants (Supplementary Figs 3 and 5). dh*adabtation* whether blocking c \mathbf{r} or the induction of induction of signal transmutation of signal transmutation, such as the s ϵ duration of signalling thro mediate region neural plate explants (Supplementary Figs 3 and 5). • Encoding and decoding the *duration* of signalling through *adaptation*

Two mechanisms that could account for the adaptation of σ

to SH signalling are the loss of a factor necessary for \mathcal{A}

 $31¹²$ Time (h)¹⁰

 $\frac{10}{10}$ $\frac{10}{10}$ $\frac{01}{10}$ 31 Time (h)

 $f(z) = 18$ 24 chick neural tube (scale bar, 50 mm). B–d, Interneural plate region neural plate region neural plate region ne

 $\frac{1}{24}$

+

+

Olig2

 $-0 - 10$ \div 4 $-0 - 1$ -6.5

 $0\frac{1}{0}$ 12 18

Relative luciferase activity

 $\frac{35}{2}$

- Spatial patterning of motoneurons in the vertebrate neural tube is based on the concentration dependent activation of target genes by a Shh gradient.
- The duration of signalling at constant concentration of Shh elicits dynamic changes in target gene activation.
- Up to 12h, there is similar signalling activation irrespective of Shh concentration
- At 24h, Shh signalling is concentration dependent.
- Signalling is down regulated over time, to a greater extent as the concentration of Shh lowers.
- **• Temporal adaptation of cells to Shh.**

ventralization of the neural tube, but no ligand-independent SHH

signalling, was observed in siNNA-transferred in siNNA-transferred embryos or inter-

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Temporal information in biological signalling $\frac{1}{2}$ 50 aical i_r .
. 4 2 Culture *in vitro* defined media leni Temporal information in biologica $\frac{c}{2}$ 200 nM cyclopamine at 12 h resulted in a twofold decrease in GLI response of neural cells to SHH (Fig. 2a), even though a diminution in the set of \mathcal{L} tiporal information in biological signaling Relative luciferase activity

Int.

0

Media Cyc.

activity and a failure to induce \mathcal{L}_2 expression (Fig. 2c, e, i) with \mathcal{L}_2

ferred to media containing cyclopamine, a small-molecule antagonist

Cyc.

TRIK NVF explants and the second control of the aing and decoding the *dul* \overline{a} and \overline{b} ion of signalling through a duration of GLI activity in NVF explants alters gene expression out inhibiting OLIG2 expression. Furthermore, addition of 400 nM ng and decoding the *duration* of signall \mathbf{F} and the profile of GLI activity evoked by SHH is suggested by SHH is supported by SHH is sup g through *adaptation* mechanism acting up of SHH signalling (Supplementary Fig. 2). Gli activity and generalling S and decoding the *duration o*f sid $\overline{}$, and two following in a two-fold decrease in a two-fold decrease in $\overline{}$ nist of SMO24 (Fig. 3a and \overline{S} alling through *adaptation* construction \mathcal{G} and \mathcal{G} are was no correlations observed in treated cells, there was no correlations of \mathcal{G} ⁰ 6 12 18 • Encoding and decoding the *duration* of signalling through *adaptation*

0

• Shh signalling requires inhibition of Ptc explants treated with the indicated concentrations of SHH for the designated receptor, which releases inhibition of Smo receptor. \mathcal{L} communication neural plate \mathcal{L} $\frac{1}{2}$ expression. $\frac{1}{2}$ expression. $\frac{1}{2}$

 $\overline{ }$

- Ptc is upregulated by Shh
- Signalling adaptation (downregulation) operates upstream of Smo receptor.
- Ptc is required for differential activation 14 of target genes at 24h Relative luciferase activity
- Adaptation via an *incoherent feedforward loop*.
- b in cells exposed to lower [Shh]. • Signal output declines (adapts) faster
- The progressive adaptation of cells to .
V. Shh transforms ligand exposure into periods of increased GLI activity, that are proportional to [Shh]

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between the rate of decrease and the concentration of σ

Signal output

0 0.06 0.12 0.25

0

0.5 1.0 2.0 4.0

signalling was induced using purmorphamine, a small-molecule ago-

4

outside cilia in the form of GPCR signalling. E. Dessaud et al and J. Briscoe, *Nature*, $450:717-720$ (2007)

Temporal information in biological signalling

- Encoding and decoding the *duration* of signalling
- Use optogenetics to perturb the dynamics of Ras signalling
- Precision sensing at the single cell level: Each cell is capable of singular and stable response over hours.
- ERK signalling is a high bandwidth low pass filter.
- Differential modular decoding downstream of Ras/ERK:
	- *Fast module* faithfully transmit Ras dynamics
	- *Slow module* is a persistence detector that only conveys long lasting signals

CLASS 3: SLOW optogenetic activation CLASS 1: Not Ras/MAPK responsive

 \Box responses (e.g. pSTAT3) Toettcher JE, Weiner OD, Lim WA. Cell 155:1422-34 (2013)

sense of the ''slow'' and '' Mangan, S., and Alon, U. Structure and function of the feed- $\frac{1}{2}$ forward loop network motif. *PNAS* 100, 11980–11985 (2003) and signaling pathward pathways. Gold arrows represent

Temporal information in biological signalling Localization (a.u.) cai sigridi \sim expansion \sim expansion \sim

- \bullet Encoding and decoding *frequency modulated* signalling $\overline{}$ ϵ $\ddot{}$ 100
- In budding Yeast, the transcription factor Crz1 mediates calcium stress response.
- Crz1 coordinates transcription of ~100 genes and cell response to changes in extracellular Ca2+.
- Crz1-GFP translocates to nucleus in response to Ca²⁺.
- Crz1-GFP shows stochastic bursts of nuclear translocation which tend to cluster.

• Ca²⁺ concentration tunes the **burst frequency** but **not** $\begin{bmatrix} \circ & \circ & \circ & \circ \\ \circ & & \circ & \circ & \circ \end{bmatrix}$ the duration of Crz1-GFP nuclear translocation.

250

Cella Cella Cella Cella Cella Cella Cella Cella

140

50

300

 $L.$ Cai, CK Dalal and M. Elowitz Nature, 455:485-490 (2008) Nc $\overline{}$ L. Cai, CK Dalal and M. Elowitz Nature, 455:485-490 (2008)

Temporal information in biological signalling 40 a in hialagical cianalli $\overline{}$ n in piological signalii dynamic range, regardless of the shapes of their input functions. $t_{\rm max}$ are continuous of switching case of switching case of switching between two swit localization levels, this would cause Crz1nuc to be either high, during a $\mathsf{\omega}$ and bursts, transcription factors to modulate the expression of multiple target on in piological signal dynamic range, regardless of the shapes of their input functions. $\frac{1}{\sqrt{1-\frac{1$ ion in biological signalling and the shapes of the sha burst, or very low, between bursts, but rarely in between, resulting in a m profogical signalit amplitude- and frequency-modulation regulation systems have on $\mathbf \sigma$ bimodal Crz1nuc histogram (Fig. 4e). The expression level of each \mathbf{t} target promoter would be determined mainly by the value of its input of its input of its input of its input

0

This hypothesis can be understood by comparing the effects that $\mathcal{L}_\mathbf{t}$

This hypothesis can be understood by comparing the effects that

two hypothetical target promoters, labelled \mathcal{A} and \mathcal{A} and \mathcal{A} and \mathcal{A} and \mathcal{A}

- \bullet Encoding and decoding *frequency modulated* signalling $\ddot{\ }$ two hypothetical target promoters, labelled A and B, with different requency moquiated sign. two europeans promoters, labelled A and inequency modulated sig ϵ in the amplitude-curves). In the amplitude-curve ϵ p treguency modulated signa \mathbf{f}
- Statistical correlation between Crz1 bursts and transcriptional activation of synthetic target gene.
- Crz1 nuclear bursts increase transcription of target gene.

Models:

- Amplitude modulation:
	- $-Ca²⁺ controls Crz1 nuclear fraction (Crz1_{nuc}).$
	- Different promoters, with different *input functions* (ie. transcription rate as a function of $Crz1_{nuc}$ concentration) have different normalised expression as a function of Crz1_{nuc} & Ca²⁺ $\frac{5}{5}$ $\frac{5}{3}$
- Frequency modulation:
	- Ca2+ controls the fraction of time that Crz1 is nuclear, not the concentration.
	- Gene expression is proportional to burst frequency
	- As Ca2+ increases, transcription of both genes increases proportionately.
	- gene expression is coordinated.

Experimental validation

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The functional role of frequency modulation $\mathcal{F}_{\mathcal{A}}$

bimodal Crz1nuc histogram (Fig. 4e). The expression level of each

function near the location of the higher histogram peak, and by the

bimodal Crz1nuc histogram (Fig. 4e). The expression level of each

Normalized expression

malized expression

Fraction of time

Fraction of time

Localization

 $\sum_{i=1}^{n}$

Temporal information in biological signalling

- Frequency-Modulated ERK Signaling in Proliferation Molecular Cell • Encoding and decoding *frequency modulated* signalling
- *transient response steady* • EGF induced ERK signalling pulses

Molecular Cell

Albeck JG, Mills GB, Brugge JS. *Mol Cell* 2013;49:249–61 (2013)

between nucleus and cytoplasm upon stimulation by the inflammatory cytokine TNFa. \mathbf{Q} $\frac{1}{1}$.
t This signalling pathway oscillates with NFkB periodically shuttling i
E • NFkB signalling has also been implicated in frequency encoding. Inhibitors added $\overline{5}$ ี
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whereas early or middle genes are also expressed at lower frequencies. The expression of late genes, like the chemokine RANTES, is only induced with high fr<mark>equency p</mark>ulses of NFkB,

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K.F. Sonnen, A. Aulehla / Seminars in Cell & Developmental Biology 34 (2014) 91–98

Quantifying information encoded dynamically

- Assess the information encoded dynamically versus statically
- Study the impact of extrinsic noise and intrinsic noise.

Accurate information transmission through dynamic biochemical signaling networks

Jangir Selimkhanov, 1* Brooks Taylor, 1* Jason Yao, 2 Anna Pilko, 2 John Albeck, 3 Alexander Hoffmann,^{4,5} Lev Tsimring,^{4,6} Roy Wollman^{2,4,7}⁺

V <u>A T D R 0 A T D R 0</u>

introduction of extrinsic noise (SM section 3), $\frac{1}{2}$, $\frac{1}{2}$

Quantifying information en $\langle \rangle \langle \rangle \langle \rangle$ (WMYM I). average of a set of numbers is less than the set $\mathbb{E}[\mathbf{X}^{(i)} \mid \mathbf{X}^{(i)}]$. This less than the set which is less than . This less n
E

• Channel capacity is the maximum of mutual information between input and \Box \Box \Box \Box \Box \Box \Box $\text{output distributions} \quad C = \text{Max}\big(H(x) - H_{\text{y}}(x)\big) = \text{Max}\text{ }I(x,\text{y})$ $\frac{1}{2}$ $\frac{1}{2}$ (D), $\frac{1}{2}$ (D), point. Yaxis in (B) to (E) is the same for each pathway and is in arbitrary units in arbitrary units in arbitrary units in \mathbb{R}

Input *X* is a scalar value

Output *Y* is a static (scalar) or dynamic variable (multivariate vector)

- Channel capacity (information transmission) is higher $\frac{1}{\sqrt{2\pi}}\int_{\frac{1}{2}}^{1}$ (>1 bit) using information encoded in the dynamics Time (min)
- following will be true: • Impact of noise:

For external noise, fluctuations are constrained by the $\frac{1}{2}$ 1 $\frac{1}{2}$ $\frac{1}{2}$ internal networks that generate the dynamics such that 1. Similarly the received set of the received set of about 15 the received sector dimensions at different time points are deterministically the members of a lowcorrelated/interdependent.

independent measurements can decode well the a priori $\begin{array}{cc} \frac{2}{5} \ 1 \end{array}$ cases internal signal distribution of the set of the se
Comparation of the set internal signal of the cell.

Dynamic (but not static) information mitigates the effect of $\frac{0}{0}$ and $\frac{2}{1}$ and $\frac{3}{2}$ and $\frac{6}{3}$ or $\frac{5}{5}$ and $\frac{10}{2}$ extrinsic noise extrinsic noise.

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<u>Iy</u>

FORMATION
SOURCE TRANSMITTER

Encoding

10-1 100 100 110 110 110 111

 α

 \overline{a} overview of single-cell data analyzed in this work. (B) Examples of single-cell data analyzed in this work. (B) Examples of \overline{a}

Selimkhanov et al., *Science* 346, 1371–1373 (2014)

Static response

Decoding

 $RECEIVER$ DESTINATION intensity of Ca2+ indicator dye Fluo-4 (D), and ratio of nuclear to cytoplasmic localization of an enhanced yellow fluorescent protein (EYFP)–p65 reporter (1) MESSAGE

equal), and point is the median response in each condition. EGF, epidermal

Dynamical information synergy in biochemical signaling networks

Distributed and dynamic intracellular organization ¹*Laboratoire de Physique de l'Ecole normale sup´erieure, CNRS, PSL University, ´* **of extracellular information** *Sorbonne Universit´e, and Universit´e Paris Cit´e, Paris, France* Biological cells encode information about their environment through biochemical signaling net-

Alejandro A. Granados^{a,b,1}, Julian M. J. Pietsch^{b,c,1}, Sarah A. Cepeda-Humerez^d, Iseabail L. Farquhar^{b,c}, Gašper Tkačik^d, and Peter S. Swain^{b,c,2}

Granados et al. *PNAS* 115, 6088 (2018). dInstitute of Science and Technology Austria, 3400 Klosterneuburg, Austria

Multidimensional representation of external signal changes in a set of 10 transcription factor dynamics Multidimensional representation of external signal changes in a set of 10 transcription factor dynamics

Drugbury information synergy in ω_j hadron different through the ω_j not ω_j ochemical signaling networks; holding to low glucos Dynamical information synergy in biochemical signaling networks i synergy in biochemical signaling networks

Lauritz Hahn,¹ Aleksandra M. Walczak,^{1, *} and Thierry Mora^{1, *} **one particular stress, but do so more quickly and for a wider range** *Laboratoire de Physique de l'Ecole normal* Sorbonne Université, and Université Paris Cité, Paris, France which represents the synthesis of the synthesis of the synthesis of the synthesis of the θ ¹Laboratoire de Physique de l'École normale supérieure, CNRS, PSL University, factors (Msn2/4, Mig1/2, μ) have pulsations μ convey and process information. Recent experiments ksandra M. Walczak, \cdot and Thierry Mora \cdot . ma^{,1}
hhn,¹
Phys
ie U1
(12):
Ilati

Hahn et al. *PRL* 131(12):128401 **tion of transcription factors thus constitute a precise, distributed internal representation of extracellular change. We predict that such multidimensional representations are common in cellular** m ic innut and output out in pacture bacpac. Biological cells encode information about their environment through biochemical signaling netdynamical patterns of the signaling molecules, rather than just their instantaneous concentrations. Analytical calculation of MI for dynamic input and output. $\frac{1}{2}$ can produce distinct dynamical responses by messengerer by mes factor kappa-B (NF-B) exhibits damped oscillations in

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studies are needed to reveal in finer detail the mo-

were different in HLS with antibiotics and plated in $\mathcal{L}_{\mathcal{S}}$

 $\overline{}$, the combination of $\overline{}$, the combination, $\overline{}$

lation, either pulsatile or continuous, induces precocious gene expression

was included in DB or DB agar. The DB or DB agar.

positive edge trigger logic circuit that is frequently

Temporal information in biological signalling logical sig<mark>r</mark> alling and fig. S10 (A to C), crac− cells or GFP-GtaC/crac− cells of GFP-GtaC/crac− cells of GFP-GtaC/crac− cells of G were pulled with different concentrations of concentrations of concentrations of cAMP and a concentrations of or at different intervals starting from 2 σ

and the early stages of developmental morphogenesis are ordered morphogenesis are or

- Decoding the number of signalling pulses: counting mechanism bunting mechanism es: counting <mark>r</mark> echanism Gene Disruption } mechanism background. The disruption construct consists of and fig. S10 \sim GFP-GFP-GFP-GFP-GtaC-crac \sim GFP-GFP-GFP-GEFP-GEFP-GEFP-GEFP-G lling pulses: countin or at different intervals starting from 2 hours. For pLPBLP (33) flanked by two genomic DNA frag m echanis m
- in the social amoeba *Dictyostelium discoideum example* for a stip and **complete** α \mathcal{D} cAMP, starvation induces social aggregation and collective motility.
- This involves waves of cAMP signalling. $\overline{}$ flanked by two generations $\overline{}$
- cAMP waves and oscillatory signalling at the single cell level induce a developmental response. Continuous signalling suppresses this response. $\qquad \qquad$ \ldots at different intervals starting from 2 hours. For $\frac{1}{2}$ hours. For $\frac{1}{2}$ was included in DB or DB agar. $\mathsf{unallina}$ at the single \mathcal{L} R response table table table R \mathcal{L}_{max} recombination, \mathcal{L}_{max} where $\frac{1}{2}$ is the first and $\frac{1}{2}$
- Decoding oscillatory cAMP signalling requires oscillatory nuclear shuttling of GtaC.
- *Corresponding author. E-mail: product author. E-mail: product author. c AMP sign \blacksquare \blacksquare signalling
- cAMP pulses induce burst of target gene activation. **Example 19 and 12 4** 5 $\frac{2}{\text{Post-starvation}}$
- The *number of pulses* tunes the accumulation
of target gene of target gene 40

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al., Science 343, 1249531 (2014). DOI: 10.1126/science.1249531 100 Cai et al., Science 343, 1249531 (2014). DOI: 10.1126/science.1249531

 \bullet Pulsatile contractions are ubiquitous in animal morphogenesis

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• Pulsatility arises from fast positive feedback (autocatalytic activation of Rho1) and slow or delayed negative feedback

C. Elegans embryo, (Munro lab) actin and myosin

Temporal information in mechanics

- $\overline{}$ $\bullet~$ From pulsatile cell deformations to irreversible tissue flows
- Irreversible and planar polarised changes in the topology of cell interfaces drive cell intercalation and tissue flow in vertebrate and invertebrate embryos.
- Similar to T1 transition in foams.
- *X. laevis* \bullet This emerges from anisotropic contractile forces at cell junctions.

Temporal information in mechanics

- From pulsatile cell deformations to irreversible tissue extension
- Polarized junction remodelling is sped up by pulsatile and flow of actomyosin contractile networks.

Myosin2 E-cadherin

• How do pulses of actomyosin contraction drive irreversible deformations? (ie. instead of pulsatile and reversible deformations)

M. Rauzi et al. *Nature*. **468**(7327):1110-4 (2010) S in elongation and my open activity results in C Collinet C, Rauzi M, Lenne PF, Lecuit T. *NCB* 17(10):1247-58 (2015)

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labeled in \mathbb{R} is labeled in cyan. (D) is labeled in cyan. (D) \mathbb{R} *The Restless Cell: Continuum Theories of Living Matter*. C. Hueschen and R. Phillips. (2024). *PUP*.

Temporal information in mechanics

- **•** From pulsatile cell deformations to irreversible tissue extension Computing different mechanical time scales determines the reversibility of deformation
- Time scale of deformation: period of actomyosin pulses ~120s.
- Dissipation time scale (emerging from turnover rate of actin, cross linkers, myosin2, E-cadherin complex binding kinetics etc) dictates junctions dynamics.
- If time scale of deformation shorter than dissipation time scale, deformation is reversible (~elastic behaviour). If longer, then deformations are irreversible.

Clément, R, Dehapiot, B, Collinet, C, Lecuit, T, Lenne, PF (2017), Curr Biol 27 3132-3142 e4. (B) Length of a cell-cell-cell-cell-cell-cell-cell junction as its length changes from an initial reference \mathbf{r} The Restless Cell: Continuum Theories of Living Matter, C. Hueschen and R. Phillips. (2024). PUP \overline{J} than the initial length is a signature of viscous relaxation. (D) P The Restless Cell: Continuum Theories of Living Matter. C. Hueschen and R. Phillips. (2024). PUP 44

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- Time scales in biology:
	- Phenomenology of time and features: nested time scales (from molecules to evolution).
	- Cycles and linear time (counting versus accumulating).
- How is time encoded: defining time scales locally and globally.

• How is temporal information decoded?

- Signalling information: information encoded in dynamics.
- Mechanical temporal information in morphogenesis.
- Segmentation clock: decoding time to encode space

Temporal information in morphogenesis

Case study: the segmentation clock

Olivier Pourquié (Harvard Medical School)

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When theory precedes experiments

A Clock and Wavefront Model for Control of the Number **of Repeated Structures during Animal Morphogenesis** *Institute of Mathematics, University of Warwick,*

J. COOKET *National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, England (Reference 2015) and <i>Alexand and <i>Ridgeway, Mill Hill, London NW7 1AA, England* AND *Coventry, Warwick, England* \triangle MDs current models for morphogenesis of repeated patterns, such as \triangle repeated pattern

explain the observed degree of constants *Institute of Mathematics, University of Warwick, Properties (i.e. number of warmick, i.e. number of cells per somite) Coventry, Warwick, England* **must adjust to the overall size of individual embryos, and one which co**number of somites in individuals of a given species. This precision requires \mathbf{r}_1 and \mathbf{r}_2 and \mathbf{r}_3 and \mathbf{r}_4 and \mathbf{r}_5 and \mathbf{r}_6 and \mathbf{r}_7 and \mathbf{r}_8 and \mathbf{r}_9 and \mathbf{r}_9 and $\mathbf{$

J. theor. Biol. (1976) 58, 455-476 \cdots is also compatible with experimental observations such as the sequence such as the sequence such as the sequence of \cdots

a mechanism where α mechanism where α is somitted (i.e. number of cells per somite) π creasing evidence for widespread existence of cellular biorhythms. The

model involves an interacting "clock" and "wavefront". The clock is ordinates an indicating clock and wavefully find clock is a smooth cellular oscillator, for which cells throughout the embryo are assumed to be phase-linked. The wavefront is a front of rapid cell change
moving slowly down the long axis of the embryo: cells enter a phase of moving slowly down the long axis of the embryo; cells enter a phase of rapid alteration in locombtory and/or adhesive properties at successively
https://www.combinal.com/organisms.html and the in-the in later times according to anterior-posterior body position. In the model, the smooth intracellular oscillator itself interacts with the possibility
of the rapid primery change at its transmission within celle that of the rapid primary change or its transmission within cells, thereby gating rhythmically the slow progress of the wavefront. Cells thus enter their rapid change of properties in a succession of separate populations,
creating the pattern. creating the pattern. The combton in locombtow and or adhesively properties at successively at successively and later times according to anterior-posterior body position. In the model,

« L'essence de la théorie des catastrophes c'est de ramener les discontinuités apparentes à la manifestation d'une évolution lente sous-jacente » René Thom.

- A model inspired by the « catastrophe theory » (R. Thom)
- A model for scaling of patterns (Turing model: wavelength is not dependent on system size)
- « Implausibility » of positional information based model: too many discrete values to respond to…
- Key features of Clock and Wavefront model: **o**
	- Wave front of *sudden* cell changes (discontinuity)
	- Clock: smooth oscillation of phase-linked cells Oscillator
	- **Slow posterior movement** of the wave front

The segmentation clock -discovery

- \bullet Formation of somites is associated with cyclic gene expression
- The mouse segmentation gene *hairy* shows very dynamic expression patterns even within the 90 min required to produce a new somite.
- Evidence of cyclic gene expression (T=90min): —split embryo in 2 halves, fix the left part immediately and let the right part develop for increasing amount of time, then fix.

—After 30 min the hairy stripe has shifted to a more anterior region

—After 90 min, the expression pattern becomes symmetric but a new segmented somite formed.

- The wave stops and is associated with the formation of a new somite the state of the state • Associated with a kinematic wave towards the anterior:
- it does not depend on a signal propagating from posterior to anterior the sominal propagation of vertebrais or The cyclic gene expression is autonomous:

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Palmeirim, I., Henrique, D., Ish-Horowicz, D., and Pourquié, O. Cell 91, drives periodic inhibition of Notch signaling necessary for the rhythmic $639-648(1997)$ \overline{A} $N = \frac{1}{\sqrt{2}}$ in the rhythmic production of embryformation. This appears unlikely because previous work occurs independently of cell movement. It also confirms \mathbf{r} stricted (Tam and Beddington, 1986; Stern et al., 1988). the mouse and of tracer injection into single PSM cells, \mathcal{L} and the last few somittally divided divided divided divided into two halves after Di

- Presomitic en de la provincia de la provi
De la provincia de la provinci • 3 signalling pathways show oscillatory signalling dynamics - mouse/chicken
- The Notch, Wnt and FGF signalling pathways show cyclic expression
- The Notch and FGF pathways are coupled
- Oscillatory dynamics of these pathways is associated with negative feedback regulation with a time delay

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Figure 2 | **The clock-and-wavefront model. a** | The segmentation clock. The segmentation clock comprises a set of

AXIN2

<u>Reviews and the second proposition</u>

NRARP

DUSP6,

bession and the emergence of a • Direct visualisation of Lfng-Venus oscillations in living mouse embryos mana dia confirms the existence of cyclic gene expression and the emergence of a kinematic wave across the PSM associated with somite formation

Nature 493, 101–105 (2012).

Lauschke, V. M., Tsiairis, C. D., Francois, P. & Aulehla, A. Hubaud and Pourquié. *Nature Rev Mol. Cell Biol.* 15: 709-721 (2014)

position

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REVIEWS AND COMPANY $CS₁$ AXIN2 :bra \bullet $\,$ 3 signalling pathways show oscillatory signalling dynamics - zebrafish

- A segmentation clock is also associated with segmentation of the mesoderm in zebrafish embryos.
- Notch and Fgf signalling are oscillatory

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- Oscillations are believed to require a Her1 transcriptional core network.
- Direct observation of Her1YFP expression dynamics reveals synchronous oscillations

50

Time (one clock period)

50

70

A''

30

50

30

60 120

HES7

 \mathcal{L} can travelling wave that progressively sharpens as it moves as it moves anteriorly along anteriorly along anteriorly along \mathcal{L}

Tg

Oscillations in isolated cells in vitro

- Dissociated cells from the PSM are oscillatory in vitro
- Oscillations are believed to require a Her1 transcriptional core network.
- Oscillations in dissociated cells are not regular in period and amplitude.

A.B. Webb et al. and A.C. Oates *eLife* 2016;5:e08438.

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Yap-dependent mechanical signal acts as a control parameter for single cell oscillations

Hubaud et al, Mahadevan, Pourquié. *Cell* 2017 171, 668–682

www.wood her1 gene

 \rightarrow V _{*MMM}</sub>* m *RNA*</sub>

 $f(p) = \frac{k}{1 + p^2/p_0}$

delay (T_{m1})

The Zebrafish Somitogenesis Oscillator

• Facts:

1401

The Zebrafish Somitogenesis Oscillator

- signalling. • Oscillations are independent of Notch
	- Oscillations are observed in isolated cells.
	- Oscillations are believed to require a Her1 transcriptional core network.
	- shown explicitly. • Model of single cell oscillator based on delayed auto inhibition (negative feedback). J. Lewis.
	- The delay may emerge from production of the Her1 mRNA and protein.
	- The dynamics of mRNA m(t) depends on protein concentration at t-delay.
	- s_{max} is the are easily solved numerically solved numerically solved numerically solved numerically solved numerical s_{max} called the process. beyond a critical value p₀ (for negative FB to manifest). Or else, damped oscillations due to degradation. The discussion of the discuss assumed that which represents the action of the action of the intervals the intervals of the interv \bullet Sustained oscillations require production rate of protein **The Period of Oscillation Is Determined**

Lewis, J. *Curr. Biol.* 13, 1398–1408 (2003).

Oscillator coupling during segmentation **Single-Cell Imaging of Segmentary Coupling ouring segment *** *phase* 1 ***** upling during segmentation

S-2 S0S-1 S1 S2

- *Her1-Venus signal* • Single cell oscillations are synchronous in the presomitic mesoderm.
- Emergence of a phase gradient along the PSM.
- \bullet In conditions that reduce Notch signalling, \overline{M} \overline{L} $\overline{$ *time (min)* cells still oscillate in the PSM, but cells are out of phase.
- 50 oscillations but for coupling of individual • Notch is not required for single cell oscillators.

B J Jiang, Y. J. et al. and J. Lewis. Notch signalling and the synchronization of the somite segmentation clock. *Nature* 408, 475–479 (2000).

0

PSM Cells

30

0 π Most Dividend Communisties 1 and β American Disruptions in C_2U 22, 005, 1005 (20) E. Delaune et al, and S. Amacher. *Developmental Cell* 23, 995–1005 (2012) A small proportion of desynchronized (antiphase) cells are

Oscillator coupling during segmentation

- Third, when protein synthesis is attenuated severely \bullet $\;\;$ Notch is not required for single cell oscillations but shows only damped oscillation, the noisy system does for coupling of individual oscillators.
- \bullet Model of coupled oscillators: J. Lewis
- σ regularity and high amplitude separated by intervals and high amplitude separated by inter • The synchronisation of 2 neighbouring cells require smaller, international stochastic effects, the behavior approximation \mathcal{L} **a specific time delay.** This delay is associated with Far from disrupting oscillation, noise helps it to occur. production of eg. Delta ligand mRNA, protein, stochastic effects become, until for *k*off ! 10 min"¹ export to the cell surface, activation of Notch in neighbouring cell.
- oscillations that continue with substantial and continue with substantial and substantial amplitude but a subs \bullet Activation of Her1 depends on delayed α scillator) and on Notch pathway in the Notch pathway α negative FB (intrinsic oscillator) and on Notch **positive input via coupling.** Depending on the spond to the latter case, with oscillation continuing noislength of the delayed coupling $T_{N_{\ell}}$ between neighbors is lost in lost in the index of \mathcal{L} synchronisation may or may not be possible.

 \mathbf{v} the molecular circuitry: the two cells are assumed to contain \mathbf{v} *Jiang, Y. J. et al. and J. Lewis. <i>Nature* 408, 475–479 (2000) Lewis, J. *Curr. Biol.* 13, 1398–1408 (2003)

her1/her7 **Oscillations in Adjacent Cells** periods. The oscillators are coupled via Notch signaling. See earlier also: Winfree AT. *J Theor Biol* ;16:15–42 (1967) $2024 - 2025$
54

$\frac{3}{4}$ Current Biology Vol 20 No 14 100 min Oscillator coupling during segements Delta-Notch Coupling Regulates Segmentation Period 1245 anterior to top. The scale bar represents 50 mm. DAPT ligands tions affecting thisVERTICAL PROPERTY OF THE REAL PROPERTY OF THE PROPERTY thearegeneschangeschange of the state of $\frac{2}{3}$ \mathbf{I} describing(B)thenization $rac{2}{3}$ (A)Figure $\mathcal{C}(\mathcal{C})$ time versus some versus some versus some plot for $\mathcal{C}(\mathcal{C})$. Linear fits of $\mathcal{C}(\mathcal{C})$ Snapshot a \mathcal{A} Delayedaddition,**A B** delay. \mathbf{z} and \mathbf{z} and \mathbf{z} and \mathbf{w} and \mathbf{w} . frequency and provided a control of r $\overline{}$ p_{max} $\sum_{i=1}^n$ del ka inand Theoreticalin $\overline{2}$ distribution of $\overline{2}$ embry on $\frac{6}{4}$
0 min fromcouplingperiod in the control of $\frac{6}{4}$ \sim 3, and (C) which (B) and (C) were taken (n \sim 12, and **A B** the component of the compo
the component of the comp \geq the $\overline{0}$ cells. Delta is the ligand for the Notch receptor, which profiles and profiles. coupling 140 $\frac{50 \text{ m}}{2}$ lir *D-N mutant* Cell A *Wild-type* .
C period. The \mathbb{R} ed
ang $\sum_{i=1}^{n}$ coupled to the coupled lel
:01 delayed \sim .
ح α ر د average**C D** ζ (E) Box-and-whisker plots of somitogenesis period: coupling coupling delayed pli loss of \overline{a} coupling $\frac{1}{2}$ \mathfrak{g} \mathcal{E}_ζ $R = 37.5$ total embryos, more than six independent trials $R = 37.5$ independent transitions. 17, $\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$ prediction of the context o \mathcal{C} Mib $p = \frac{p}{2}$ $\overline{\mathcal{L}}$ altereded
Pr percent oscillators
a
co $\overline{}$ $\ddot{}$ coupled the coupled of period instantaneous lators and nof/raldh2, for which n R 16 total embryos, two inde-Delta in
I stantaneo
coupling pattern $p_{\rm s}$ per experimental condition. Het denotes per experimental condition. Het denotes $p_{\rm s}$ 120 |
|
| autonomousheterozygote. *** p = 0.001, Student's t test. Figures S1, Student's t test. Figures S1, Student's traditional for1
} **Notch** $\overline{}$ Delta-Notchperiod.and S2 show that general developmental rate is unaf-Movie $\frac{e}{x}$ the \blacksquare DAPT fected in the conditions with slower period. The central wavelength accountingparti Period 7 senegotibox covers the interpretation range with the mean individual range $\frac{1}{T_{A \text{ min}}}$ $\frac{1}{T_C} = \frac{1}{T_A}$ $\frac{1}{T_{A \text{ max}}}$ segmentationio
I of $\overline{}$ \overline{a} cated by the small square and the median by the lines. $\overline{}$ 22 somites oscillators in predicts and $\frac{1}{T_C}$ $\frac{1}{T_{A min}}$ $\frac{1}{T_C} = \frac{1}{T_A}$ $W_1 = \frac{1}{2}$, $W_2 = \frac{1}{2}$, $W_3 = \frac{1}{2}$ wt *mib* intercellular
J $\dot{\tau}$ $T_{A max}$.
In percentiles, and small bars depict the most extreme of α Cell B different ϵ corresponding to the corresponding of the correspondin solutionvalues. $\begin{picture}(18,14) \put(0,0){\line(1,0){10}} \put(10,0){\line(1,0){10}} \put(10,0){\line(1$ results*TA1 TA3* uncoupled wt *mib* $\bigcup_{\mathcal{T}_A}$ instantaneousinstalle in de arrest front coupling; to)
C frontonline). $\overline{}$ the*TA2* v nan $\frac{9}{2}10$ there 160 ** withincreased the that Shorteningdelayedg no fin (raldh2) mutants, which affect the control of the $\overline{1}$ 140 $\overline{}$ was $\ddot{}$ m \overline{a} inhibitorFGF, Wilson and RA pathways, respectively, respectivel \mathbf{I} *D-N mutant* ** ** ** $\overline{}$ loss of and detected no change (Figure 2E). Although i
I \mathbb{I} $\overline{}$ in coupling not excluding roles for the these pathways in ntrol period mib i
I $\overline{}$ somites arrest from the some presentation of the some presentation of the some presentation % control period \parallel period setting, these results indicates control peric well \overline{I} increased somitogenesis period is not protocolا and 2E),120 in 1911.
Nati attenuatesFigure 1. Theoretical Description of Collective and Spatial Properties of Oscillators in the Segmentation Clock a general consequence of defective intercelas \vert \mathbf{r} presomitic mesoderm (A) Delayed coupling can alter collective period. Uncoupled oscillators with random phase and unimodal symmetric distribution of autonomous periods TA1, \overline{R} and \overline{R} signalize pathways. We conclude \overline{R} embryosas 100 1
أ $\overline{}$ Ta \mathcal{A} instantaneous weak coupling (green arrows) results in a collective period TC \mathcal{A} $\frac{1}{2}$ that Delta-Notch coupling regulates somito- $\overline{\mathcal{C}}$ thel
.1 thenization by delayed coupling (red arrows) can result in TC different to TA. Shortening or lengthening of TC relative to TA is possible depending on the value of |
ה \sim togenesis period. $\overline{1}$ $\left\lceil \frac{1}{2} \right\rceil$ $\overline{\mathbf{3}}$ $\overline{}$ the delay. \mathbf{r} result $\begin{bmatrix} \text{B} & \text{B} & \text{B} \end{bmatrix}$ theory describes the segmentation clock as an array of coupled phase oscillators $\begin{bmatrix} 20 & \text{B} & \text{C} & \text{D} & \$ $\frac{1}{1}$ \overline{a} treated formed $\overline{\mathsf{I}}$ describing embryonic elongation with velocity v, comoving with a front that arrests oscillations on the anterior side of the PSM; (2) local coupling of oscil-6 \mathbf{L} Segment Length Is Increased by Reduction in and type signals lators, with strength 3, accounting for Delta-Notch intercellular coupling; (3) a time delay t in coupling, due to synthesis and trafficking of molecules; *mib* 3%of Delta-Notch Coupling (4) a frequency profile uⁱ $\frac{1}{\infty}$ (t) across the PSM accounting for the slowing of cellular oscillators as they approach the arrest front, characterized by decay phenotype,**Mi**b
m_i m^{*m*} DAPTSegment length in the elongating embryo is $\frac{1}{2}$ length r and the period of the fastest autonomous oscillators TA, located in the posterior PSM. with**high-precise** somitogenesisFight $\frac{1}{2}$ los wt.1a 80

a independent of the CAST of the Miller of the Miller of the Miller $\frac{1}{3}$ thought to be determined by interaction of $80 - 365$ ick
J wt tap du_l concentrations $4\pi\frac{1}{2}$ some some some confidence synchrony, \mathcal{Q} and the total segment length due to the to t

- Model of coupled oscillators: F. Jülicher.
- Delayed coupling is expected to modify the collective period of oscillation.

Experimental observation of increased period in conditions where Notch signalling is reduced consistent with the model.

L. Herrgen et al., F. Jülicher and A. Oates *Current Biology* 20, 1244–1253 (2010)

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\blacksquare From *time* encoding to *space* decoding

A Clock and Wavefront Model for Control of the Number of Repeated Structures during Animal Morphogenesis *Institute of Mathematics, University of Warwick,*

National Institute for Medical Research,

J. COOKEr *National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, England (Reference) and <i>Ridgeway, Mill Hill, London NW7 1AA, England Coventry, Warwick, England* Λ MDs current models for morphogenesis of Λ

AND vertebrate somites, cannot explain the observed degree of constancy for the

E. C. ZEEMAN *Institute of Mathematics, University of Warwick, Properties (i.e. number of warmick, i.e. number of cells per somite) Coventry, Warwick, England* **must adjust to the overall size of individual embryos, and one which co**number of somites in individuals of a given species. This precision requires \mathbf{r}_1 and \mathbf{r}_2 and \mathbf{r}_3 and \mathbf{r}_4 and \mathbf{r}_5 and \mathbf{r}_6 and \mathbf{r}_7 and \mathbf{r}_8 and \mathbf{r}_9 and \mathbf{r}_9 and $\mathbf{$

J. theor. Biol. (1976) **58,** 455-476 \cdots is also compatible with experimental observations such as the sequence such as the sequence such as the sequence of \cdots

a mechanism where α mechanism where α is somitted (i.e. number of cells per somite) π creasing evidence for widespread existence of cellular biorhythms. The

model involves an interacting "clock" and "wavefront". The clock is ordinates an indiadring dock and wavenum in the dock is a smooth cellular oscillator, for which cells throughout the embryo are assumed to be phase-linked. The wavefront is a front of rapid cell change
moving slowly down the long axis of the embryo: cells enter a phase of moving slowly down the long axis of the embryo; cells enter a phase of rapid alteration in locombtory and/or adhesive properties at successively
https://www.combinal.com/organisms.html and animal model and animal model and animal model of the intervals of the intervals of the intervals of the later times according to anterior-posterior body position. In the model, the smooth intracellular oscillator itself interacts with the possibility
of the rapid primary change or its transmission within cells, thereby of the rapid primary change or its transmission within cells, thereby gating rhythmically the slow progress of the wavefront. Cells thus enter $\left\{\right\}$ their rapid change of properties in a succession of separate populations,
creating the pattern. creating the pattern. The combton in locombtow and or adhesively properties at successively at successively and later times according to anterior-posterior body position. In the model,

• Key features

- Wave front of *sudden* cell changes (discontinuity)
- Clock: smooth oscillation of phase-linked cells
- Slow posterior movement of the wave front **o**

From *time* encoding to space decoding o *space* decodino: parne activities \mathbf{I} : \mathbf{A}

• The clock and wave front model - the principle

Time (one clock period)

Time (one clock period)

- Antero-posterior gradient of FGF protein.
- As the PSM grows, it shifts towards the posterior.
- This leads to the posterior shift of the FGF scale invariant gradient.
- The clock (orange) and wavefront (blue line) are independent entities that determine the segments.
- Only one phase of the clock (orange) triggers segment determination (pink).
- The position of the wavefront determines the position of the posterior boundary of a newly determined segment.

determination front position moves posteriorly with elongation of the body axis. **c** | Clock topologies. Oscillations are

Hubaud and Pourquié. Nature Rev Mol. Cell Biol. 15: 709-721 (2014) $m_{\rm T}$ and fibroblast growth factor (FGF). Binding of the WNT ligand to its receptor results in $r_{\rm T}$ Hubaud and Pourquié. *Nature Rev Mol. Cell Biol.* 15: 709-721 (2014)

Her7–Hes6

Her7–Hes6

Hes6–Hes6,

Hes6–Hes6,

From *time* encoding to space decoding

From time encoding to space decoding odicato da controlled and somita in somi oscillator—the segmentation clock—which drives the periodic $U_{\rm{max}}$ and $U_{\rm{max}}$ is the myod (Supplementary Fig. 1) were closed and their contract their contract their contract to the interaction of the $\lim_{n \to \infty}$ SPRY2) were expressed in domains comparable to those observed in $\mathcal{F}_{\mathcal{F}}$ or amni $\mathcal{F}_{\mathcal{F}}$ or amni $\mathcal{F}_{\mathcal{F}}$, supporting the existence of ex genesis in all four species (support that similar processes (scaled that similar processes (scaled that simila proportional controvering to space decounty elongation to charged decoding pace decounig b cd *FGF8 SPRY2 DUSP6*

pathways in the PSM1,2,4, \sim The periodic signal of the segmentation \sim

- Variations in segment number : snakes is in Segment number . Sid \mathcal{L} in concert with axis elongation \mathcal{L} $\mathcal{L}_{\mathcal{A}}$ with the dynamics of this gradient in snake with that in snake with that in snake with that in the other species. As a readout for the posterior gradients, we used the posterior gradients, we used the pos \bullet Variations in seqment number : snakes number : snakes. No dynamic exp DUSP6 (ref. 4) or AXIN2 (ref. 7) was evident in the snake PSM $\texttt{I} \texttt{m} \texttt{p} \texttt{e} \texttt{r}$: snakes
- Snakes have a large number of vertebrae (315 in corn snakes). a
- The segmentation clock in snakes is presumably the same as in chick embryos… $\mathop{\mathsf{ame}}\nolimits$ as in chick $\mathop{\mathsf{embryos}}\nolimits$ *...*
	- clock genes: Notch, LFng.
	- wave front: FGF8, Wnt3A that re front

between corn snake and the other species examined.

amniote segmentation clock. No dynamic expression of SPRY2,

a Wint/FGF posterior gradient opposing an anterior $\mathcal{O}_\mathcal{F}$ positive and anterior retinoic action $\mathcal{F}_\mathcal{F}$

Gomez C, et al. J. Lewis and O. Pourquié, Nature, 454(720) ϵ in chicken or ϵ is chicken or line of ϵ . Gomez C, et al. J. Lewis and O. Pourquié, *Nature*, $454(7202):335-9$ (2008). relative to the development rate, the clock ticks much faster in snake

Figure 2 [|] The corn snake determination front and segmentation clock.

From *time* encoding to *space* decoding c Percentage of total somite number ICCO'

 \bullet Variations in segment number : computing the difference between clock and developmental time scales. 10 puting the differen 30

40

- The clock period in corn snake embryos is 90 min, similar to chick and mouse embryos.
- The growth of the PSM is slower in snakes (3-3.5x) but lasts longer.
- Thus, the posterior movement of the wavefront is presumably slower than in chick.
- The relative time constant of the clock with respect to cell/tissue growth accounts for smaller size of somites in snakes over the same embryonic time window.
- Since development lasts longer, the number of segments is much larger.

Gomez C, et al. J. Lewis and O. Pourquié, *Nature*, $454(7202):335-9$ (2008).

6. Sawada, A. et al. Fgf/MAPK signalling is a crucial positional cue in somite

 P —
as
II Modulation of Phase Shift between Wnt and Notch signaling oscillations controls segmentation

 $\frac{1}{\sqrt{2}}$

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next anterior boundary and the control of the cont
The control of the c

From *time* encoding to *space* decoding

Phase-shift model of segmentation

- Ex vivo cultured mouse PSM cells produce kinematic waves and segments.
- Both Notch and Wnt oscillate and produce kinematic waves.
- Relative phase-shift between Wnt and Notch signaling oscillations is changing along the PSM length.

Sonnen et al. and A. Aulehla, *Cell* 172, 1079–1090 (2018)

 $\overline{}$

 $\bigcap_{n=1}^{\infty}$ $\bigcap_{n=1}^{\infty}$

 Ω

D \overline{D}

1

DMSO

Time (min)

(A–C) or simultaneous pulses (E–G) of 2 mM DAPT

2 na matataga pulses na matataga p
2 na matataga pulses na matataga p

From *time* encoding to space decoding _{ace d} The *Mesp2* interface sets ϵ m *time* enc alternating pulses *ace* decoum

Mesp2 positions the Phase-shift model of segmentation \overline{a}

1

• Using microfluidic, entrainment of Wnt and Notch oscillations by drugs that activate Wnt (Chiron) or inhibit Notch (DAPT). FGF–pERK FGF–pERK

T<mark>axaan dagaal dagaal</mark>

- **•** Cross-entrainment between two oscillators. **Phase-shift model**
	- resulted in anti-phase Wnt and Notch signalling
……………………………………………………………………………………… oscillations in anterior PSM, and led to • Entraining the endogenous rhythms with simultaneous pulses of Chiron and DAPT, segmentation defects.
	- $\rm \, oscillations$ is critical for segmentation. $\rm \, Time$ • Relative timing of Wnt and Notch signaling

 Λ Autoble C_2H 172, 1070, 1000 (2019) 11.1 Mucha, CC*u* 172, 1072 1090 (2010). μ , μ , μ , μ , μ , σ , μ , σ , Sonnen et al. and A. Aulehla, *Cell* 172, 1079–1090 (2018)

and its downstream target Ripply2 (Morimoto et al., 2007) were

FGF–pERK defines

From *time* encoding to *space* decoding F_{max} time of a new diner to eneceded decoding ment space de mandat space de mandat de
2011 : le posse de mandat de m 40 40 0 $\frac{1}{2}$ ld
|
|

• Scaling of segmentation based on phase-gradient encoding interconnected by the following relationship: v~LQ=Lt parameter plays during the scaling process, we performed temperaturetion based on phase gradient one mascu on phase gradient

*R*2 = 0.89737 *R*2 = 0.63104

• Ex vivo cultured mouse PSM cells the method of model is the matrix of the method segment size (Fig. 3b, c). The segment size of the segment size parameters are parameters and segment size \sim 50 μ segment size \sim 50 μ segment size \sim 50 μ se segments. There is a phase shift between mete is a phase sime serveen.
 neighbouring cells and a phase
 $\begin{array}{ccc}\n\text{velocity} & \text{clock} & \text{phase} \\
\text{of wave} & \text{frequency} & \text{gradient}\n\end{array}$ gradient across the PSM. velocity (v) and the slope of the phase-gradient (LQ=Lx), that scale segments.
 $\begin{aligned} v &= \frac{\partial \varphi}{\partial t} \Big|_{\partial \varphi} \Big|_{\partial x} \end{aligned}$ Scaling mechanism: **In all a change in zebrafish it has been previously shown that a change in a chang** • As the PSM length shortens, segments $\frac{1}{2}$ in the mail of the mouse matrix $\frac{1}{2}$ sizes $\frac{1}{2}$ and $\frac{1}{2}$ • This indicates scaling of segments to $\frac{2\pi \text{ rad}}{3}$ indicates scaling of segments to • The velocity of the wave also scales with $\frac{1}{\sqrt{1-\frac{1}{n}}}$ $\frac{1}{\sqrt{1-\frac{1}{n}}}$ $\frac{1}{\sqrt{1-\frac{1}{n}}}$ tical correlation to many correlation to many correlation of the state of the state which is a second to the state of • The amplitude of the phase gradient is 2π irrespective of tissue size. $\qquad \qquad \qquad \blacksquare$ • Therefore, the phase gradient scales with tissue size. shift assays. In zebrafish it has been previously shown that a change in $t_{\rm eff}$ in fluences the rate of segmentation with α $\frac{1}{\sqrt{2}}$ $\frac{1}{\sqrt{2}}$ vivo cell culture model; segmentation proceeded more slowly at 33 uC, $\frac{1}{2}$ 60 and followed the identity $\frac{1}{2}$ $\frac{1}{12}$ 40. $\sum_{i=1}^{\infty}$ $R^2 = 0.89737$ lation dynamics in the temperature-shift assay. First, we found that the overall oscillation period of the state of 400 mPSM length (μm) $\frac{1000 - 200}{\pi}$ $(3, 3)$ $\begin{bmatrix} 5 \ 1 \end{bmatrix}$. In addition, we found that although the phase-wave velocity $\begin{bmatrix} 1 \ 1 \end{bmatrix}$ $\left| \begin{array}{ccc} \varepsilon & \varepsilon & \varepsilon \\ \varepsilon & \varepsilon & \varepsilon \end{array} \right|$ $\frac{d}{dt}$. Therefore, phase-wave velocity $\frac{d}{dt}$. Therefore, phase-wave velocity $\frac{d}{dt}$. $\mathbb{E}_{\mathbb{E}_{\mathbb{E}_{\mathbb{E}}}[\mathbb{E}_{\mathbb{E}_{\mathbb{E}}}[\mathbb{E}_{\mathbb{E}_{\mathbb{E}}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{E}_{\mathbb{E}}[\mathbb{$ /elocity (um min⁻¹) $\begin{array}{c|c|c|c|c|c} \hline \multicolumn{1}{c|}{\textbf{0}} & \multicolumn{1}{c|}{\textbf$ $\frac{200}{\pi}$ root $\frac{200}{\pi}$ uC $\frac{330}{\pi}$. $\frac{1}{2\pi}$ $\frac{1}{2}$ $\frac{d}{dx}$ 2π . $\frac{1}{2}$ segment size definition is encoded at the level of phase differences differences of phase differences $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ order, that is, a phase gradient, can provide spatial information for α 0 100 200 0 100 200 300 400 1 phase by the phase velocity clo *R2* R *R2 10.600 R2* R *R2 10.600* R of wave frequency 0π rad $2π$ rad 1 mPSM length 0π rad 2π rad mPSM length $v = \frac{\partial \varphi}{\partial t} \Big|_{\partial \varphi} \frac{\partial x}{\partial x}$
velocity clock phase
of wave frequency gradient e m α –c, e–g, Experiments were performed at α –c) or 37.3 uC (a–c) or 33.3 uC (a–c) of wave clock **gradient** become smaller. tissue size PSM length. Phase gradient \widehat{q} ed) 2π
application
design 3π 1π $0\frac{1}{0}$ 1 2 3 0 100 200 300 400 Velocity (μm min–1) $0 +$ 20 40 60 0 100 200 300 400 Segment width (μm) Segment width (um) | $R^2 = 0.89737$ $R^2 = 0.5861$ $\mathcal{L} = \mathcal{L} \left(\mathcal{L} \right)$ and $\mathcal{L} \left(\mathcal{L} \right)$ and $\mathcal{L} \left(\mathcal{L} \right)$ $R^2 = 0.5861$

0 100 200 300 400

mPSM length (μm)

0 100 200 300 400 mPSM length (μm) $\frac{52}{53}$ e \overline{H} and morphological and morphological and morphological and morphological analysis of the experimental culture model using in situ hybridization after $\frac{18}{10}$ target gene T (a) and the Fgf-target gene Dusp4 (b) are expressed centrally. c, Mesp2, indicative for the onset of mesoderm differentiation, is activated in the periphery of the cell culture assay. d, Bright-field image indicating segment formation. e, Magnification of region indicated by the red box in d, showing sharp boundaries between segments. S1–S3 denote segments in the order of formation. F, Scheme illustration. F, Scheme illustration of the embryonic original reorganization of the embr anterior–posterior axis in a central–peripheral direction. When \mathcal{P}_max genes are upregulated centrally and downregulated peripherally, the inverse is true for the retinoic acid (RA) target gene Aldh1a2 (Supplementary Fig. 6). LPSM $10₂$ $10₃$ $10₃$ ©2013 **Macmillan Publishers Limited. All rights reserved**

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Lauschke, V. M., Tsiairis, C. D., Francois, P. & Aulehla, A. Nature 493, 101-105 (2012). length of mPSM in which they occur (P , 0.0001, n 5 42 waves; n 5 7

m PSN length (um)

- Time can be *encoded* locally and globally in variety of ways:
	- Chemical systems (diffusion, trigger wave), mechanical systems (advection, material properties)
	- o Importance of energetics/metabolism.
- How is temporal information *decoded*?
	- Signalling: information decoded in *dynamics* of signal.
		- signal duration
		- signal frequency
		- signal burst counts etc
	- Mechanical deformation in morphogenesis: information decoded through *comparison of different time scales*.
		- eg. deformation and viscous relaxation, or growth and relaxation.
	- Developmental patterning
		- The segmentation clock: decoding time to encode space
		- Neuronal identity: temporal encoding of transcription factor series.

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