Epistemological bases
Definitions and applications

Epistemological bases

Epistemology: the philosophical study of the nature, origin, and limits of human knowledge

- The term is derived from the Greek *epistēmē* (“knowledge”) and *logos* (“reason”), and accordingly the field is sometimes referred to as the theory of knowledge.

- Epistemology has a long history within Western philosophy, beginning with the ancient Greeks and continuing to the present.

- Along with metaphysics, logic, and ethics, it is one of the four main branches of philosophy, and nearly every great philosopher has contributed to it.

From: https://www.britannica.com/topic/epistemology

Is there a unique definition of “Scientific method”?

Experiments

Observations

Conclusions

Scientific laws

AI ?

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

¹ Fraser, R. D., Gosling, R., and Jevons, W., *Phil. Mag.*, **42**, 149 (1951).

² Longuet-Higgins, H. C., *Mem. Nat. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).

³ Cox, Arn., E. A., Woods Hole Papers in Phys. Oceanog. Meteor., **12**, 151 (1949).

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MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

This figure is purely diagrammatic. The two ribbons symbolize the sugar–phosphate backbone, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the *z*-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical *z*-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge. April 2.

¹ Pauling, L., and Corey, R. B., *Nature*, **171**, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).

² Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).

³ Chargaff, E., for references see Zamenhof, S., Hurwitz, J., and Chargaff, E., *Biochim. et Biophys. Acta*, **9**, 402 (1952).

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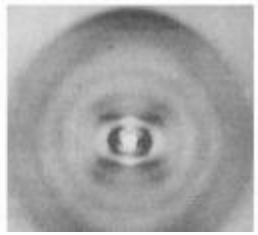

Article

Bridge RNAs direct programmable recombination of target and donor DNA

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Check for updates

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Genomic rearrangements, encompassing mutational changes in the genome such as insertions, deletions or inversions, are essential for genetic diversity. These rearrangements are typically orchestrated by enzymes that are involved in fundamental DNA repair processes, such as homologous recombination, or in the transposition of foreign genetic material by viruses and mobile genetic elements[1,2]. Here we report that IS110 insertion sequences, a family of minimal and autonomous mobile genetic elements, express a structured non-coding RNA that binds specifically to their encoded recombinase. This bridge RNA contains two internal loops encoding nucleotide stretches that base-pair with the target DNA and the donor DNA, which is the IS110 element itself. We demonstrate that the target-binding and donor-binding loops can be independently reprogrammed to direct sequence-specific recombination between two DNA molecules. This modularity enables the insertion of DNA into genomic target sites, as well as programmable DNA excision and inversion. The IS110 bridge recombination system expands the diversity of nucleic-acid-guided systems beyond CRISPR and RNA interference, offering a unified mechanism for the three fundamental DNA rearrangements—insertion, excision and inversion—that are required for genome design.

Evolution has dedicated a vast number of enzymes to the task of rearranging and diversifying the genome. This process enables the emergence and functional specialization of new genes, the development of immunity[3] and the opportunistic spread of viruses and mobile genetic elements (MGEs)[1,2]. MGEs are abundant throughout all domains of life and often mobilize through a transposase, integrase, homing endonuclease or recombinase. These enzymes typically recognize DNA through protein–DNA contacts and can be broadly classified by their target sequence specificity, which ranges from site-specific (for example, Cre and Bxb1 recombinases)[4,5] to semi-random (for example, Tn5 and PiggyBac transposases)[6,7].

Insertion sequence (IS) elements are among the most minimal autonomous MGEs, and are found abundantly across bacteria and archaea. Many characterized IS elements use a self-encoded transposase that recognizes terminal inverted repeats (TIRs) through protein–DNA interactions[8]. IS elements have been categorized into approximately 28 families on the basis of their homology, architecture and transposition mechanisms, but they can be broadly grouped by the conserved catalytic residues of their encoded transposases. These include DDE, DEDD and HUH transposases, and, less frequently, serine or tyrosine transposases[8].

IS110 family elements are cut-and-paste MGEs that scarlessly excise themselves from the genome and generate a circular form as part of their transposition mechanism[9,10]. Given what is known about this mechanism and life cycle, IS110 transposases are more accurately described as recombinases. Although circular intermediates are found in other IS families, IS110 is the only family that uses a DEDD catalytic motif in its recombinase. The N-terminal DEDD domains of IS110 recombinases share homology with RuvC Holliday junction resolvases, suggesting that they have a unique mechanism of action compared with other IS elements. IS110 elements typically lack TIRs and appear to integrate in a sequence-specific manner, often targeting repetitive elements in microbial genomes[11]. Although the mechanism of DNA recognition and recombination for IS110 elements remains unclear, previous studies have suggested that the non-coding ends of the element flanking the recombinase ORF regulate recombinase expression[12,13].

Here we show that the IS110 circular form drives the expression of a non-coding RNA (ncRNA) with two distinct binding loops that separately recognize the IS110 DNA donor and its genomic insertion target site. By bridging the donor and target DNA molecules through direct base-pairing interactions, the bispecific bridge RNA facilitates DNA recombination by the IS110 recombinase. Each binding loop of the bridge RNA can be independently reprogrammed to bind and recombine diverse DNA sequences. We further show that this modularity

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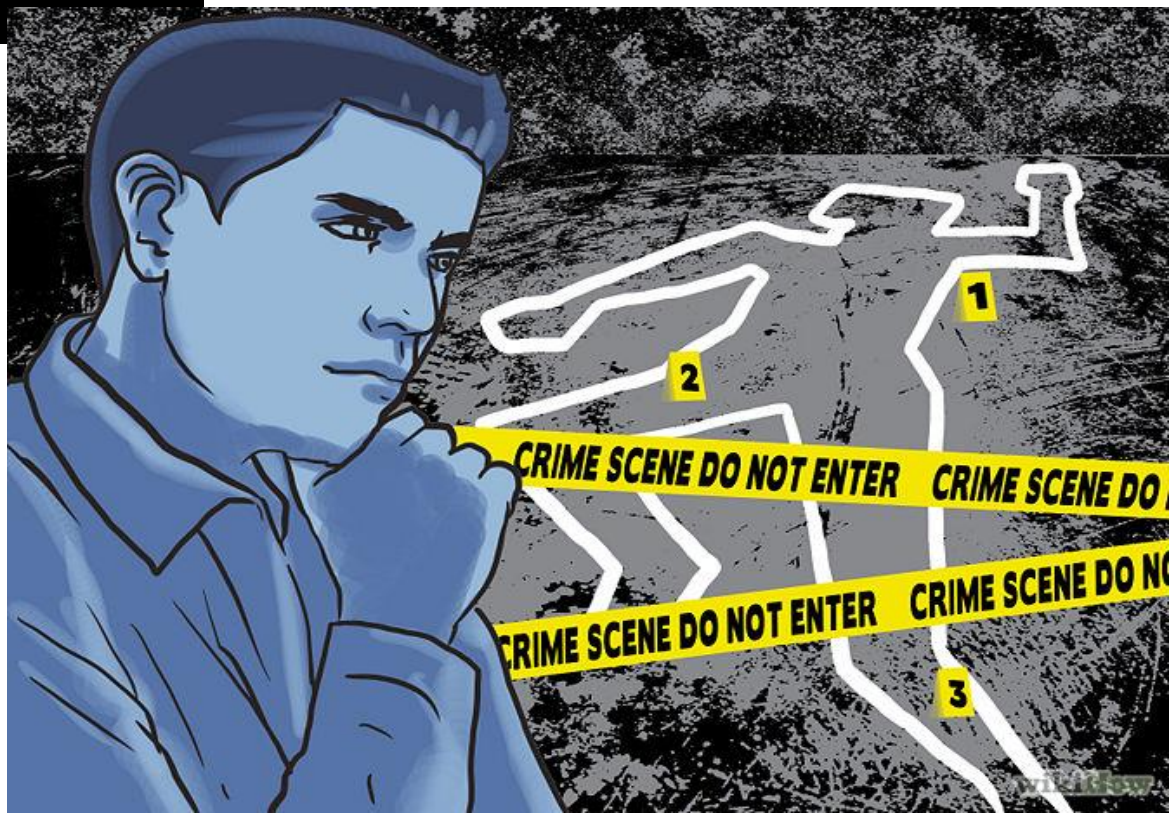
Paper + ext data
17+10 pages
6+8 figures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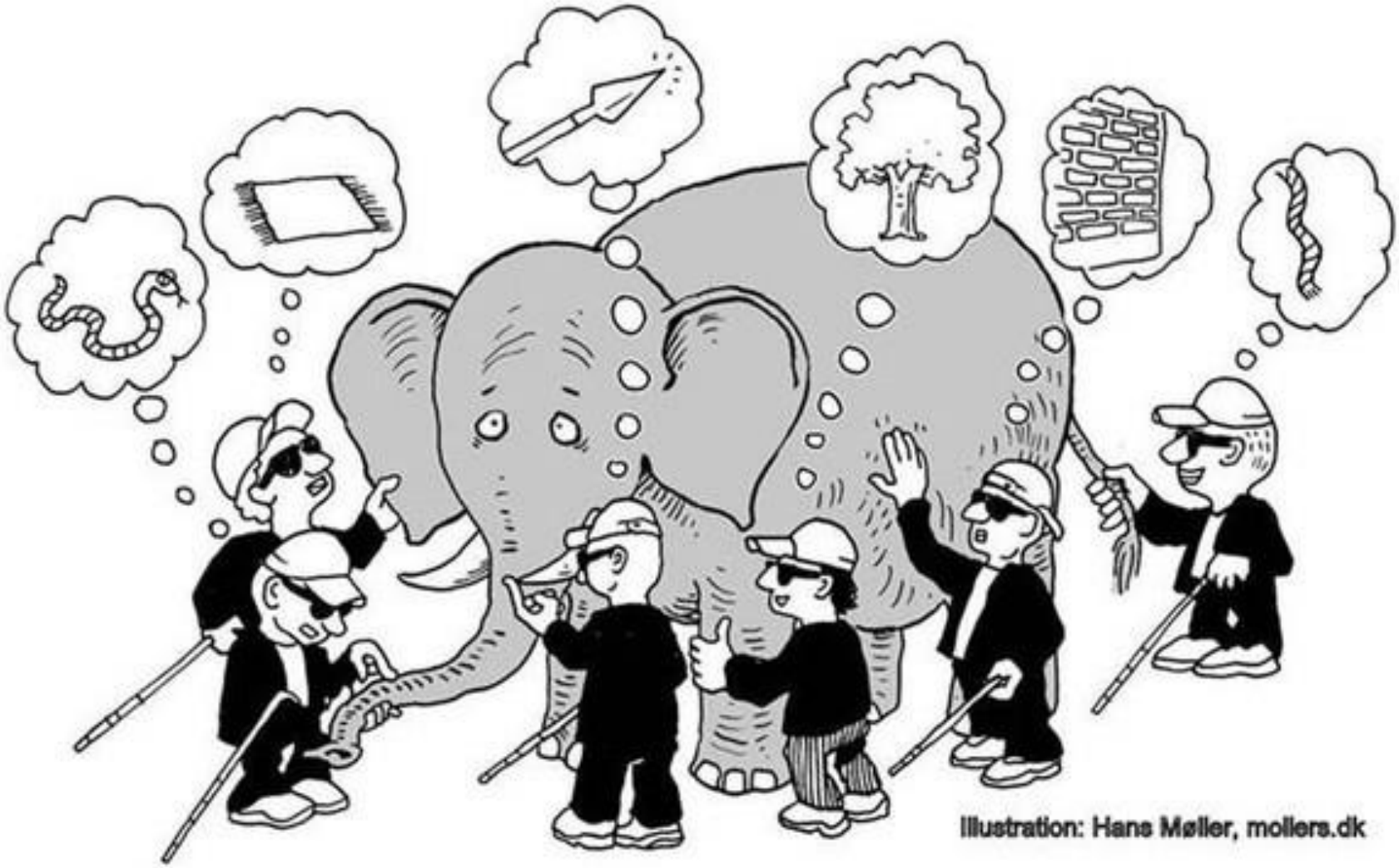
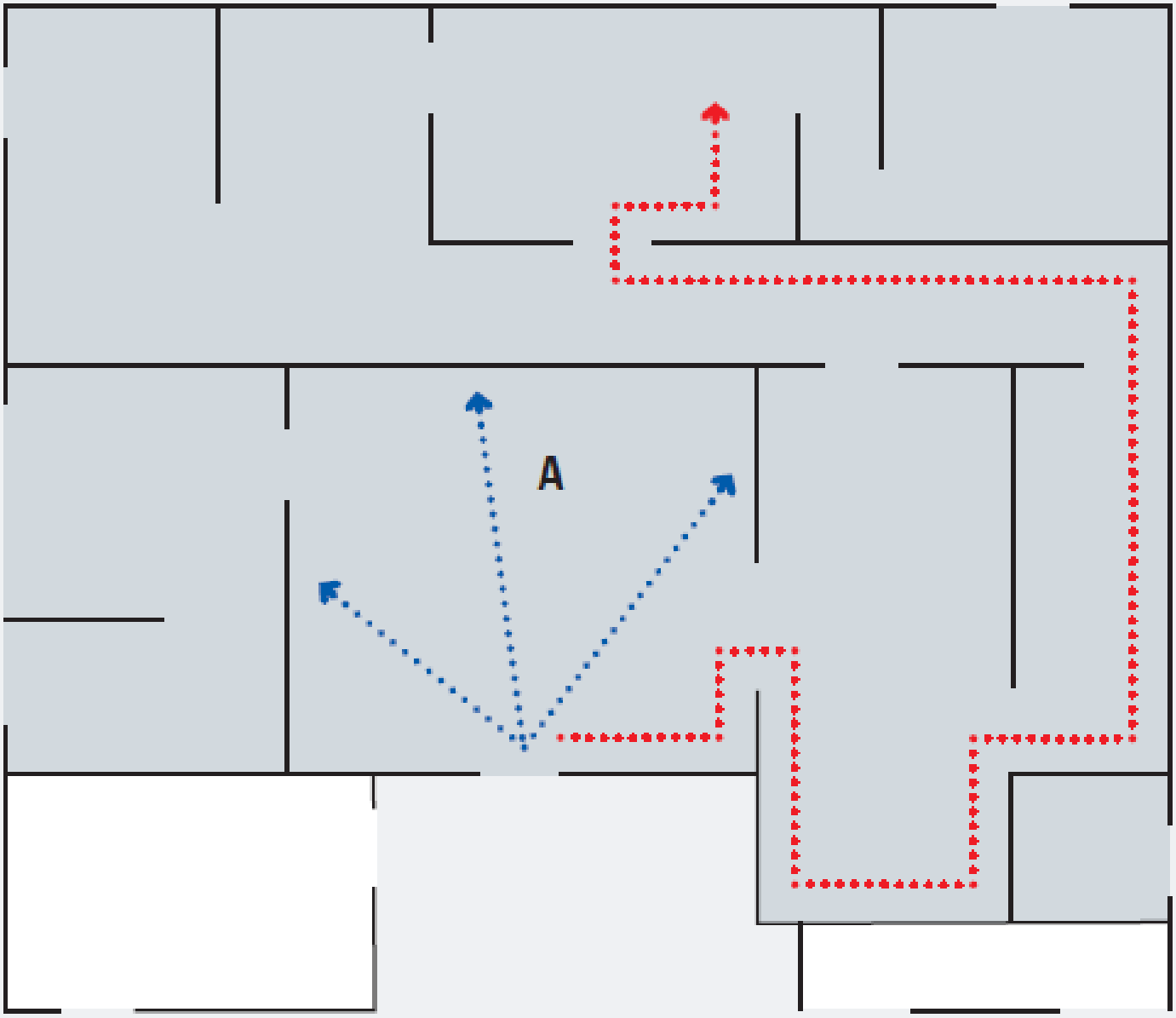
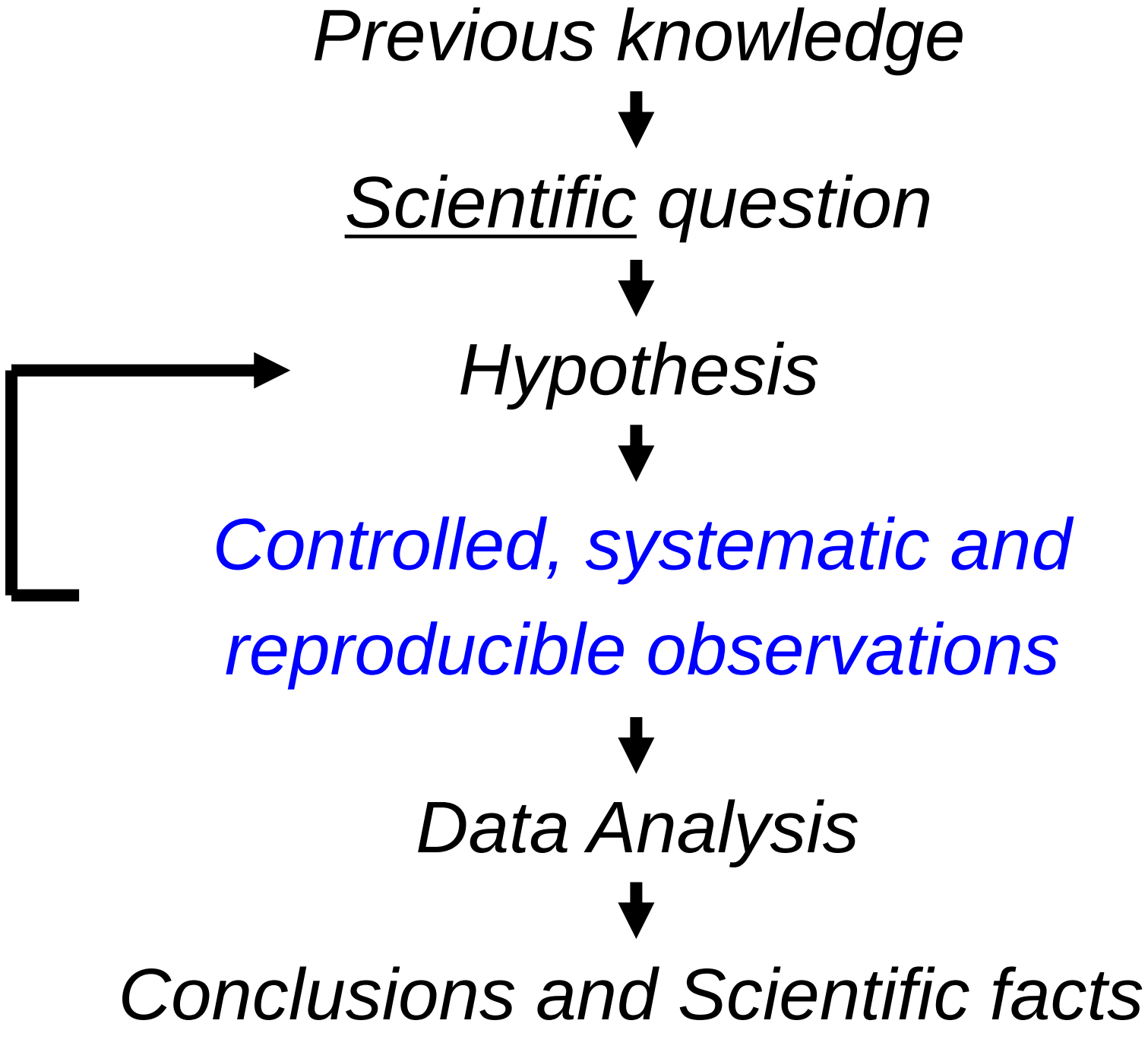


Illustration: Hans Møller, mollers.dk

What's the best way to investigate?

Figura 1.1
Per esplorare la stanza A, una strategia casuale (frecce blu) può essere più efficace di una che segua una regola sistematica, come quella di attenersi sempre alla destra (percorso in rosso).




Previous knowledge
Scientific question
Hypothesis
Controlled, systematic and reproducible observations
Data Analysis
Conclusions and Scientific facts

> Proc Natl Acad Sci U S A. 2015 Sep 22;112(38):E5246-52. doi: 10.1073/pnas.1512869112. Epub 2015 Sep 8.

Caspase 3 cleavage of Pax7 inhibits self-renewal of satellite cells

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Affiliations + expand

PMID: 26372956 PMCID: PMC4586827 DOI: 10.1073/pnas.1512869112

Abstract

Compensatory growth and regeneration of skeletal muscle is dependent on the resident stem cell population, satellite cells (SCs). Self-renewal and maintenance of the SC niche is coordinated by the paired-box transcription factor Pax7, and yet continued expression of this protein inhibits the myoblast differentiation program. As such, the reduction or removal of Pax7 may denote a key prerequisite for SCs to abandon self-renewal and acquire differentiation competence. Here, we identify caspase 3 cleavage inactivation of Pax7 as a crucial step for terminating the self-renewal process. Inhibition of caspase 3 results in elevated Pax7 protein and SC self-renewal, whereas caspase activation leads to Pax7 cleavage and initiation of the myogenic differentiation program. Moreover, in vivo inhibition of caspase 3 activity leads to a profound disruption in skeletal muscle regeneration with an accumulation of SCs within the niche. We have also noted that casein kinase 2 (CK2)-directed phosphorylation of Pax7 attenuates caspase-directed cleavage. Together, these results demonstrate that SC fate is dependent on opposing posttranslational modifications of the Pax7 protein.

Keywords: Pax7; casein kinase 2; caspase; satellite cells; self-renewal.

Review > Eur J Epidemiol. 2023 Jan;38(1):31-38. doi: 10.1007/s10654-022-00946-6. Epub 2023 Jan 3.

Decrease of cancer diagnosis during COVID-19 pandemic: a systematic review and meta-analysis

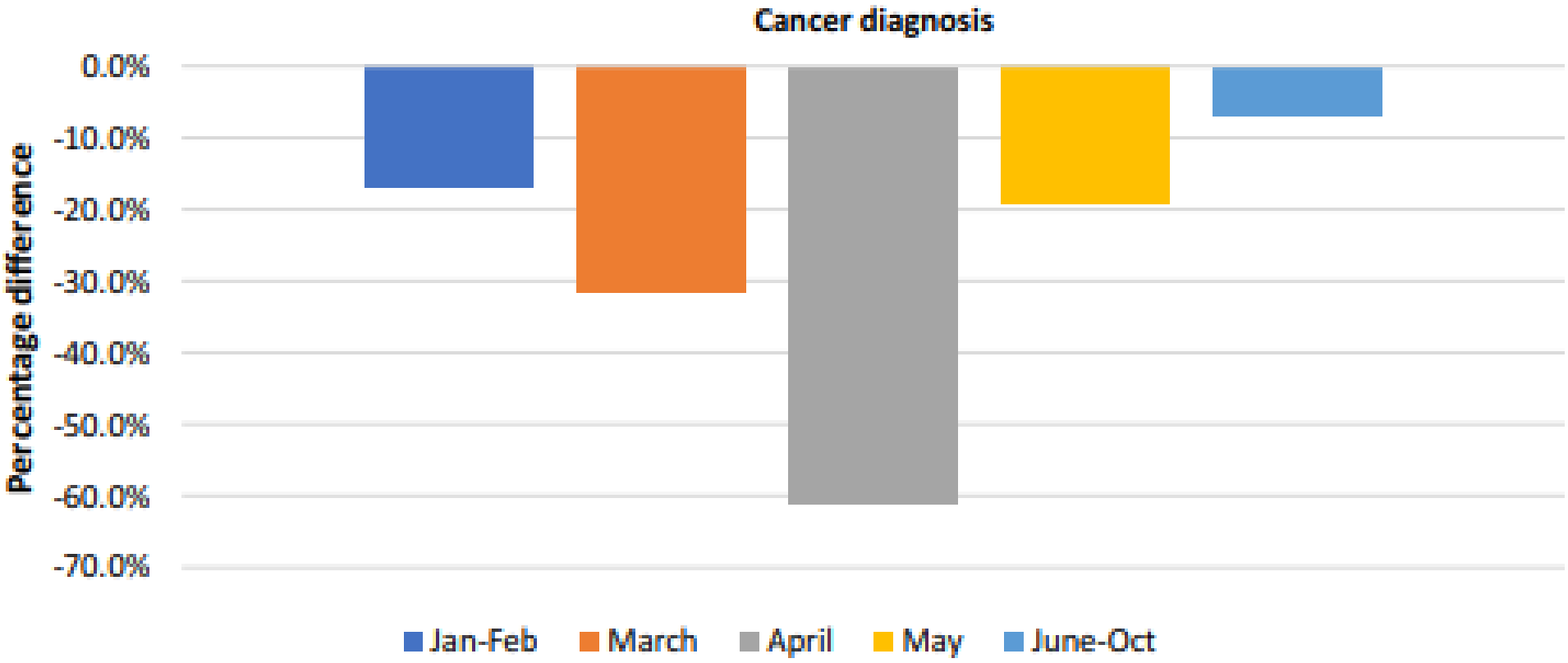
Marco Angelini [1], Federica Teglia [1], Laura Astolfi [1], Giulia Casolari [1], Paolo Boffetta [2 3]

Affiliations + expand

PMID: 36593334 PMCID: PMC9807424 DOI: 10.1007/s10654-022-00946-6

Abstract

Many health services, including cancer care, have been affected by the COVID-19 epidemic. This study aimed at providing a systematic review of the impact of the epidemic on cancer diagnostic tests and diagnosis worldwide. In our systematic review and meta-analysis, databases such as Pubmed, Proquest and Scopus were searched comprehensively for articles published between January 1st, 2020 and December 12th, 2021. Observational studies and articles that reported data from single clinics and population registries comparing the number of cancer diagnostic tests and/or diagnosis performed before and during the pandemic, were included. Two pairs of independent reviewers extracted data from the selected studies. The weighted average of the percentage variation was calculated and compared between pandemic and pre-pandemic periods. Stratified analysis was performed by geographic area, time interval and study setting. The review was registered on PROSPERO (ID: CRD42022314314). The review comprised 61 articles, whose results referred to the period January-October 2020. We found an overall decrease of - 37.3% for diagnostic tests and - 27.0% for cancer diagnosis during the pandemic. For both outcomes we identified a U-shaped temporal trend, with an almost complete recovery for the number of cancer diagnosis after May 2020. We also analyzed differences by geographic area and screening setting. We provided a summary estimate of the decrease in cancer diagnosis and diagnostic tests, during the first phase of the COVID-19 pandemic. The delay in cancer diagnosis could lead to an increase in the number of avoidable cancer deaths. Further research is needed to assess the impact of the pandemic measures on cancer treatment and mortality.


Cancer diagnosis
Percentage difference
0.0%
-10.0%
-20.0%
-30.0%
-40.0%
-50.0%
-60.0%
-70.0%
Jan-Feb
March
April
May
June-Oct

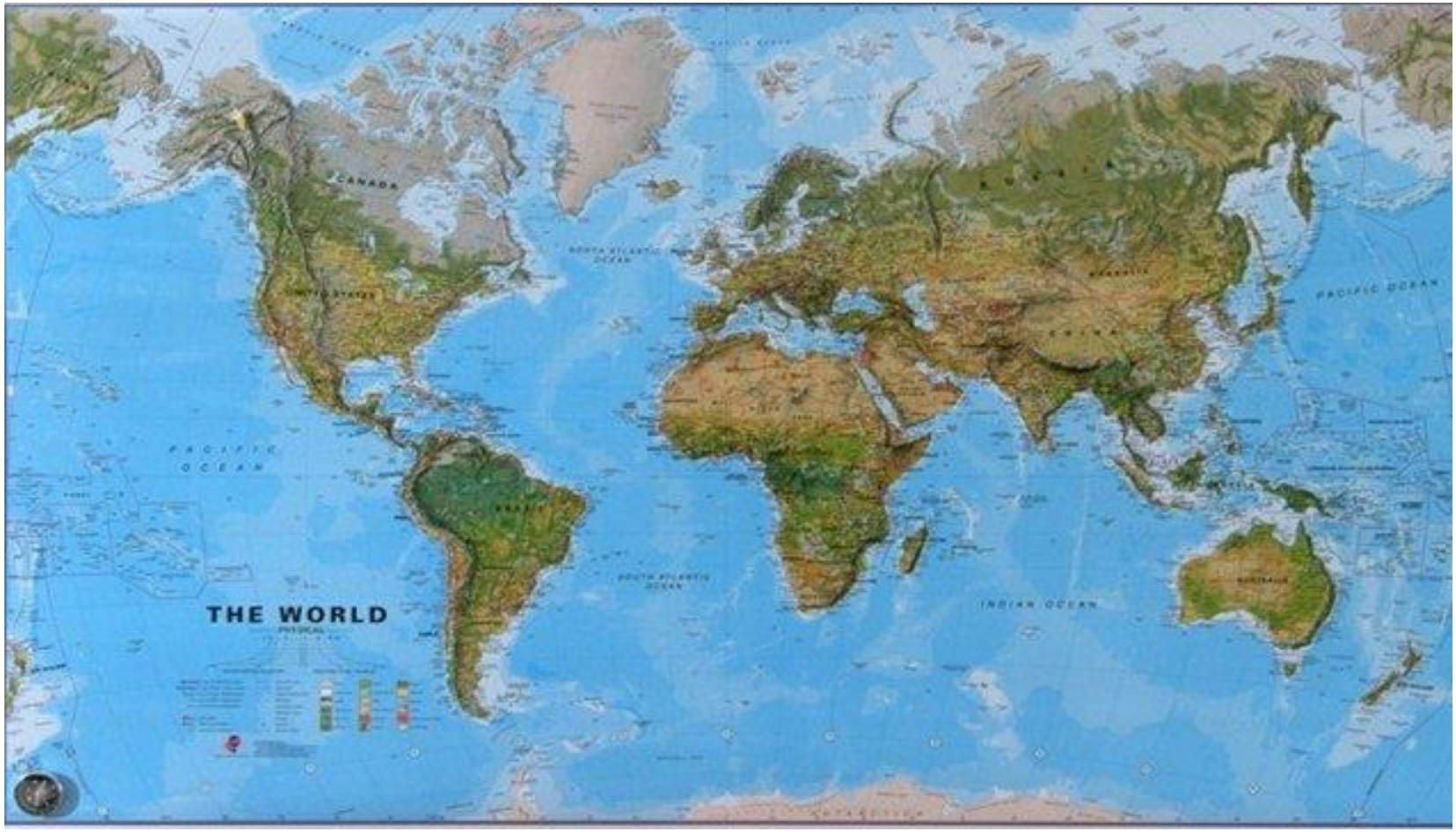
HYPOTHESIS

Conjecture or explanatory proposal, developed on the basis of limited evidence, as a starting point for further investigations

MODEL

Simplified representation of a real object or phenomenon, based on some of its characteristics, deemed relevant:

- **Conceptual** models – useful to understand, to further investigate
- **Operational** models – to define practical rules to approach an object of investigation
- **Mathematical** models – to quantify phenomena, predict behavior
- **Grafic** models – to visualize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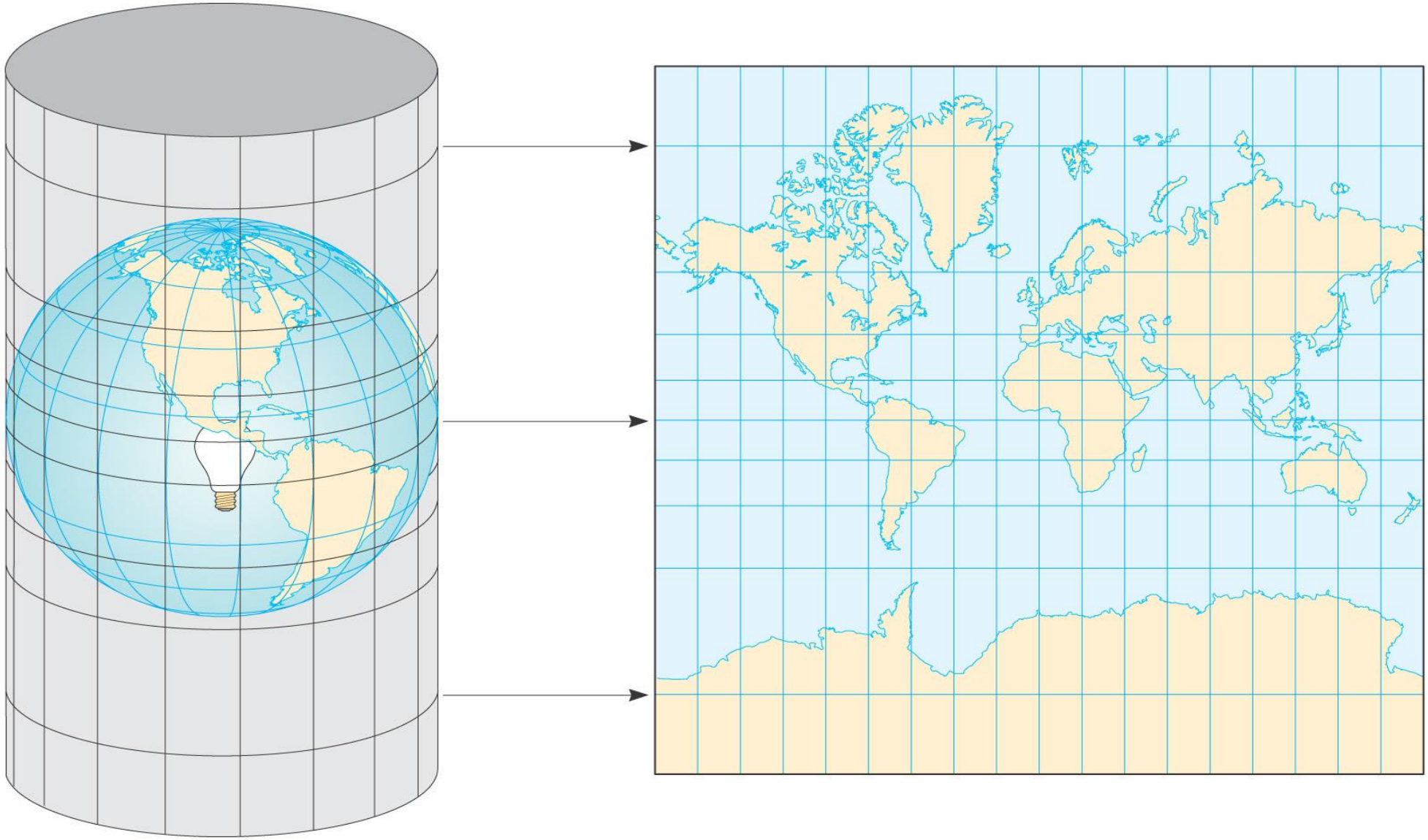
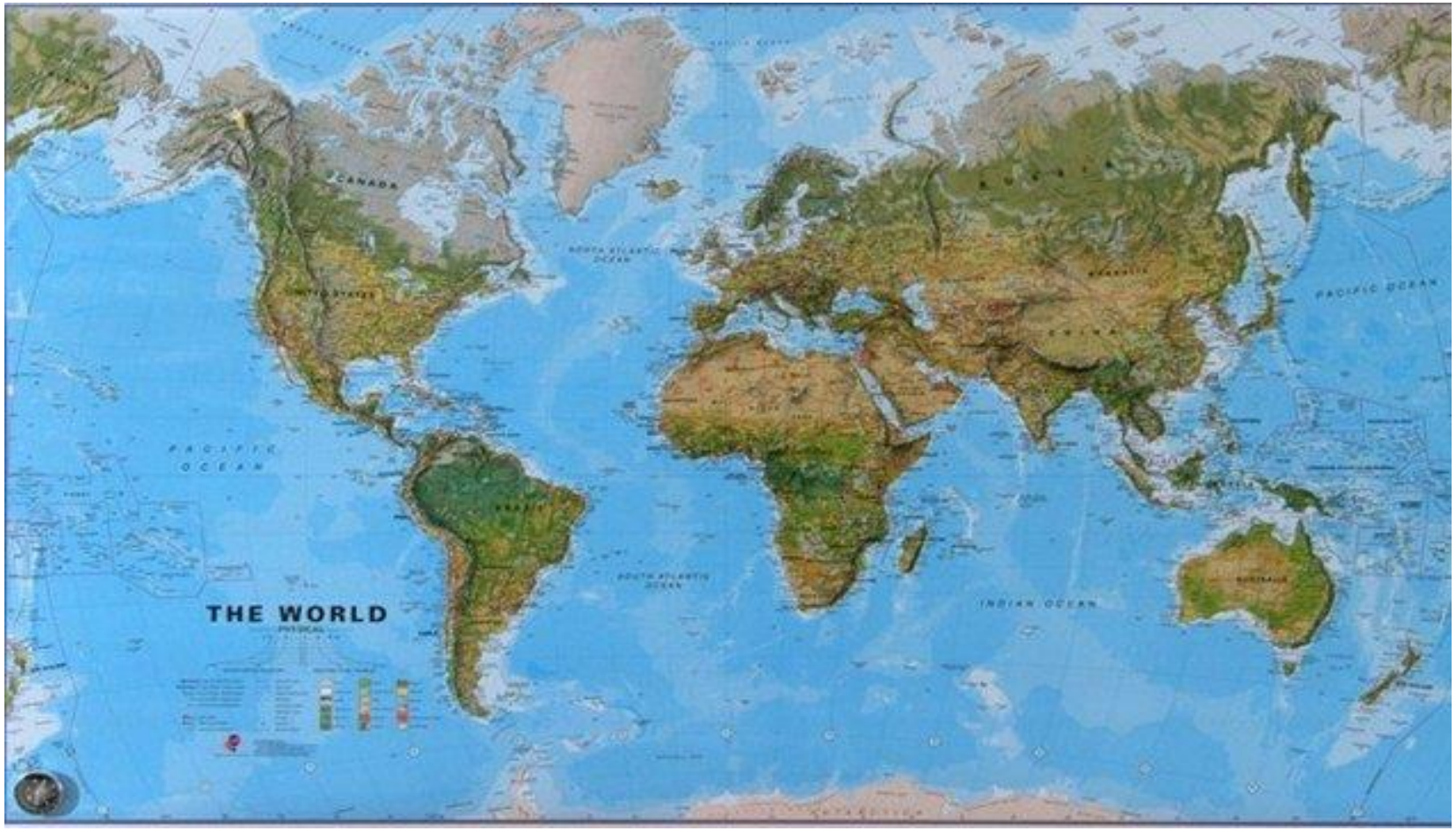
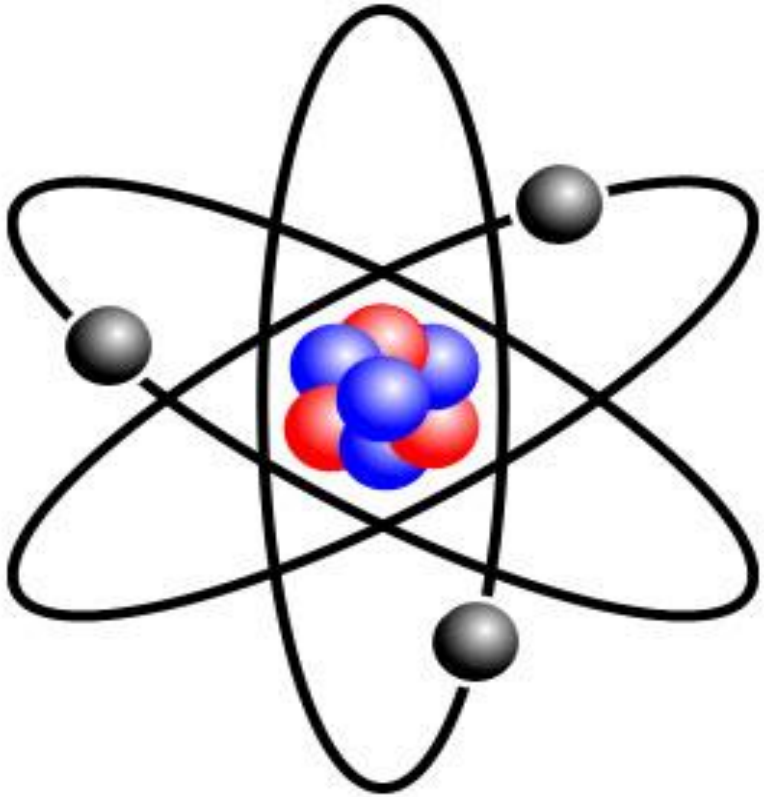
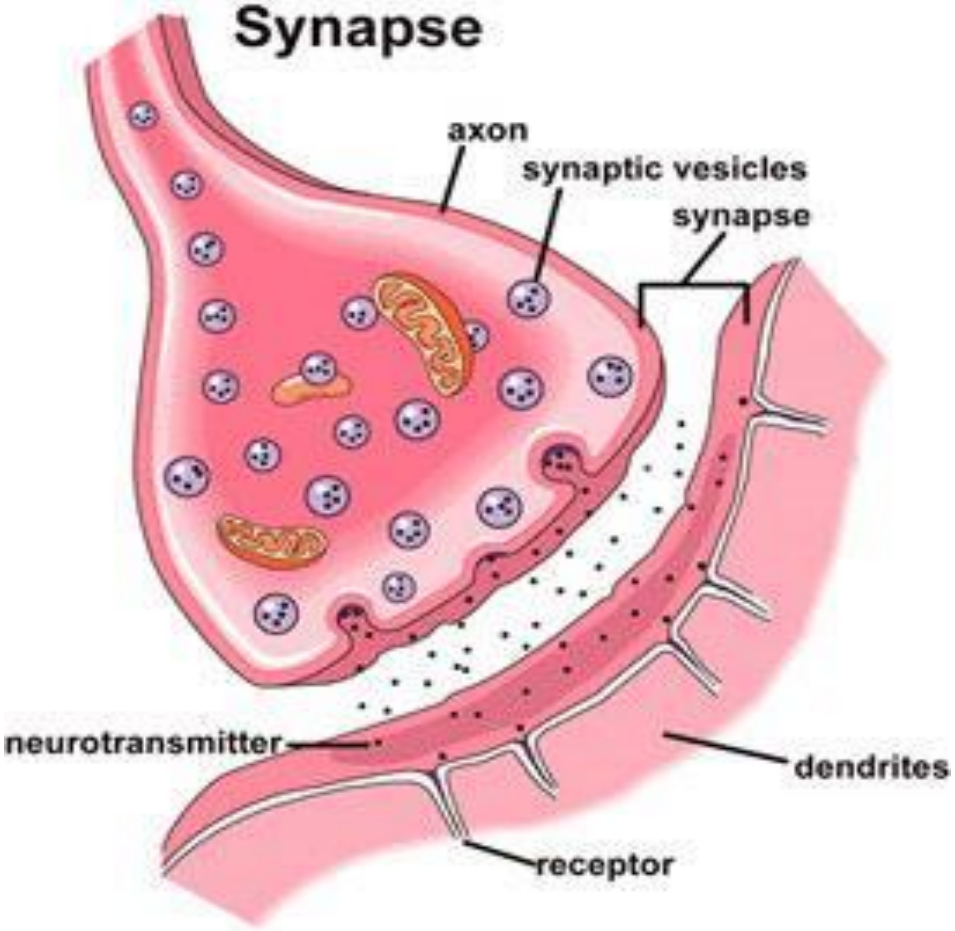


(a) (b)



Continent	Area (km^2 x 1000)		
Asia	43.810	S. America	17.840
Africa	30.370	Antarctica	13.720
N. America	24.490	Europe	10.400
Greenland	2.166	Australia	7.703
		Oceania	9.010

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synapse
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dendrites
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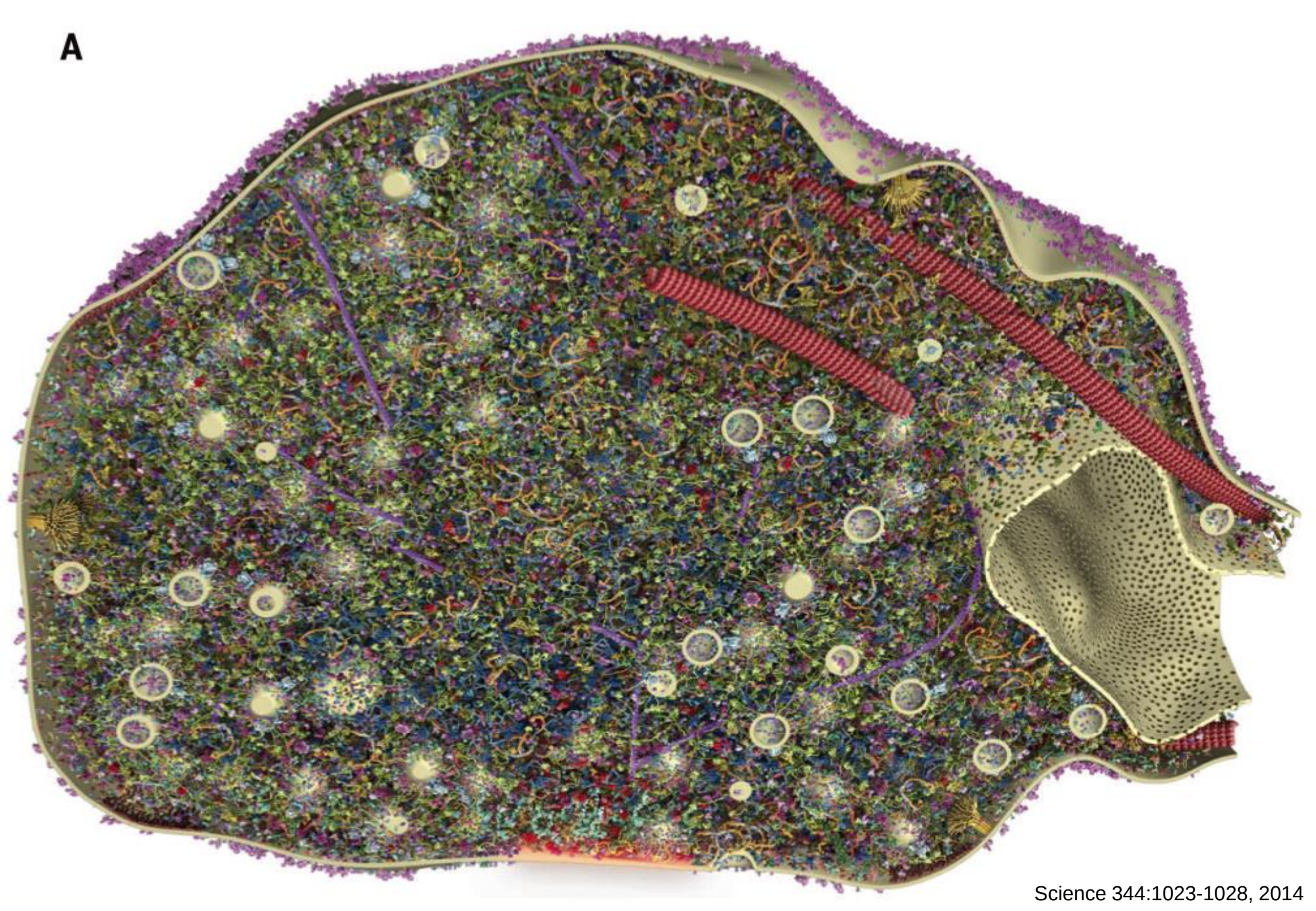
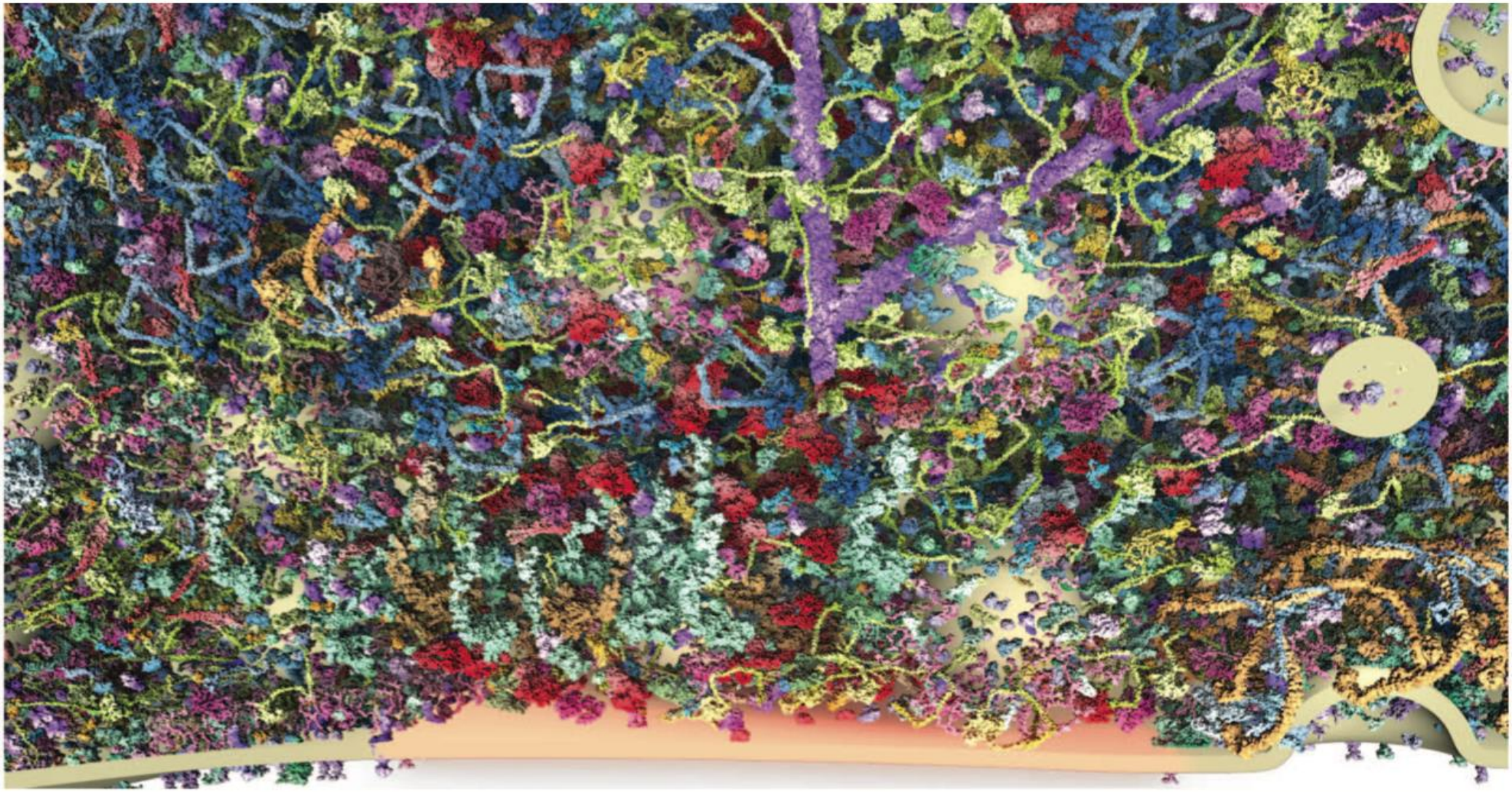


Science 344:1023-1028, 2014



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- Mathematical models – to quantify phenomena, predict behavior
- Graphical models – to visualize

Theory

Explanation of specific aspects of the natural world, based on solid scientific bases (e.g. Evolution; Continental drift; Relativity)

Note: the colloquial use of this word, often does not reflect this definition

Law

Short statement on natural facts, strongly based on scientific evidence, with strong predictive power; usually it can be expressed in mathematical form; makes quantitative predictions (E.g. Hardy-Weimberg)

Principle

A theorem or a scientific law applicable to a wide part of reality (e.g. Heisenberg)

Dogma

A settled or established principle