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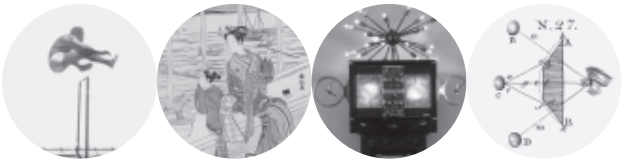

The Life of Movement: From Microcinematography to Live-Cell Imaging

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Abstract

How do we see life after the century of the gene? This article argues that the post-2000 postgenomic turn was and is a thoroughly visual turn, as well as a theoretical and practical shift away from the central dogma of DNA as master molecule. Live-cell imaging is a rapidly expanding area of scientific visualization of living things whose practice is central in postgenomic biological research and theory. Fluorescent probes enable the visualization of the movement *in vivo*, over time, of a wide range of vital molecules, for example the movement of motor proteins along the cellular skeleton. Despite its prominence in the life sciences, these moving images have attracted little critical attention outside the scientific community. Comparison with microcinematography of the early 20th century, another time-based medium that also placed the capture of movement at the center of the technique, is used here to frame the emergence of live-cell imaging in the late 20th century and discuss its theoretical significance. This article argues that live-cell imaging was at its origins an animation of a theory of life dominated by the gene. However, focused as it is on the life of proteins, the practice actually facilitated a move away from such dominance, with a rise of a 'molecular vitalism': an interest in all cellular molecules as knitted together in a complex moving net in the time and space of the cell. As such, the present moment echoes early 20th-century tensions between the study of structure and function in cellular anatomy versus physiology and puts the focus on molecular movement just as cellular movement was central to earlier practices. Contemporary live-cell imaging does not depict a structure described in a unique moment that explains a life process, but rather visualizes a continuity of movement that constitutes life processes.

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What does the study of the biological moving image bring to the cluster of humanities disciplines concerned with visuality? This question is particularly puzzling when the visual objects and visual technologies in question have very little public presence, do not function as art, entertainment, advertising or education, and most of the people who make and see these images are research scientists. Take the 'film' made with live-cell imaging: a fluorescent probe is inserted into a living cell or body – usually using genetic engineering to insert a DNA sequence encoding a fluorescent protein so that the body itself produces the visual probe along with its own proteins.[1] The digital moving images resulting from viewing the specimen through highly specialized microscopes and light detectors are documents recording the movement of molecules in time through cells or bodies. In fact, the image of the cell produced with such technology is of a cellular body made visible by its constituent molecules, molecules lit up like strings of Christmas lights, trailing their fluorescent tags around as they go about their ordinary business (see Figure 1). Just by way of example, a European Union funded project called MitoCheck at the European Molecular Biology Laboratory (EMBL) produced 190,000 films of human cells whose chromosomal proteins had been transgenically tagged with green fluorescent protein (GFP), 'providing time-resolved records of over 19 million cell divisions' (Neumann et al., 2010: 721). Who will see these images, other than the machines that have been trained to analyze them and divine which movement patterns represent anomalies?[2]

These moving images are important even if no one watches them. The very paradox of life being watched by machine, life that has been engineered to express the means of its own luminosity, should cue the postgenomic, postcybernetic moment to which this article attends. Live-cell imaging has become a constitutive and routine tool in biomedical and life science research; a textbook on the subject notes dryly: 'It is hard to imagine an active academic research department, pharmaceutical or biotechnology company without access to this technology and without using it on a regular basis' (Papkovsky, 2010: v). My consideration of the use of moving images in bioscience today – which is necessarily an encounter with live-cell imaging – is driven by this basic reason: after 2000, *it becomes difficult to imagine life without it*.

The life sciences after 2000 have been going through transformations that are often described as 'postgenomic'. The typical narrative is that with the complete sequencing of the human genome in 2000, it became apparent that the approximately 22,000 genes therein could not possibly account for the complexity of the body arising from the genome. Thus post-translational

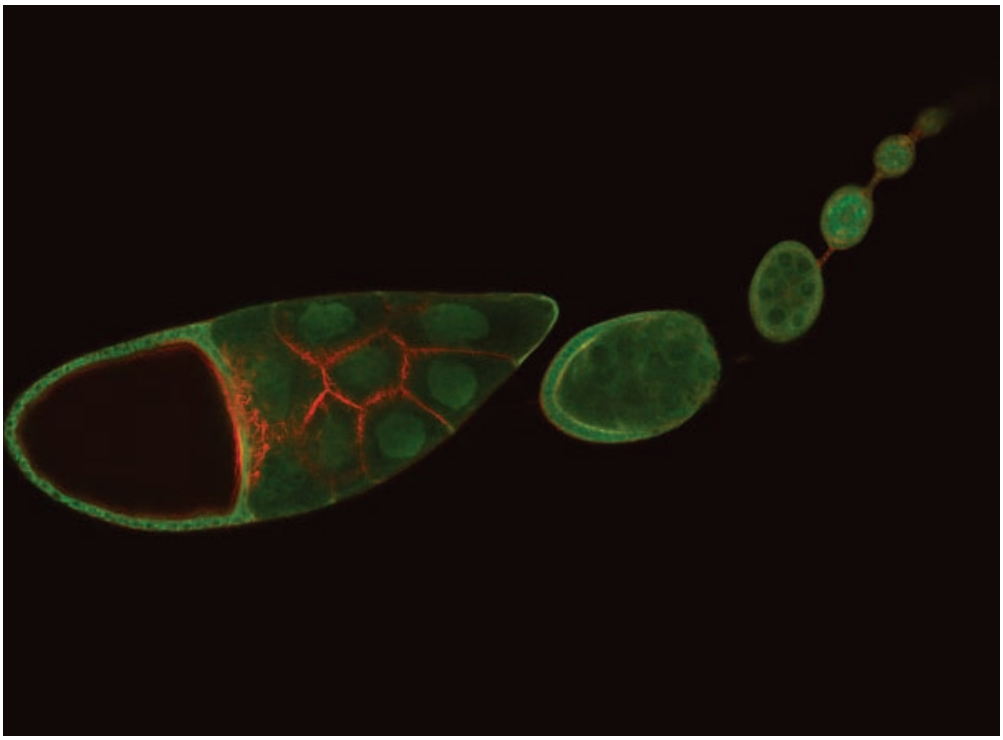

Figure 1 This still image shows a tube dissected out of the fruit fly ovary, called an ovariole. Insect ovaries are made of these tubes – ovarioles – in which eggs develop. Each round structure in the picture is an egg chamber made of up 15 nurse cells and one developing egg, all surrounded by about one thousand follicle cells. As the egg chambers move along the ovariole and out into the fly uterus, they move through progressive stages of development, with the egg chamber at front left the most developed. These structures are made visible by labeling different cell components with different fluorescent markers. In this case, the red is specific to actin filaments, which are part of the cell skeleton or cytoskeleton, and the green is specific to a protein called Spire, which is active in helping build the cytoskeleton. Notable about this image is that even though it is a still photograph of a stained specimen, the time course of development is visible from right to left, intimating past to future. Viewers feel as though they are seeing cells, but because of the specificity of the labels, they are seeing the cells' constituent proteins – in this case cytoskeletal proteins. © Margot Quinlan. Reproduced with permission.

events – what happens with RNA and proteins after they are translated and moved around cells and bodies interacting with one another in complex networked ways – began to occupy scientists (Powell and Dupré, 2009). These *events* – and it is important to emphasize their temporal qualities – are highly context-dependent, occurring at very specific times and places in the living cell. Where sequencing efforts sought answers in the double-

helical structure and base-pair sequence of DNA, the rise of systems biology, or integrative biology, focuses on interaction. It is a time of the dissolution of one of the great fundaments produced by the 20th century: the gene as *the* primary determinant of all living things. Borrowing from a set of scientists who 'lightheartedly' apply the term to their own work, this may be understood as the emergence of a *molecular vitalism*, in which the emergent and functional qualities of molecules in interaction in time and space begin to depose DNA as a master molecule whose structure dictated everything that unfolded from it (Kirschner et al., 2000).

It might be difficult for general visual studies readers to feel that they care much about molecular coups in a set of scientific disciplines far from them. It can be hard to interest humanists in apparently arcane matters occurring at the foreign scale of angstroms in the uncongenial acronym-laden language of biological molecules without even an immediate medical application to tie it to human concerns. Thus an immodest claim, here at the outset: the postgenomic turn is a visual turn, as much as a conceptual one. A recurrence of a new vitalism is unfolding on these screens.[3] The moving image of the living cell is a fertile site for characterizing both emergent theories of life and emergent lives of theory. This life of theory is of as much consequence for humanists as it is for biologists, just as for a previous generation of theorists, from Derrida to Deleuze, 20th-century Life and life sciences shaped, informed and troubled the discourse they were a part of (Doyle, 1997). The part of visual technologies in thinking life, particularly in the recent millennial transition from genomic to postgenomic sciences, is the focus of the historical narrative that follows.

The genome to phenome turn is not the first time the ground of static, structure-oriented images of life has given rise to the moving image of life (Curtis, 2004). As the philosopher Georges Canguilhem (2008) has noted (in a very relational, processual vein himself), biological theory is characterized by a kind of 'permanent oscillation', a history in which 'Mechanism and Vitalism confront one another on the problem of structures and function.' Moving from 1907 to 1994, and then from 1994 to the present, this article follows segments of that oscillation, folding early 20th-century technologies of time-lapse microcinematography up against the ascendance, a century later, of live-cell imaging, in order to tell the story of how, never very photogenic to begin with, the gene has paradoxically been eclipsed by efforts to visualize it.

Fixing and Animating: 1907

In 1907, Julius Ries, a Swiss biologist, made one of the first time-lapse microcinematographic films, a two-minute unfolding of the fertilization and development of the sea urchin.[4] Sea urchin embryos were large and transparent, and easy to keep alive in seawater, so that all the cell divisions of early development could be watched. Their particular biology had come to stand for the theories of cellular life developed using them. Ries lamented

that students couldn't see sea urchins for themselves – not everyone could get to the seaside marine biological stations to observe them – and therefore they couldn't experience and witness the truth of *omnis cellula e cellula*: cell theory. According to Ries (1909: 1), the ability to witness the truth and profundity of the fact that all cells arise from cells was so limited that it remained 'for the student something true that he must believe, without being able to convince himself of it'.

Before turning to film, Ries recounted, he attempted to capture sea urchin development by fixing as many stages as possible through classic histological methods. By adding a fixative to a developing sea urchin, he could stop development at precise points, and the killed specimen could be mounted on a microscope slide. If enough individual specimens were fixed at enough time points, they could be ordered so that the series of slides represented each moment of the developmental process – each significant stage of cellular begetting – between fertilization and morula stage. Even so,

> there is still an enormous difference between the best fixed preparation and the living one. Aside from the many artifacts that are stuck to the dead fixed preparation, it also differs from the living in its motionlessness. (p. 2)

The pursuit of a way for the student to 'convince himself' of the truth that all cells come from other cells led Ries to experiment with the new medium of film. He wrote that 'my interest is not concentrated solely on separated images, but on the possibility of reconstructing the complete phenomenon of fertilization through projection' (Ries, 1910: 225). It was through projection that a preparation could retain motion and thus greater proximity to life.[5] *Made to be projected,* the film combined the observer's access to motion with the investigator's access to motion as an experimental tool. In Ries's case, the particular constraints of film provided room for an editorial maneuver – an intentional derangement of the time of observation – that condensed the 14-hour course of development into two minutes. 'One really believes one has a living developing egg before one,' wrote Ries (1909: 6), in direct comparison to the series of fixed stages that depended on killing many discrete individuals to make one series.

Meanwhile, also in Paris, Louise Chevreton and Frederic Vlès made a nine-minute film of the sea urchin from egg to larva (1909). Although working directly in the chronophotographic tradition of Jules Marey, Chevreton and Vlès commented that in the end they could not mentally or graphically grasp the thousands of stills of their production in the chronophotographic mode. The film had to be projected for its content to be fathomed by the viewer; there was no other access to the various phenomena of cellular life. It was movement itself, the movement-image, of film cells and organic cells that made life visible.[6]

Thus two of the very first time-lapse micro-cinematographic films made to be projected were made in the same year in the same city using the

same organism, by two sets of investigators working independently of each other without knowledge of the others' production until the two films were finished.[7] This simultaneous production poses a puzzle since there are a lot of organisms in the world, even if you only count those visible through a microscope. The history of cinema might indicate to us why Paris, but why the sea urchin? This coincidence may be understood by asking what these films do, other than depict sea urchins, and the answer lies in the relation between cinematography and histology. Sea urchins were favored model organisms, and the illustration, proof, and capture of cells to that point was a mass of static images: fixed and stained cells, microphotographs, diagrams of stages. Rather than probing the unknown, the film-makers sought to re-animate something quite familiar, in fact very well known, but *in time* instead of in static form.

That sea urchins were an obvious choice for animation with film makes sense in the context of this previous cycle of codification of observation: these microcinematographers saw a theory of the living illustrated by dead images and set out to animate those images, resulting in the doubled perception of the living thing and the theory of the living thing on screen.[8] Ries, Chevreton, and Vlès were not surprised by observing the particular sea urchin they had under the microscope on a fine day in 1907. Rather, they understood themselves to be watching a sea urchin that stood in for all sea urchins, whose cells were all Cells. Thus they were watching Development, Cell Theory, Life, Movement – all of which had been previously codified as curves, sections, fixed series, and diagrams, and in being codified, had literally been stilled.

Film, histology, drawing, and photography all represent the thing, and each in its own way was understood as accurate or truthful. The move from fixed specimens to filmed ones is not a question of true and false representations. Rather, this anatomy of the attractions of cinema for biologists in these early days is a detailed section of a much longer and still ongoing cycle of representation propelled by the competing demands of perceptibility and intelligibility within biology.[9] The cycle proceeds this way: theory animates observation, and then observation is preserved, quantified, pinned down to make the perceptible intelligible within scientific conventions of (objective) proof, evidence, and demonstration (Daston and Galison, 1992: 2007). But then each round of codification is met with some dissatisfaction for its lifeless representation of life; a machine is built to animate observation's codification, and the resulting moving image is perceived as an animation of theory.

In this cycle, film *makes a difference* in relation to previous representations of life.[10] In 1909, medical students already knew about cell division from looking at static images, by looking at fixed specimens; they knew the developmental stages delineated by embryologists. They had perhaps seen microphotographs of these stages. What these films did was to animate these still images – to produce the illusion of movement in the projection on a screen and demonstrate what they could not otherwise see: life. In order

to believe, in order to convince observers of the truth of life, both the image and the cell must be animated. This is not a leap of faith, but precisely that 'enormous difference', that unquantifiable quality by which a still image 'differs from the living in its motionlessness'.[11]

Fixing and Animating: 1994

Nearly exactly a century after the first films of sea urchin development, life science is passing through another cycle of reanimation of stilled life. In 2008, the Nobel Prize for Chemistry was awarded to three scientists involved in the discovery and development of green fluorescent protein (GFP) as a tool of visualization in life science. The first recipient, Osamu Shimomura, isolated green fluorescent protein from a particular species of jellyfish called *Aequorea Victoria* in the 1960s in an attempt to answer the question of why jellyfish and other aquatic animals glowed. The second recipient of the prize, Martin Chalfie, was recognized as the first to insert the gene for GFP into the genome of another species in the 1990s, as a tool for visualizing gene expression.

In his Nobel acceptance speech, Chalfie talked about his work to engineer GFP into the nematode worm *Caenorhabditis elegans*. He commented that 'if I had not worked on *C. elegans* and constantly told people that one of its advantages was that it was transparent, I am convinced I would have ignored GFP when I first heard of it' (Chalfie, 2009: 10073). Like the sea urchin, the nematode became a favored model organism in part because of the ability to see cells in the body as they moved and divided during development. Transparency had endured as a desirable quality in the model organism, but in the 1990s it took a specific historical form that has been described as a desire for 'genetic transparency: the power to visualize pure information' (Stacey, 2008: 108). Cell theory was not something that needed to be demonstrated any more – rather, transparency was understood as direct access to a resolutely late-20th-century genetic form of cell theory: how all cells come from genes and are the vehicles for genes arising from themselves (Stacey, 2010).

The fate of every single cell could be traced as it divided and moved, from egg to adult organism. Richard Doyle has described this cell-fate work in *C. elegans* as a kind of apogee of molecular biology's organization around the concept and practice of DNA as code. For Doyle (1997: 13), *C. elegans* was the paradigmatic 'postvital' organism, 'a body in which the distinct, modern categories of surface and depth, being and living, implode into the new density of coding … a transparent sequence with nothing behind or beyond it'. The worm body was seen as a window onto the genetic program, a way to see the genome:

> With C. elegans we can say that the postvital organism is nothing but coding. It is coding in its noun form, in the sense that the ability to say 'that is all there is' relies upon a physical genetic map. At the same time, it is coding in its sense as a verb in that cell lineage is seen as an algorithm of a worm's own development, which is itself the act

> of instantiating code. That is, the 'code,' the genome of *C. elegans*, implicitly codes and decodes 'itself'. (p. 17)

Despite all the sequence talk, of course, watching a verb means watching something in action, and the gene action that accompanied the gene sequence was actually quite difficult to 'see' in time. One could see cells through the microscope, but following gene activity required elaborate visualization techniques, and all of these required that the animal be killed. Prior to GFP, scientists used three different methods for visualizing gene expression and the production and movement of proteins in worm cells. There were radioactively labeled antibodies that would stick very specifically to proteins, there was a bacterial gene construct whose protein product could be detected with a dye, and there was a technique for visualizing messenger RNA, called in-situ RNA hybridization. Chalfie (2009: 10074) discussed the shortcomings of these three ways to record gene expression in the body of the worm before his success with GFP in a manner uncannily resonant with Ries discussing the drawbacks of fixation of sea urchin embryos a century before:

> The animals had to be fixed and then permeabilized so either the antibody, the X-gal substrate, or the DNA probe could enter the tissue. This preparation, which needed to be done with each batch of animals, meant that we could only look at dead tissues, giving us a static picture of expression. If we wanted to understand changes during development, we had to compare images from many different individuals.

As with the fixed embryos, change over time was a compilation of still moments, each represented by a different dead body stopped in its tracks by a chemical stain or fixative. Thus for Chalfie, the idea of co-generating a fluorescent protein with a native protein and watching it as it moved in *one* living transparent body of *one* worm over time was extremely attractive.

Live-cell imaging is very literally postgenomic, since it could only happen after comprehensive genome sequencing. The genetic engineering necessary to insert a fluorescent protein coding sequence into the worm genome in precisely the position to ensure its coexpression with a selected protein that the researcher wanted to follow could not have happened without the previous decades' elaboration of those sequences. Chalfie wanted to know how the nerve cells responsible for the worm's sense of touch developed and how they worked; in particular, he wanted to know which genes making which molecules were responsible for the 'transduction' of sensation from the mechanical signal in the worm's environment. By fusing GFP DNA to (already known) genes linked to touch, Chalfie could see the expression pattern of these genes in the body, when in development expression happened, where in cells the proteins went, and, by using different colors of fluorescent proteins, when several genes were co-expressed, indicating close interaction. Unlike the DNA sequence information or the cell-fate map, this representation of gene action occurs in time and space.

Thus the painstaking detail of genomic elaboration, a static form of representation of a string of As, Ts, Cs and Gs, is put to work in making a moving image. The reanimation of sequence data by fluorescent imaging echoes the desire of Ries a century before to make the knowledge amassed in sections and photographs and drawings move again, in an image that was closer to life because it encompassed movement. A theory of life seemed inadequately represented by such dead images as permeabilized worm corpses mounted on microscope slides or the strings of letters that are sequence data.

If we can say about live-cell imaging that it is as much an animated image of theory as it is an image of a nematode, what theory is this? At its origin point in the 1990s, with the first transgenic placement of the fluorescent molecule in the body, we see the classic genetic techniques of the previous half-century being set into motion. What emerges, then, is a kind of cinematic genome, in which the genetic code can be seen, as a genetic 'reporter' in the form of a translated protein, on the screen of the living body. The worm visualized with the fluorescent reporter is not so different from the body described by Doyle: 'the body stuffed into the molecule', one with no surface or depth. Watching the fluorescent protein's movements was understood to be like watching the code running; the protein is taken to be the proxy of what the gene is doing. Originally then, live-cell imaging was an image of the genetic code unfolding itself – an *in vivo* demonstration of the 'central dogma' in the form of DNA making RNA making protein making light.

From Gene Reporter to Lively Protein: 2000

Inserting the DNA that codes for fluorescent proteins into organisms is a 'visual fabrication of animal form' that has caught the attention of viewers well beyond the sciences (Davies, 2003: 410). The primary instance is the work of Eduardo Kac and the object of Alba the bunny. Alba is, in Kac's words, an artwork that 'comprises of the creation of a green fluorescent rabbit, the public dialogue generated by the project and the integration of the rabbit into the social environment' (Kac, 2003: 97). GFP Bunny 'Alba' was then a subject of artistic elaboration and media interest, as the artist who had 'commissioned' the rabbit to be made and the scientists who 'made' her disagreed about Kac's plan to take the rabbit home and integrate her into his family and disagreed about the veracity of the bright green image of Alba Kac was circulating. For Kac, this organism was part of, and an enduring symbol for, the very idea of 'transgenic art', defined as a new art form involving the transfer of synthetic or natural genes into organisms to create new and unique living beings. Because of Kac's work, the discussion of GFP in scholarly realms outside of biology has generally focused on the fact of transgenesis and the ethics, aesthetics, and public reception of the generation of cross-species hybrids: 'As an icon, Alba tends to indeed function as a sort of neon sign for transgenesis' (Doyle, 2007: 75). In Alba and Kac's subsequent work *The Eighth Day*, fluorescence highlights the

engineered status of the whole organism, whether a bacterium or a plant or a rabbit; the organisms literally glow with their man-made condition.[12]

That was 2000. In Kac's work and the response to it, we see the previous decades' focus on DNA as essence: the transgenic animal is interesting to Kac because its very thingness has changed through changing its genetic structure: it has jellyfish genes in it, and those were put there by humans. Illuminated with blue light, it glows with green light. Kac has been criticized about the photograph he circulated of Alba, as it is claimed that only the ears and other areas where living skin shows through would fluoresce; the fur, being composed of dead cells, would not be actively making GFP (Davies, 2003). But, for Kac, this distinction between the live and dead parts of the animal hardly matters, because it is the fundamental structure underlying the picture that (he) has changed. Insofar as the rabbit is a process, the process lies only in the human discussions that arise from it and the human integration of this object into social life. Perhaps it represents the expansion of the artistic palette to biological matter; artists along with scientists can tinker with essence and make new forms. The rabbit's glow is the atemporal glow of the gene.

This particular rabbit has loped off into history and, in its going, provides a convenient departure point for the third section of this story, which turns to the question of the specificity of the life of movement rather than the life of (genetic) structure in biological theory after 2000. What begins to matter is not what the rabbit is, but what the rabbit does; or more precisely, what the rabbit's proteins do. Neither visualization nor theory stand still. The core irony of fluorescent proteins as gene reporters is that they do not show the life of genes; they show the life of proteins. Moreover, these proteins do not show up by themselves. The fluorescent organism literally produces one of the conditions of its own visibility, but this should not dazzle us *too* much. A concurrent explosion in new kinds of microscopy and software produces many of the other necessary conditions for these images and ensures that not just proteins, but proteins-in-interaction over time are made visible. This fluorescent life form does not exist separately from its articulation in time-based media. It is not the transgenic thing per se that comes into sight after 2000, but the thing in motion, the thing as a moving set of relations. Moving away from an icon of transgenesis, Alba becomes 'er, *living* proof that machines, signs, and organisms, in their newest promiscuities, no longer dwell in definable, taxonomical domains, but are instead differentials of intensity: networks' (Doyle, 2007: 74–75).

As live-cell imaging has grown exponentially as a technique, changed, and become routinized as part of the biosciences after the turn of the century, the practice has been part and parcel of a decisive undermining of the very theoretical stances out of which it was first generated. For all the certitude that scientists were close to decoding the code, to knowing everything, to completely resolving the story of life, to uploading sequence information into databases and proceeding to a biology without bodies, that was of course not all there was. Even as complete sequence information for many

organisms came into reach, dissatisfaction grew with the static nature of such information. Roger Tsien, the third recipient of the 2008 Nobel Prize in Chemistry, put it this way: 'genome sequences alone lack spatial and temporal information and are therefore as dynamic and informative as census lists or telephone directories' (Tsien, 2003: SS16).[13]

As in previous turns of biological science, animation of stilled life provides a renewed round of observation, of perception of life in time. With the millions of observations of live cells lit up by their constituent molecules has come a broadening of what is being sought and proved and observed in these films. This has led to a kind of democratization of molecular life caused in part by live-cell imaging; DNA is no longer the only molecule that matters, its status as prime mover degraded by a redistribution of vitality among the many other species of molecules in the cell such as RNA and proteins, as well as smaller entities such as calcium ions that participate in the cascades of signals that constantly move across and between cells.

As noted above, because the visible entity is not the genetic sequence itself but the resulting *protein,* fluorescent markers show protein action. Watching these proteins, researchers rapidly came to realize that the dynamism and density of protein movements and interactions are not captured by the gene sequence information they may have started out with. Proteins interact with one another, they cross membranes, they split into pieces, they form complexes, they are 'post-translationally' modified – for instance, phosphorylated and dephosphorylated (altered in form and function by having a phosphate group PO_4 added or taken away by another protein) – they are shipped around in vesicles, they 'walk' along the cytoskeleton, they constitute complex nets of signaling cascades that transduce an extracellular event to an intracellular one. Scientists interested in how mechanical stress changes cell behavior might tag cytoskeletal proteins with fluorescence and watch how their actions change with changes to the cell's physical environment, for example.

Live-cell imaging continues to change rapidly, with intense engineering and manipulation of both the qualities of fluorescent markers and the microscopes used to observe and capture them. Even the fact that fluorescent molecules are extinguished – photobleached – by the light used to make them fluoresce has been turned into a tool for measuring protein movement. A spot on the cell can be photobleached, and as non exposed fluorescent molecules move back into the area, fluorescence reappears, giving a rate of movement of the proteins in the cell. Another way the contortions of the protein itself are part of visual practice is in the advantage researchers have taken of the ability of fluorescent molecules to excite one another, as long as they are close enough together. An organism genetically engineered to contain two different fluorescent DNA sequences fused to two different proteins can be used to visualize the interaction of these two proteins. When exposure to light excites one fluorescent molecule, it will only light up the second when the two proteins are within 10 angstroms of one another. An angstrom is 0.1 nanometers, or one ten billionth of a meter, a unit about the size of an atom

or the length of a chemical bond. In other words, the organism *and* the probe can both be exquisitely engineered to show the functional interaction of proteins in time and space, not just protein expression or co-localization of several proteins. Research into protein kinetics in the cell is intimately tied to manipulations of the fluorescent protein's chemical/visual qualities and its properties in interaction with light and other fluorophores. The life of cellular proteins is enacted in concert with the life of fluorescent proteins; one observes what the former is doing via the actions and interactions of the latter.

Due to these developments, a three- and four-dimensional body of visual and temporal depth has spilled back out of the molecule in live-cell imaging, even as the molecule remained the luminous focus of observation. How does an image of a molecule produce an image of a body? The three-dimensional look of the cell on screen is due to the kind of machines that detect the fluorescent signal and reassemble the collected information into an image. Confocal and multiphoton microscopes are central to time-lapse imaging in three dimensions – repeated imaging over time of multiple focal planes. Originally developed by Marvin Minsky in the 1950s to attempt live imaging of neural networks, confocal microscopy involves illuminating a specimen with a focused beam of light, often a laser, producing what is called an 'optical section' (to distinguish it from cutting a physical section through a specimen). The light emitted from the illuminated specimen is in turn collected through a pinhole in front of a photodetector – this mode of collection cuts down the amount of out-of-focus light. As the beam moves across the specimen, the optical sections are reconstructed (by a computer) to form the image sent to a screen. Sometimes called 4D microscopy, time-lapse images of fluorescent molecules are collected as sequential three-dimensional data sets, not sequential single images in a single focal plane as was the case in classic microcinematography (Roux et al., 2004).[14]

While this might seem an overly technical discussion to get enmeshed in, the generation of such an 'embodied' image for the molecule is central to the distinctiveness of these techniques for rendering a body in time. Thick, living specimens can be imaged at high resolution, with innumerable optical sections being reassembled over and over again to capture both space and time. The images produced look like a body (even if it is a cellular body) suspended in space; moreover, the technology has allowed for imaging molecules moving in live animals, meaning that the narrative given to the molecule's movement is that it is a representation of life as it is actually lived – molecules as they actually move about in bodies and produce its life. Genes coding for phytochromes from bacteria have been engineered into mice because these molecules excite and emit in the near-infrared part of the electromagnetic spectrum 'where animals are less opaque' (Rice and Contag, 2009: 624). Multiphoton microscopes use laser pulses of infrared light and are particularly good for imaging thick specimens; the infrared light they employ is lower energy and thus less damaging to tissues than light in the visible spectrum. Transparency is thus not in the eye of the observer

but in his or her microscopic technology. It is a penetrating vision that takes a different form from the x-ray, but the excited discourse around live-cell imaging recalls nonetheless the early days of that imaging technology. What will we *not* be able to see, as the previously opaque opens to sight (Tsivian, 1996)?

What is being animated is not just genomic knowledge, as proteins are followed as part of functional genomics, but a vast body of biochemical knowledge built up over the 20th century. Very precise modes of molecular imaging have been applied to the structure of biomolecules, but these were extracted from ground-up cells (Myers, 2006, 2008). Paraphrasing Ries, we might say that molecules investigated in solution in test tubes differed from the living in their contextlessness:

> We understand that the milieu of the cell is fundamentally different from an in vitro solution in several ways … a biochemical reaction in a single cell could have different thermodynamic and kinetic properties from the same reaction in a test tube. (Xie et al., 2006: 228)

Many changes in proteins are very quick and transient; visualizing them at the level of a single cell instead of emptying out the contents of many cells into a test tube adds temporal and spatial specificity to protein interaction, turning it from a fact of binding specificity to a momentary event of binding.

The nature of the resulting image depends on what kind of molecules the fluorescent markers are joined or attached to, and where those molecules go and what they do, and how ubiquitous they are in a cell. Images of calcium waves moving through the cell interior look quite different from images generated by tagging a protein that is part of the cytoskeleton. Often these images are reminiscent of the original *A. Victoria* jellyfish from which green fluorescent protein was first isolated – floating in a dark sea, undulating, membranous, and diaphanous. Also quite often, these images are rather unintelligible to anyone but the scientists making them, as it is necessary to have specialized knowledge of just what is lighting up to understand its significance (as is the case with other forms of microscopy). Manuals exhort film makers to 'keep your cells alive … avoid producing crisp showcase images but aim for live cells' (Papkovsky, 2010: 7). These movies show a cell that *is* its constituent molecules – literally, the cell interior, its movements and its mechanisms are seen because of fluorescent proteins resident in the cell membranes, or chromosomes, organelles, or skeleton. The depicted cell seems a kind of endlessly dynamic molecular sea, where even those 'structures' elaborated by a century of biochemical analysis are constantly being broken down and resynthesized (see Figure 2).

The cell or organism of live-cell imaging appears as a body composed of signals and transductions, and the network of specific possible relations crosses the boundary of the cell or organism – into the environment, whether that is the microenvironment of the cell or the macroenvironment of the organism. Martin Chalfie's own research shows the path that live

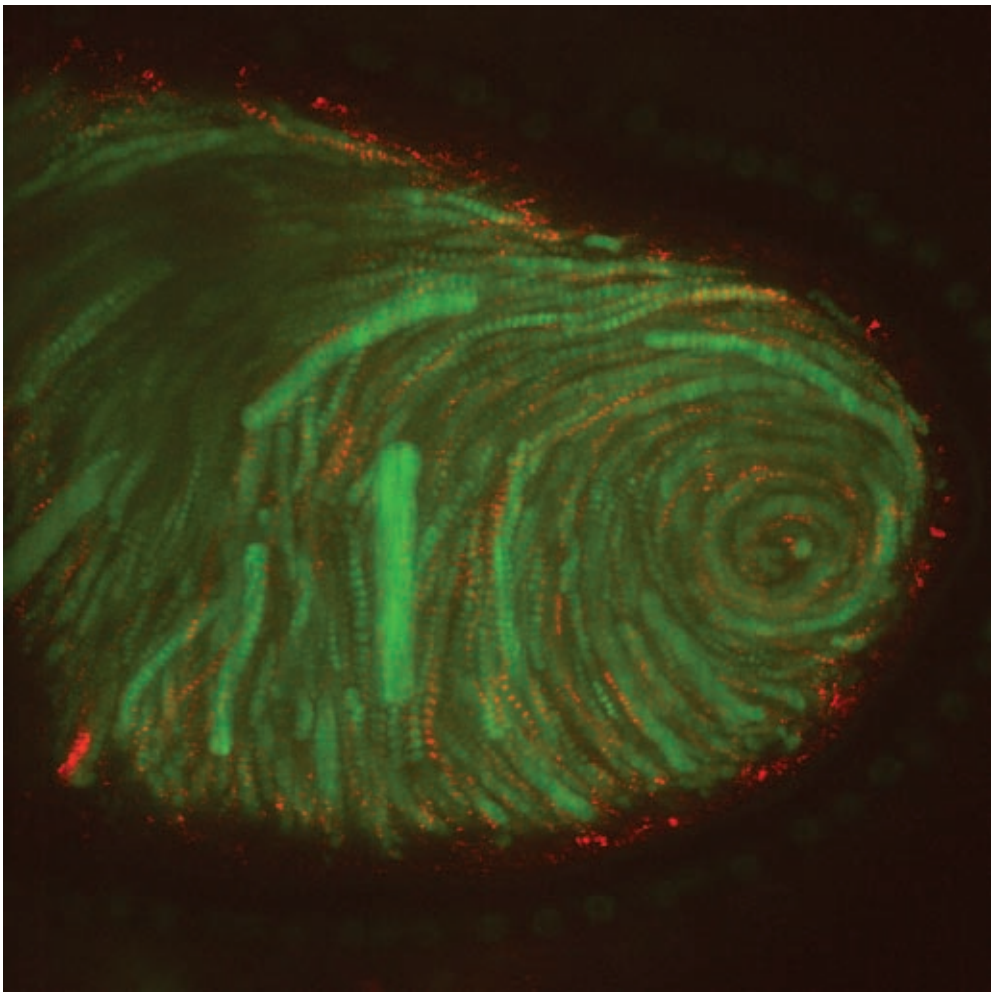

Figure 2 This still is composed by 'stacking' images from a movie taken over time to show the changing position of objects. In this case, what is shown is a fruit fly oocyte (a developing egg). Yolk granules are stained green, and tiny red fluorescent polystyrene beads have been injected into the egg to show the dynamism of the flow in the egg body over time. © Margot Quinlan. Reproduced with permission.

cell imaging demarcates for research: from the *genes* linked to touch to the visualization of proteins moving and interacting *in relation to* the worm's external environment. Thus live-cell imaging is used to visualize the formation and flux of synaptic connections in mice after their whiskers are stimulated (Miller, 2003); the cascade of signaling molecules that fire after a cell is subject to mechanical stress (Wang et al., 2008); the movement of HIV in and out of cells and the reaction of those cells to the virus (Campbell and Hope, 2008); the circadian rhythms of gene expression as cells respond to

changes in light and temperature around the organism; and many events that occur in development, the time of life when organisms and cells are moving and changing at a rapid pace as tissues differentiate and organs are formed.

Molecular Vitalism

The gene has lost some of its privilege as the ultimate end of representation, but the molecule, a larger class of entities of which the gene is one part, has gained potency. Live-cell imaging is not solely responsible for these shifts. It is through many 'new technologies of visualization that life has been made amenable to thought at the molecular level, as a set of intelligible vital mechanisms among molecular entities', which range widely from the X-ray crystallography through which the first three-dimensional representation of the atomic structure of organic molecules were produced to the development of radioactive tracers to follow biological molecules through living cells, bodies and ecosystems (Creager, 2009; Dumit, 2004; Myers, 2008; Rose, 2007: 14). Live-cell imaging, however, is the most dynamic of these modes of molecular visualization, the most rooted in the time and space of the cell or tissue. Molecular structures enumerated by previous methods, when visualized through fluorescence and over time, reveal themselves to be as much events as structures. These are not vital mechanisms *among* molecular entities, as if the entities and their actions are somehow separable, but molecular entities in interaction *as* vitality.

Indeed, the term 'molecular vitalism' has been proposed as a description of a style of investigation that considers the gene as one molecule amongst others rather than the primary molecule by which all others will be fathomed (Kirschner et al., 2000). 'How close are we to understanding how a single cell operates or an embryo develops? If the answer is not so close, will true understanding come from further annotating the database of genes, or must we explore the physicochemical nature of living systems?' The scientists posing this question mean it rhetorically – for them, it is clear that, although 'proteins, cells and embryos are manifestly the product of genes, the mechanisms that promote their actions are often far removed from sequence information', and therefore 'true understanding' must be sought elsewhere, in the chemical principles of macromolecular assembly and self-organization (Kirschner et al., 2000: 79). Tellingly, one can determine the principles of interaction only by understanding many entities in action together over time rather than the code or determining information being intrinsic to some part of the living being. This research into integrative cell and organismal physiology they call – albeit 'lightheartedly' – *molecular vitalism*. For these authors, vitality resides in the time and space of all molecular interaction not just in the genetic blueprint.

It would be unreasonable to ascribe such shifts away from the genetic blueprint ideas of the 1990s solely to live-cell imaging; in fact, most critical attention to these developments in biology from historians or philosophers has narrated them as the rise of systems biology – focused on complex systems of interactions among biological entities and the properties emergent

from those interactions (Fox Keller, 2010; Griffiths and Stotz, 2006; Powell and Dupré, 2009). Such analyses are focused on conceptual change and do not consider the role of imaging practices. If the technologies of live-cell imaging are considered part of the 'thinking machinery' of contemporary life science, the necessity for unidirectional causal claims falls away, and ideas of proteins in networks of interaction (the 'interactome') can be seen as intrinsic to live-cell imaging as live-cell imaging is to such conceptual shifts (Rheinberger, 1992, 1997). Where classic cell theory posited that all cells come from other cells, and all organisms are composed of nothing but cells, 21st-century cell theory thought through live-cell imaging might look something like this passage from a contemporary textbook: 'No cell lives in isolation. Cellular communication is a fundamental property of all cells and shapes the function and abilities of every living organism' (Lodish and Berk, 2008). Life as molecular network is a theory with origins, causes and practices that reach well beyond live-cell imaging, but at the same time, the role of imaging in giving life to theory should not be underestimated. As Julius Ries observed, a film can be understood to move in various ways, including moving the viewer to a position of belief.

Live-cell imaging hangs the molecule in a living but empty (unstained) background, and the image is of the cell as a skein of movement – a network not of molecules that stand in place as nodes or strings connecting nodes, but a network of very specific possible relations with actual entities moving in and out of various states or conformations of being. Over and over again, processes which were thought to be programmed, set in the genetic code and thus orchestrated or prearranged – particularly those unfolding in organismal development – are shown by live-cell imaging to arise out of a messier, looser set of molecular relations and interactions: 'it now appears that cells are not locked into a rigid choreography but behave more like football players with a set of rules and options at every play' (Beckman, 2003: 76). Observers following gene expression and cells are surprised to see that cells are not predestined or programmed to become one thing or another but move in and out of fields of molecular signals generated internally and externally. At stake is more than the map of development; it is the molecular foundation of life. This new foundation is a much expanded version of the late 1990s 'postvital' body, one that lives in time and space, one whose study requires integration, not dissection, an attitude of 'molecular vitalism'.

It will perhaps seem odd to readers to see even the half-joking invocation of this term. In the 20th century, vitalism was strongly associated with imprecision and mysticism, with ideas of a perhaps unknowable special quality or vital principle in living things that can only be approached by studying phenomena as a whole. Mechanism, by contrast, has been associated with the ascendant sciences of the 20th century: biochemistry, molecular biology and genetics. Georges Canguilhem observed in 1965 that vitalism carried such a pejorative value that 'there are few biologists who, classified as vitalists by their critics, willingly accept this label' (Canguilhem, 2008: 60). Why then would we see contemporary biologists willingly applying it to themselves?

With live-cell imaging and a host of other developments in protein sciences, it seems that the cell composed of functional structures is dissolving into molecular entities that constantly but always changeably constitute structures. It is not so much that the structures begin to move, but movements – for example in the assembly and self-organization of the cytoskeleton – begin to constitute structure. It is perhaps not so surprising that in 2000, during a turn away from genetics and biochemistry's fundamentally structural orientation, to a functional genomics and an integrative cell physiology, vitalism should reappear as a valid millennial critique of the definition of the living as that which is capable of accurately transmitting a genetic blueprint (Kirschner et al., 2000: 79).

Conclusion

While this portrayal of networks of protein interactions might recall the informational network of 1990s gene-talk, there is one difference that live-cell imaging embodies: matter and energy are literally part of the picture. These developments could be understood quite apart from the relation between cell theory and microcinematography in the early 20th century, but it is my hope that one turn that places movement at the center of life provides a useful contrastive frame for a turn that we are still in the midst of. It is early yet in the generation of this oddly holistic reductionism, this fluorescent temporal body composed of its molecules and their lives, but one may speculate on some consequences for visual culture in particular of a new emergence of vitalism, where the vital entity is the molecule-in-interaction.

First, there are the implications for long-held conventions of medical imaging of the physical manifestation of disease. Traditional imaging in radiology relied on 'nonspecific macroscopic physical, physiological or metabolic changes' to differentiate pathological from normal tissues; by contrast, molecular imaging aims to uncover the molecular events in 'pathways and mechanisms responsible for disease within the context of physiologically authentic and intact environments within living subjects' (Massoud and Gambhir, 2007: 183). With these developments, medical imaging and therapies promise to become (even) more focused, literally, on the molecule rather than the tissue or the organ and more on process and event than on structure. With this change, the concept of the lesion and the iconography of pathology will shift.

The body produced by live-cell imaging is one of signals and transductions, where the cell is the center of integration; if life is a set of cascades and interactions, then visualization of these events leads to a very particular narrative of control on the part of the observer who places a manipulable probe in the middle of events. If you can see aberrant proteins collecting in the nuclei of brain cells in patients with a known genetic mutation, the place of intervention is not at the gene itself – this is not genetic engineering – or even 'the brain' as an organ, but somewhere in the processes of protein manufacture and translocation. A signal may be interrupted, mimicked, enhanced or diminished; in this way, the perhaps overwhelmingly

irreducible specter of biological complexity is at least imagined to be amenable to pharmaceutical intervention and medical control (Wynne, 2005). Perhaps one of the greatest demarcations between 1910 and 2010 is that representation in the contemporary period is seen as a means of *remaking* the thing through its image, not reproducing it (whatever the actual efficacy of that remaking might be).

A second rather prosaic consequence for visual culture of live-cell imaging can be characterized as the rise of a fluorescent aesthetic. Not the black and white and gray of light microscopy, of light reflected from the living surface, but living things as the emitters of meaningful signal, as they go about the biosemiotic business of communicating to, within and about themselves. One can already see the rise of the fluorescent aesthetic in the public visual culture of science; stills of cells imaged with fluorescence and confocal microscopy routinely illustrate news stories about cancer research, pharmaceutical advertisements, movies, and science popularizations. Where *The Hulk* once glowed green due to gamma radiation, he now transgenically fluoresces. While the penetrance of the complexity of systems biology, epigenetics, cell signaling or proteomics into the public presentation of science is to date rather insignificant, the images being generated in their pursuit are nonetheless filtering through.

Finally, at a more abstract level, comparing these cinemas of life one hundred years apart highlights the waxing and waning of the centrality of movement to understanding, perceiving, visualizing and theorizing life. At the heart of early microcinematography was the deceptively simple assertion that the fixed preparation 'differs from the living in its motionlessness' (Ries, 1909: 2). Early microcinema, instead of giving us 'a figure described in a unique moment', provided 'the continuity of the movement which describes the figure'; contemporary live-cell imaging equally does not give us a structure described in a unique moment that explains a life process but rather provides a continuity of movement that constitutes life processes (Deleuze, 1986: 5). Even those cellular organelles that seem the most constant are 'inherently steady-state structure(s) in which continuous fluxes of material and energy are inherent to spatial organization' (Kirschner et al., 2000: 82); thus the 'robust' stable patterns of a rather constant-looking physiology and embryology are recognized as composed of movement. Accordingly, what it means to see 'inside' things has reopened, as everything bodily is transparent in its becoming to the right time-based instrument. Instead of skeletons or organs or genomes, live-cell imaging produces a vision of the moving net of the phenome. Far from being specific to molecular biology or pharmaceutical development, such fluorescent movies are an image of contemporary thought, amenable to all kinds of observation, from science to film theory.

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Notes

1. Not all live-cell imaging is based on transgenic insertion of the DNA coding for a fluorescent marker, and there are sophisticated techniques for tagging RNA or small molecules such as calcium with fluorescence. Quantum dot probes (extremely small semiconductor crystals) are also used. A comprehensive review and explanation of all the probes and microscopic techniques is far beyond the scope of this article. For the sake of simplicity, my discussion focuses mostly on transgenic fluorescent proteins.
2. The project website, including the database of films, is available at http://www.mitocheck.org/ (accessed 29 June 2011).
3. The same vitalism never recurs, but a new vitalism inevitably does (Canguilhem, 2008).
4. This story is also told – in somewhat different form – in Kelty and Landecker (2004), as part of a consideration of the relationship between microcinematographic imaging to mathematical formalization in 20th-century life science.
5. Previous projection practices in the life sciences had cast an image of what was happening on the microscope stage onto a screen for an audience to see, but the 14-hour course of development made this approach impractical (Schmidgen, 2004). Other methods had recombined the separate images of chronophotographic sequences back into a moving image (Gaycken, 2011). By the time of Ries's writing, film cameras had become commercially available, and these were designed to make films for projection in projectors. Tinkering with the time of photographing in relation to projection was key to Ries's distinction between his production and still photography and histology.
6. See Gilles Deleuze, *Cinema 1: The Movement-Image* (1986: 1–11) for a description of the movement-image.
7. Chevreton and Vlès report that they worked on this film without knowledge that Ries was doing the same thing at the same time ('La cinématique', 1909: 1). Time-lapse imaging of very slow movements had been done well before 1909, by Marey and others, but the aim of these efforts was in general to reconstruct movement as it would have been perceived by the naked eye if watched without the mediation of photographic technology; the aim in part was to educate the observer's eye as to the work done by chronophotographic analysis (Gaycken, 2011). Thus the films of Chevreton, Vlès and Ries were among the first that were made for the sole purpose of projection, in order to show accelerated movements of microscopic organisms to the viewer.
8. Efforts were also made to visualize cell division and development by injecting embryos or particular cells of embryos with so called 'vital' stains that did not kill them, allowing observers to trace the fate of cells over time as development progressed, a technique known as cell lineage studies (see Maienschein, 1978: 129–158, and Galperin, 1998: 301–350).
9. For an extended version of this argument, see Kelty and Landecker (2004).
10. This analysis is indebted to the work of Hans-Jörg Rheinberger (1997). The experimental system as a basic unit of experimental reasoning plays out in a space of representation, and in this space, the generation of differences is necessary to the temporality of investigative shifts in experiment, to the ability of the experiment to produce surprises. Theory is part of the experimental system and is not understood to exist in opposition to experiment. Rheinberger (1992: 307), drawing on Gaston Bachelard, writes that 'scientific activity is a game with things', and 'that theories, concepts and ideas are not

the Other to things.' Rather, the things that constitute experimental systems can be understood as 'material instances' of theories, concepts and ideas.

11. Here the questions of the history and philosophy of science – the generation of difference as part of the experimental system – come together with questions from the history and philosophy of film: what difference does film make?
12. Videos and discussion of The Eighth Day are at http://www.ekac.org/ (accessed 29 June 2011).
13. Metaphors abound for the difference moving images make:

> Static images – until now, the source of most data in developmental biology – give an incomplete view … Imagine trying to determine the rules for American football … by examining 1000 snapshots taken at different times during 1000 games. The importance of the football would be evident, but not why players are obsessed with its position. And it would be tough to make sense of the halftime marching band. The rules of the game would probably remain utterly obscure. (Beckman, 2003: 76)

Or: 'Imagine the performance of a great symphony orchestra reduced to periodic samples of the sound produced at a few time points.' Genetically encoded fluorescent indicators 'serve as the microphones that allow us to listen to individual components of the cellular symphony in live performance' (Kotlikoff, 2007: 55).

14. Roux et al. (2004) also speak of '5D' imaging – multiwavelength-dimensional imaging, in addition to 3D (volume) and 4D (time). Multiwavelength imaging basically means collecting signals of different kinds at different wavelengths of light emitted by specimens/probes.

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