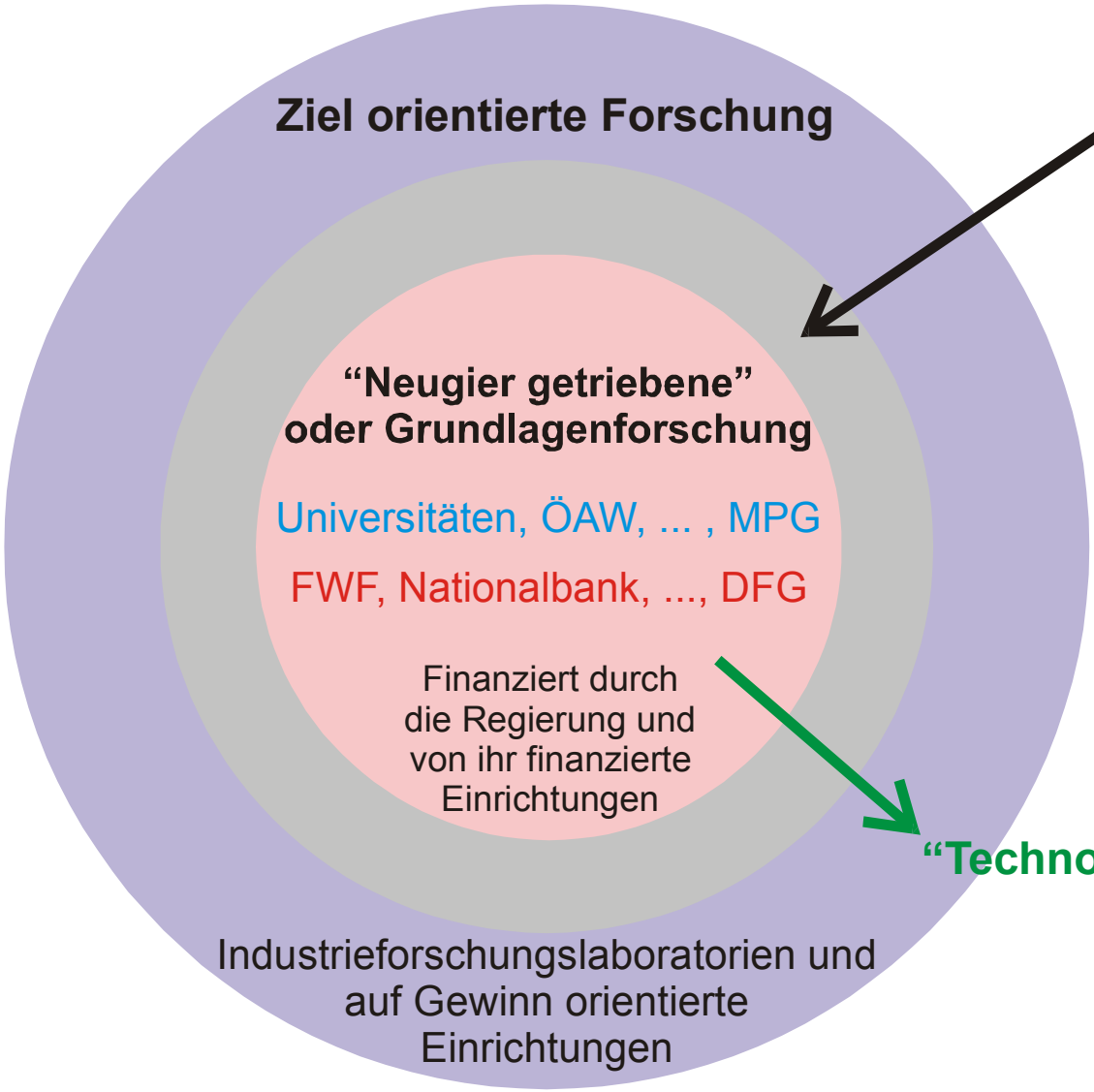
Ziele der biologischen Forschung und Erwartungen an die Wissenschaft

Peter Schuster
Österreichische Akademie der Wissenschaften

Trends in Biotechnologie, 21.- 22.11.2002

World Trade Center, Vienna Airport



Erfordert
eigene Programme und
besondere Einrichtungen

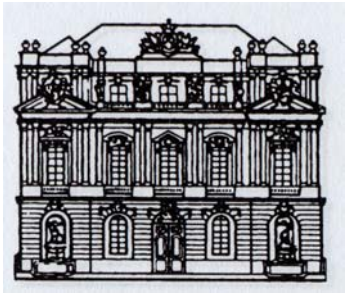
Beispiele: **FFF**, "GENAU"

"BioRegio" und andere
BMBF-Programme

Austrian Research Seibersdorf
Johaneum Research

Fraunhofer Institute

Konventionelle Vorstellung der Forschungslandschaft



Österreichische Akademie
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Institut für Biomedizinische Alternsforschung
Innsbruck

Institut für Biophysik und Röntgenstrukturforschung
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Institut für Molekularbiologie
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Research Institute of Molecular Pathology

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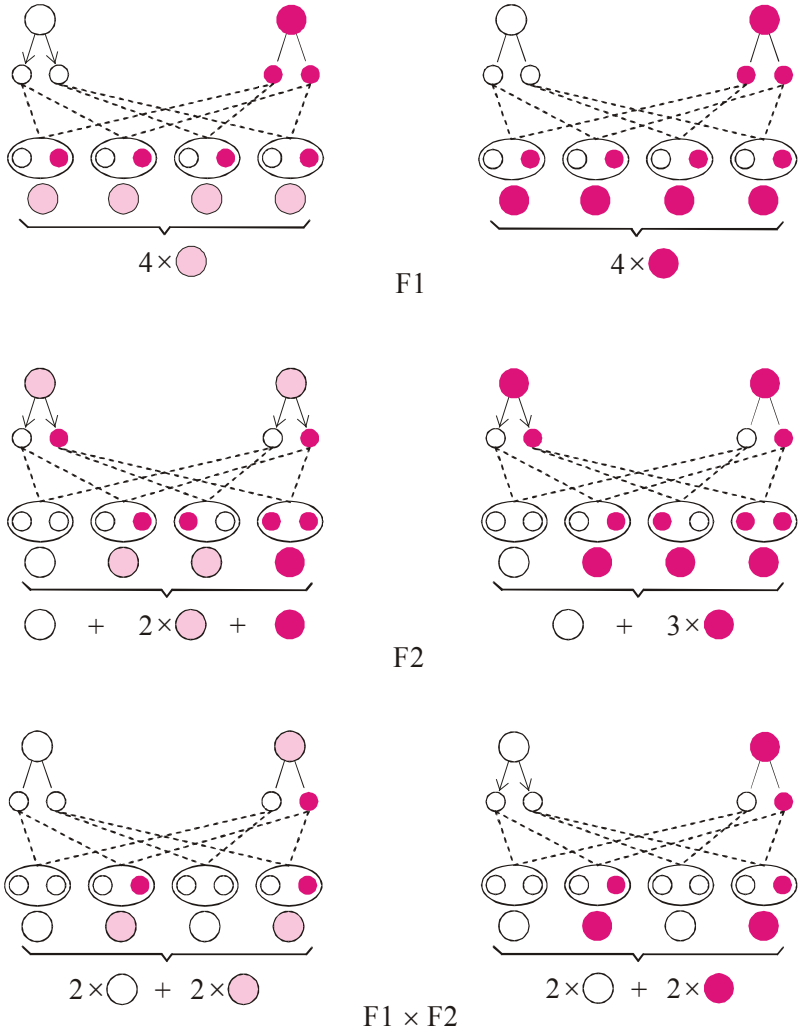
Ziel der biologischen Forschung ist das Verstehen von Arten und Organismen als robuste Einheiten, die ihre Eigenschaften durch die **Dynamik** der in ihnen auf **verschiedenen Zeitskalen** und in ständigem **Energie**- und **Material-austausch** mit der Umgebung ablaufenden Vorgänge aufrechterhalten. Das Wissen um diese Vorgänge ist gleichzeitig die Basis für die Erklärung und die Behebung von pathologischen Fehlfunktionen.

Vier aktuelle Beispiele für die Vorteile und die Notwendigkeit einer dynamischen Sicht anstelle des konventionellen statischen Bildes:

1. Genbegriff,
2. Datenexplosion,
3. Netzwerkkonzepte und
4. Evolutionäre Biotechnologie.

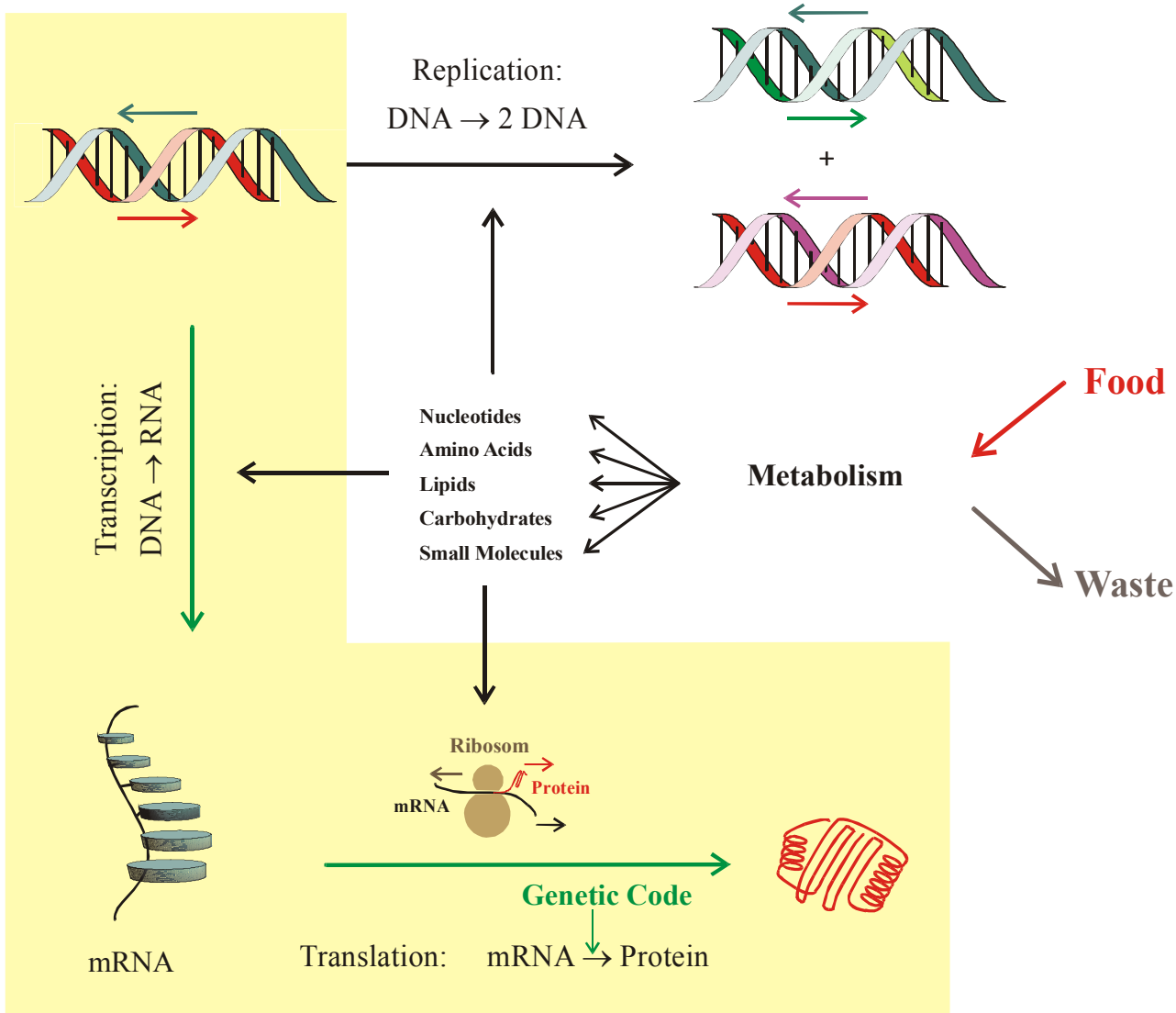


Intermediäres Allelpaar

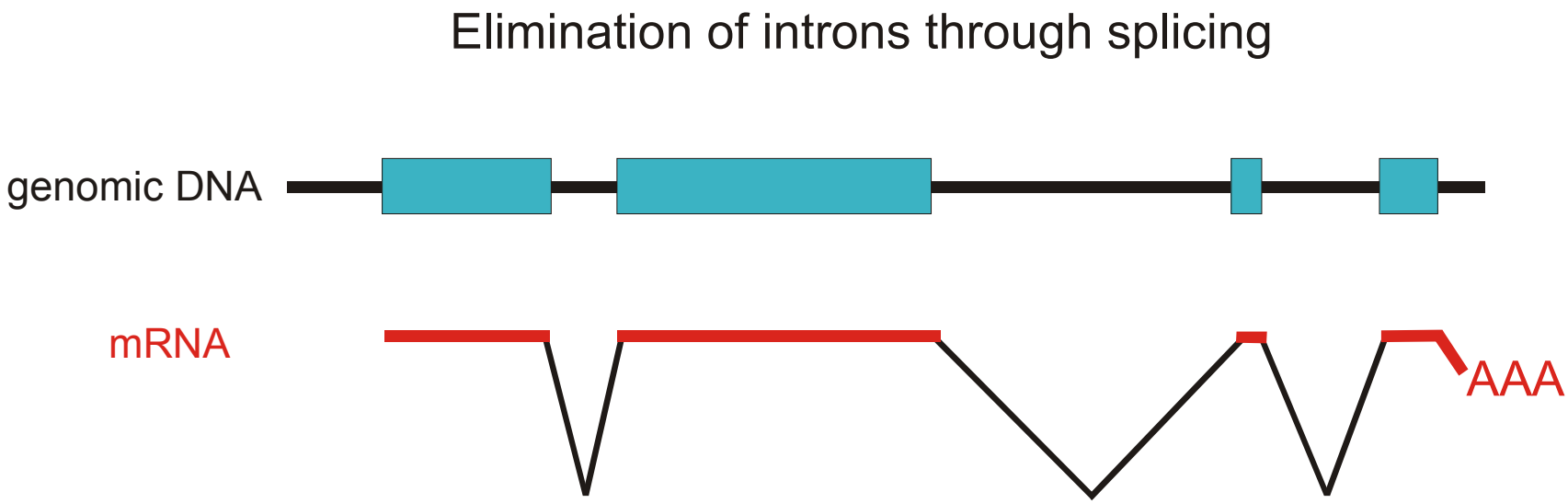
Dominant/rezessives Allelpaar

Gregor Johann Mendel (1822-1884)
Quelle: Bildarchiv der Österreichischen Nationalbibliothek

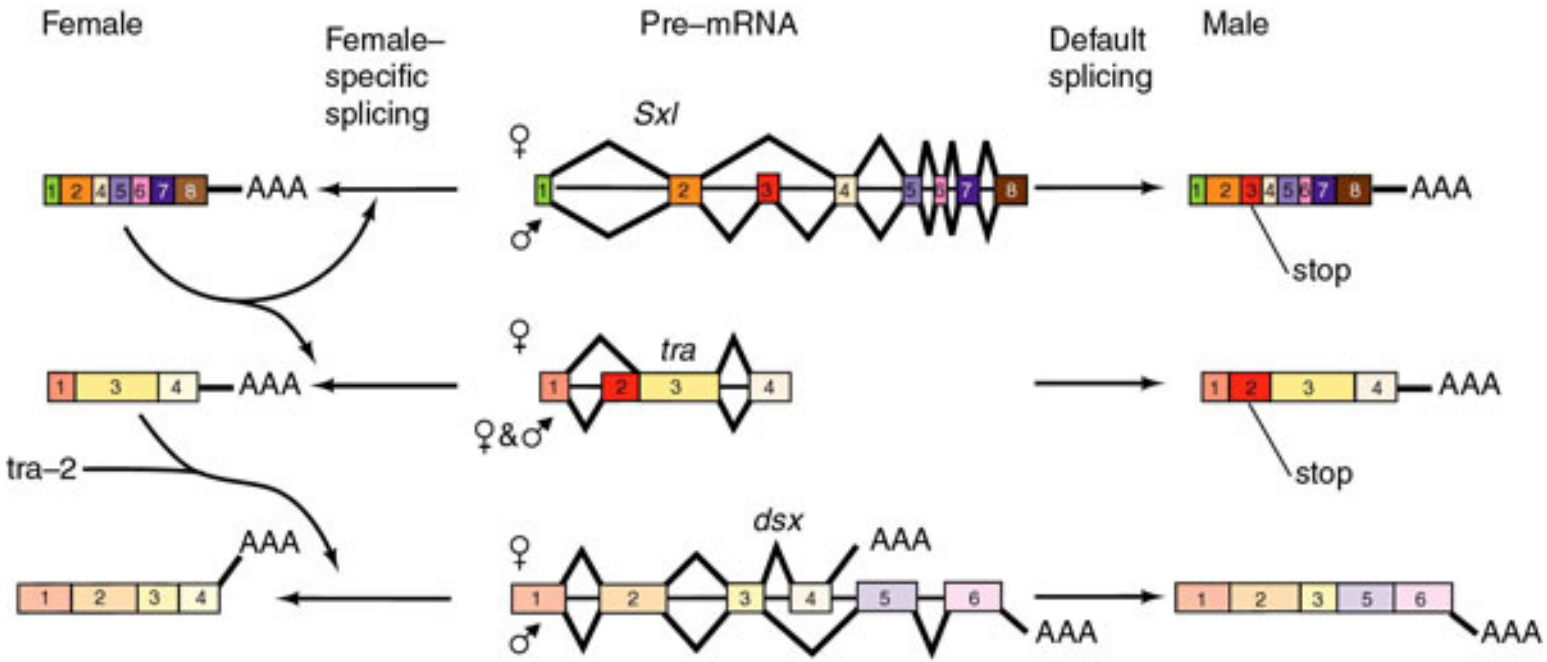
The „gene“ is an abstract element or atom of inheritance



The gene is a stretch of DNA which after transcription gives rise to a mRNA

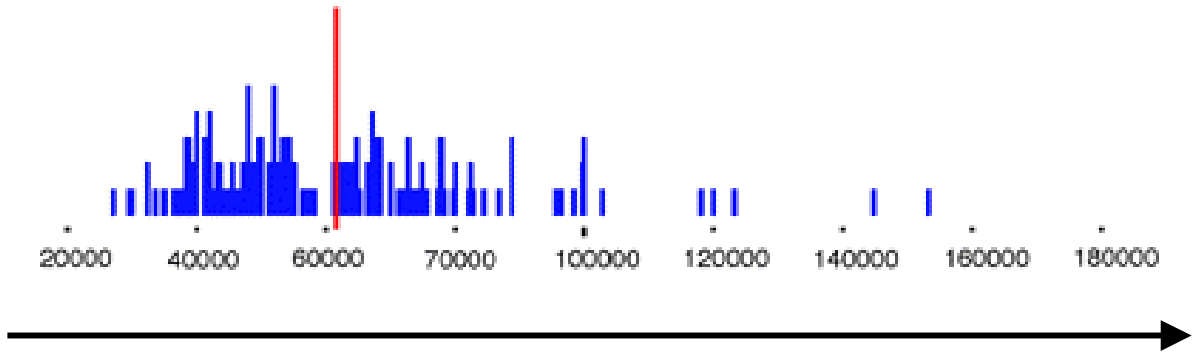


The gene is a stretch of DNA which after transcription and processing gives rise to a mRNA



Sex determination in ***Drosophila*** through alternative splicing

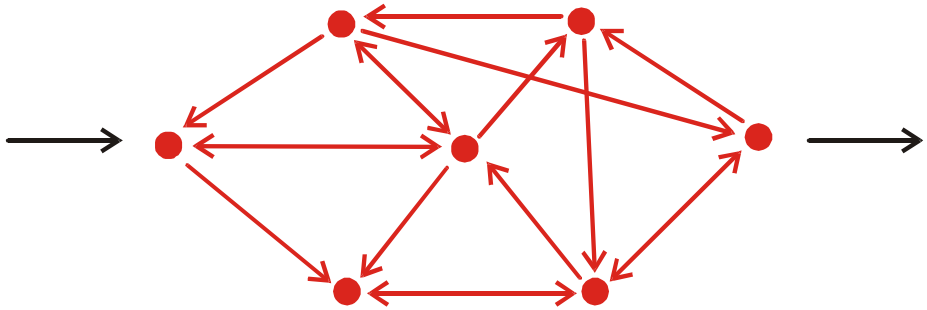
The process of protein synthesis and its regulation is now understood but the notion of the gene as a stretch of DNA has become obscure. The gene is essentially associated with the sequence of unmodified amino acids in a protein, and it is determined by the nucleotide sequence as well as the dynamics of the the process eventually leading to the m-RNA that is translated.



Number of genes in the human genome

The number of genes in the human genome is still only a very rough estimate

Linear chain



Network

Processing of information in cascades and networks

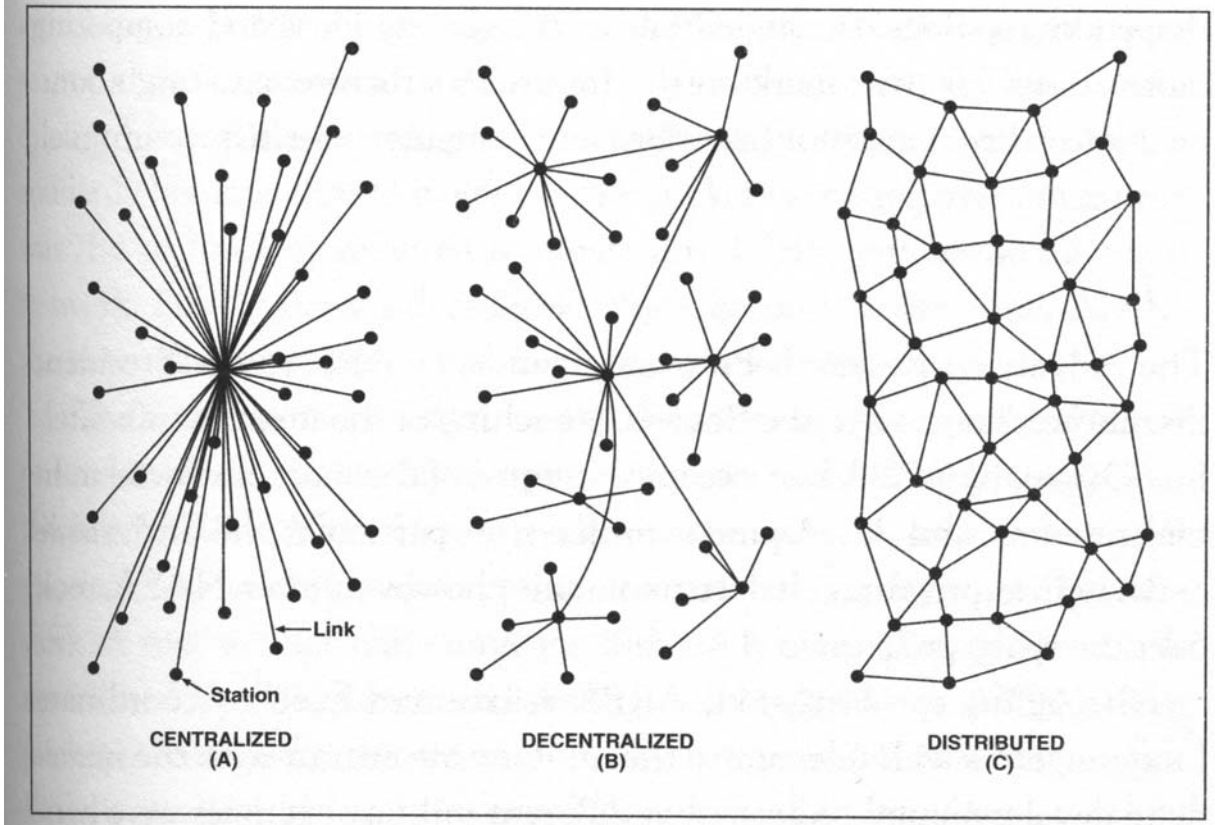


Figure 11.1 Paul Baran's Networks. *In 1964, Paul Baran began thinking about the optimal structure of the Internet. He suggested that there were three possible architectures for such a network—centralized, decentralized, and distributed—and warned that both the centralized and decentralized structures that dominated communications systems of the time were too vulnerable to attack. Instead, he proposed that the Internet should be designed to have a distributed, mesh-like architecture. (Reproduced with permission of Paul Baran.)*

Albert-László Barabási, Linked – The New Science of Networks. Perseus Publ., Cambridge, MA, 2002

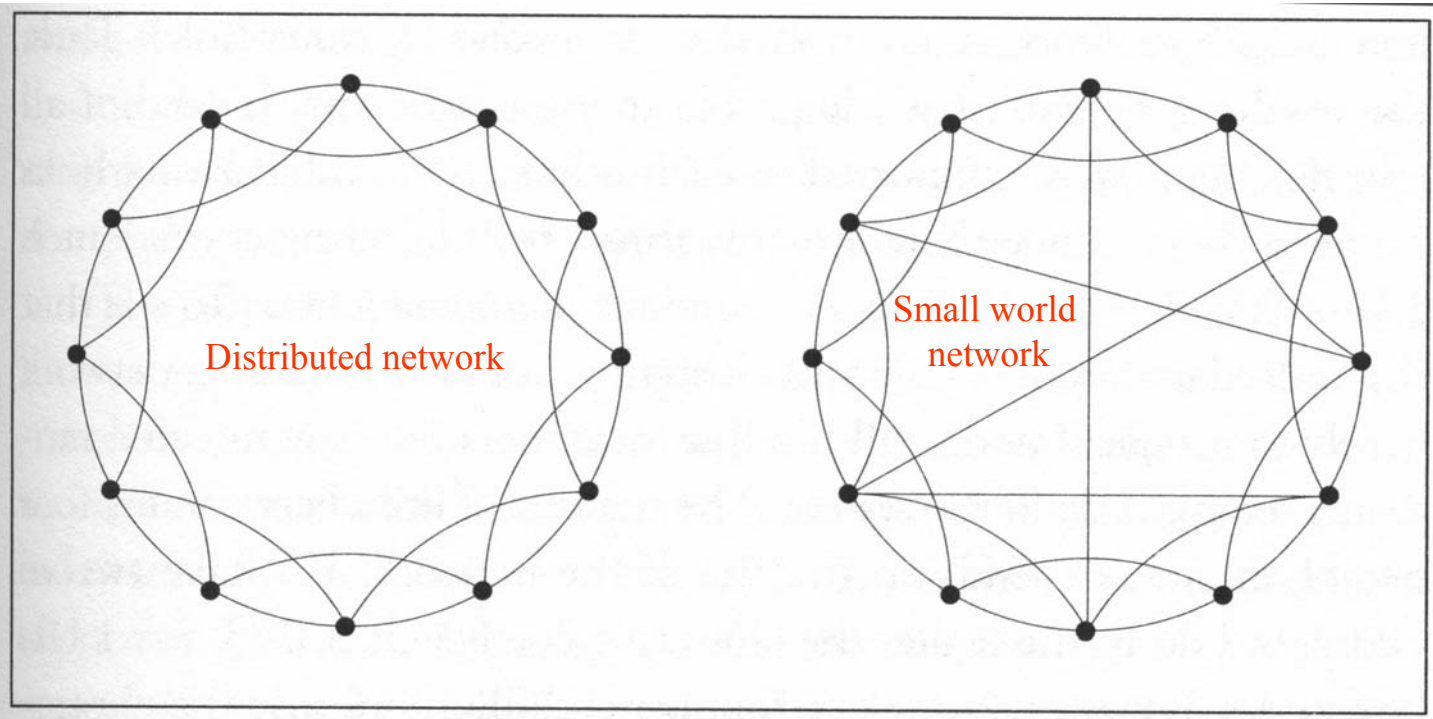


Figure 4.2 A Small and Clustered World. *To model networks with a high degree of clustering, Duncan Watts and Steven Strogatz started from a circle of nodes, where each node is connected to its immediate and next-nearest neighbors (left). To make this world a small one, a few extra links were added, connecting randomly selected nodes (right). These long-range links offer the crucial shortcuts between distant nodes, drastically shortening the average separation between all nodes.*

Albert-László Barabási, Linked – The New Science of Networks. Perseus Publ., Cambridge, MA, 2002

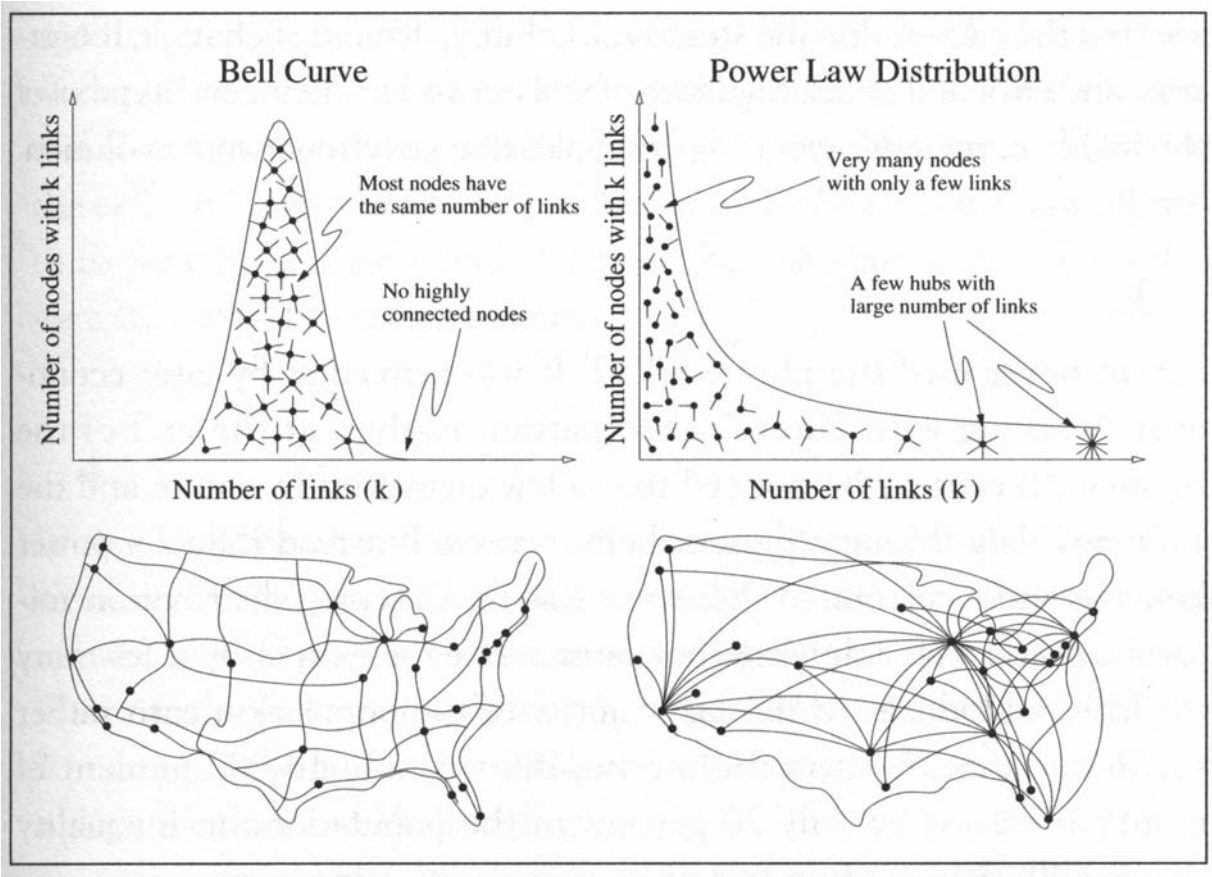
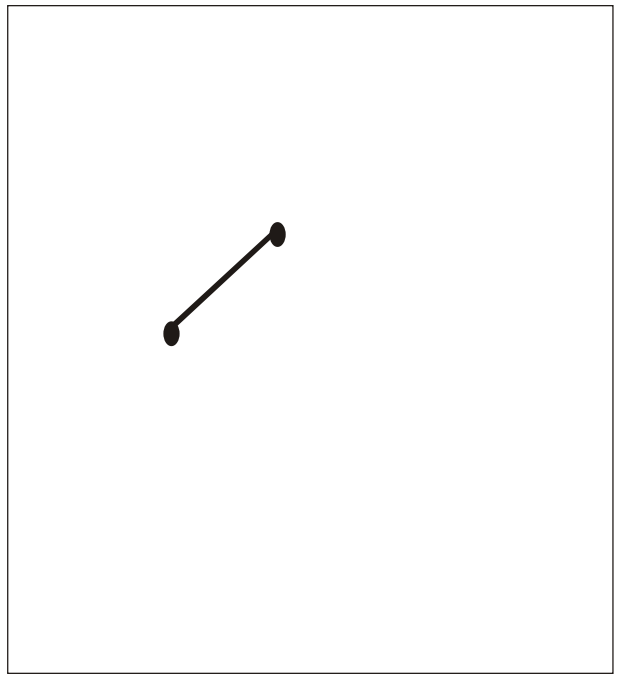
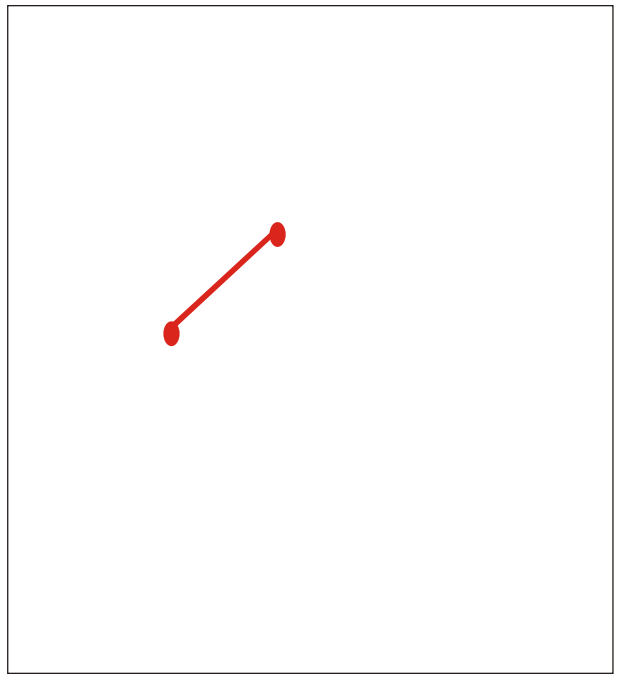


Figure 6.1 Random and Scale-Free Networks. *The degree distribution of a random network follows a bell curve, telling us that most nodes have the same number of links, and nodes with a very large number of links don't exist (top left). Thus a random network is similar to a national highway network, in which the nodes are the cities, and the links are the major highways connecting them. Indeed, most cities are served by roughly the same number of highways (bottom left). In contrast, the power law degree distribution of a scale-free network predicts that most nodes have only a few links, held together by a few highly connected hubs (top right). Visually this is very similar to the air traffic system, in which a large number of small airports are connected to each other via a few major hubs (bottom right).*

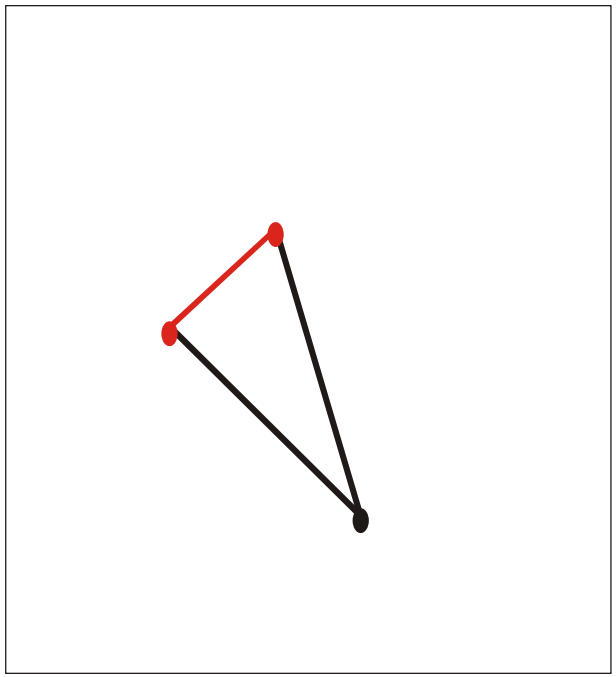
Albert-László Barabási,
Linked – The New Science of Networks
Perseus Publ., Cambridge, MA, 2002



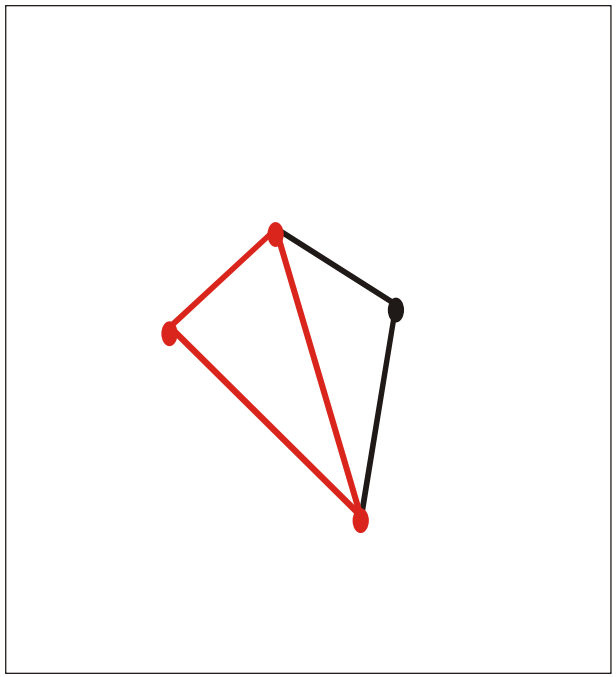
Formation of a scale-free network through evolutionary point by point expansion: Step 000



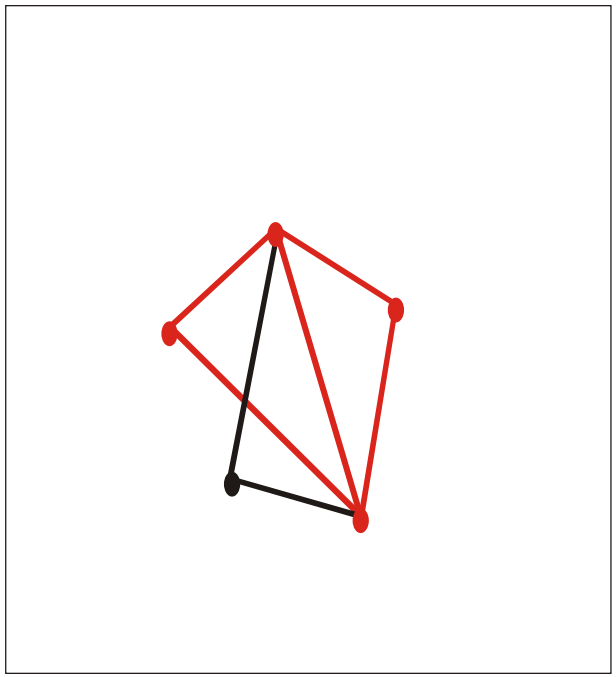
Formation of a scale-free network through evolutionary point by point expansion: Step 001



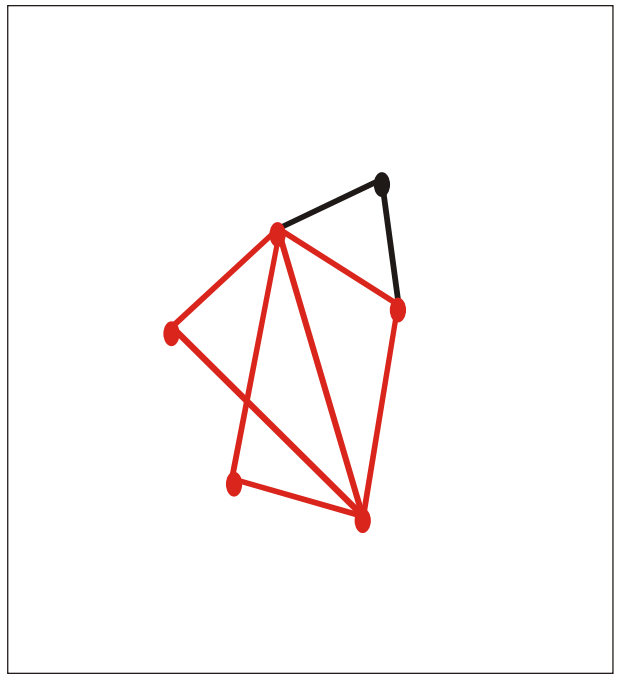
Formation of a scale-free network through evolutionary point by point expansion: Step 002



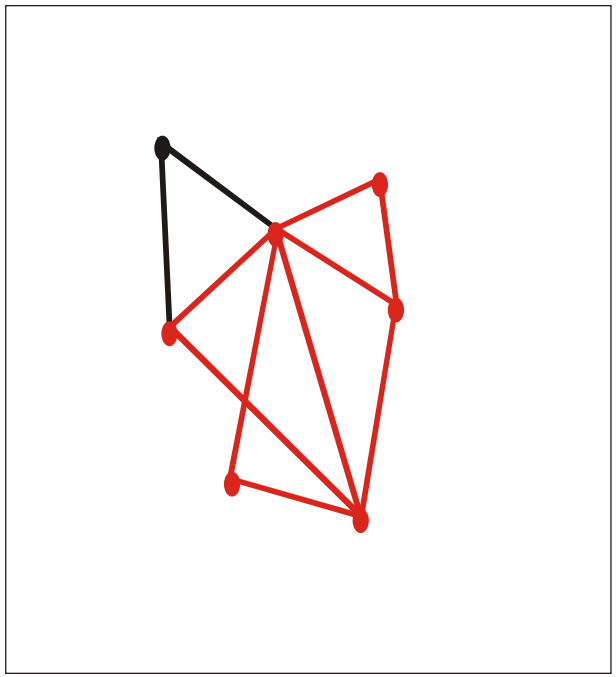
Formation of a scale-free network through evolutionary point by point expansion: Step 003



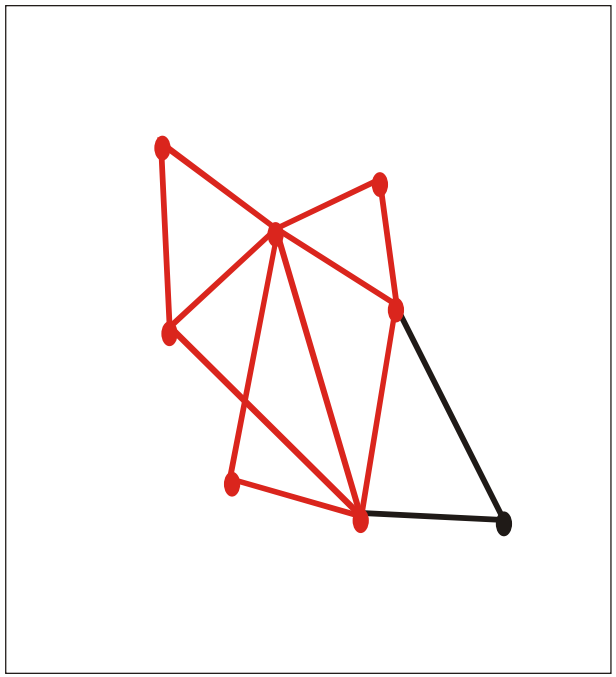
Formation of a scale-free network through evolutionary point by point expansion: Step 004



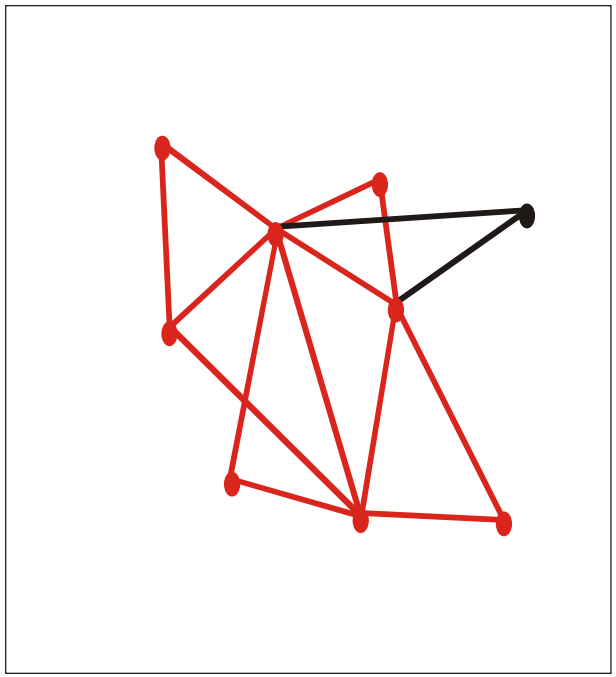
Formation of a scale-free network through evolutionary point by point expansion: Step 005



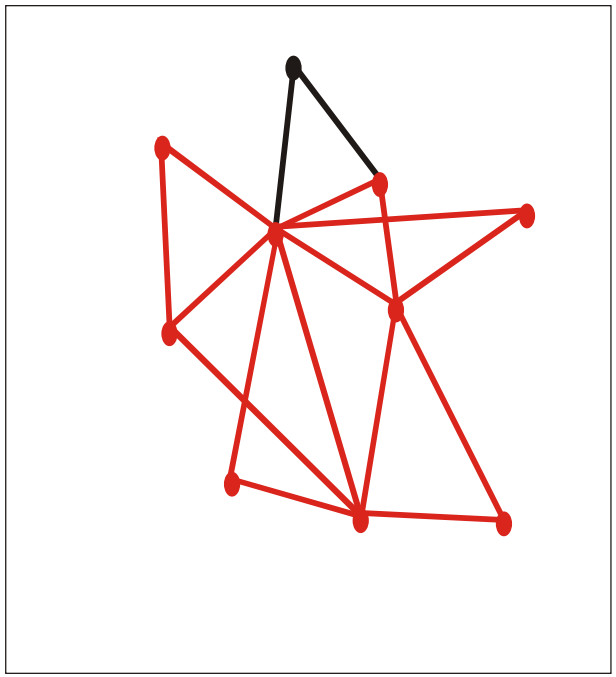
Formation of a scale-free network through evolutionary point by point expansion: Step 006



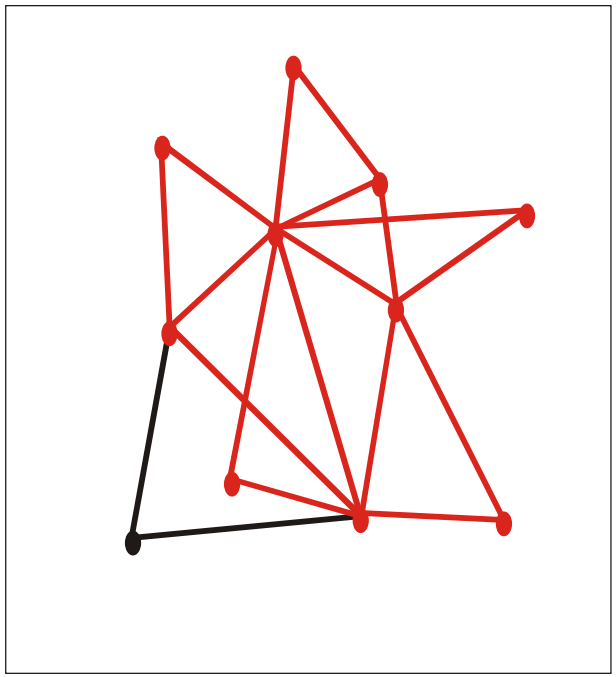
Formation of a scale-free network through evolutionary point by point expansion: Step 007



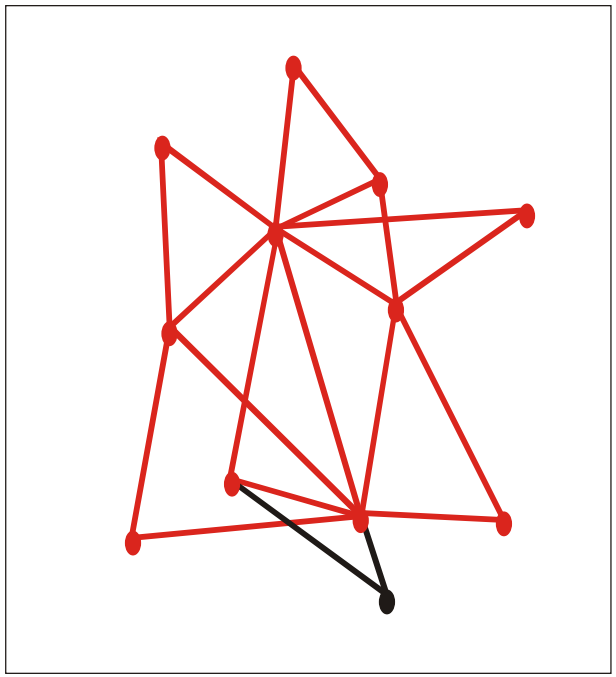
Formation of a scale-free network through evolutionary point by point expansion: Step 008



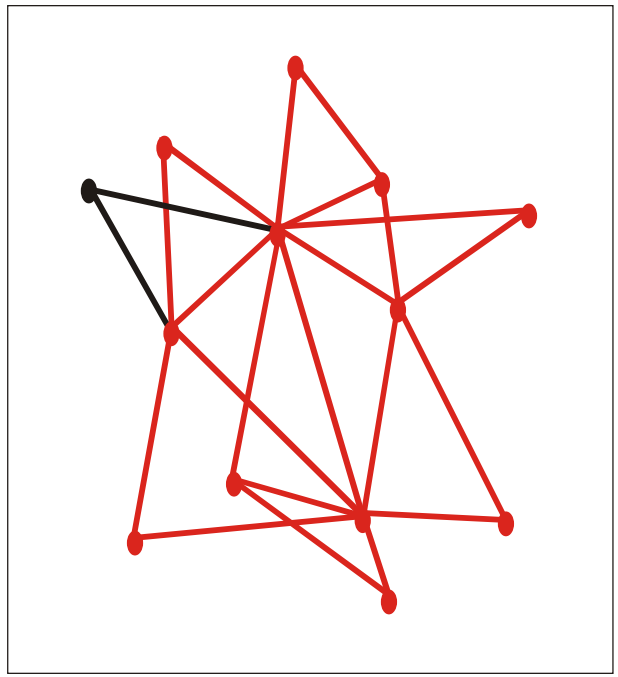
Formation of a scale-free network through evolutionary point by point expansion: Step 009



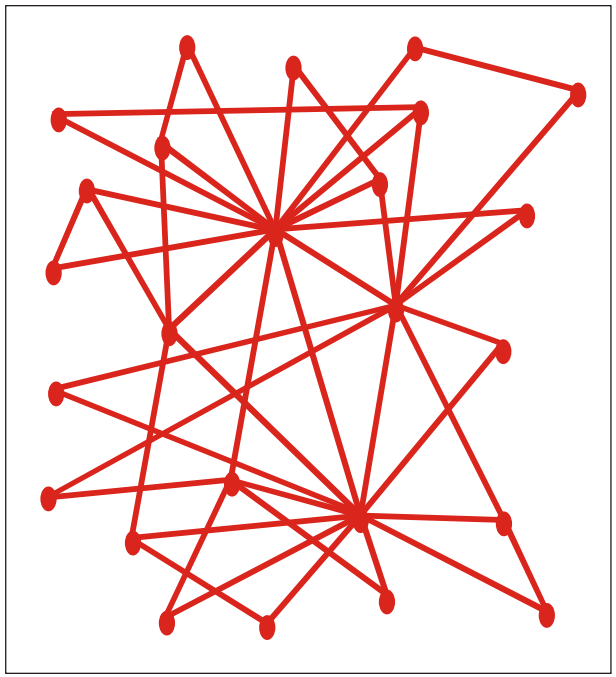
Formation of a scale-free network through evolutionary point by point expansion: Step 010



Formation of a scale-free network through evolutionary point by point expansion: Step 011

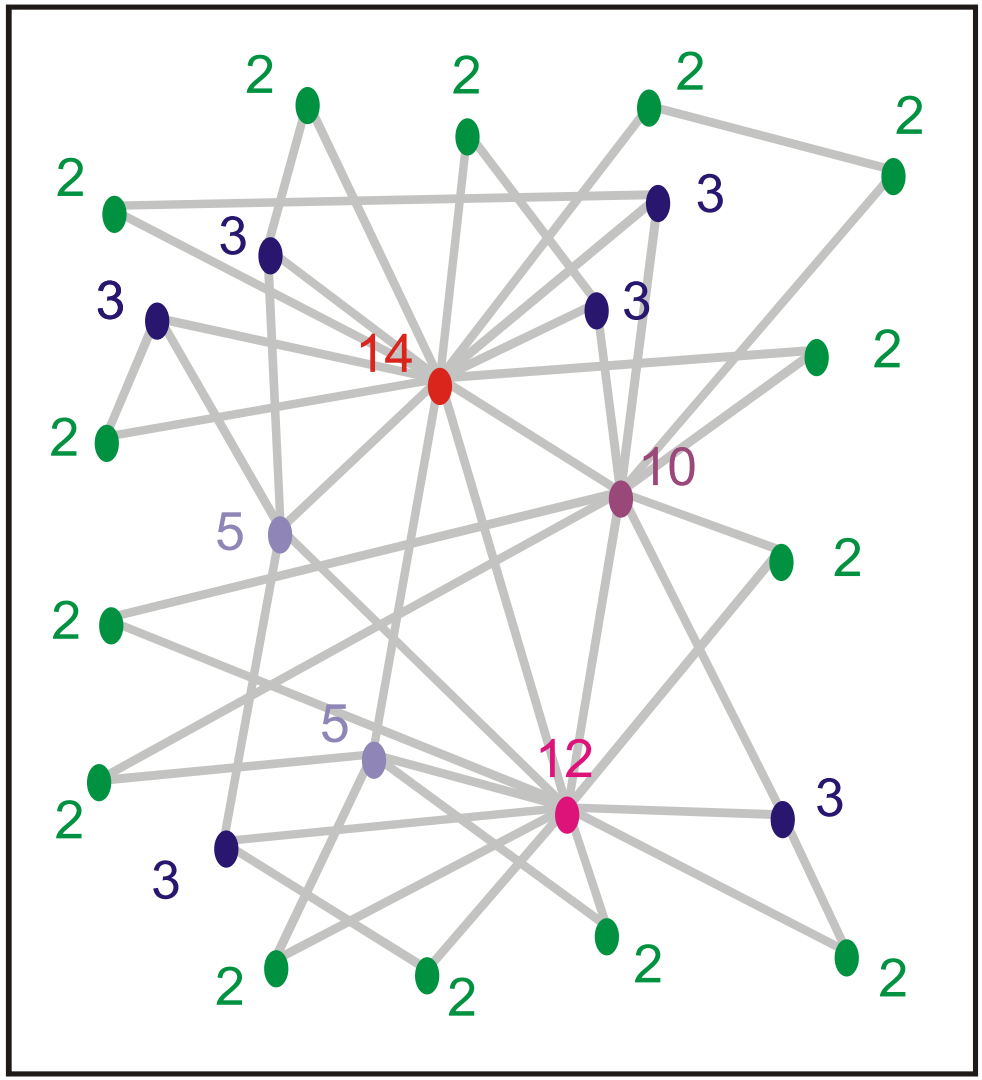


Formation of a scale-free network through evolutionary point by point expansion: Step 012



Formation of a scale-free network through evolutionary point by point expansion: Step 024

links	# nodes
2	14
3	6
5	2
10	1
12	1
14	1



Analysis of nodes and links in a step by step evolved network

Structures in **Directed Networks**

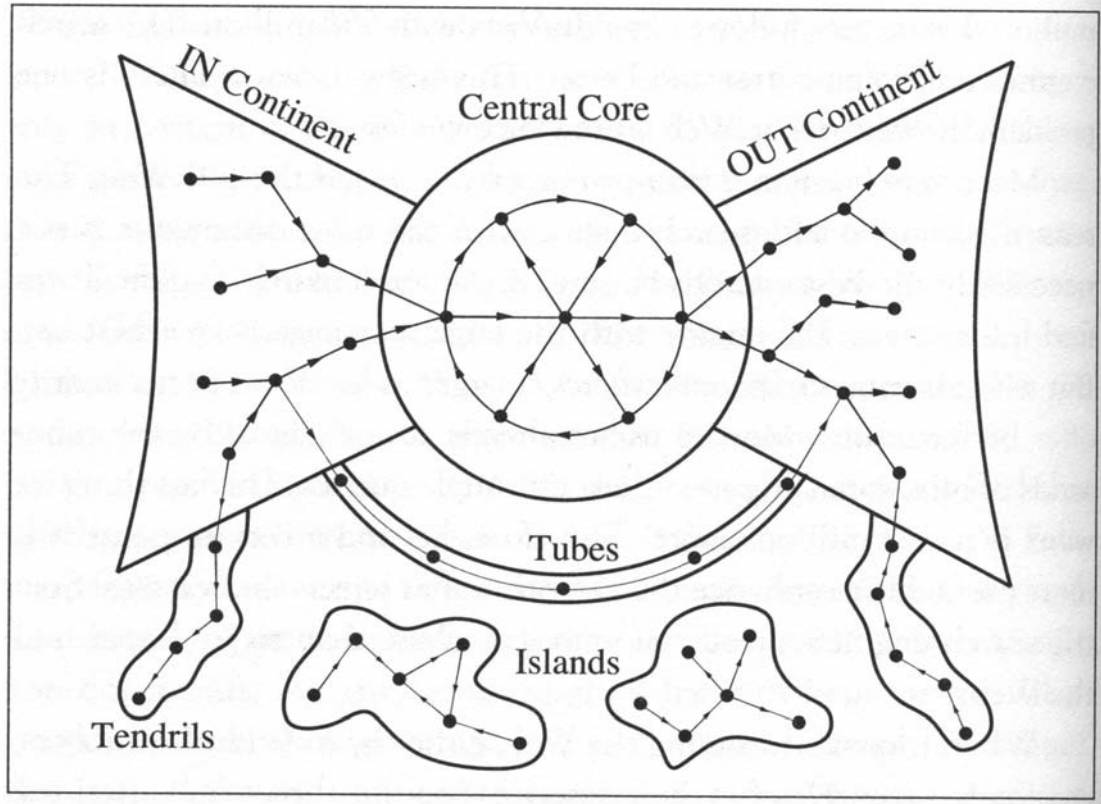
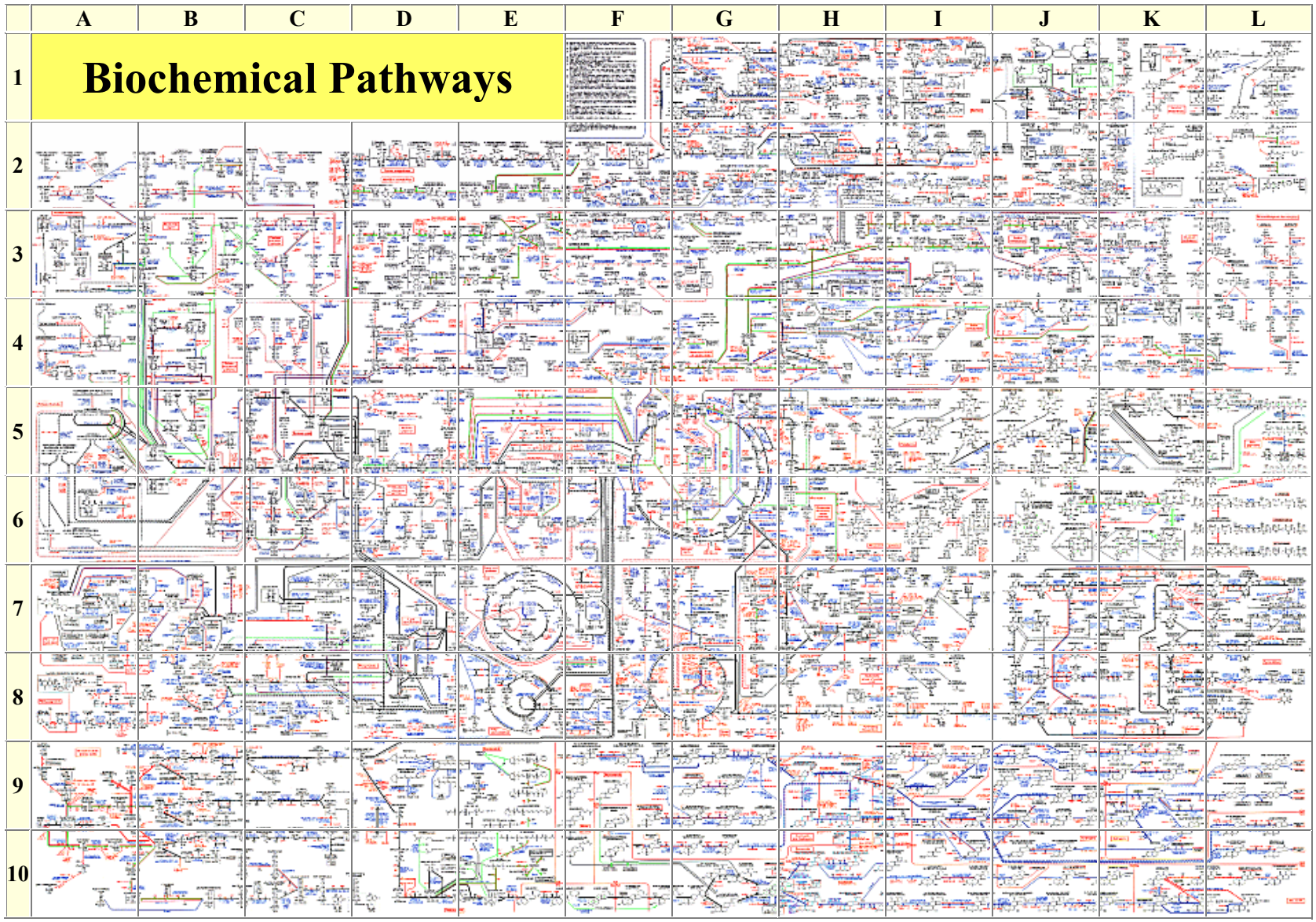


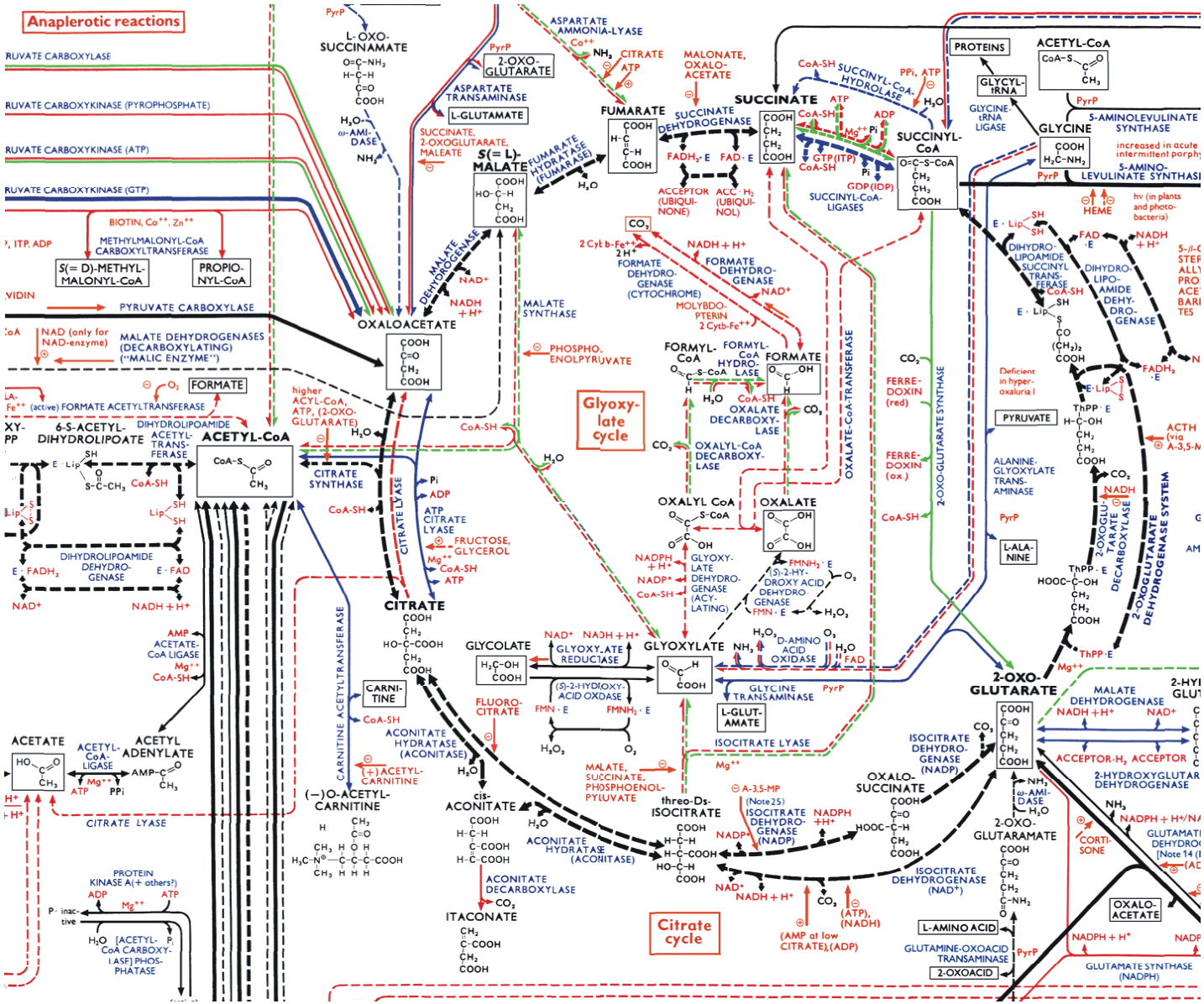
Figure 12.1 The Continents of a Directed Network. *Directed networks such as the World Wide Web naturally break down into several easily identifiable continents. In the central core each node can be reached from every other node. Nodes in the IN continent are arranged such that following the links eventually brings you back to the central core, but starting from the core doesn't allow you to return to the IN continent. In contrast, all nodes of the OUT continent can be reached from the core, but once you've arrived, there are no links taking you back to the core. Finally, tubes directly connect the IN to the OUT continent; some nodes form tendrils, attached only to the IN and OUT continents; and a few nodes form isolated islands that can't be accessed from the rest of the nodes.*

Albert-László Barabási,
Linked – The New Science of Networks.
Perseus Publ., Cambridge, MA, 2002

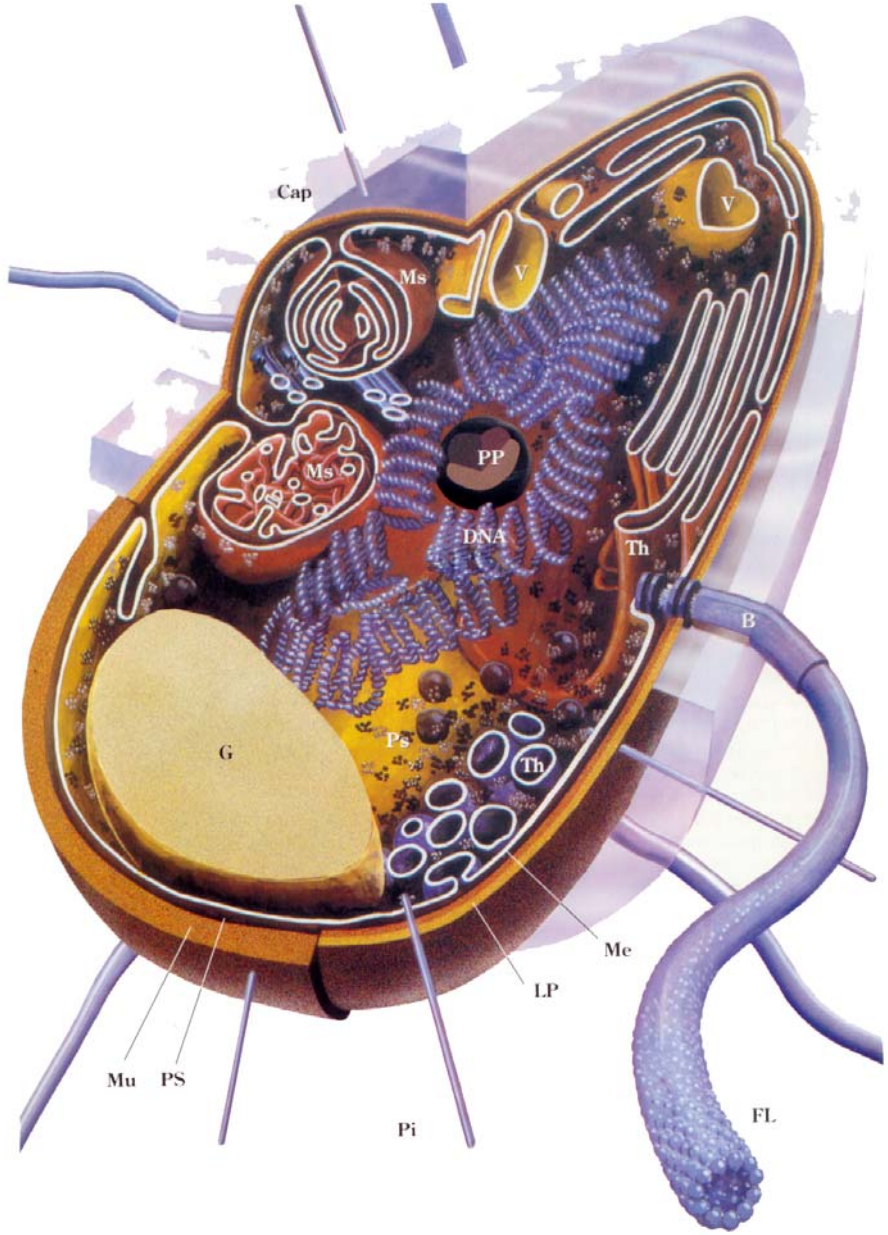


The reaction network of cellular metabolism published by Boehringer-Ingelheim.

The citric acid or Krebs cycle (enlarged from previous slide).



The bacterial cell as an example of an optimized nanostructure



Taming of sequence diversity through selection and evolutionary design of RNA molecules

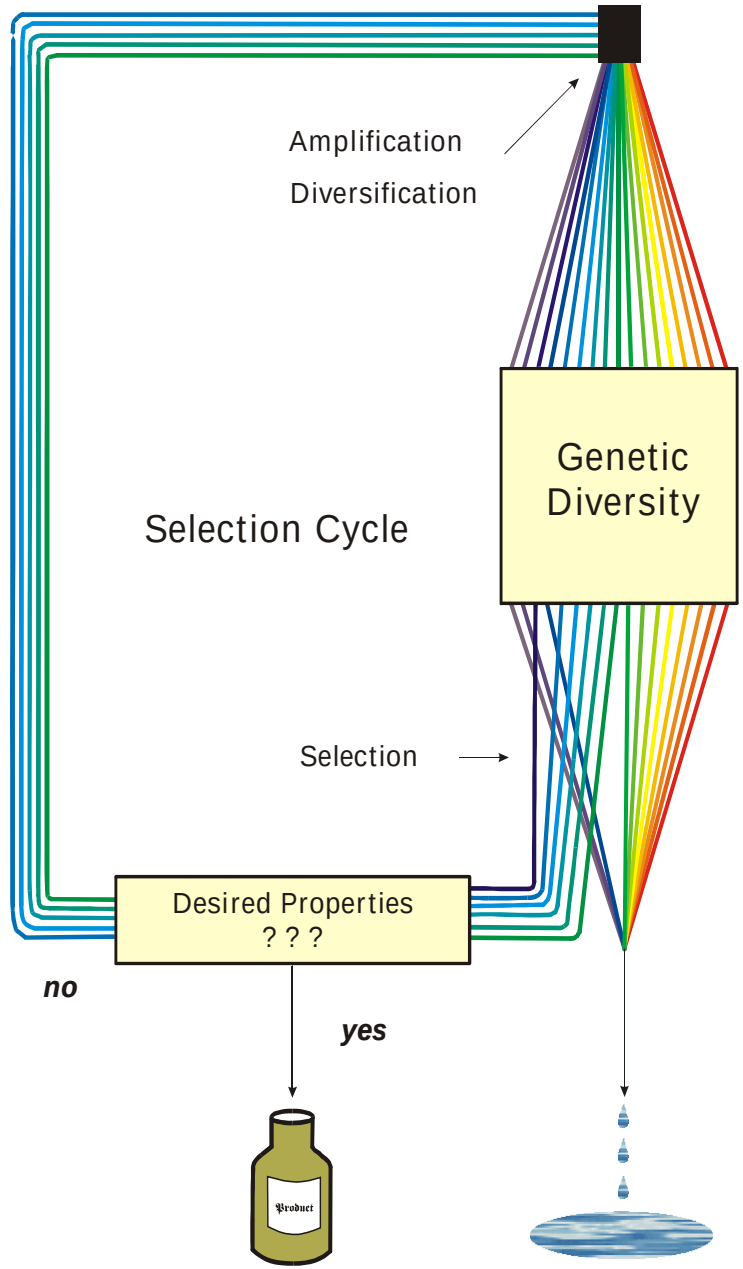
D.B.Bartel, J.W.Szostak, **In vitro** ***selection of RNA molecules that bind specific ligands***. Nature **346** (1990), 818-822

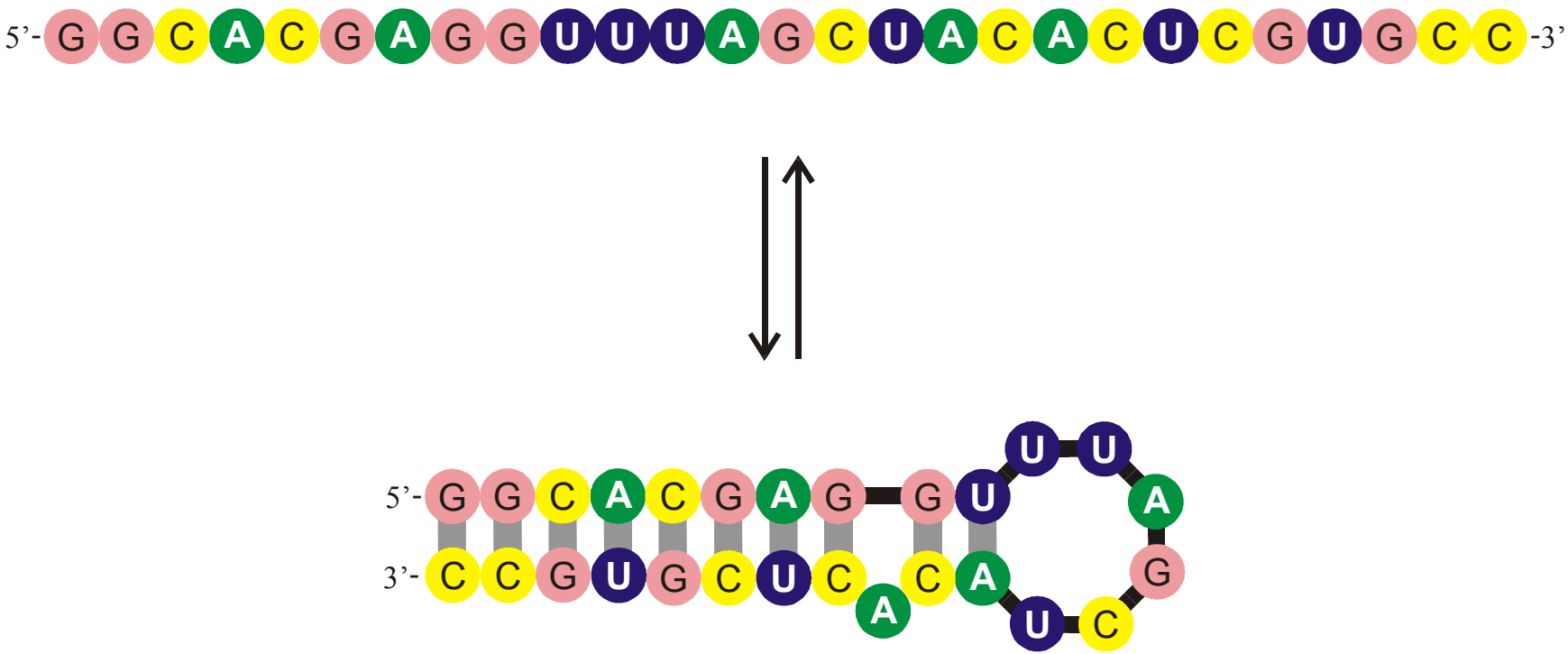
C.Tuerk, L.Gold, **SELEX** - ***Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage*** **T4** ***DNA polymerase***. Science **249** (1990), 505-510

D.P.Bartel, J.W.Szostak, ***Isolation of new ribozymes from a large pool of random sequences***. Science **261** (1993), 1411-1418

R.D.Jenison, S.C.Gill, A.Pardi, B.Poliski, ***High-resolution molecular discrimination by RNA***. Science **263** (1994), 1425-1429

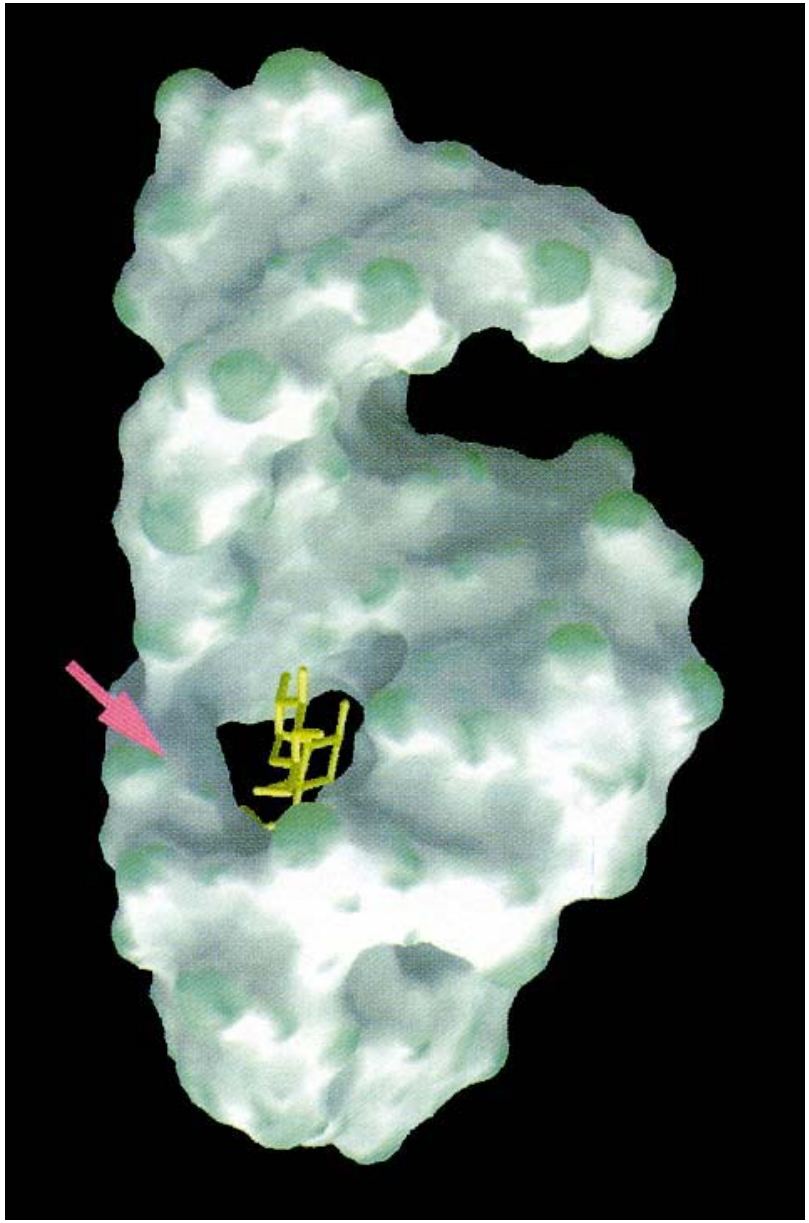
Selection cycle used in applied molecular evolution to design molecules with predefined properties





Formation of secondary structure of the tobramycin binding RNA aptamer

L. Jiang, A. K. Suri, R. Fiala, D. J. Patel, Chemistry & Biology **4**:35-50 (1997)

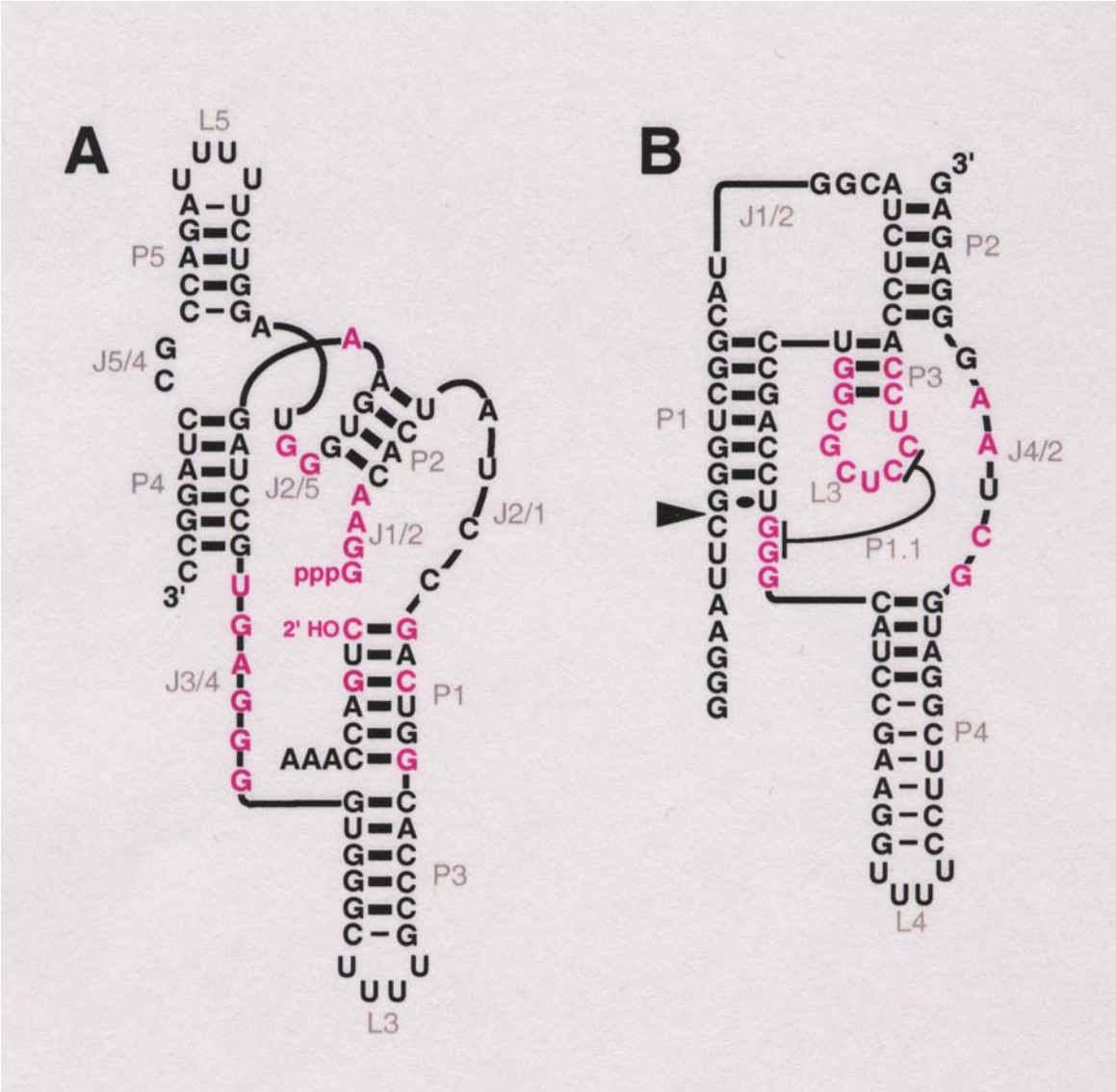


The three-dimensional structure of the tobramycin aptamer complex

L. Jiang, A. K. Suri, R. Fiala, D. J. Patel, Chemistry & Biology **4**:35-50 (1997)

A ribozyme switch

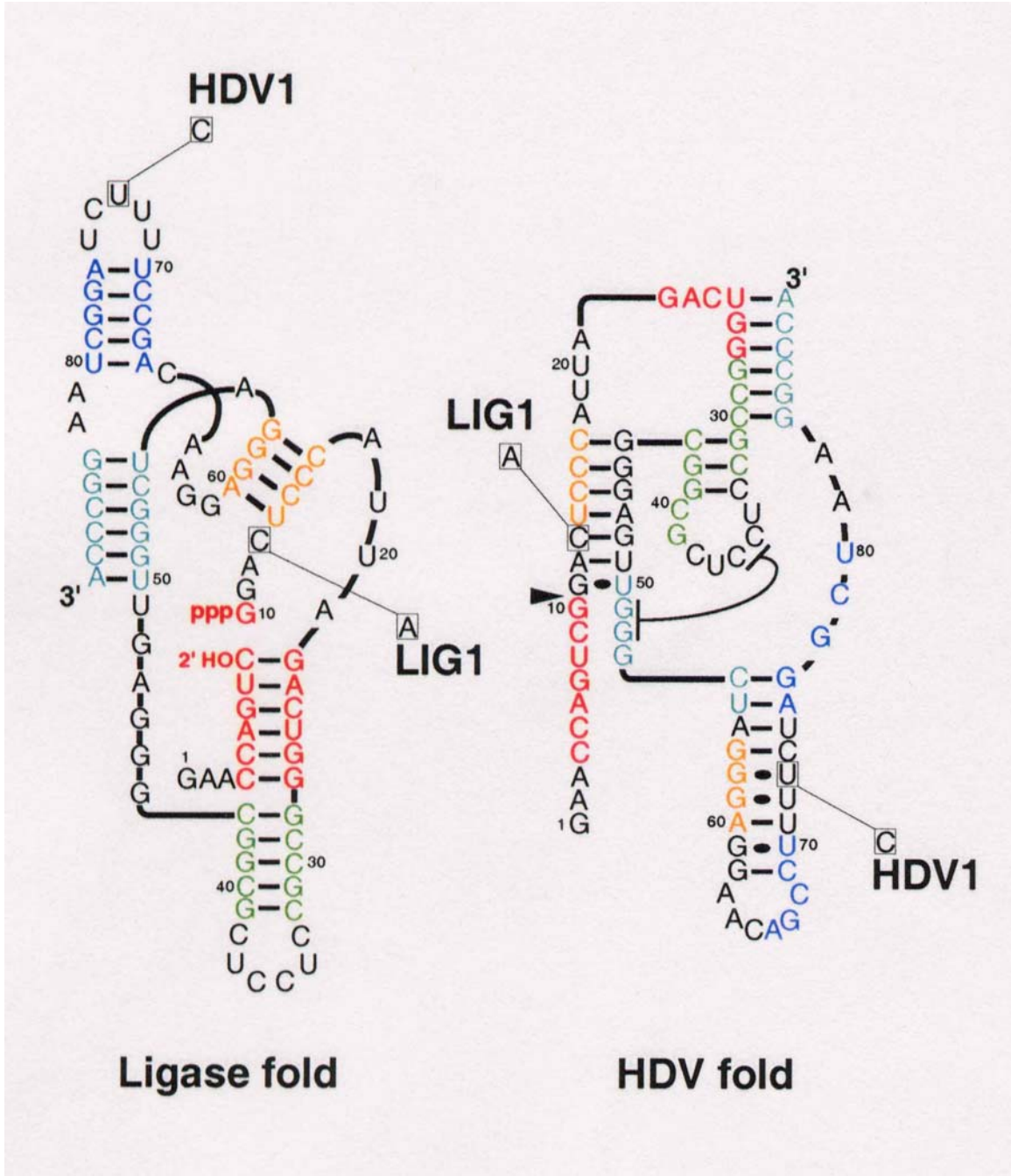
E.A.Schultes, D.B.Bartel, ***One sequence, two ribozymes: Implication for the emergence of new ribozyme folds***. Science **289** (2000), 448-452



Two ribozymes of chain lengths n = 88 nucleotides: An artificial ligase (**A**) and a natural cleavage ribozyme of hepatitis-d-virus (**B**)

The sequence at the ***intersection***:

An RNA molecules which is 88 nucleotides long and can form both structures



Bulletin of Mathematical Biology, Vol. 59, No. 2, pp. 339–397, 1997
Elsevier Science Inc.

0092-8240/97 $17.00 + 0.00

S0092-8240(96)00089-4

GENERIC PROPERTIES OF COMBINATORY MAPS: NEUTRAL NETWORKS OF RNA SECONDARY STRUCTURES[1]

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Random graph theory is used to model and analyse the relationships between sequences and secondary structures of RNA molecules, which are understood as mappings from sequence space into shape space. These maps are non-invertible since there are always many orders of magnitude more sequences than structures. Sequences folding into identical structures form *neutral networks*. A neutral network is embedded in the set of sequences that are *compatible* with the given structure. Networks are modeled as graphs and constructed by random choice of vertices from the space of compatible sequences. The theory characterizes neutral networks by the mean fraction of neutral neighbors (λ). The networks are connected and percolate sequence space if the fraction of neutral nearest neighbors exceeds a threshold value ($\lambda > \lambda^*$). Below threshold ($\lambda < \lambda^*$), the networks are partitioned into a largest "giant" component and several smaller components. Structures are classified as "common" or "rare" according to the sizes of their pre-images, i.e. according to the fractions of sequences folding into them. The neutral networks of any pair of two different common structures almost touch each other, and, as expressed by the conjecture of *shape space covering* sequences folding into almost all common structures, can be found in a small ball of an arbitrary location in sequence space. The results from random graph theory are compared to data obtained by folding large samples of RNA sequences. Differences are explained in terms of specific features of RNA molecular structures. © *1997 Society for Mathematical Biology*

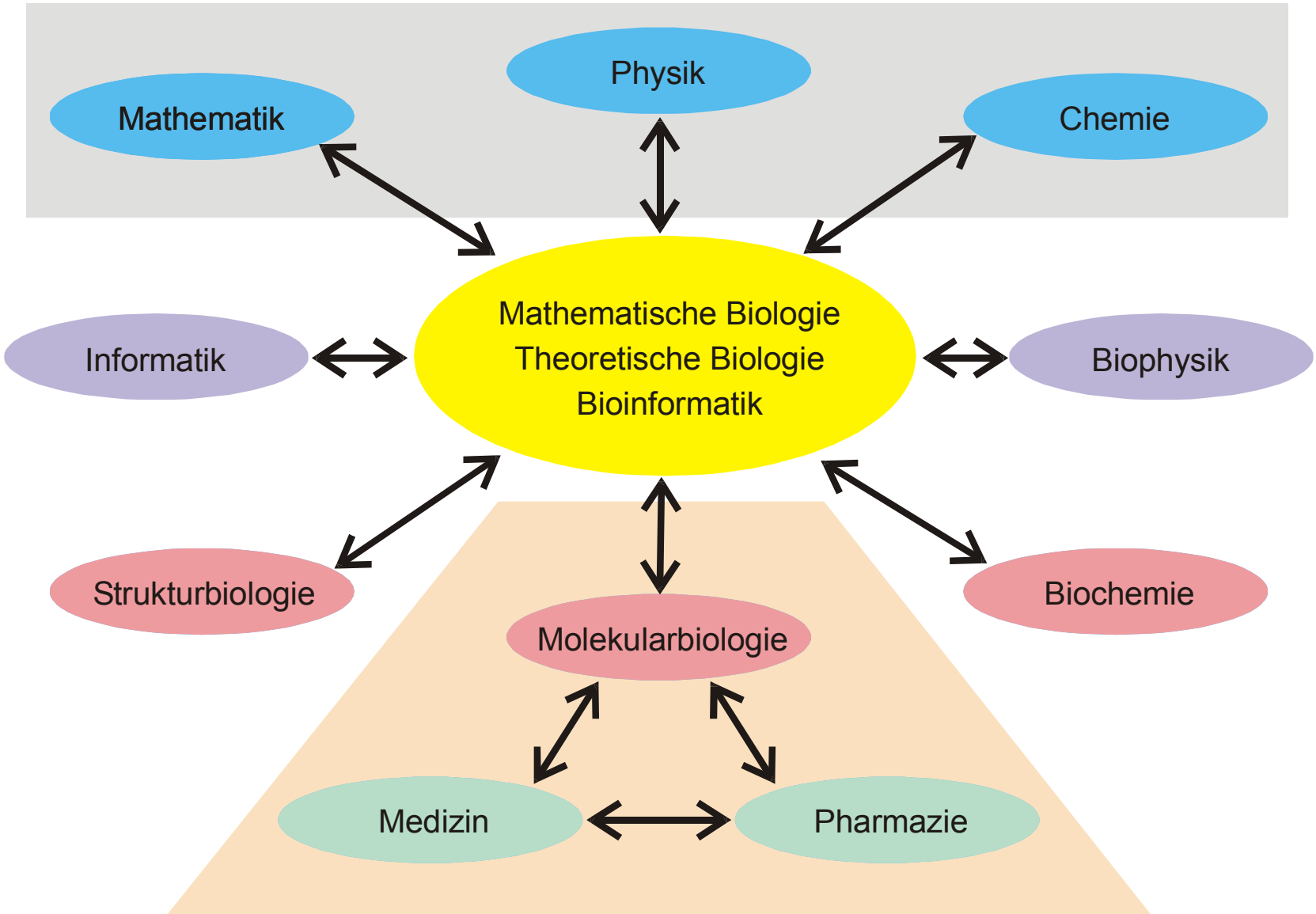
THEOREM 5. INTERSECTION-THEOREM. *Let* s *and* s′ *be arbitrary secondary structures and* **C**[s], **C**[s′] *their corresponding compatible sequences. Then,*

$$\mathbf{C}[s] \cap \mathbf{C}[s'] \neq \varnothing.$$

Proof. Suppose that the alphabet admits only the complementary base pair $[XY]$ and we ask for a sequence x compatible to both s and s'. Then $\gamma(s, s') \cong D_m$ operates on the set of all positions $\{x_1, \ldots, x_n\}$. Since we have the operation of a dihedral group, the orbits are either cycles or chains and the cycles have even order. A constraint for the sequence compatible to both structures appears only in the cycles where the choice of bases is not independent. It remains to be shown that there is a valid choice of bases for each cycle, which is obvious since these have even order. Therefore, it suffices to choose an alternating sequence of the pairing partners X and Y. Thus, there are at least two different choices for the first base in the orbit. ■

Remark. A generalization of the statement of theorem 5 to three different structures is false.

Reference for the definition of the intersection and the proof of the ***intersection theorem***



Vernachlässigte und überbewertete Fächer in der Ausbildung der Molekularbiologen

Zur gleichen Zeit schreien viele nach einer neuen Biologie. Man liest, sie wollen „Integrative Biologie“ machen, oder „Systembiologie“. Kaum einer nennt es beim richtigen Namen: Theoretische Biologie. Weil diese einen schlechten Klang hat. Ich jedoch denke, ich kann die Sünden der Vergangenheit vergeben und nehme das Wort: Wir brauchen eine Theorie, die das alles einschließt. Stellen Sie sich doch nur mal vor, wir müssen am Ende all dieses Zeug nicht nur unter Fachleuten besprechen, sondern müssen es an Universitäten lehren, in der Schule, und es der Öffentlichkeit erklären. Wie sollen wir das machen ohne umfassende Theorie? Das, denke ich, ist die Herausforderung, der wir uns stellen müssen.

At the same time people are crying for a new biology. They say, they want to make “Integrative Biology” or “Systems Biology”. Hardly anyone calls it by its proper name: Theoretical Biology. Because it has a bad reputation. I think, however, I can remit the sins of the past and declare: We need a theory, which comprises all that (*Molecular, Structural, Cellular, Developmental, …… , and Evolutionary Biology*). Imagine, eventually, we not only need to discuss all this stuff with our expert colleagues, but we have to teach it at universities, at schools, and to the public. How could we manage without a comprehensive theory? This is the challenge we have to meet.

Sydney Brenner im Gespräch: „*Eine einsame Stimme aus der Prägenomik Ära*“. Laborjournal 2002, Heft 4:28 – 33.

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Time to free tomorrow's biologists from pre-med tyranny?

10 September 2002 17:35 EST

by *Lois Wingerson*

Quality training for the biologists of the future depends on liberating life-science programs from the pre-med template and especially from the criteria of the Medical College Admissions Test (MCAT), according to a report from the US National Academy of Sciences (NAS), released today.

Asking colleges to rethink their entire undergraduate life-science curricula, the NAS committee also called for a greater focus on chemistry, physics, and math, more interdisciplinary subject materials, and mathematical curricula that go beyond calculus and statistics to embrace other quantitative skills relevant to life science not only today but tomorrow.

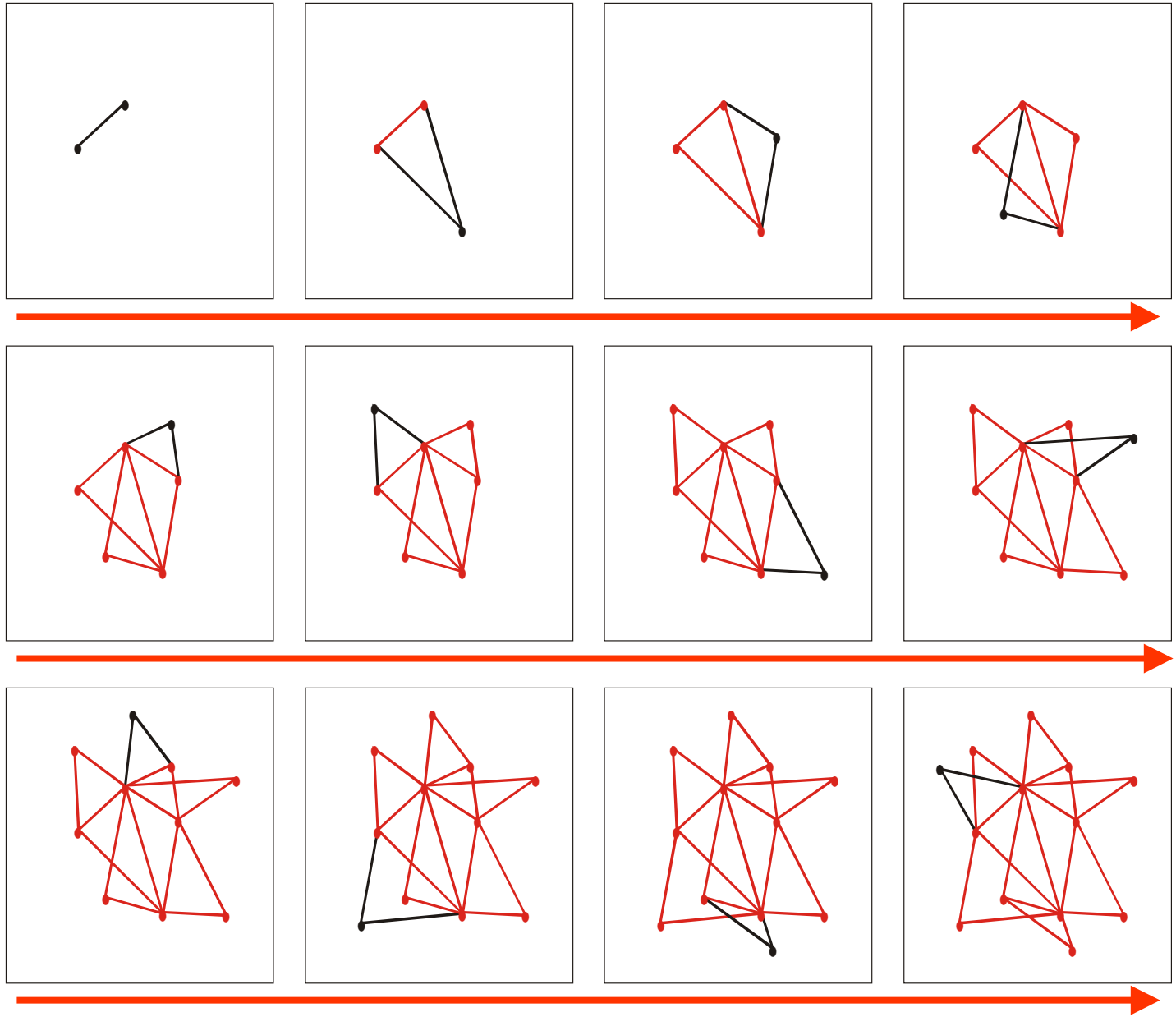
"Most biology students of today are being prepared for the biology of the past, not the future," said Stanford University neurology professor Lubert Stryer, chairman of the committee that wrote the report. Experiments such as imaging molecular motors, unimaginable 20 years ago, are now being carried out by graduate students, he noted, yet many Bio 101 students learn little more than "factoids."

See also:

Comparison of problem-and lecture-based pharmacology teaching
[Opinion]
Martin C. Michel, Angela Bischoff and Karl H. Jakobs
Trends in Pharmacological Sciences, 2002, 23:4:168-170

Teaching the scientific thrill
[In brief]
Stephanie Bono de
Trends in Biochemical Sciences, 2001, 26:11:647

Biochemistry and molecular biology teaching over the past 50 years
E.J. Wood
Nat Rev Mol Cell Biol, 2001 Mar 2:217-21



Formation of a scale-free network through point by point expansion