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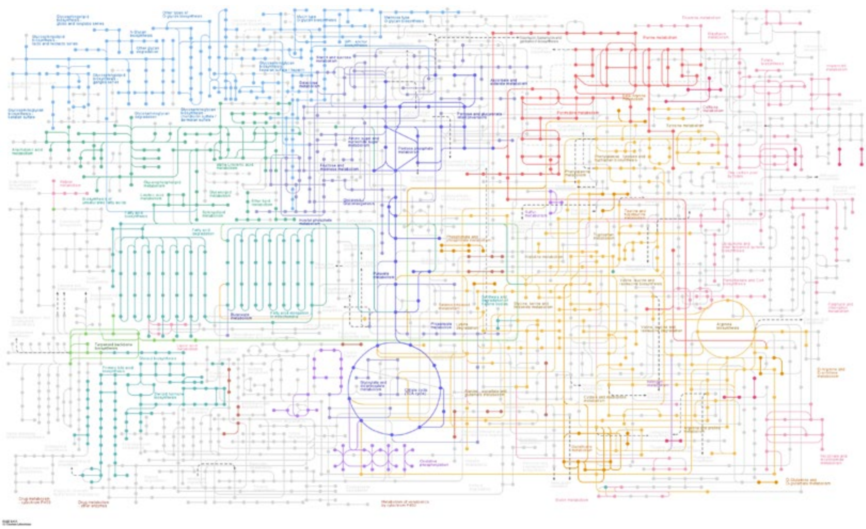
Diagrammatic Traditions: Color in Metabolic Maps



1: The metabolic map *Kyoto Encyclopedia of Genes and Genomes*.

Within a fine black frame of approximately 2:1 width to height, the image above (FIG. 1) shows a large number of well-ordered fine parallel vertical and horizontal lines against a white background, connected to one another by half-circular curves, sometimes also by circles and ovals. Where they run parallel, these lines are peppered with dots at symmetrical altitudes. All lines are depicted in eleven different soft pastel and brilliant colors, which dominate specific areas of the drawing; few additional lines are in gray. Salient are two groups of thirteen parallel vertical lines in a bluish-green in the left center. Their design is reminiscent of abstract floral art deco graphics. Apart from the circular forms that build connections between lines, all lines are either strictly vertical or strictly horizontal (in a ninety degree to one another). While the specific areas of the map appear in a specific color, the respective color is repeated in an oval nametag to the respective zone of the graphic that bears the name (written in white against the colorful background) of a metabolic pathway (e. g., on the violet tag: "Energy Metabolism"). In the very center, a long vertical line ending in a large circle in the lower part of the center depicted in violet-blue captures one's attention, bearing the tag "Carbohydrate Metabolism," and on the top

2–7: Cutouts from the metabolic map *Kyoto Encyclopedia of Genes and Genomes* (see fig. 1).

right, a tag of strong light-red, nearly apricot color attracts our gaze ("Nucleotide Metabolism" is written on it in white letters), while from there red vertical lines with their dots seem to seep downwards into the drawing like blood. Several details of the overall graphic by their symmetry and circular forms remind one of abstracted organismic, sometimes floral forms (FIG. 2–7).

This graph (FIG. 1) is a metabolic map, published in the year 2000 by a Japanese laboratory and labelled *Kyoto Encyclopedia of Genes and Genomes*.[1] The image is subtitled with the acronym, KEGG, in dark green letters, with G for genes and genomes that seem to be tumbling out of the E for Encyclopedia.

The metabolic map and the color question

Metabolic maps like the KEGG map depict the myriad ways (chemical pathways) molecules can take inside of organisms during anabolism or catabolism. Scientists have been drawing chemical pathways since the end of the nineteenth century. A chemical pathway, as more explicitly visible in FIGURE 8, in one or several steps, depicts the transition of a molecule from one state to another, often by adding or substracting one or several atoms and with the help of enzymes.

The first chemical pathways were simple reaction pathways entailing only a few visual elements. In those days, they were not referred to this way – the terminology "biochemical pathway" or "metabolic pathway" first appeared in the 1940s, labeling charts such as the first metabolic path, the Glycolysis, which was then for the first time fully completed. In the following decades, more and more charts of different metabolic paths in humans, animals and plants were published. As noted above, a metabolic map, which is the topic of this article, shows more than just one path; it

1 Minoru Kanehisa, Susumu Goto: KEGG: Kyoto Encyclopedia of Genes and Genomes. In: *Nucleic Acids Research 28 (1)*, 2000, pp. 27–30; http://www.genome.jp/kegg-bin/show_pathway?scale=0.70&query=Glyoxylat-cycle&map=cge01100&scale=0.35&auto_image=&show_description=hide&multi_query=&show_module_list=, acc. 03-15-2019.

shows the entanglement of various paths that intersect, combining to construct the map together. It is relevant to note that the metabolic map is an ambivalent type of map: it is neither topological, nor is it simply conceptual. Instead, it guides scholars through the real world of biochemical substances by depicting the relationship between the substances.

The KEGG map by Kanehisa Laboratories is one of the most successful online tools in biochemical mapping that has emerged since the end of the 1990s.[2] It is a surface for large databases that can be accessed by clicking on the different dots and pathway tags.

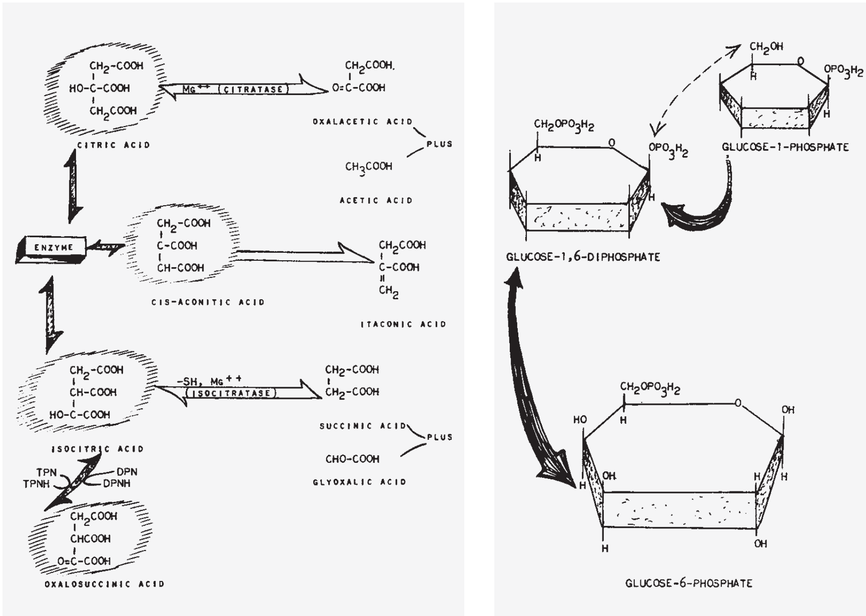
The choice of colors and overall layout of this rapidly spreading KEGG map (in 2002 it already appeared in the Stryer, a biochemistry textbook of near worldwide circulation)[3] meant a break with the color code known up to then in biochemistry textbooks and most common wall charts, where a triad of primary colors (the achromatic color black and in addition red, blue and yellow or green)[4] dominate to this day.

As most symbols and graphs are standardized in chemistry (see the following section), it is only fair to assume that this is the case for color as well; however, there is no such color standard. Looking for reasons for the specific color choices, listeners at presentations I gave on (polychrome) diagrams in the sciences tend to suggest that the selection of red, blue and green in such diagrams was simply because it was those colors that the respective printing house had on site or could produce. Is this the case? Does technology (alone) govern the color choices in diagrams? Often this suggestion of technical reasons is followed by a reference to CMYK (cyan, magenta, yellow and k for key, which is black) that are used in professional printing as basic colors, which began with the illustrator William

2 Kanehisa, Goto (s. fn. 1).

3 Jeremy M. Berg, John L. Tymoczko, Lubert Stryer: *Biochemistry,* New York: W.H. Freeman, 2002.

4 The European color tradition during different times knew the combinations red and blue and in addition yellow or green as primary colors, resulting in either three or four of them, when yellow and green were both added to red and blue as primary colors. After the end of the gothic color system which favored red, blue and yellow, according to Thürlemann in Italy, a four-color system including green appeared and became the standard in the north, while painters in the Netherlands stuck to the trichromatic red, blue, green (Felix Thürlemann: Grün – die verstoßene Vierte. Zur Genealogie des modernen Farbpurismus. In: Bernhard Bürgi (ed.): *Rot – Gelb – Blau: die Primärfarben in der Kunst des 20. Jahrhunderts*, Kunstmuseum St. Gallen, Friedericianum, Kassel. Stuttgart: Gerd Hatje, 1988, pp. 11–28). Briefly after 1600 though, different color theoretical tractates were published which brought the trias red, blue and yellow back into focus and on the canvasses for the rest of modernity, especially when – as in the Bauhaus tradition – primary colors were seen as "pure." In natural science teaching material, we find green replacing yellow frequently given that the light color yellow is difficult to read on white paper.



8: Examples of pathways in Umbreit's *Metabolic Map*, 1960.

Kurtz, who patented the first color-separation technique with these colors in 1892.[5] Yet, the color tones vermillion, ultramarine blue and yellow (alternatively green) that dominate in (bio-)chemistry textbooks differ strongly from the tones we refer to with CMYK. In offset printing with CMYK, the red, blue and green (or yellow) used in scientific textbooks are the result of mixed printing, which could be used to produce any shade of any color.[6]

In all scientific disciplines, there are historical and current diagrams in which color is used without any reference to nature (i. e., they are not mimetically resonant). Still, there is little theoretical literature on color in scientific diagrams that could help clarify the question of color choices in the scientific practice of diagram drawing. Theoretical reflections on color in scientific images have so far mainly

5 University of Michigan: American Printer and Lithographer, vol. 36, Michigan: Moore Publishing Company, 1903.

6 This is also true in our common use of desktop printers: the ink or toner cartridges may be CMYK, still the European and American user tends to choose RGB colors on the computer screen which will then be the colors printed.

been published in the field of history of science. These studies can be divided into five types: the history of the ontology of color, which most frequently belongs to the history of physics;[7] studies on the history of the color map for standardization in science and technology;[8] studies on the analysis of the history of color as a material substance;[9] those that refer to the mimetic use of color to reproduce the aspects of living zoological or botanical objects;[10] as well as those that consider the mimetic use of color in other disciplines such as geology, meteorology or medicine.[11] However, diagrams do not imitate the colors of nature, but at best symbolize them mimetically, i. e., they are then "semantically resonant."[12] For example, the color green may represent botany. Even the extensive literature in the humanities on diagrams as such sheds no light on the use of color in science.

To discuss reasons for specific color choices in diagrams, we will need to think beyond technological determination, taking into consideration that starting from the first days of three-color print by LeBlon in 1710 and textbook lithography, in image printing any color choice was possible. There was (and is) obviously no technical need for the reliance on primary colors,[13] as atlases and medical textbooks from the eighteenth to twentieth century depict images of the most diverse skin tones and organ colors in often drastically lifelike (or morbid) images. Asking those contemporary scientists who draw such maps (see below), yields the response that

7 See e. g., Klaus Hentschel: Verengte Sichtweise. Folgen der Newtonschen Optik für die Farbwahrnehmung bis ins 19. Jahrhundert. In: Vera Dünkel (ed.): *Farbstrategien. Bildwelten des Wissens,* 4.1. Berlin, Boston: De Gruyter, 2006; Magdalena Bushart, Friedrich Steinle: *Colour Histories, Science, Art, and Technology in the 17th and 18th Centuries,* Berlin, Boston: de Gruyter, 2015.

8 See e. g., André Karliczek: Zur Herausbildung von Farbstandards in den frühen Wissenschaften. In: *Ferrum,* 90 (Nachrichtenblatt der Eisenbibliothek), 2018, pp. 36–49; Ann Temkin, Briony Fer, Melissa Ho, Nora Lawrence: *Color Chart: Reinventing Color, 1950 to Today,* The Museum of Modern Art, 2008; Edward R. Landa, Mark D. Fairchild, Mark D.: Charting Color from the Eye of the Beholder. In: *American Scientist,* 93 (5), 2005, pp. 436–443.

9 See e. g., Jan Altmann: Färbung, Farbgestaltung und früher Farbdruck am Ende der Naturgeschichte. In: Dünkel (s. fn. 7), Alexandre Métraux: Farbstoffchemie, Farbexperimente und die französische Malerei. In: Dünkel (s. fn. 7).

10 Kärin Nickelsen: The Challenge of Colour: Eighteenth-century Botanists and the Hand-colouring of Illustrations. In: *Annals of Science,* 63 (1), 2006, pp. 3–23.

11 See e. g., Tawrin Baker, Sven Dupré, Sachiko Kusukawa, Karin Leonhard: Early Modern Color Worlds. In: *Early Science and Medicine*, 20 (4–6), 2015, pp. 289–591; Klaus Hentschel: *Visual Cultures in Science and Technology: A Comparative History*, Oxford: Oxford University Press, 2014; Dünkel (s. fn. 7).

12 Vidja Setlur, Maureen C. Stone: A Linguistic Approach to Categorical Color Assignment for Data Visualization. In: *IEEE Transactions on Visualization and Computer Graphics,* 22 (1), 2016, pp. 698–707; Sharon Lin et al.: Selecting Semantically-Resonant Colors for Data Visualization. In: *Computer Graphics Forum,* 32 (3), 2013, pp. 401–410.

13 Thürlemann (s. fn. 4).

the choice is rather ad hoc. Yet, the continuity and persistence of a specific color code are still impressive.

How can we make sense of color in diagrams when we cannot turn to explicit statements by their authors? In the absence of studies on the meaning and connotations of color in science, we may draw on art history: art historians such as Heather Pulliam, John Gage, Michel Pastoureau, Liz James and Herbert Kessler have demonstrated the context dependency of the meaning of color throughout the centuries and various communities.[14] As we can't rely on literature in history, theory or sociology of science to uncover more about color choices, the aim of this article is to investigate a possible tacit background for such choices: cultural coding and socio-historical connotations of the respective color systems. Comparing the two most famous metabolic maps (the KEGG map above in FIGURE 1, and another one by Gerhard Michal,[15] introduced below) we will also be able to discuss the different roles of color as a symbolic vehicle.[16]

The following section introduces the history of the metabolic map and its symbolic elements. Section three and four detail the comparison between the KEGG map and Michal's map regarding the graphic symbolism (section three) and the color use (section four). The concluding section discusses the resulting aspects and consequences for the use of color as a symbolic vehicle in metabolic maps and diagrams in general.

14 Such cultural codes and diachronically shifting meanings of color in general have been investigated by the art historians John Gage: *Color and Meaning: Art, Science, and Symbolism*, Berkeley: University of California Press, 1999; Rolf G. Kuehni: *Color: An Introduction to Practice and Principles,* New York: Wiley, 2012; Michel Pastoureau: *Dictionnaire des couleurs de notre temps: Symbolique et société*, Paris: Christine Bonneton, 2007; and on individual colors for instance by Doran on yellow: Sabine Doran: Die Kunst des Skandals und die Ambivalenz des Gelben. In: Margrit Vogt, André Karliczek (eds.): *Erkenntniswert Farbe*, Jena: Institut für Geschichte der Medizin, Naturwissenschaften und Technik, 2013, pp. 151–170; on blue specifically again by Pastoureau (see above), on pink and its strong late modern gender connotation in diverse studies separately by Grisard (in this volume), Paoletti (on pink and blue): *Pink and Blue. Telling the Boys from the Girls in America*, Bloomington: Indiana University Press, 2012; Veronika Koller: 'Not Just a Colour': Pink as a Gender and Sexuality Marker in Visual Communication, *Visual Communication,* 7 (4), 2008, pp. 395–423; Barbara Nemitz (ed.): *Pink: The Exposed Color in Contemporary Art and Culture*, Ostfildern: Hatje Cantz, 2006; on green see Michael Rossi in this volume. Interview conducted by the author with Gerhard Michal, Munich, September 2, 2018.

15 Gerhard Michal: *Biochemical Pathways,* Poster, Mannheim: Böhringer, 1963.

16 Frederic Jameson: Reification and Utopia in Mass Culture. In: *Social Text,* 1, 1979, pp.130–148.

History of the metabolic map and its elements

Basically, diagrams organize knowledge.[17] Their simple forms are easy to grasp and to use as placeholders for the real object under study,[18] and diagrams, like models, are easy to transport.[19] Another aspect that makes them particularly suitable for educational purposes[20] is that diagrams appeal to our ability to recognize patterns[21] and perceive shapes ("*Gestaltwahrnehmung*").[22]

When we look at the biochemistry textbooks of highest circulation that in most cases were edited in Europe or the United States, metabolic maps seemed, until recently, to be highly conventionalized diagrams. As introduced above, they entail symbols such as letters, numbers and arrows following rules established during the past one-hundred years. They apply inter-subjectively a consistent, more or less reliable symbolic language in which authors of these diagrams summarize empirical chemical findings of the past seven decades.

Biochemical pathways and maps consist of several diagrammatic elements, the history of which goes back to the early nineteenth century.[23] In 1814, Berzelius suggested alphabetical atomic symbols instead of the earlier alchemical symbols.[24] Lavoisier, still applying the full names to the substances, introduced an equation symbol to link a product with the reactants. Soon both, the equation sign and the alphabetical system, appeared together in chemical writings. The combination of both became common in the 1860s. In 1884, Van't Hoff introduced the double arrows for reactions in both directions. In 1874, Gustavus D. Hinrichs, at the University of Iowa, introduced the single arrow, making it possible to depict longer

17 David Kaiser: *Drawing Theories apart: The Dispersion of Feynman Diagrams in Postwar Physics*, Chicago: University of Chicago Press, 2009; Ursula Klein: Berzelian Formulas as Paper Tools in Early Nineteenth-Century Chemistry. In: *Foundations of Chemistry*, 3 (7), 2001, pp. 7–32.
18 Andrea I. Woody: Putting Quantum Mechanics to Work in Chemistry. The Power of Diagrammatic Eepresentation. In: *Philosophy of Science*, 67, 2000, pp. 612–627.
19 Kaiser (s. fn. 17).
20 Brian Hand, Aeran Choi: Examining the Impact of Student Use of Multiple Modal Representations in Constructing Arguments in Organic Chemistry Laboratory Classes. In: *Research in Science Education,* 40 (1), 2010, pp. 29–44; Kaiser (s. fn. 17); Stephen G. Brush: The Reception of Mendeleev's Periodic Law in America and Britain. In: *Isis*, 87, 1996, pp. 595–628; Roger Krohn: Why Are Graphs So Central in Science? In: *Biology and Philosophy*, 6 (2), 1991, pp. 181–203.
21 Krohn (s. fn. 20).
22 Michael Lynch: Science in the Age of Mechanical Reproduction: Moral and Epistemic Relations Between Diagrams and Photograph. In: *Biology and Philosophy,* 6, 1991, pp. 205–226.
23 Alvarez Santiago: Chemistry: A Panoply of Arrows. In: *Angewandte Chemie*, 51, 2012, pp. 590–600.
24 Jacob Berzelius: Essay on the Cause of Chemical Proportions and on Some Circumstances Relating to Them: Together with a Short and Easy Method of Expressing Them. In: Thomas Thomson (ed.): *Annals of Philosophy 3*, London: Robert Baldwin, 1814, p. 51.

sequences of reactions, including the idea of mechanism; around 1900, sequential arrows became common to indicate the paths between reactions.

Parallel to the first use of arrows, molecular diagrams emerged in chemistry publications, although they can be traced back to the eighteenth century. In 1874, Arthur Cayley was probably the first to publish results that consider molecular graphs.[25] The subsequent decades saw the development of the skeletal formulas, stereochemical formulas, Newman projection and sawhorse projection, Haworth projection (for sugars), the Fischer projection as well as others.

In addition, attempts at standardization of the elements in chemical writing and diagrams date back to the nineteenth century. With August Kekulé's efforts in 1860, a forerunner of the International Union of Pure and Applied Chemistry (IUPAC) was founded and with that the continuous attempts of standardization continued.[26] As we will see, however, up until the present, they do not embrace the question of color. Apart from color, with the historic developments described above, we have the usual constituents of the biochemical pathway map.[27]

After all these steps, the need to obtain a broader overview similar to a map rose, as is described in the history of chemistry unanimously, with the push by technology in the 1930s and during the war:[28] The availability of stable and radioactive isotopes led to labeling as a productive tool in the study of pathways of biochemical change in living organisms, so that soon the citric circle, the glycolysis and other similarly complex pathways were constructed.

In 1952 Wayne Umbreit who taught microbiology at various universities in the US, published the first metabolic map. Umbreit's map is a collection of different entangled pathways, depicted page by page and describing the links between them, bound together in one book, incorporating the most recent bibliography. Figure 8 shows an image of the 1960 second edition of Umbreit's book. This collection of maps could thus be called an atlas.[29]

In his introduction, Umbreit explains at length the use of his maps: "metabolic maps or charts can and do summarize widely scattered and unrelated information

25 A. Cayley, *Phil. Mag.*, 47, 1874, pp. 444–446, as quoted in Norman L. Biggs, E. Keith Lloyd, Robin J. Wilson: *Graph Theory 1736–1936*, Oxford: Clarendon Press, 1976; Oxford University Press, 1986.

26 Evan Hepler-Smith, paper presented January 31, 2018, Harvard History of Modern Science Working Group, Cambridge/Massachussetts.

27 Donald Nicholson: From Metabolic Pathway Charts to Animaps in 50 Years. In: *The International Union of Biochemistry and Molecular Biology,* Vol. 33 (3), 2005, pp. 156–158, p. 156.

28 Marcel Florkin: *A History of Biochemistry. Part V. The Unravelling of Biosynthetic Pathways*, Amsterdam, Oxford, New York: Elsevier Science Ltd, 1979, p. 367.

29 See Moser and Meyer on geographic maps in this volume.

in biochemistry and […] from such summaries one may discern relationships that are otherwise obscure."[30]

Umbreit begins his book with *two* introductions, apparently envisioning different types of readers: in the title of his second introduction, which he published beside the first on the same pages, he referred to such a map as "[a] device for the orderly assembling of useful contemporary information without employing extensive files."[31] Thus in these terms, the metabolic maps are a tool for *research*. As Umbreit found no such map published during his day – and he had been drawing such maps for ten years for his personal use –, he argued "[…] I wanted such a volume to use myself; the only way to get it, was to write it."[32]

Another widely distributed map shows that metabolic maps were also used as tools in education to help memorize typical pathways of relevance.[33] In any case, whether used as tools in research or teaching, metabolic maps follow different diagrammatic traditions and corresponding color uses, as discussed in the following.

Diagrammatic traditions in metabolic maps: two case studies

In the description of the map in FIGURE 1, Minoru Kanehisa stated that the KEGG, launched as a website and with a journal article in 2000,[34] was a source for understanding parts of the biological system up to the ecosystem on the basis of genome sequencing and other big data technology. In May 1995, the project was initiated as part of the Human Genome Program of the Ministry of Education, Science, Sports and Culture in Japan.[35] As described above, the KEGG is a surface for large databases that can be addressed by clicking on the different dots and pathway tags. The ending "-ome" in genome signifies that this database is not only about specific genes but also about the entirety of all the genes of one organism. In another publication, which accompanied the launch of the KEGG in 2000, Susumu Goto, Takaaki Nishioka and Minoru Kanehisa stated that it was due to the progress in the study of

30 Wayne William Umbreit: *Metabolic Maps*, Minneapolis: Burgess Publishing, 1952, p. 1.

31 Umbreit (s. fn. 30).

32 Umbreit (s. fn. 30).

33 Donald Nicholson: From Metabolic Pathways Charts to Animaps in 50 Years. In: *The International Union of Biochemistry and Molecular Biology,* Vol. 33 (3), 2005, pp. 156–158, p. 156; the same holds for Michal's map, Gerhard Michal: *Biochemical Pathways.* Poster, Mannheim: Böhringer, 1963; Gerhard Michal, Dietmar Schomburg (eds.): *Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology*, Hoboken, NJ: John Wiley & Sons, Inc., 2012, Gerhard Michal: On Representation of Metabolic Pathways, 1999. In: *Biosystems*, 47 (1–2), 1998, pp. 1–7.

34 Kanehisa, Goto (s. fn. 1).

35 Minoru Kanehisa: A Database for Post-Genome Analysis. In: *Trends in Genetics*, 13 (9), 1997, pp. 375–376.

the results of transcriptions of DNA to RNA and protein in a cell (the transcriptome and proteome) that a large amount of data on messenger RNA and protein-protein interaction became available.[36] This served, they said, to predict gene functions from the complete genome sequence and to reconstruct the biochemical pathways of an organism. Metabolic pathways, however, were a specific class of biochemical pathways for which information on chemical compounds and reactions was also required. This is why they needed to build the respective databases to ensure that the map worked interactively. Consequently, KEGG consists of three databases: the database called PATHWAY contains information on the network of interacting molecules; GENES entails the collection of gene catalogues for all the sequenced genomes; and LIGAND has a collection of chemical compounds in the cell, enzyme molecules and enzymatic reactions.[37] The aim of the KEGG was summarized by its makers, then at Kyoto University, as follows:

> *"We wish to automate human reasoning steps for interpreting biological meaning encoded in the sequence data. We consider the problem of predicting gene functions as a process of reconstructing a functioning biological system from the complete set of genes and gene products. Thus, it is critical to understand how genes and molecules are networked to form a biological system."*[38]

The databases behind the digital map entail approximately 90 pathway maps. These maps and the overall maps of the metabolism of each out of 17 different organisms were drawn by hand and continuously updated. In the KEGG map, with this focus on nucleotides, i. e., DNA and RNA, are set at the top of the map. In addition, we see that the chemical substances are connected by dots – there are no arrows. The eleven chromatic colors used in Kanehisa's map distinguish between different metabolic pathways within the map. They are the same for the respective metabolic pathways in all KEGG maps of different organisms.

The design of the KEGG map as described in the prelude to this article – the straight, fine, always parallel vertical and horizontal lines on white, terminating in connecting (semi-)circular lines with their little knots in symmetrical positions that result in, sometimes floral, graphic patterns – corresponds with today's characteris-

36 Susumu Goto, Takaaki Nishioka, and Minoru Kanehisa: LIGAND: Chemical Database of Enzyme Reactions. In: *Nucleic Acids Research,* 28, 1, 2000, pp. 380–382.

37 Kanehisa, Goto (s. fn. 1).

38 Hiroyuki Ogata, Susumu Goto, Kazushige Sato et al.: KEGG: Kyoto Encyclopedia of Genes and Genomes. In: *Nucleic Acid Research*, 27 (1), 1999, pp. 29–34, p. 29.


9, **10:** Japanese stencil design.

tics of Japanese graphic design, especially with typical aspects such as the organic (floral) patterns, circles and symmetry, high-information density, custom typography and, last but not least, the choice of colors discussed in the next section.[39] While graphic design, e. g., of posters in Japan, in the revival of the economy after the Second World War was predominately guided by Western modernism, it became more common from the 1970s onwards to draw on local pictorial traditions.[40]

In historic Japanese painting and drawing, artists tended to eliminate elements deemed secondary or unnecessary and thereby developed what Shūji called an "aesthetics of omission."[41] A major stream of traditional Japanese arts was early on of formalized nature instead of attempting to recreate a three-dimensional illusion of reality.

39 Natalie Avella: *Graphic Japan: From Woodblock and Zen to Manga and Kawaii,* Hove: Roto Vision, 2004. See also: Joseph D'Addetta: *Traditional Japanese Design Motifs,* North Chelmsford, MA: Courier Corporation, 1984.

40 Kiyonori Muroga: *Japan – Nippon: Poster Collection 26*, Zürich: Museum of Design Zürich, 2014; Friedrich Deneken: *100 Japanese Stencil Designs*, New York: Dover, 2006; Clarence Hornung: *Traditional Japanese Stencil Designs*, New York: Dover, 1984.

41 Takashina Shūji: *The Japanese Sense of Beauty,* Tokyo: Japan Library, 2018, p. 96.

Japanese visual and material culture is said to be influenced by classical poetry, called *waka*, with its pronouncement of seasonal and natural associations.[42] With its zenith in the Heian period (714–1185), *waka* was still popular up until the late Edo period (1600–1867) and still inspires Japanese design today.

Repetitive round, often circular forms abstracting from nature and resulting in patterns as depicted in the stencils in FIGURE 9 AND 10 laid the ground for the Western adoption of Japanese graphic design as in the Art Nouveau and Art Deco of the early twentieth century, as well as for today's Japanese graphic design resonating in the repetitive linear and circular graphics in the KEGG map.

As already indicated, in all its features, the KEGG map contrasts with the conventional color traditions and graphics in the metabolic map widely used until at least the end of the twentieth century.

One of, if not *the* internationally most well-known way to depict metabolic pathways and probably the first polychrome metabolic map published is the metabolic map by the Böhringer Company in Mannheim, Germany (today Roche). It was a map designed by Gerhard Michal, then a Ph.D. student working there, apparently on the basis of other local traditions than the KEGG map.[43]

In Michal's map, each line is an arrow. Arrows are usually an important distinguishing feature in the diagrammatic elements in metabolic pathways: As one introduction to a metabolic atlas explains, chemical pathways indicate the way to get from one place to another.[44] Philosopher of science Paul Thagard described these pathways therefore as *explanations*. Explanations in biochemistry frequently make reference to mechanisms, Thagard claims, with "'mechanism' here meaning entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions. […] The arrows […] represent the chemical activity of the molecules that together with the enzymes produce new molecules."[45] Mechanisms reveal regularity and productivity and "[t]hus biochemical pathways explain by showing how changes within a cell take place as the result of the chemical activities of the molecules that constitute the cell."[46]

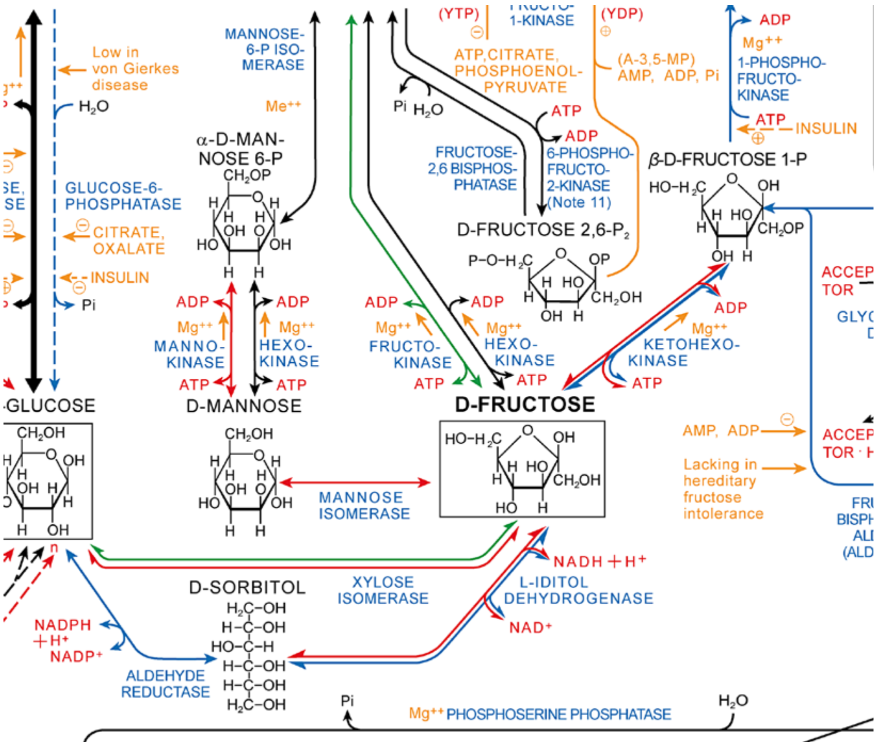
42 Haruo Shirane: *Japan and the Culture of the Four Seasons,* New York: Columbia University Press, 2012.

43 Donald Nicholson: From Metabolic Pathways Charts to Animaps in 50 Years. In: *The International Union of Biochemistry and Molecular Biology,* Vol. 33 (3), 2005, pp. 156–158, p. 156.

44 Jack G. Salway: Metabolism at a Glance, London: Blackwell, 1994, p. 10.

45 Paul Thagard: Pathways to Biomedical Discovery. In: *Philosophy of Science,* 70 (2), 2003, pp. 235–254, p. 238.

46 Thagard (s. fn. 45). It should be added that, of course, the diagram cannot stand alone and without text (and be it text that is chronologically or geographically far from the diagram) in order to unfold its explanatory power.



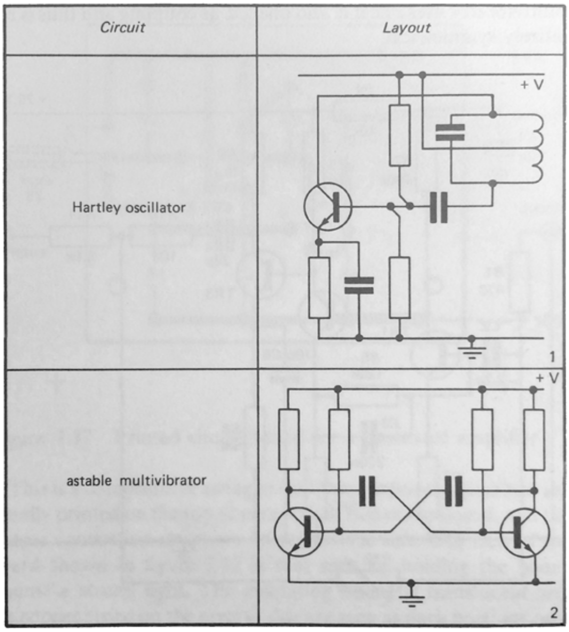
11: Cutout from Michal's *Biochemical Pathways*, 1993 edition.

The way Gerhard Michal's map was distributed worldwide was by being frequently recommended and sold as a large poster together with the abovementioned biochemistry textbook Stryer. Until 2005, this map was published in four revised and extended editions.

Figure 10 shows a cutout from the 1993 version. Just as in earlier versions, together with the achromatic black, we find three further colors: the primary colors red and blue and in addition green. Michal used the colors to distinguish between the "kingdoms" in nature: between bacteria, plants and animals.[47] Until 2002, these maps were exclusively drawn by hand. The 1993 map took the working group one-and-half years to complete.[48]

47 Michal: *Biochemical Pathways* (s. fn. 15).

48 Gerhard Michal: On Representation of Metabolic Pathways. In: *BioSystems,* 47, 1998, pp. 1–7.



12: Examples of standard circuit layouts.

Contextualizing Michal's map with diagrammatic traditions in the twentieth century shows that the layout of the lines and angles in his map corresponds to the standardized fashion of electrical circuits (FIG. 12).

Simplification is the most repeated aim of the rules for drawing these diagrams. As the author of a text book for electrical drawing explains:

> *"Circuit diagrams show the way in which the components in an electrical or electronic system are connected together. When reading or drawing circuit diagrams it is important to remember two points. (1) The symbol used to represent each component depends only on its function, and has no relation to its shape, size or electrical rating. (2) The symbols are placed on the drawing to make the diagram as clear and easy to follow as possible. Their position bears no relationship to the layout of the components in the corresponding equipment."*[49]

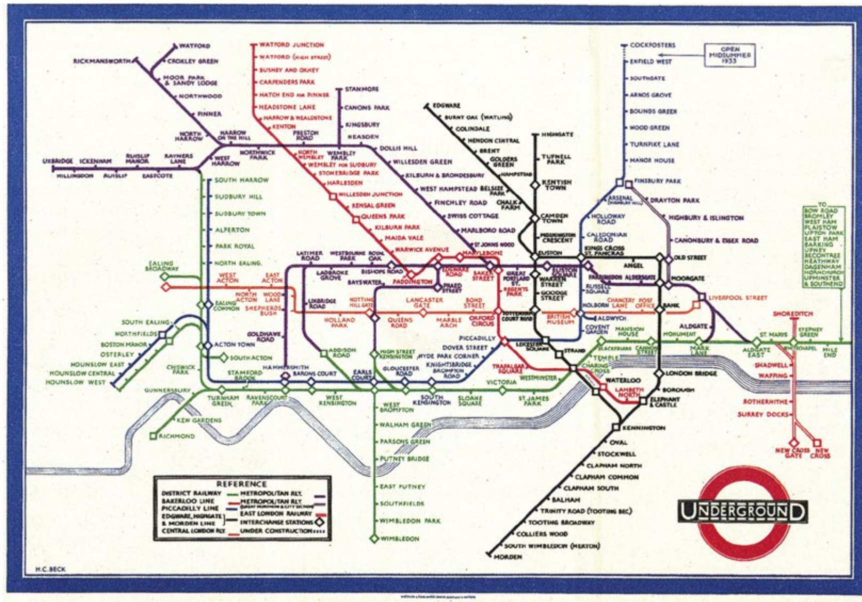
49 John Charles Cluley: *Electrical Drawing I*, London and Basingstoke: Macmillan, 1979, p. 40. According to Cluley, until the 1971 agreement on British Standards (by the British Standards Institution) many different standards in different international enterprises existed. Another important set of standards are those used by American firms which follow the MIL-STD-806C (Cluley, p. 37f.).

13: London Underground map 1932.

In the twentieth century, the electrical circuit inspired diverse complex diagrams, including sewing patterns and subway maps. Most iconic is the result of this graphic transfer in the first abstract, semi-topographical London tube map drawn in 1931 by Henry Charles Beck based on, as the engineer himself mentioned, electrical circuits.[50] Before 1933, London's various underground lines had been laid out geographically over the roadway of a city map, as in the example of 1932 in FIGURE 13.

Beck believed that geographical accuracy was not needed in an underground map, but that passengers were more interested in how to get from one station to the next, and where to change lines. He therefore suggested presenting the ever-expanding network as a circuit diagram rather than a geographical map. When Beck designed the iconic London tube map in 1931 (FIG. 14), he was partly inspired by circuit board schematics he had worked with as an engineering draftsman at the Signal Office of the London Underground.

50 Ken Garland: *Mr Beck's Underground Map,* Harrow Weald: Capital Transport, 1994.



14: London underground map by Henry Charles Beck 1931, realized 1933.

To consider Michal's map as part of this diagrammatic tradition suggests understanding his map in the – since the eighteenth century common – fashion of equating the living organism with a machine.[51] Equating metabolism with an electrical circuit, or otherwise of the body with a machine, had become even more plausible in modern science upon the introduction of the first computers as well as the publication of Norbert Wiener's *Cybernetics or Control and Communication in the Animal and the Machine* in 1948, which became a model for thinking about control circuits.[52]

To summarize, with the KEGG map, we have for the first time a metabolism chart that renounces giving the individual transformations a direction using arrows. It is possible to see the transformation of one molecule into another (and vice versa) as a continuous flow that has no direction. Obviously, the Kyoto Encyclopedia is meant as primarily that: an encyclopedia, not a diagram to explain mechanisms. The

51 Laura Otis: The Metaphoric Circuit: Organic and Technological Communication in the Nineteenth Century. In: *Journal of the History of Ideas*, Vol. 63, 1, 2002, pp. 105–128; Philipp Sarasin: *Reizbare Maschinen: eine Geschichte des Körpers 1765–1914,* Frankfurt: Suhrkamp, 2001.

52 Norbert Wiener: *Cybernetics: or Control and Communication in the Animal and the Machine,* Cambridge, MA: MIT Press, 1948.

graphic design of the KEGG map calls on local organismic traditions and depicts the organism as an open system including extra organismic substances while Michal's map shows metabolism as a closed electrical machine. As the following section demonstrates, the color choices underline these graphic concepts.

Color choices in metabolic maps

Presented in London 1864, one of the first color uses in chemistry documented in the history of science is that of the color choices for atoms in the ball-and-stick-model of molecules which have remained the same until today: white for hydrogen and black for carbon, red for oxygen and green for chlorine.[53]

While this color code remains quite stable, this is not the case for elements, atoms and molecules in chemistry publications. A scan of chemistry journals and textbooks reveals that primary or European basic colors are the most frequent in European and American chemical textbooks in the twentieth century. Mainly, the primary colors red and blue are employed. When further distinctions are needed, the primary colors green and yellow are used. There is, however, no fixed code for the color use regarding different kinds of reactions, atoms or molecules apart from the fact of the common use of the primary colors red, blue, green/yellow.[54]

A glance at the KEGG map easily reveals that its colors are very different: the eleven colors used in the KEGG map, without any resonance with European RGB-based color systems, are peach-red, violet, pink, light blue, violet-blue, bright pastel green, dark green, ocher, brown, orange and a red-brown.

Drawing on local tradition in Japanese arts and design, European primary colors are usually absent.[55] Japanese color favoritism goes back to Shinto, in which both Yin-Yang and Five Agent Theory coalesce.[56] According to the art historian Mary McClintock Dusenbury, these concepts entered Japan from China via Korean political advisors and clerics together with the technical knowledge, pigments and dye materials in the sixth and seventh centuries, to be employed "as a political tool within the newly

53 Christoph Meinel: Molecules and Croquet Balls. In: Soraya De Chadarevian, Nick Hopwood: *Models: The Third Dimension of Science,* Stanford: Stanford University Press, 2004, pp. 242–275; Colin A. Russell: The Changing Role of Synthesis in Organic Chemistry. In: *Ambix,* 34, 1987, pp. 169–180.

54 Also, the rare cases of polychrome periodical system diagrams up to the 1960s were usually held in primary colors only, in accordance with the Newtonian color scheme with primary and secondary colors (red, blue, green and yellow); see Andreas von Antropoff: Eine neue Form des periodischen Systems der Elemente. In: *Angewandte Chemie, 39,* pp. 722–725; Alcindo Flores Cabral: Classificação Natural dos Elementos. Boletim Didático nº 1, Escola de Agronomia Eliseu Maciel, Pelotas, 1951.

55 Shirane (s. fn. 42).

56 Mary McClintock Dusenbury: *Radiance and Darkness: Color at the Heian Court*, University of Kansas, dissertation, Ann Arbor, MI: Bell & Howell, 1999.

emerging imperium."[57] In the Five Agent Theory – as well as in state rituals – five pure, so-called correct colors, which were worshiped as powers and extracted from their respective dye plants, exist: red, blue, yellow, white and black. Yet, as Dusenbury and sinologist Haruo Shirane stress, these "correct" colors are very different in hue and concept from European primary colors. They were not pure colors in the sense that they didn't need mixing or were the purest color in visible light, i. e., in the rainbow, but rather derived from the respective plant they were made from – e. g., the correct red would be the light, slightly orange red from the madder plant. This madder plant red is different from cinnabar or vermillion red, which comes closer to the tone of the primary color red in the European system. According to ancient Chinese tradition, red is the color for the passage from life to death and burials can be found sprinkled and skeletons painted with red.[58] In Japan up until present day, red is the color of the sacred as on gates to shrines, e. g., the famous gateway to the Inari Shrine in Kyoto. *Akane* (madder), a peachy red, is the indigenous local red, with "aka" meaning brilliant light, also referring to the sun in Japan and Korea. Dyes for *shu* (vermillion) for official seals were imported from China and symbolized the authority of the rulers of ancient times.[59] Together with red, purple is a high-ranking color: it symbolizes the great cosmic unity between yin and yang as told in an eighteenth-century Japanese lexicon.[60] In the imperial bureaucracy involving twelve ranks indicated by color, purple was the highest and is still today the supreme color, the archetypical noble color for Buddhist priests and the color in which one would wrap the most valuable objects.[61] Also, within the most used colors in Japan, there is no favoritism for navy blue. Instead, without ever confusing blue and green where a distinction is necessary, blue is not an individual color but overlaps with green.[62]

The KEGG map bears the connection to its local conditions in its name: the *Kyoto* Encyclopedia of Genes and Genomes. There's a map of another institution in Kyoto which instead of primary colors uses the typical local colors, madder-red and a greenish blue: the Kyoto subway and train map (FIG. 15). While in contrast, Tokyo's tube map embraces all primary and secondary colors, in that resembling European and American subway maps, Kyoto's subway map adheres to the local correct color scheme.

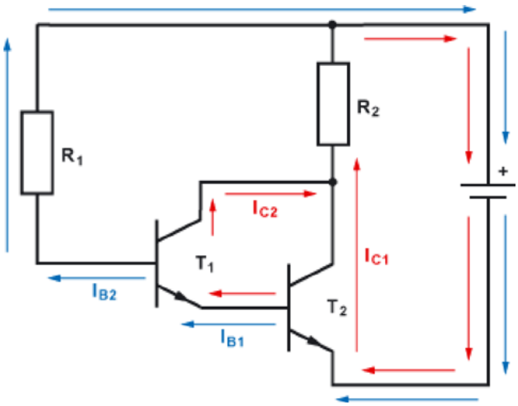
57 Dusenbury (s. fn. 56), p. 60.
58 Dusenbury (s. fn. 56).
59 Sadao Hibi, Kunio Fukuda: *The Colors of Japan,* Tokyo: Kodansha International, 2000.
60 Dusenbury (s. fn. 56).
61 Hibi, Fukuda (s. fn. 59).
62 Hibi, Fukuda (s. fn. 59), Dusenbury (s. fn. 56).

15: Subway and train map, City of Kyoto.

To refer to local conditions in Kyoto also means to see that it is a town built around the Japanese imperial palace, seat of the emperor for more than eleven centuries until 1868. The town of Kyoto represents the national treasury and traditions. Taking this and the hint to the town in the name of the KEGG map into consideration, it seems not too far-fetched to conceive the idea to interpret the colors used in the map with the color code of the local correct colors. In the metabolic map in the *Kyoto Encyclopedia of Genes and Genomes*, we find the DNA at the top, set in bright red, the color of the gods.[63] Following this interpretative trace, the energy metabolism, depicted in violet, shows the color of the emperor. Far from anything usual in European and American chemistry textbooks, we even find pink, in the KEGG map the color for co-factors and vitamins, those elements needed to catalyze chemical reactions. Instead of referencing femininity,[64] pink in Japan historically denotes the cherry blossom to the venerated Japanese Samurai, who fell in the liberation war

63 Hibi, Fukuda (s. fn. 59). In the case of this KEGG map, we don't know yet whether in this case those who drew the map and chose the colors made such connections voluntarily.

64 See the article by Grisard in this volume.



16: Electron flow through the Darlington Circuit.

with China in medieval times.[65] While pink in the European-American tradition of the past decades is the color of love and strongly feminized, in Japan it symbolizes masculine strength and violent power. When we put the three together, the relationship between the three works as an analogy of the relationship between the Samurai, the emperor and the gods: between the co-factors, the energy-metabolism they enhance and make possible, and the genes that provide the matrix for their structure.

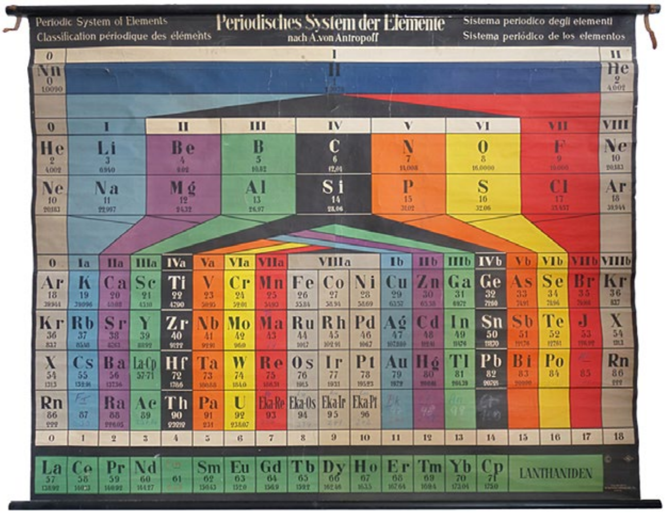
As indicated above, there is no correlation in color between the map by Michal and the KEGG. The colors in Michal's map are semantically resonant, green for plants, red for the other multicellular organisms and the one metabolic map embraces all organisms.[66] In contrast to Michal's metabolic map, in Kanehisa's map each metabolic pathway has its own fixed color, disregarding the organism in which it appears. This map underlines the *similarities* between organisms, even between plants and animals. Different from Michal's map, it depicts an open system that includes extra-organismic substrates.

When looking at the diagrammatic tradition in the background, we find that not only the layout of the lines and angles correspond to the standardized fashion of electrical circuits as said above, but the colors as well (FIG. 16).

The RGB color model strengthens the conceptual interpretation of organisms as (electrical) machines. This is a familiar concept in physics and it also appears in

65 Barbara Nemitz: The Exposed Color: Pink. https://www.uni-weimar.de/projekte/rosa/index.php?inhalt=issue, acc. 03-15-2019; Barbara Nemitz 2016: personal communication, 06-30-2016.

66 Michal: On Representation (s. fn. 48).



17: Antropoff's periodical system as a wall chart.

Michal's map whose diagrammatic style goes back to the electrical circuit (and the London subway map). Such maps, including the arrows that are meant to show the actions of the reactants in the cell, not only catalogue and summarize, but explain what occurs in these organic machines as well. In addition, the use of colors – blue for procaryotes, red for eucaryotes, multicellular organisms and animals, green for plants – distinguishes three different realms in the organismic world.

If the color scheme of the KEGG map easily relates to the local scheme of the correct colors, does this apply to the RGB-related color choice in Michal's iconic map, in the diagrams in the most used biochemistry textbooks of the twentieth century as well as in electrical drawings?

In the early twentieth century, the education at technical schools in German-speaking Europe and beyond was influenced by the Bauhaus school, and in the 1920s, by the De Stijle movement. The polychrome wall chart of a periodical system designed by Andreas Antropoff (FIG. 17) illustrates this impressively.

The interaction between scientific knowledge and technical design and again, the – not only applied – sciences completed a circle: Bauhaus teachers Johannes Itten, Wassily Kandinsky, Paul Klee and Oskar Schlemmer, with added influence by Piet Mondrian,[67] believed it necessary for the advancement of arts and design

67 Rolf Bothe et al. (eds.): *Das frühe Bauhaus und Johannes Itten*, Ostfildern-Ruit: Hatje, 1994; Wassily Kandinsky: *Punkt und Linie zur Fläche*, München: Langen Verlag, 1926; Paul Klee: *Pädagogisches*

to simplify design to the most elemental in order to make it more readily available to the masses. Any aesthetic decision that drew design nearer to the sciences was favorable. In terms of color, they advanced the use of primary, deemed pure, colors, which we then also frequently find in the works of the De Stijl artists, the fauvistes and in (technical) design starting in the late 1910s. While around the turn of the century, light and opaque colors were still the trend,[68] in the natural sciences and in mathematics, since the 1920s in technical drawings and prints such as electrical circuits, when depicted in color, the use of the primary colors vermillion, strong green and ultramarine blue was favored. The idea of the De Stijl artists was to go back to the most elementary – and what was the most basic or elementary in terms of color had its cultural tradition: primary colors, in classical, later Christian tradition, were red, yellow and blue in addition to black and white.[69] Since early Christianity, icons of the Virgin Mary typically depict her with a primary color blue and red manteau and a yellow, if not golden aureole.[70]

Leonardo da Vinci naturalized this favoritism to the claim that these were the colors that resulted without mixing.[71] This color-trio was overridden by the idea of pure colors in physiology: with Ewald Hering and Hermann von Helmholtz's three-color perception theory came the replacement of yellow by green, resulting in the modern acronym RGB for the three primary colors red, green and blue.[72] It followed that, when more than three colors (the primary colors suggested by both the dominant color theories of Goethe and Newton, red, blue and yellow) were needed in technical or natural science images, first green as a fourth, and then the so-called secondary colors (orange and violet) were used, giving the seven base colors as suggested by Goethe. These were the ones propagated by the Bauhaus and also, perhaps in an overlap with Newton's spectral colors which included light blue as another secondary color, inspired technical diagrams internationally as we see in the London tube map, produced in 1933 by the technician Henry Charles Beck.[73]

Skizzenbuch, München: Langen Verlag, 1925; Paul Klee: *Das bildnerische Denken*, Basel, Stuttgart: Schwabe & Co, (1981); Oskar Schlemmer: *Der Mensch: Unterricht am Bauhaus*, Berlin: Gebrüder Mann, 2014; Piet Mondrian: *Neue Gestaltung, Neoplastizismus, Nieuwe Beelding*, München: Langen,1925; Magdalena Droste: *Bauhaus 1919–1933*, Köln: Taschen, 2013/2019; Jeannine Fiedler, Peter Feierabend (eds.): *Bauhaus*, Rheinbreitbach: H.F. Ullmann Publishing, 2013.

68 See images of mathematical models in Friedman in this volume.

69 Ingrid Bennewitz, Andrea Schindler: *Farbe im Mittelalter. Materialität – Medialität – Semantik*, Berlin: Akademie Verlag, 2011; Thürlemann (s. fn. 4).

70 Thürlemann (s. fn. 4).

71 Thürlemann (s. fn 4); see also Lawson in this volume.

72 Thürlemann (s. fn. 4).

73 Garland (s. fn. 50).

Concluding discussion: color as a symbolic vehicle in metabolic maps

Biochemical maps are intended for research purposes as well as for teaching. As Umbreit stated, with the aid of such maps the reader can discern relationships that are otherwise obscure; the maps assemble and order information using limited space in contrast to extensive files.

Color, in the maps discussed above, is used as a differentiator and could not be replaced by other graphic signifiers. To include even more gray-scale graphic symbols in the metabolic maps would lead to an overload of graphic signs and corrupt the gestalt aspect of the respective diagram. In contrast to other symbolic graphic vehicles, color is able to add one more dimension to the same graphic form of a line. In addition to working as a simple operator, the use of colors can advance the gestalt aspect of the image – even more so, when fitting the specific traditionally common color scheme in the respective style of the diagram.

When comparing the different color schemes used, it seems that the colors underline and make explicit different cosmologies entailed in the respective diagrams: in one diagram it is the aspect of the organism as an (electric) machine and differentiated in three organismic realms, in the other a fluid open organism with pronounced similarities between all species.

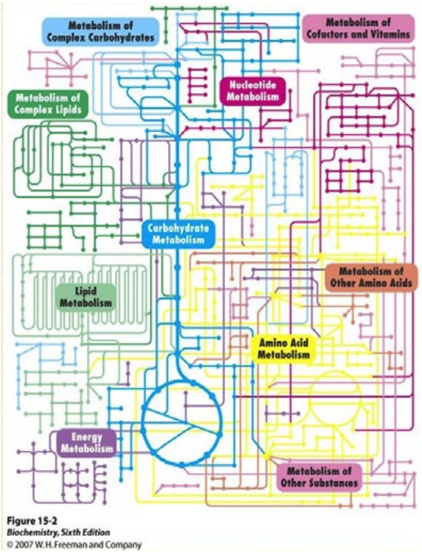
Interestingly, the makers of metabolic maps themselves tend not to see and make any connection between their color choices and corresponding color traditions.[74] Michal knew of no earlier polychrome pathways to draw upon.[75] His map was the first published polychrome metabolic map, thereby setting a standard for decades of authors of biochemistry textbooks and their polychrome pathways.[76]

Even though Michal doesn't make the semantic resonance (red for reactions in multicellular organisms, green for those in plants) explicit in an accompanying text, this iconic use of color is obvious for everyone acquainted with this symbolism. This is not so much the case for the Japanese KEGG diagram – again, at least for the non-shinto observer. These statements raise questions regarding the reading of these maps: do the color codes help the understanding and memorization and will the learned cultural context play a role in this? If such diagrams transport implicit cosmologies, are scholars who do their studies on the basis of Michal's map restrained in their horizons of research questions and interpretations by the tacit separations of the realms of plants and animals? Would those trained on the

74 Michal: On Representation (s. fn. 48); Alan Viel: Interview conducted by the author with Alain Viel, Harvard University, Cambridge, MA, April 4, 2018.

75 Michal: On Representation (s. fn. 48).

76 Viel (s. fn. 74).



18: KEGG in Stryer 2002.

basis of the KEGG map see more similarities in the organisms instead of divisions between them? Such and many more research questions relate the use of color to the epistemology of diagrams.

Today, both types of representation, pathways and charts in the typical primary colors, as well as the KEGG map with a very different choice of color, meet on the pages between the same two covers of a book (FIG. 18). Of course, without this new color scheme ever being mentioned, the Stryer (which prior to 2002 did not show colors other than primary colors) displays the KEGG map on its textbook pages.[77]

The author's special thanks go to Alexandre Métreux, Ulrike Boskamp, Ian Lawson and participants of the author's workshop in 2017 that preceded the publication of this edited volume for their invaluable comments.

77 Berg, Tymoczko, Lubert Stryer (s. fn. 3), figure 15-2.

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MEANINGFUL COLORS IN THE SCIENCES