Seeing things: From microcinematography to live cell imaging

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Hannah Landecker

From histology to microcinematography, from cytochemistry to live cell imaging, the history of visualization technology in the life sciences may be understood as a series of cycles of action and reaction between static and dynamic modes of representing life.

In the relatively new field of molecular epigenetics, understanding the dynamics of chromatin is of central importance. In his introduction to the first textbook dedicated to epigenetics, published in 2007, Daniel Gottschling commented that "on the basis of static images of chromatin and the refractory nature of silent chromatin, I was convinced that once established, a heterochromatic state was solid as granite." Further, although "chromatin precipitation has been important in establishing which components reside in a structure, it has temporarily blinded us to the dynamics"[1].

It is indeed easy to forget that chromatin—exhaustively analyzed biochemically, histologically detailed for over a century, that appears in such characteristic form in electron and light microscopy—is actually always moving and undergoing constant change. What is true in a cell at one moment in time may not be true at another moment under different conditions, such that methods that produce a snapshot of gene expression or methylation might not give a good picture of process over time.

Epigenetics, it is safe to say, is a field characterized by the search for methods that allow the visualization of biological structure—but structure that is now understood to be in perpetual flux. Processes such as methylation and acetylation are reversible and may change quickly, rendering the genome a much more plastic entity than previously suspected. We may also understand this as the genome being a much more plastic entity than previously *depicted*.

Much the same point about biologists' perception of chromatin was made almost a hundred years ago by the French biologist and cinematographer Jean Comandon. In the years 1913 and 1914, writing and giving lectures about films of cell division that he made together with his colleague Justin Jolly, Comandon noted that the stages of cell division that biologists used in order to describe the phenomenon were arbitrary steps in what was actually a continuous process[2]. Watching dividing cells filmed with time-lapse microcinematography, he remarked, was to be amazed by the ferocity of continuous movement of the chromatin. One should remember, he said, that the very name chromatin derives from the histological procedures used to see it—the colored dyes and fixatives that rendered the chromatin and its structure more visible under the light microscope, but at the same time rendered it dead. In short, the method of visualization—chromatization—had become substituted in biologists' understanding for the thing itself, and they had forgotten that chromatin was a living entity. Time-lapse cinematography could remind them that chromatin was a lively thing, undergoing constant change and movement, as much a process as a structure. It all depended on how you looked at it.

Juxtaposing the perception of chromatin in these two eras, one might conclude that the more things change, the more they stay the same. But surveying the history of visualization techniques from the late nineteenth century to today, a more complex picture emerges: a cycle of technical invention that has for more than a hundred years been a process of action and reaction between analytical, quantitative biochemical or mathematical methods and more qualitative, observational methods.

The late nineteenth century was a period of ascendance for histological methods. After 1870, Paul Ehrlich (1854–1915) was instrumental in the energetic adaptation of industrially available synthetic dyes as biological stains, and in efforts to understand the chemistry of their selective action on different tissue and cell components. Ehrlich's famous "magic bullet" concept behind the development of arsphenamine (Salvarsan) for the treatment of syphilis emerged from the chemistry of selective staining: if organisms could be selectively stained (and thus killed) on a microscope slide, they should also be selectively killed in the body.

Ehrlich championed the various fixatives and stains as providing much more visual detail than could be seen in wet specimens; he also trumpeted the ability of histological techniques to free the investigator from the constraints of time and place. Whereas a wet specimen had to be examined when and where it was obtained, a stained and fixed slide could be kept for months at a time and examined repeatedly[3]. It was exactly the ability to stop time that made histology desirable to its practitioners around the turn of the twentieth century. Although a few agents permitted live cell staining (used extensively in embryology for cell fate mapping) the refinement of treatments that killed the specimen were at the center of histology. Halting biological process at a

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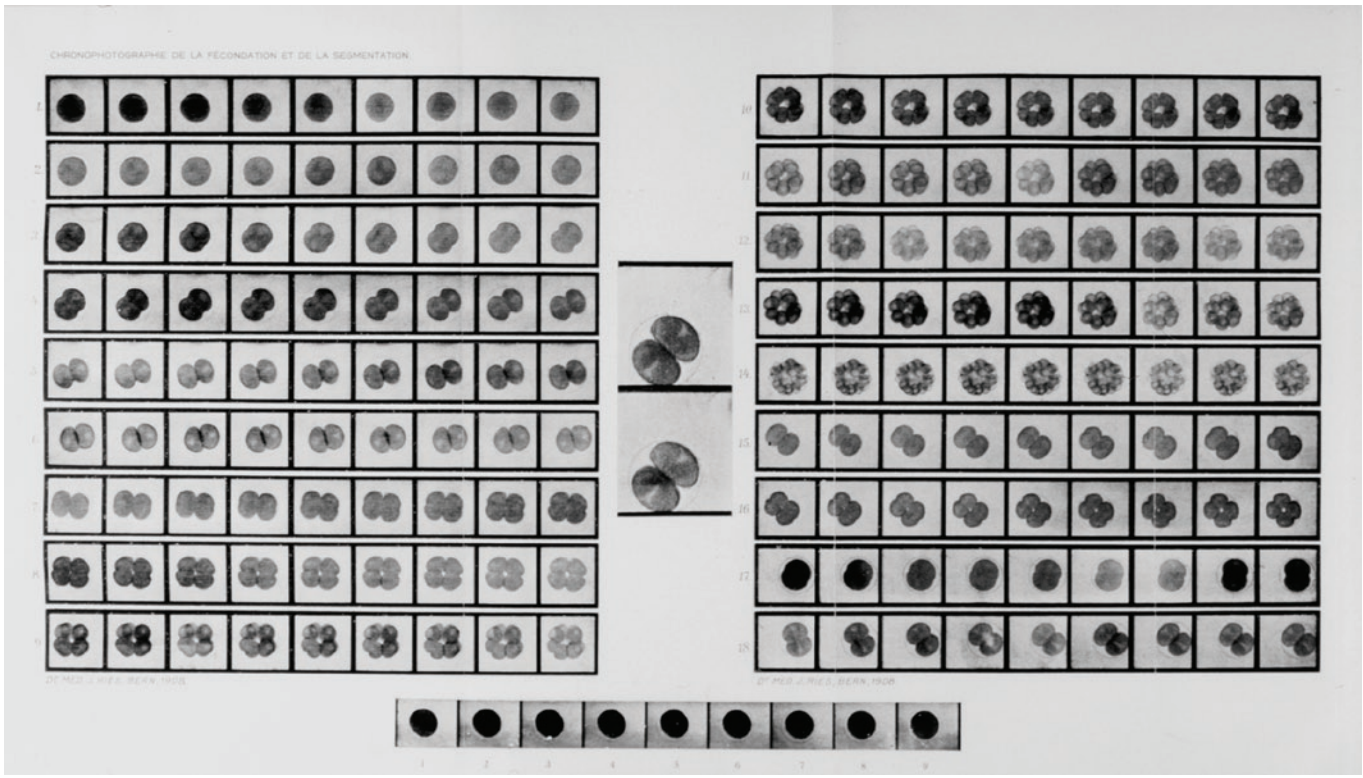

Figure 1 | Stills from *Fertilization and Development of the Sea Urchin Egg* by Julius Ries, one of the earliest time-lapse microcinematographic films ever made, filmed in Paris in 1907. Using the moving image for teaching and research was novel, but Ries still had to meet the constraints of paper publishing. He illustrated his paper on the topic with this photograph of the filmstrips, all that now remains of the original film. Reproduced from ref. 10.

particular point was seen as a mark of forward progress over older ways of pursuing microscopy.

What was left unremarked was the shift in emphasis from process to structure and from behavior to morphology that accompanied the rise of these methods. This is understandable enough, for it was the great strength of using histological stains that previously imperceptible details of cellular and tissue structure were now visible. But this strength would later become a perceived shortcoming, a springboard for innovation for a later generation that pushed in the opposite direction. Although functional analysis of organs or animals was strong at the beginning of the twentieth century, many noted the need for methods that would allow a functional analysis of cells. Comandon and other scientists working with tissue culture (see accompanying article) and microcinematography were reacting to the static nature of histology when they sought to find ways to study the cell in its living state, over time. In their writings, one sees frequent comparisons of histology to the practice of autopsy; microcinematography, in contrast, was the tool for vivisection and for seeing physiology at the scale of the cell.

The first time-lapse films of embryonic development and cultured cells were made in France in 1907. At first, films were made of the fertilization and development of the sea urchin egg as a way of teaching medical students cell theory. Julius Ries, maker of one of the first of these films (**Fig. 1**), thought that students would never believe that all cells came from other cells, and that organisms were made up of nothing but cells, unless they had moving, living evidence in front of their eyes. But a very small percentage of medical students had access to the marine biological stations where one might be able to observe sea urchins; in addition, the whole process of development took about 14 hours. It was much easier to film development and allow it to unfurl on the screen in two minutes. Drawings and fixed sections were in Ries's opinion inadequate, exactly because they "differed from the living in their motionlessness"[4].

Upon making films to demonstrate known phenomena in a more convenient format, researchers quickly realized that they could also now see things not visible in any other way, as the movement of many cells was so slow as to be below the threshold of human perception. The first purpose-built microcinematographic apparatuses became commercially available in Europe in 1914. Time-lapse microcinematography has been used to study cellular behavior *in vitro* ever since, from the early work of Warren Lewis demonstrating pinocytosis as a basic cellular phenomenon to the later cellular movement studies of Michael Abercrombie[5,6]. The practice was reinvigorated with the invention in the 1930s of phase contrast microscopy. Coupled with a film camera or, later, video technology, phase contrast allowed the observers into the cell: intracellular organelles and their previously imperceptible movements could now be seen in much greater detail.

The visualization efforts in microcinematography were explicitly directed at making structures elucidated by static methods, such as chromatin or mitochondria, move again, to observe their behavior over time or their reaction to injury or pharmacological agents. However, dynamic modes of imaging were in their turn critiqued as inexact and unscientific precisely because of their qualitative nature. Nobelist Peter Medawar, writing in his memoir about biology in the 1940s, scolded a previous decade

of film-making cell biologists for having been "delighted, distracted, and beguiled by the sheer beauty" of cells on film, and as a result having missed the opportunity to use cytological methods to—as he put it—"solve biological problems"[7]. The criticism voiced by Medawar is only one specimen of a constant call to formalization: what good will "just looking" at life do, when there are immune reactions to figure out, forces to quantify, DNA to sequence, regularities to ferret out? All would agree that phenomena were exquisitely visible on film, but what kind of explanation did it provide?

The disparagement of inexactitude has been a productive force in efforts to represent life for analysis. New methods and technologies come about for many disparate reasons, but one of them is the desire to make biology a more exact science, to produce laws or at least mechanisms such as are found in other sciences. J.H. Woodger, for example, attempting to construct a theoretical biology in the late 1930s by importing mathematical logic into biology, assigned logical operators to components of biological knowledge to produce axioms from which biological theories could be generated. This he pursued because "an intense interest in, and intimate first-hand acquaintance with organisms, indispensable as it is, will not *alone* lead biology to the goal of an exact science"[8]. This was a reference not just to microcinematography, but to all observation-based methods. Just watching something happen, he felt, must be transformed—formalized—before the observation could be part of an exact science. Although Woodger's notation system did not persist, his drive to formalize qualitative observation was influential in the early years of mathematical and theoretical biology.

In their turn, all static depictions of structure or process eventually come under fire as an inadequate representation of life. Labeling molecules with radioisotopes and then visualizing their passage through cells, tissues and ecosystems was greeted in the 1950s as a radically new form of perception exactly because it allowed the visualization over time of the molecular entities enumerated and fixed by x-ray crystallography, the ultracentrifuge and the electron microscope (see accompanying article).

It may be argued that we are at present experiencing yet another sea change, a shift in practice and perception from the static to the dynamic. In epigenetics, in the study of dynamic protein structure and in cell biology, to mention a few instances, entities that have been depicted as static structures are moving again. Perhaps most notably, the rise of live cell imaging in the past decades has been meteoric, with intense technical innovation both in the insertion of fluorescent probes into living cells and in the microscopy used to visualize their expression and movement. Roger Tsien, recognized along with Martin Chalfie and Osamu Shimomura last year with the Nobel prize in chemistry for founding work in fluorescent labeling, voiced a sentiment that precisely echoed the spirit of microcinematographers's critiques of histology a century ago: "genome sequences alone lack spatial and temporal information and are therefore as dynamic and informative as census lists or telephone directories"[9].

Judging from history, the beautiful, beguiling images of live cells produced by the new labels and microscopes will spur a new generation of biochemical and analytical methods in the effort to pin down the observed phenomena. Although those who concentrate on structure and those who concentrate on process have not always seen eye to eye, they nonetheless depend on one another in this cycle of action and reaction. It is not just theories that change in relation to technical innovation; the trajectory of biological science over the past century shows us that the development of technique also generates a kind of momentum in which instruments of visualization constantly evolve in relation to one another. The tension between the still and the moving image has been, and will no doubt remain, a highly productive force in the generation of new scientific knowledge.

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