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**A mathematical theory proposed by Alan Turing in 1952 can explain the formation of fingers**

**Jul 31, 2014**



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Like strips and dots in many animals, fingers can be considered as patterns that can be predicted by the Turing model. Credit: Luciano Marcon and Jelena Raspopovic

Alan Turing, the British mathematician (1912-1954), is famous for a number of breakthroughs, which altered the course of the 20th century. In 1936 he published a paper, which laid the foundation of computer science, providing the first formal concept of a computer algorithm. He next played a pivotal role in the Second World War, designing the machines which cracked the German military codes, enabling the Allies to defeat the Nazis in several crucial battles. And in the late 1940's he turned his attention to artificial intelligence and proposed a challenge, now called the Turing test, which is still important to the field today.

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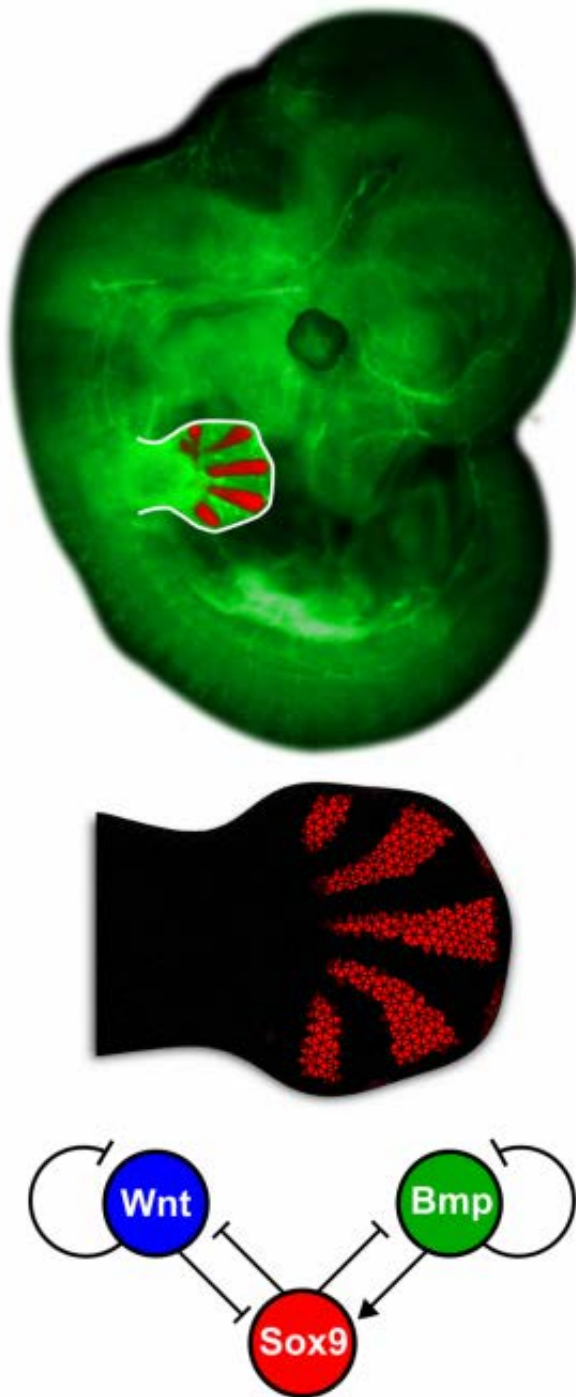
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His [mathematical equations](#) showed that starting from uniform condition (ie. a homogeneous distribution – no pattern) they could spontaneously self-organise their concentrations into a repetitive spatial pattern. This theory has come to be accepted as an explanation of fairly simple patterns such as zebra stripes and even the ridges on sand dunes, but in embryology it has been resisted for decades as an explanation of how structures such as fingers are formed.

Now a group of researchers from the Multicellular Systems Biology lab at the CRG, led by ICREA Research Professor James Sharpe, has provided the long sought-for data which confirms that the fingers and toes are patterned by a Turing mechanism. "It complements their recent paper (*Science* 338:1476, 2012), which provided evidence that Hox genes and FGF signaling modulated a hypothetical Turing system. However, at that point the Turing molecules themselves were still not identified, and so this remained as the critical unsolved piece of the puzzle. The new study completes the picture, by revealing which signaling molecules act as the Turing system" says James Sharpe, co-author of the study.

The approach taken was that of systems biology – combining experimental work with computational modelling. In this way, the two equal-first authors of the paper were able to iterate between the empirical and the theoretical: the lab-work of Jelena Raspopovic providing experimental data for the model, and the computer simulations of Luciano Marcon making predictions to be tested back in the lab.



[Enlarge](#)

This is the detailed embryo limb and the network topology of the Bmp-Sox9-Wnt (BSW) model. Credit: Luciano Marcon and Jelena Raspopovic.

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**Explore further:** [Turing's theory of chemical morphogenesis validated 60 years after his death](#)

**More information:** *Science*, 2014. [DOI: 10.1126/science.1252960](https://doi.org/10.1126/science.1252960)

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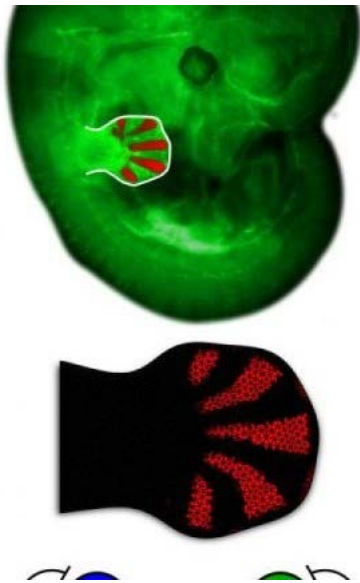




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✍ **A MATHEMATICAL THEORY PROPOSED BY ALAN TURING IN 1952 CAN EXPLAIN THE FORMATION OF FINGERS** ([HTTP://WWW.ASTRONOMY-ASTROPHOTOGRAPHY.GR/WORDPRESS/?P=9255](http://www.astronomy-astrophotography.gr/wordpress/?p=9255))

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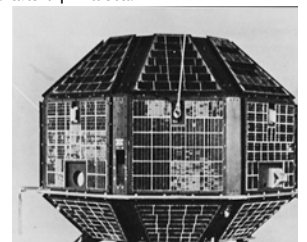
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«Κάνουμε ένα βασικό λάθος όταν διαχωρίζουμε τα μέρη από το όλον: Το λάθος να εξατομικεύουμε αυτό που δεν εξατομικεύεται η ενότητα και η συμπληρωματικότητα συνιστούν την πραγματικότητα.» Werner Heisenberg

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Η πρώτη λεπτομερής Φωτογραφία της Στραβήχτηκε από τον Αμερικανό (Γεννημένο στην Αγγλία) Αστρονόμο, Φιλόσοφο, Για Ιστορικό και Φωτογράφο John William Dr. στις 23 Μαρτίου 1840.



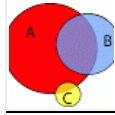
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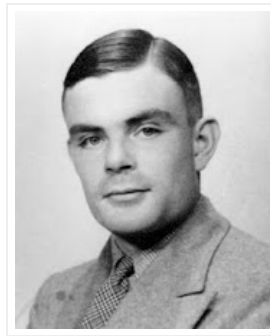
## Turing's morphogenesis and the fingers' formation

By Gianluigi Filippelli on [Friday, August 01, 2014](#)

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On today *Science's* issue it is published a paper about the application of Turing's morphogenesis to the formation of fingers. In this period I'm not able to download the papers, so I simple publish the editor's summaries. First of all I present you the incipit of the paper by Aimée Zuniga, Rolf Zeller<sup>(2)</sup>

Alan Turing is best known as the father of theoretical computer sciences and for his role in cracking the Enigma encryption codes during World War II. He was also interested in mathematical biology and published a theoretical rationale for the self-regulation and patterning of tissues in embryos. The so-called reaction-diffusion model allows mathematical simulation of diverse types of embryonic patterns with astonishing accuracy. During the past two decades, the existence of Turing-type mechanisms has been experimentally explored and is now well established in developmental systems such as skin pigmentation patterning in fishes, and hair and feather follicle patterning in mouse and chicken embryos. However, the extent to which Turing-type mechanisms control patterning of vertebrate organs is less clear. Often, the relevant signaling interactions are not fully understood and/or Turing-like features have not been thoroughly verified by experimentation and/or genetic analysis. Raspopovic *et al.*<sup>(1)</sup> now make a good case for Turing-like features in the periodic pattern of digits by identifying the molecular architecture of what appears to be a Turing network functioning in positioning the digit primordia within mouse limb buds.



And now the summary of the results:

Most researchers today believe that each finger forms because of its unique position within the early limb bud. However, 30 years ago, developmental biologists proposed that the arrangement of fingers followed the Turing pattern, a self-organizing process during early embryo development. Raspopovic *et al.*<sup>(1)</sup> provide evidence to support a Turing mechanism (see the Perspective by Zuniga and Zeller). They reveal that Bmp and Wnt signaling pathways, together with the gene Sox9, form a Turing network. The authors used this network to generate a computer model capable of accurately reproducing the patterns that cells follow as the embryo grows fingers.

(1) Raspopovic, J., Marcon, L., Russo, L., & Sharpe, J. (2014). Digit patterning is controlled by a Bmp-Sox9-Wnt Turing network modulated by morphogen gradients *Science*, 345 (6196), 566-570 DOI: [10.1126/science.1252960](https://doi.org/10.1126/science.1252960)

(2) Zuniga, A., & Zeller, R. (2014). In Turing's hands--the making of digits *Science*, 345 (6196), 516-517 DOI: [10.1126/science.1257501](https://doi.org/10.1126/science.1257501)

### About

Master degree in Physics in scattering theory. PhD in Physics in group theory (ray representation in quantum mechanics). After a master in e-learning I'm instructional designer for Italian Astronomical Olympiads at Brera's Astronomical Observatory (Italy).



#### Gianluigi Filippelli

Instructional designer for Italian Astronomy Olympiads, INAF - Osservatorio Astronomico di Brera Milano, Italy

### Research field

Physics

### Publications

#### Moodle for Italian Astronomy

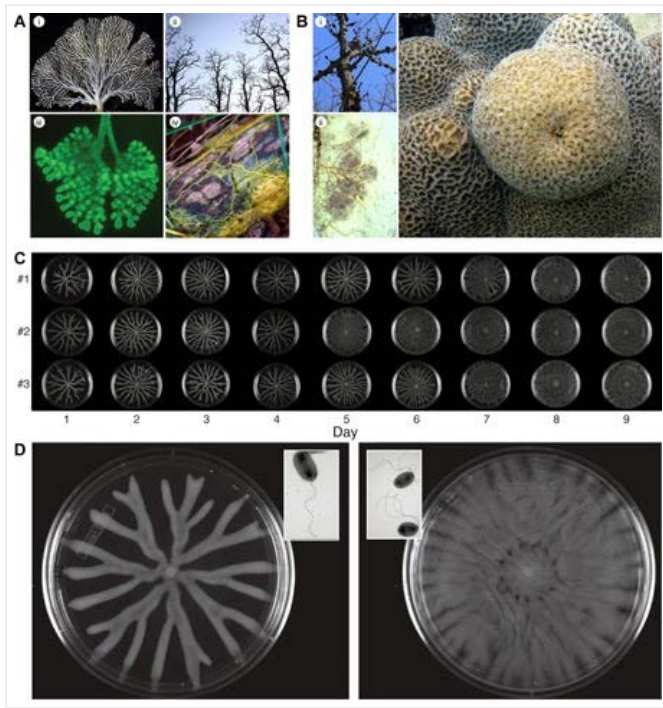
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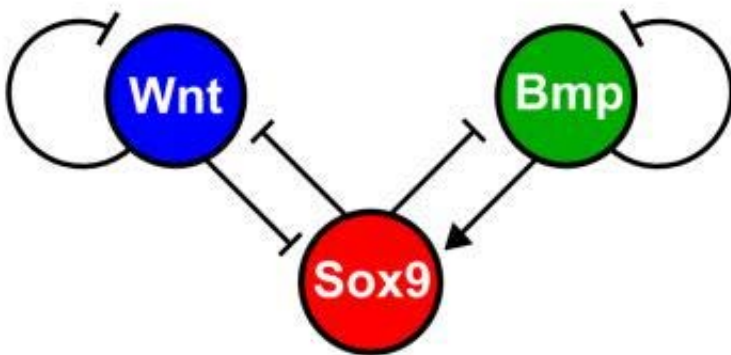
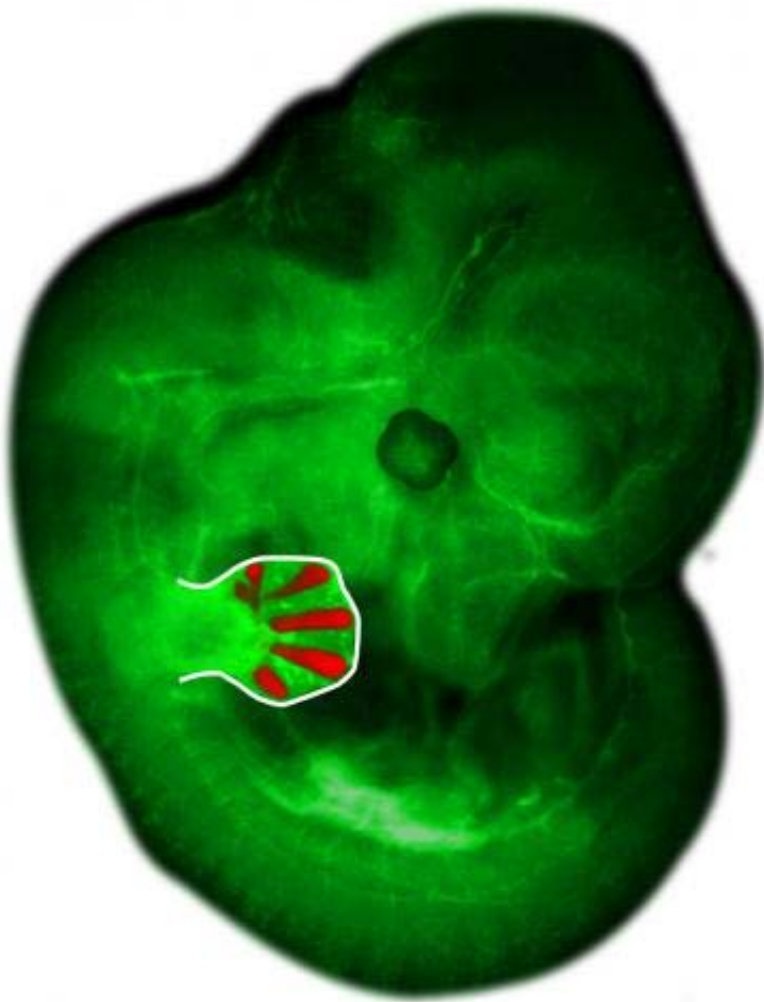
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Category: LATEST (/lastest-news) Published: Thursday, 31 July 2014 16:42 Written by Tyler O'Neal

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## A MATHEMATICAL THEORY PROPOSED BY ALAN TURING IN 1952 CAN EXPLAIN THE FORMATION OF FINGERS

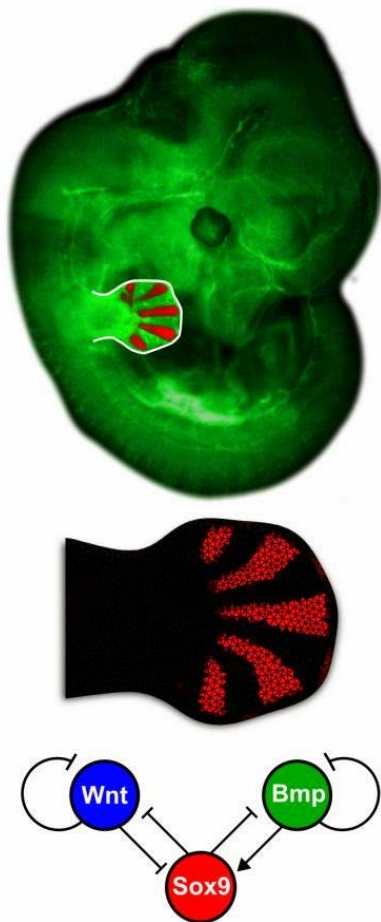
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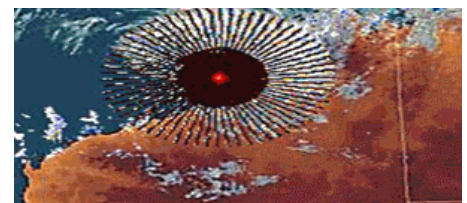
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pattern) they could spontaneously self-organise their concentrations into a repetitive spatial pattern. This theory has come to be accepted as an explanation of fairly simple patterns such as zebra stripes and even the ridges on sand dunes, but in embryology it has been resisted for decades as an explanation of how structures such as fingers are formed.

Now a group of researchers from the Multicellular Systems Biology lab at the CRG, led by ICREA [Research](#) Professor James Sharpe, has provided the long sought-for data which confirms that the fingers and toes are patterned by a Turing mechanism. "It complements their recent paper (Science 338:1476, 2012), which provided evidence that Hox genes and FGF signaling modulated a hypothetical Turing system. However, at that point the Turing molecules themselves were still not identified, and so this remained as the critical unsolved piece of the puzzle. The new study completes the picture, by [revealing](#) which signaling molecules act as the Turing system" says James Sharpe, co-author of the study.

Like strips and dots in many animals, fingers can be considered as patterns that can be predicted by the Turing model.



Credit: Luciano Marcon and Jelena Raspopovic

The approach taken [was that](#) of systems biology – combining experimental work with computational modelling. In this way, the two equal-first authors of the paper were able to iterate between the empirical and the theoretical: the lab-work of Jelena Raspopovic providing experimental data for the model, and the computer simulations of Luciano Marcon making predictions to be tested back in the lab.

By screening for the expression of many different genes, they found that two signalling pathways stood out as having the required activity patterns: BMPs and WNTs. They gradually constructed the minimal possible mathematical model compatible with all the data, and found that the two signalling pathways were linked through a non-diffusible molecule – the transcription factor Sox9. Finally, they were able to make computational predictions about the effects of inhibiting these 2 pathways – either individually, or in combination – which predicted how the pattern of fingers should change. Strikingly, when the same experiments were done on small pieces of limb bud tissue cultured in a petri dish the same alterations in embryonic finger pattern were observed, confirming the computational prediction.

This result answers a long-standing question in the field, but it has consequences that go beyond the development of fingers. It addresses a more general debate about how the millions of cells in our bodies are able to dynamically arrange themselves into the correct 3D structures, for example in our kidneys, hearts and other organs. It challenges the dominance of an important traditional idea called positional information, proposed by Lewis Wolpert which states that cells know what to do because they all receive information about their "coordinates" in space (a bit like longitude and latitude on a world map). Today's publication highlights instead that local self-organising mechanisms may be much more important in organogenesis than previously thought.

Arriving at the correct understanding of multicellular organization is essential if we are to develop effective strategies for regenerative medicine, and one day to possibly engineer replacement tissues for various organs. In the shorter term, these results also explain why polydactyly – the development of extra fingers or toes – is such a common birth defect in humans: Turing systems are mathematically known to have slightly lower precision in regulating the number of "stripes" than alternative models.

At first glance, the question of how an embryo develops seems unrelated to the problems of computing and algorithms with which Turing is more commonly associated. In reality however, they were both expressions of his interest in how complex and clever biological "machines" arise in nature. In a sense, he sought the

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algorithms by which life builds itself. It is fitting that this study, which has confirmed Turing's 62 year-old theory on embryology, required the development of a serious computer model. It brings together two of his major life achievements into one satisfying result.

Contacts and sources:

- [Juan Manuel Sarasua](#)
- [Center for Genomic Regulation](#)

Citation: J. Raspopovic; L. Marcon; L. Russo; J. Sharpe. Digit patterning is controlled by a Bmp-Sox9-Wnt Turing network modulated by morphogen gradients. Science, 2014. DOI: 10.1126/science.1252960

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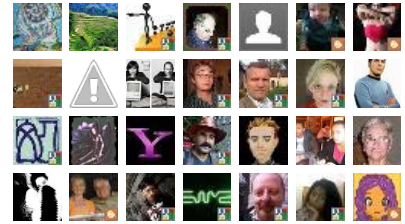
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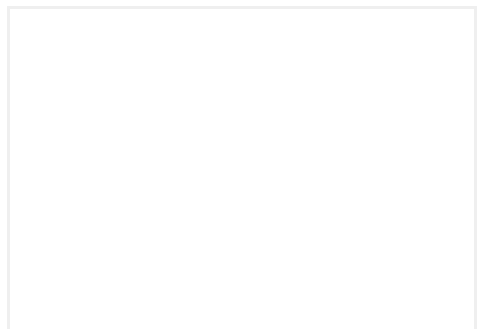
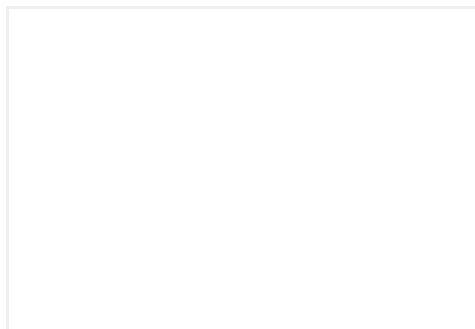
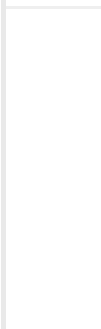
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Mathematical equations showed that starting from uniform condition (ie. a pattern -- no pattern) they could spontaneously self-organise their characteristic repetitive spatial pattern. In this way, the two equal-first authors of the paper bridge the gap between the empirical and the theoretical: the lab-work of Jelena Stojanovic provided experimental data for the model, and the computer simulations of the model's predictions to be tested back in the lab.

Mathematical theory

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## Las matemáticas de Turing explican la formación de los dedos

CRG Álef



Patrones animales y para la formación de dedos - Luciano Marcon y Jelena Raspopovic

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El científico británico Alan Turing (1912-1954) contribuyó a la biología matemática con la publicación, en 1952, de un solo un artículo (The Chemical Basis for Morphogenesis, en Philosophical Transactions of the Royal Society of London) que provocó el desarrollo de toda una nueva área de investigación relacionada con la creación de patrones en la naturaleza.

El matemático descubrió un sistema de dos moléculas que podían, al menos en teoría, crear patrones de manchas o de rayas si las moléculas se difundían e interactuaban químicamente de una determinada manera.

Las ecuaciones matemáticas mostraban que, partiendo de una condición de uniformidad (p.ej. una distribución homogénea, sin patrones o diseños), estas moléculas podrían autoorganizar su concentración de manera espontánea en un repetitivo patrón. Esta teoría ha sido aceptada como explicación de patrones sencillos, como las manchas de las cebras o incluso de las crestas que se forman en las dunas de arena, pero en el campo de la embriología aún no había servido como explicación satisfactoria de cómo se forman estructuras como los dedos.

Ahora, un grupo de investigadores del laboratorio de Biología de Sistemas Multicelulares del Centro de Regulación Genómica (CRG), coordinados por James Sharpe, coautor del estudio, ha conseguido los tan anhelados datos suficientes para confirmar que los dedos de manos y pies siguen el modelo descrito por el mecanismo de Turing.

"Este estudio complementa uno anterior del mismo grupo que mostraba que los genes Hox y el factor de crecimiento de fibroblastos (FGF, en inglés) seguían un hipotético patrón de Turing. Sin embargo, en ese momento las moléculas de Turing no habían sido identificadas aún y la pieza clave del rompecabezas seguía sin ser descubierta. Este nuevo estudio resuelve el enigma al demostrar qué moléculas actúan como el científico predijo", comenta James Sharpe.

El acercamiento al problema se realizó a través de la biología de sistemas. Los investigadores combinaron datos descubiertos en el trabajo experimental con datos del modelo matemático. Así, los primeros autores del estudio pudieron comprobar su hipótesis basándose en datos empíricos y en datos teóricos. El trabajo proporcionó los datos experimentales para el modelo y las simulaciones por ordenador dieron las predicciones que debían ser comprobadas con los experimentos.



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#### Dos vías metabólicas clave

Al revisar la expresión de determinados genes, los investigadores encontraron dos vías metabólicas que cumplían con los requisitos: BMP y WNT. Gradualmente fueron construyendo el modelo matemático mínimo compatible con los datos y encontraron que las dos vías estaban relacionadas a través de una molécula, el factor de transcripción Sox9.

Posteriormente calcularon los efectos de la inhibición de estas vías metabólicas, tanto individualmente o por combinación de las dos, que predecían el cambio en el patrón de los dedos (predecían cuantos dedos iba a tener el embrión). Cuando los mismos experimentos fueron realizados en las yemas de extremidades cultivadas en una placa de Petri, se observaron las mismas alteraciones en los patrones de los dedos que fueron observadas en el modelo por ordenador.

Este resultado efectivamente resuelve una pregunta del campo de la embriología, pero sus consecuencias afectan a muchas áreas más allá del desarrollo de las extremidades. Permite abordar el debate de cómo las millones de células de nuestro cuerpo son capaces de auto organizarse en una estructura tridimensional. Desafía pues el dominio de una idea muy arraigada denominada "información de posición" (positional information en inglés), que dice que las células saben qué hacer porque reciben información sobre sus coordenadas en el espacio (como la longitud y la latitud en un mapa de la tierra).

El estudio publicado hoy resalta que, por el contrario, los mecanismos más locales de autoorganización son más importantes de lo que se creía. Entender perfectamente la organización de un organismo multicelular es esencial si queremos desarrollar estrategias efectivas para la medicina regenerativa y, por ejemplo, poder crear un día tejidos de reemplazo para nuestro cuerpo. A corto plazo estos resultados explican porqué la polidactilia, el desarrollo de dedos de mas en pies y manos, es un defecto muy común en humanos: ahora sabemos que el sistema de Turing tiene una precisión casi igual que el modelo alternativo a la hora de regular el número de manchas, rayas, dedos o cualquier patrón.

Según los autores, la pregunta sobre cómo se desarrolla un embrión parece no estar relacionada con los problemas informáticos o los algoritmos con los que se relaciona más a Turing. Sin embargo, responde a sus legítimos intereses por entender las complejas e ingeniosas máquinas presentes en toda la naturaleza. De una forma, Turing buscaba los algoritmos que la vida utilizó para desarrollarse. Este estudio, que ha confirmado una teoría de la embriología propuesta hace 62 años, reúne los dos más grandes intereses del científico.

#### Un genio poco valorado en su época

Alan Turing es en la actualidad reconocido mundialmente por una serie de descubrimientos que alteraron profundamente el siglo XX. En 1936 publicó un artículo que se convirtió en la base de la informática al crear el primer concepto formal de un algoritmo informático.

También desempeñó un papel crucial en la Segunda Guerra Mundial al diseñar las máquinas que resolvieron los códigos secretos de la Alemania Nazi. Y al final de la década de los años 40, se dedicó a profundizar en la inteligencia artificial y propuso un desafío, ahora llamado El Test de Turing, que sigue siendo muy utilizado hoy en día.

#### Referencia bibliográfica:

J. Raspopovic; L. Marcon; L. Russo; J. Sharpe. Digit patterning is controlled by a Bmp-Sox9-Wnt Turing network modulated by morphogen gradients. Science, 2014. DOI: 10.1126/science.1252960



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