

CHAPTER 9

A Mess of Causes

The difficulties in talking about causes in biology have been recognized for over two centuries.¹ It's just that the issues were largely set aside in the era of molecular biology due to the expectation that our rapidly growing powers of minute analysis would bring full causal understanding. Biology would soon be rid of its troublesome language of life in favor of well-behaved molecular mechanisms. And yet today, after several decades of stunning progress in molecular research, the struggle to fit our understanding of living activity into the comfortable garb of familiar causal explanation looks more hopeless than ever.

On one hand, most biologists seem unaware that there is a problem here — or, at least, they are unwilling to betray their awareness in professional circles. On the other hand (as we will see in this chapter), their scientific descriptions could hardly signal more dramatically the failure of the usual causal explanations. We seem to be looking here at another illustration of blindsight.

In Chapter 7 we considered epigenetics, which is commonly taken to be about the way epigenetic “marks” on chromosomes alter gene expression. But no sooner did epigenetics gain biologists' attention than researchers began puzzling over the question, “Do epigenetic marks alter gene expression, or do changes in gene expression alter the marks?” (see Box 9.1). And the question is still with us. According to Luca Magnani, a cancer researcher at Imperial College London,

It's an absolutely legitimate question and we need to address it. The answer is either going to kill the field [of epigenetics], or make it very important (quoted in Ledford 2015).

“Either kill the field or make it very important”. The comment expresses absolute confidence that we can discover unambiguous causation, which will in turn settle the matter: either epigenetic changes *cause* gene activity (in which case they are very important), or they are *mere effects* of that activity, with little causal significance of their own. It must be one way or the other. The general idea is that, if something is to contribute to scientific understanding, it must be the indisputable cause of an indisputable effect. And yet, as we will now see, this stubborn insistence on causal clarity continually prods biological researchers (we will focus on molecular biology) to offer embarrassingly incoherent explanations.

The seductive appeal of master controllers

Consider the following remarks about a protein known rather blandly as “p53”. The remarks issue from a perfectly reputable source who is clearly aware of the subtleties and interwoven intricacies of coordinated, molecular-level activity in the cell. And yet this expert is lured by the mirage of unambiguous causation into offering a wondrously self-annihilating description:

The tumor suppressor p53 is a master sensor of stress that controls many biological functions, including [embryo] implantation, cell-fate decisions, metabolism, and aging ... Like a complex barcode, the ability of p53 to function as a central hub that integrates defined stress signals into decisive cellular responses, in a time- and cell-type dependent manner, is facilitated by the extraordinary complexity of its regulation. Key components of this barcode are the autoregulation loops, which positively or negatively regulate p53's activities.

To start with, then, we have a *master sensor* (p53) that *controls* various fundamental cellular processes, and yet is itself wholly dependent on the signals it receives and is subject to “extraordinarily complex” *regulation* by certain autoregulation loops. While all these loops regulate p53 (some positively and some negatively), one of them, designated “p53/mdm2,”

is the master autoregulation loop, and it dictates the fate of an organism by controlling the expression level and activity of p53. It is therefore not surprising that this autoregulation loop is itself subject to different types of regulation, which can be divided into two subgroups ... (Lu 2010).

So the *master controlling* sensor is itself subject to a *master controlling* process (one of several regulatory loops) that *dictates* the fate of the organism. But this master loop, it happens, is in turn *regulated* in various manners (as the author goes on to say in the rest of the article) by a whole series of “multi-layered” processes, including some that are themselves “subject to direct regulation by mdm2” — that is, they are regulated by an element of the regulatory loop they are supposed to be regulating.

It is hard to believe that the confusion here is unavoidable. By now every biologist knows how regulatory processes extend outward without limit, connecting in one way or another with virtually every aspect of the cell. But this only underscores the undisciplined terminological confusion continuing to corrupt molecular biological description today. When key regulators are in turn regulated, and controllers have their fates underwritten or redirected by other players, where within the web of mutual interaction can we single out a *master* controller capable of *dictating* cellular fates? And if we can't, what are reputable scientists doing when they claim to have identified such a controller, or, rather, various such controllers?

More than an innocent abuse of language

Here is a comment from another paper on p53:

Following DNA damage, the transcription factor p53 determines whether cells undergo apoptosis [self-induced cell death] or cell cycle arrest and DNA repair. To enable different cellular outcomes, p53 is regulated through its temporal expression dynamics and post-translational modification, and by interactions with chromatin, chromatin regulators and transcription factors.²

Here again we have the same terminological confusion, with p53 *determining* cellular outcomes, while it is itself regulated by many pervasive cellular processes. But the authors conclude their paper with these remarkably sensible statements:

The large number of p53 regulatory mechanisms and their cooperation in triggering specific expression programmes remain open areas for investigation. Systematic measurements in multiple conditions together with models integrating the multiple layers of regulation on p53 activity will be required to decipher the complexity of p53 function.

Why not leave the matter there, with this admirable spirit of openness to the research results as given, together with an acknowledgment of almost unsurveyable complexity? Why are so many researchers driven to paste on top of this picture a contradictory assertion of open-and-shut causal determination?

And I do mean *driven*. How else to explain a comment that could serve as a fitting postscript to our discussion of RNA splicing in [Chapter 8](#). Brenton Graveley, a geneticist at the University of Connecticut Stem Cell Institute, reported in 2011 on the discovery of a splice variant of the protein known as FOX-P1 — a variant that has a role in the generation of stem cells. After usefully elucidating some of what goes on, he offers this as his conclusion:

What controls the [FOX] splicing switch? What splicing factors are responsible for flipping this switch, and how are their expression and activities regulated? Answering these questions is like hunting down the “chicken-or-the-egg” paradox, but they will ultimately uncover the master regulator of stem cell pluripotency (Graveley 2011).

So in the very act of acknowledging the fundamental “chicken-or-egg” paradox of all biological causation, he reflexively reverts to a kind of creedal affirmation of a still-hidden, but eventually-to-be-found Master Regulator.

If all those who use the language of biologically omnipotent control are really trying to describe something like “important influencers,” then that’s perfectly fine. But influence is not about mechanism and control; the *things* at issue just don’t have controlling powers. Nor, despite Graveley’s suggestion, is it about a simple flipping of yes-or-no switches. What we see, rather, is a continual mutual adaptation, interaction, and coordination explicable only in terms of the functional ideas through which we grasp the contextualized *meaning* of what is going on ([Chapter 6](#), “Context: Dare We Call It Holism?”).

What we see, that is, once we start following out all the interactions at a molecular level, is not some mechanism *dictating* the fate or *controlling* an activity of the organism. Rather (as I have been emphasizing throughout the preceding chapters), we observe an organism-wide, [narrative coherence](#) — a functional, end-directed, story-like coherence impossible to elucidate

in terms of strictly physical interactions that make no reference to the *meaning* of events. Only so far as they are caught up in and sensitive to this functional story do the individual molecular players find their proper roles.

The misrepresentation of this organic and rational coherence in favor of supposed controlling mechanisms is not an innocent inattention to language; it is a fundamental misrepresentation of reality at the central point where we are challenged to understand the character of living things.

Biological clocks: who is keeping time?

Pick any topic in biology and you will encounter an egregious failure to “tie down” biological causes. Clockwork mechanisms are nowhere to be found — a fact that becomes particularly poignant in the investigation of “biological clocks” such as the circadian (daily) rhythms that figure so prominently in human and other forms of life. Biologists, of course, set out to

identify the “master clock mechanism” that was presumed to “control” these rhythms, and, yes, they found a rhythmic feedback loop involving genes and transcription factors in a certain area of the brain that seemed the perfect candidate. It quickly came to be viewed as the decisive governor of circadian rhythms in the body:

In mammals, the anatomical structure in the brain that governs circadian rhythms is a small area consisting of approximately 15,000 neurons localized in the anterior hypothalamus, called the suprachiasmatic nucleus (SCN). This “central pacemaker” in the SCN receives signals from the environment and, in turn, coordinates the oscillating activity of peripheral clocks, which are located in almost all tissues (Berger and Sassone-Corsi 2016).

And yet (as this statement already indicates), ongoing research has revealed distinct “clocks” in different mammalian organs and tissues, and indeed in every cell. These “clocks”, it turns out, are not merely on the receiving end of a central, governing coordination, but rather are themselves participants in that coordination, and also, it now seems, are interwoven with just about all aspects of the organism’s physiology — metabolism, reproduction, cell growth and differentiation, immune responses, central nervous system functions ...

In each of these areas the quest for causes and master controllers leads to the usual perplexity about who’s doing what to whom. For example: “Although metabolism is thought to be primarily downstream of the cellular clock, numerous studies provide evidence that metabolic cycles can operate independently from or even influence circadian rhythms” (Kumar and Takahashi 2010). At the molecular level, one research team remarks that the enzymatic function of a certain clock protein “may be controlled by changing cell energy levels, or conversely, could regulate them” (Doi et al. 2006). In general: “It seems that connections between the circadian clock and most (if not all) physiological processes are bidirectional” (Yang 2010).

What we’re gaining from all this research is a wonderful portrait of the organism as a rhythmic being. Investigators have not found controlling mechanisms that single-handedly establish or govern the circadian rhythms of the organism, but rather are discovering how those

rhythms come to expression at every level and in every precinct of the organism — perhaps more centrally here and more peripherally there, but altogether in a single, organism-wide harmony that is also linked to environmental rhythms. There is no sensible way, as a scientist, to speak of particular mechanisms that *explain* this harmony. Instead, every isolated “mechanism” is found to be a *reflection* of the harmony, and we thereby gain further, detailed understanding of how the whole organism functions as a being in time.

Is any of this a surprise? Should we expect, say, that a “master regulator” of digestion exists? Would it be the stomach? The small intestine? The large intestine? The pancreas? The liver and gall bladder? The metabolism taking place in every cell? The brain that sends various coordinating nervous signals to different organs? The mouth that initiates everything? We would certainly look more to the stomach than, say, to the heart, but the fact remains that the organism as a whole is the closest thing we have to a “master regulator”. What we see in the separate, “mechanistic” clocks and regulators of circadian rhythms is simply the functioning of those rhythms in the most recognizable or most focal places. But they merely put on more obvious display the rhythmic functioning of the entire body.

A well-studied worm

Or, we can choose a different example. If there was any place where biologists expected a causal explanation of the organism to emerge clearly, it was in the study of *Caenorhabditis elegans*, a one-millimeter-long, transparent roundworm whose private molecular and cellular affairs may have been more exhaustively exposed than those of any

other organism. The adult hermaphrodite has exactly 959 cells, each precisely identified as to origin and type: for example, 302 cells belong to the nervous system. The developmental fate of every somatic cell, from egg to adult, had already been mapped out by 1980. But this mapping and the associated molecular studies did not produce the expected explanations.

Sydney Brenner — who received a 2002 Nobel prize for his work on *C. elegans* — acknowledged that development “is not a neat, sequential process ... It’s everything going on at the same time”. Even regarding the carefully mapped cell lineages of this “simple” roundworm, “there is hardly a shorter way of giving a rule for what goes on than just describing what there is”. In other words, the only “rule” for the development of this worm is the entire developmental description of it.

When critics suggested he had not really come to an understanding of the worm, but had “only” described it, Brenner wisely responded, “I’m not sure that there necessarily is anything more to understand than what it is”. British science writer Roger Lewin quoted this remark by Brenner in an article titled, “Why Is Development So Illogical?” with the subtitle, “The more biologists learn about development, the less it appears that organisms are assembled by neat, sequential processes; we should not be surprised” (Lewin 1984). Actually, it’s not even true that organisms are *assembled* from pre-existing parts. They grow from within through processes of self-transformation, not mechanical assembly.

The difficulties of linear, causal explanation encountered by the *C. elegans* researchers were not accidental. You can't explain an organism of meaning, and you don't need to. You need only allow it, like any meaningful text, to speak ever more vividly and profoundly, in ever greater detail, so as to yield up its unique and unrepeatable story.

The separate processes do not make tidy explanations because they are not really separate and are not doing just one thing. They are harmonizing with everything else going on in the organism. We gain understanding when we learn to recognize this harmony in every aspect of the organism. Various analyses can play a crucial role in bringing clarity to our understanding, but the full picture takes shape only when the analytical threads are woven back into the larger fabric of meaning.

Of crosstalk, horror graphs, and collaboration

One final example. Molecular biologists speak about *signals* arriving at *receptors* on the cell surface. The signals are said to bear *messages*, which are then transferred (as it often happens) from the receptors to a series of further *messengers* internal to the cell, which may, among other possibilities, finally

convey the message to the cell nucleus. There the message may be *interpreted* to require the increased or decreased *expression* of a gene *coded* for a particular protein. The players in the signaling are, of course, molecules, with proteins being the usual focus of research.

The terminology so naturally resorted to here — and italicized in the preceding paragraph — vividly evokes language, meaning, and communication — something we saw exemplified in Chapter 2 (“The Organism’s Story”). But, of course, this usage is typically treated as “mere metaphor”. Signaling pathways have long been regarded as neat, linear sequences of molecular interactions by which an initial encounter — say, the binding of a hormone to a cell membrane receptor — leads to a predetermined result. It's almost as if the language of molecules and cells were merely one of mechanism and logic — not a true language at all.

But the language is in fact much richer than that. Signaling pathways help to maintain a coherence of meaning within and between cells. Take, for example, the work by a team of molecular biologists at the Free University of Brussels. They investigated how signaling pathways interact or “crosstalk” with each other. Tabulating the cross-signalings between just four such pathways yielded what they called a “horror graph”, and quickly it began to look as though “everything does everything to everything” (Dumont et al. 2001), much like the way any given term in a meaningful text can modify the meanings of many other terms. Other researchers speak of a “collaborative” process that can be “pictured as a table around which decision-makers debate a question and respond collectively to information put to them” (Levy et al. 2010).

Even considering a single membrane receptor bound by a hormonal or other signal, you can find yourself looking, conservatively, at a billion possible states, depending on how that receptor is modified by its interactions with other molecules. Despite previous belief, there is no

simple binary rule distinguishing deactivated receptors from those activated by some combination of signals in a particular context. “The activated receptor looks less like a machine and more like a ... probability cloud of an almost infinite number of possible states, each of which may differ in its biological activity” (Mayer et al. 2009).

Our problem lies in adequately imagining the reality. When a single protein can combine with several hundred different modifier molecules, leading to practically infinite combinatorial possibilities, and when that protein itself is an infinitesimal point in the vast, turbulent molecular sea of continual exchange that is the cell, and when the cell is one instance of maybe several trillion cells of some 250 different major types in the human body — in muscle and bone, liver and brain, blood and artery — well, it would be understandable if some of those seeking mechanistic or computer-like “controllers” preferred not to stare too long at this picture.

Nevertheless, we should keep in mind that the “collaborative” process mentioned above involves not just one table with “negotiators” gathered around it, but countless tables with countless participants, and with influences radiating in all directions as countless local “decisions” are made in a manner somehow disciplined by the immaterial unity (Chapter 6, “Context: Dare We Call It Holism?”) and multidimensioned *interests* of the organism as a whole.

In other words, not only are the elements of an individual signaling pathway extremely flexible and adaptive; the individual pathway itself, once thought of as discrete and well-defined, doesn’t really exist — certainly not as a separate “mechanism”.

In sum: messages are not physically discrete, and they do not fly back and forth as elements of a predefined cellular logic. They move as dynamically sculptured, interwoven patterns of force and energy. Their meanings are mimed or gestured — neither translated into, nor reduced to, a kind of expressionless Morse code, nor impelled along precisely incised channels like computer instructions. And what holds them together amid the ceaseless flow and crosstalk and molecular transformation of the cellular plasm is the unity of meaning that is the whole cell and whole organism. This unity is there for us to observe directly, and we all recognize it, whether with blindsight or otherwise.

Box 9.1 illustrates the problems we’ve been discussing, with specific reference to a single aspect of cellular function: the molecular biology of gene expression.

Box 9.1

Cause — Or Effect? Ambiguities related to gene expression

In trying to articulate the idea of a machine-organism, molecular biologists are forever chasing “causal mechanisms”, forever lamenting the difficulty of teasing apart cause and effect, and forever failing to see that the sought-for mechanisms don’t exist in any stable and reliable sense.

In the following quotations, you needn’t worry about the technical details; the general sense of the remarks is all that matters here.

“Together, these results further emphasize the role for RNA polymerase in shaping the chromatin landscape of the genome and point toward the difficulty in disentangling cause and effect in the relationship between chromatin and transcription” (Weiner et al. 2010).

“Epigenetic modifications in Alzheimer’s disease: cause or effect?” — title of a paper. The conclusion: “Further studies are necessary” (Piaceri 2014).

“While several studies using next-generation sequencing have revealed genome-wide associations between epigenetic modifications and transcriptional states, a direct causal relationship at specific genomic loci has not been fully demonstrated ...” (Fukushima et al. 2019).

“Despite the difficulties in proving cause and effect, these examples convincingly illustrate how chromatin crosstalk can functionally increase the adaptive plasticity of the cell exposed to the changing microenvironment” (Göndör and Ohlsson 2009).

“A related unresolved question is whether chromatin loops are the cause or the effect of transcriptional regulation” (Deng and Blobel 2010).

“The enthusiasm for establishing whether epigenetic mechanisms link the environment with disease development must be tempered by the knowledge that the epigenome is dynamic and has as much potential to respond to disease as respond to the environment. Therefore it is very difficult to disentangle cause from consequence when studying epigenetic variation and disease” (Relton 2012).

“Despite abundant evidence that most kinds of tumor cells carry so-called epigenetic changes, scientists haven’t yet worked out exactly whether such glitches are a cause or a consequence of disease” (Kaiser 2010).

“The clarification of the cause-and-effect relationship of nuclear organization and the function of the genome represents one of the most important future challenges. Further experiments are needed to determine whether the spatial organization of the nucleus is a consequence of genome organization, chromatin modifications, and DNA-based processes, or whether nuclear architecture is an important determinant of the function of the genome” (Schneider and Grosschedl 2007).

“Although there is widespread agreement that genome form [such as folding and topological domains] and function [gene expression] are intimately connected, their causal relationship remains controversial” (Stadhouders et al. 2019).

“The spatial organization of the genome into compartments and topologically associated domains can have an important role in the regulation of gene expression. But could gene expression conversely regulate genome organization? ... Recent evidence suggests a dynamic, reciprocal interplay between fine-scale genome organization and transcription, in which each is able to modulate or reinforce the activity of the other” (Steensel and Furlong 2019).

“Transcription itself alters loops and consequently requires their continual reformation. Together, [this and other chromatin] properties suggest extensive feedback between chromatin structure and gene activity, rather than a simple cause-and-effect relationship” (Misteli and Finn 2021).

The problem of causation is fundamental to biology

The powerful compulsion to identify decisive causes, even at the expense of painfully self-contradictory language, strongly suggests that a one-sided and unrealizable ideal of biological explanation is at work. Under its influence we aim to discover a physical lawfulness reflecting, above all, our experience with machines

— a lawfulness of precise, unambiguous *control*, where one thing can be said, without unwelcome qualification, to make another thing happen.

Think of a machine. Having conceived what we want it to do, we design it to be a closed system whose intended functioning is more or less immune to contextual interference. And we try to do much the same in many scientific demonstrations. For example, we can create a vacuum in a chamber, and then release a leaf from the top of the chamber. It falls like a stone.

Of course, leaves in nature often travel upward. But the experiment in the chamber enables us to observe the singular and lawful play of gravity, without any disturbing “interference” from the resistance or movement of air. We can then — and only then — say that gravity appears to *make* the leaf fall, just as the simple laws governing the gears and springs of a mechanical watch *make* the watch perform as a reliable keeper of time.

But when the biologist tries to see an animal in the same mechanistic light, as a closed system without interfering factors, the attempt fails miserably. This is because, for the animal, *contextual interference is the whole point*. As the meaning of its activity shifts from moment to moment, so, too, does the contextual significance of all the details of its life.

For example, when a deer is grazing in a meadow, its glimpse of a vaguely canine form in the distance changes the meaning of everything from the flowers and grass the deer was eating, to its own internal digestive processes, to the expression of its genes. This happens, not because the distant form is exerting some strange physical force upon the deer, but because that form becomes part of a now suddenly shifted pattern of meaning.³

Or (to focus on the cellular level): when a cell enters into mitosis, just about every detail of its physiology and chemistry takes on an altered meaning in light of the changing narrative context. Everything is now heading toward a different outcome. Molecules that had been participating in one set of interactions (and could easily still do so in purely physical terms) now enter into very different intermolecular relations. Similarly with a cell experiencing heat shock, oxygen deprivation or other stress, a cell coming into contact with new neighbors, or a cell proceeding along a path of embryonic differentiation.

Certainly we can still identify unambiguous causes in the organism. It is always possible to narrow the conditions of our experiments so severely that a consistent “causal arrow” for a particular interaction emerges *under those conditions*. But the whole point of life’s adaptability is to seek (or help create) *altered conditions* according to present needs and interests. This is why there can be no fixed syntax, no mechanical constancy of relations among the parts. The organism is forever abandoning the coordinating principles of its old context in favor of a new and ever-changing meaning. Its story is always evolving.

I titled this section, “The Problem of Causation is Fundamental to Biology”. The problem I had in mind was that of getting clear about the very nature of causation in biology. It differs from the problem of causation in the physical sciences. Organisms manifest a fluid, integral, harmonizing sort of causation that is more like a play of the multi-dimensional *reasons* for things than a set of one-dimensional mechanical interactions. It is more like the rich interplay of meaning in an unfolding poem than a rigid syntax or logic.

Biologists, on the other hand, seem to be fixated on the “fundamental issue” of distinguishing clear-cut cause from clear-cut effect in the usual physical sense:

Despite intensive studies of genome organization in the past decade, a fundamental issue remains regarding genomic interactions and genome organization as a cause or a consequence of gene expression. This problem is also pertinent to RNAs, which may have

regulatory functions in transcription rather than being simply products of transcription (Li and Fu 2019).

Unfortunately, there is little if any effort to elucidate just what hangs upon this “fundamental issue” — or what might be the implications of the fact that the issue appears irresolvable so long as we insist upon unambiguous physical causation as the basis for biological understanding.

WHERE ARE WE NOW?

We Need a Biology Beyond Definitive Causes

If the preoccupation with controlling causes reflects, as I have now suggested, an unrealizable ideal of biological explanation, then it also reflects a more or less false understanding of biological reality. I have, in the preceding chapters, been trying to point toward some primary aspects of a more adequate understanding — one that needn't bring us into conflict with what we know. Here is a brief retrospective:

- It has turned out, as we saw in “[What Brings Our Genome Alive?](#)” and “[Epigenetics: A Brief Introduction](#)”, that genes — those supposed *prime causes* of the organism's life — are in fact the focus of almost incomprehensible powers of coordination working from the whole of the cell and organism into the cell nucleus. And the principle of coordination was equally evident in “[The Sensitive, Dynamic Cell](#)”, where we looked at the membranes and cytoskeleton of cells.

- We have seen, courtesy of the work of the twentieth-century cell biologist, Paul Weiss, that molecules interacting according to physical law in the fluid medium of the cell possess countless “degrees of freedom” that must be curtailed, or disciplined, by the cell as a whole. Similarly, vast numbers of cells must be “held together” according to the functional needs of particular organs. And so, too, the disparate organs and organ systems are harmoniously subordinated to the needs and interests of the organism as a whole. (See especially the chapter, “[Context: Dare We Call It Holism?](#)”)

- We have also seen (in that same chapter) that biologists incessantly appeal to the “context-dependence” of biological activity. The appeal amounts to a tacit recognition of a kind of causation that works “downward” from the integral unity of a larger whole, into the parts. This causal unity is inseparable from the *ideas* that define a context and hold its elements meaningfully together, thereby posing “[The Mystery of an Unexpected Coherence](#)” (Chapter 8).

- Again, in the present chapter, we have been alerted to the confusion of causes that makes it impossible to explain organisms in the usual causal terms. That is, it is impossible to explain them *biologically* in this way, as opposed to merely elucidating their physics and chemistry. The life-like coordination of physical interactions involves what I referred to above as the “multi-dimensional *reasons* for things rather than a set of one-dimensional mechanical interactions. It is more like the rich interplay of meaning in an unfolding poem or novel than a rigid syntax or logic”.

• And, finally, it is hard not to notice that all these themes come together in what we can usefully think of as the organism's story. That is, every organism spins, or cooperates in spinning, the narrative of its own life. Future-directedness, purposiveness, context-sensitivity, the meaningful interweaving of ideas, the subordination of isolated events and physical causes to the needs, interests, and purposes of active agents — these features that we have noted in organisms are also the features of stories (Chapter 2).

In the next two chapters, dealing with problems of form, we will see how the form of organisms offers us an avenue toward biological understanding that can be a useful corrective to the usual preoccupation with cause and effect. Then, in Chapter 12 (“Is a Qualitative Biology Possible?”), we will work at reconceiving biological causation as a matter of form and idea.

Notes

1. In his 1790 work, *Kritik der Urteilskraft* (subsequently published in English as *Critique of Judgment*), the philosopher Immanuel Kant wrote of the organism that “every part not only exists *by means of* the other parts, but is thought as existing *for the sake of* the others and the whole ... also [the] parts are all organs reciprocally *producing* each other” (Kant 1790, Div. 1, para 65).

In speaking of purely physical causation, we certainly would not say that parts exist *for the sake of* each other. But Kant's treatment of these issues was central to a great deal of biological discussion during the following decades — and still surfaces frequently today, at least among philosophers of biology. But the technically oriented training of biologists themselves no longer encourages a familiarity with decisive issues at the foundation of their own discipline.

2. The quotation is from a Table of Contents description in *Nature Reviews Molecular Cell Biology* for Hafner, et al. 2019.

3. I make this same point with the wildebeest and lion in the chapter on “The Organism's Story”.

Sources

Berger, Shelley L. and Paolo Sassone-Corsi (2016). “Metabolic Signaling to Chromatin”, *Cold Spring Harbor Perspectives in Biology* vol. 8, no. 11. [doi:10.1101/cshperspect.a019463](https://doi.org/10.1101/cshperspect.a019463)

Deng, Wulan and Gerd A. Blobel (2010). “Do Chromatin Loops Provide Epigenetic Gene Expression States?”, *Current Opinion in Genetics and Development* vol. 20, pp. 548-54. [doi:10.1016/j.gde.2010.06.007](https://doi.org/10.1016/j.gde.2010.06.007)

Doi, Masao, Jun Hirayama and Paolo Sassone-Corsi (2006). “Circadian Regulator CLOCK Is a Histone Acetyltransferase”, *Cell* vol. 125 (May 5), pp. 497-508. [doi:10.1016/j.cell.2006.03.033](https://doi.org/10.1016/j.cell.2006.03.033)

Dumont, Jacques E., Frédéric Pécasse and Carine Maenhaut (2001). “Crosstalk and Specificity in Signalling: Are We Crosstalking Ourselves into General Confusion?”, *Cellular Signalling* vol. 13, pp. 457-63. [doi:10.1016/S0898-6568\(01\)00168-1](https://doi.org/10.1016/S0898-6568(01)00168-1)

- Fukushima, Hiroto S., Hiroyuki Takeda and Ryohei Nakamura (2019). "Targeted in Vivo Epigenome Editing of H3K27me3", *Epigenetics and Chromatin* vol. 12, no. 17. doi:10.1186/s13072-019-0263-z
- Gilbert, David M. (2002). "Replication Timing and Transcriptional Control: Beyond Cause and Effect", *Current Opinion in Cell Biology* vol. 14, no. 3 (June 1), pp. 377-83. doi:10.1016/S0955-0674(02)00326-5
- Göndör, Anita and Rolf Ohlsson (2009). "Chromosome Crosstalk in Three Dimensions", *Nature* vol. 461 (September 10), pp. 212-17. doi:10.1038/nature08453
- Graveley, Brenton R. (2011). "Splicing Up Pluripotency", *Cell* vol. 147 (September 30), pp. 22-24. doi:10.1016/j.cell.2011.09.004
- Hafner, Antonina, Martha L. Bulyk, Ashwini Jambhekar and Galit Lahav (2019). "The Multiple Mechanisms That Regulate p53 Activity and Cell Fate", *Nature Reviews Molecular Cell Biology* vol. 20, no. 4 (April). doi:10.1038/s41580-019-0110-x
- Kaiser, Jocelyn (2010). "Genes Link Epigenetics and Cancer", *Science* vol. 330, no. 6004 (October 29), p. 577. doi:10.1126/science.330.6004.577
- Kant, Immanuel (2000). *Critique of Judgment*, translated by J. H. Bernard. Amherst NY: Prometheus Books. Originally published in German in 1790. Available at <https://www.gutenberg.org/ebooks/48433>
- Kumar, Vivek and Joseph S. Takahashi (2010). "PARP around the Clock", *Cell* vol. 142 (September 17), pp. 841-43. doi:10.1016/j.cell.2010.08.037
- Ledford, Heidi (2015). "The Genome Unwrapped", *Nature* vol. 528 (December 3), pp. S12–S13. doi:10.1038/528S12a
- Levy, Emmanuel D., Christian R. Landry and Stephen W. Michnick (2010). "Signaling through Cooperation", *Science* vol. 328 (May 21), pp. 983-84. doi:10.1126/science.1190993
- Lewin, Roger (1984). "Why Is Development So Illogical?" *Science* vol. 224 (June 22), pp. 1327-29. doi:10.1126/science.6374894
- Li, Xiao and Xiang-Dong Fu (2019). "Chromatin-Associated RNAs as Facilitators of Functional Genomic Interactions", *Nature Reviews Genetics* vol. 20 (September), pp. 503-19. doi:10.1038/s41576-019-0135-1
- Lu, Xin (2010). "Tied Up in Loops: Positive and Negative Autoregulation of p53", *Cold Spring Harbor Perspectives in Biology* (December 9). doi:10.1101/cshperspect.a000984
- Mayer, Bruce J., Michael L. Blinov and Leslie M. Loew (2009). "Molecular Machines or Pleiomorphic Ensembles: Signaling Complexes Revisited", *Journal of Biology* vol. 8, no. 9, article 81. doi:10.1186/jbiol185
- Misteli, Tom and Elizabeth H. Finn (2021). "Chromatin Architecture Is a Flexible Foundation for Gene Expression", *Nature Genetics* vol. 53, no. 4 (April), pp. 426-7. doi:10.1038/s41588-021-00813-2
- Piaceri, Irene, Beatrice Raspanti, Andrea Tedde et al. (2015). "Epigenetic Modifications in Alzheimer's Disease: Cause or Effect?", *Journal of Alzheimer's Disease*, vol. 43, no. 4, pp. 1169-73. doi:10.3233/JAD-141452
- Relton, Caroline (2012). "Epidemiology and Epigenetics — A Marriage Made in Heaven?", *Oxford University Press Blog* (March 28). <https://blog.oup.com/2012/03/epidemiology-epigenetics-journal/>
- Schneider, Robert and Rudolf Grosschedl (2007). "Dynamics and Interplay of Nuclear Architecture, Genome Organization, and Gene Expression", *Genes and Development* vol. 21, pp. 3027-43. doi:10.1101/gad.1604607
- Stadhouders, Ralph, Guillaume J. Filion and Thomas Graf (2019). "Transcription Factors and 3D Genome Conformation in Cell-Fate Decisions", *Nature* vol. 569 (May 16), pp. 345-54. doi.org/10.1038/s41586-019-1182-7
- Steensel, Bas van and Eileen E. M. Furlong (2019). "The Role of Transcription in Shaping the Spatial Organization of the Genome", *Nature Reviews Molecular Cell Biology* vol. 20, pp. 327-37. doi:10.1038/s41580-019-0114-6

- Weiner, Assaf, Amanda Hughes, Moran Yassour et al. (2010). "High-Resolution Nucleosome Mapping Reveals Transcription-Dependent Promoter Packaging", *Genome Research* vol. 20, pp. 90-100. doi:[10.1101/gr.098509.109](https://doi.org/10.1101/gr.098509.109)
- Yang, Xiaoyong (2010). "A Wheel of Time: The Circadian Clock, Nuclear Receptors, and Physiology", *Genes and Development* vol. 24, pp. 741-47. doi:[10.1101/gad.1920710](https://doi.org/10.1101/gad.1920710)