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ORIGINAL ARTICLE

Tissue culture and biological time: Alexis Carrel, Henri Bergson and the plasticity of living matter

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Abstract Taking the early tissue culture experiments of Alexis Carrel in the 1910s–1930s as its example, the article explores the relationship between advances in biotechnological control over living matter and a holistic ontology of life, which stresses the temporal specificity of living things. With reference to Henri Bergson, Carrel argued that physiological time depends on an organism's relationship to its milieu. By developing a laboratory apparatus and culture media, new objects of investigation could be made to live outside the organism and be brought to behave in novel temporal ways. In difference to recent biotechnological advances, like for example genome editing, which seek to 'engineer' living organisms by rebuilding them from their DNA up, then, early twentieth century interventionist laboratory practices were often linked to an understanding that biological plasticity results from organismic complexity and interactions between organism and milieu. These notions contributed to shaping laboratory apparatuses and techniques; they also helped to establish an understanding of environmental control that would allow for the production of novel 'living things'.

Keywords Alexis Carrel · Henri Bergson · Holism · Cell culture · Ontology · Time

Introduction

In the past decades, a returned emphasis on epigenetics for an understanding of phenotypic difference has not only stressed the importance of the surrounding environment or *milieu*, it has also drawn attention to the plasticity and temporality of

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living things. Instead of concentrating on the stability, and thus 'timelessness' of the genetic code, the development of the organism as a spatio-temporal process, open to perturbation and variation, is highlighted (Lappé and Landecker 2015). In many ways the ideas expressed in this 'new' epigenetics relate to an earlier period of biological and medical inquiry. Before the discovery of DNA as the carrier of genetic information, anti-reductionist, holistic and organicist notions flourished in opposition to the pervasive reductionism of modern biology. This period from roughly the late 19th century until the beginning of World War II, was also a time in which interventionist laboratory practices took shape. The development of the laboratory apparatus as an artificial and relatively controllable environment would become central to the contemporary life sciences. By concentrating on the ideas of two prominent figures of this period, Alexis Carrel and Henri Bergson, this article seeks to argue that interventionist notions in the life sciences which have sought to bring 'nature' under human control, have not always taken an 'engineering' approach to living things. Instead, organicist and holistic ideas provided a program for the manipulation of organisms which focused on the temporal and relational nature of living things. Here, scientists could gain control over 'nature', not by rewriting the 'code of life,' or rebuilding organisms from their constituent parts, as in contemporary biotechnology and synthetic biology, but by controlling the *milieus* to which living things are connected by necessary, relational processes.

Alexis Carrel's work on the temporal properties of living cells provides an excellent example of this approach. As a pioneer in tissue culture, his work in developing a technical apparatus for cell culture had a lasting influence on the life sciences. Carrel understood cell culture in terms that intermingled mechanist and holistic ideas, drawing heavily on the vocabulary of Henri Bergson. Despite often being taken for a vitalist, this is not a fitting description of Bergson's thought. Vitalism, in this context, can be defined as a dualistic position that purports a difference in substance between the living and the inanimate.[1] Bergson, a philosopher who followed the development of the natural sciences closely, however, argued that living and nonliving matter differ from each other not in substance but in their temporal extension, which in turn depends on their degree and form of organization. The idea that time is memorized by living matter led Bergson to formulate a theory of 'creative evolution' which, in turn, was influential on evolutionary biologists in the early 20th century, like for example the young Julian Huxley (Herring 2018). Via Deleuze, Bergsonian ideas also found their way into a prominent strain of poststructuralist theory.

[1] As organicist philosopher of biology J.H. Woodger explained it, both vitalists and mechanists held on to a "materialist" understanding of nature as described in Newtonian physics—"a theory which believes the physical world or nature to consist of little hard lumps, too small to be visible to the naked eye pushing each other about" (Woodger 1929, p. 271). While mechanists, however, "insisted that this quantitative, atomistic view of the universe could in the end account for all other phenomena", vitalists would argue "that other forces from outside of the natural system were needed in order to grant the complexity that living things exhibited." As we will see below it is precisely this shared atomism, Bergson set out to critique (Peterson 2016, p. 66).

Similar ideas today resurface in process-oriented philosophy of biology[2] (see e.g. Dupré and Nicholson 2018).

By exploring how Carrel drew on Bergson for his understanding of the role of time in the study of living systems, I hope this article can contribute to the exploration of the connections between biological ontologies, research practices in the life sciences, and the idea of biotechnological control over living things. Biotechnological intervention does not simply reduce living beings to the status of inanimate machines, which can be re-engineered at will; it can also highlight the plasticity and temporality of relationships between organisms and their environments. In particular, the idea that biotechnological control over nature can be targeted not at a organism or species of interest directly, but instead intervene in their environments, might have important implications for contemporary notions of 'nature' in the Anthropocene.[3]

Alexis Carrel and the beginnings of tissue culture

In 1907, the embryologist Ross Harrison showed that small pieces of tissue could survive *in vitro* for several weeks. Harrison embarked on these first successful experiments in animal tissue culture, because he wanted to study embryonic nerve development. To do so, events that take place in the "dark inside and obfuscating covet of the solid complex body" had to be brought "into the simplified transparent technical body where it could be continuously observed" (Landecker 2007, p. 70). Among the many scientists deeply impressed by Harrison's work was Alexis Carrel, a French surgeon employed by the Rockefeller Institute in New York (Reggiani 2007, pp. 33, 43). In difference to Harrison, Carrel turned his attention to tissue culturing not primarily because he wanted to find answers to a specific question about cell development. Instead, as Albert Fischer, author of one of the first text books on tissue culture, noted, Carrel was fascinated by the possibilities of the new technique itself (Fischer 1925, p. 21). Developing the technical apparatus of tissue culture, he hoped, would at some point allow for whole organ culture. This, in turn, could facilitate organ transplantation, his main research interest. Carrel was awarded the Noble Prize in Medicine or Physiology in 1912 for developing a technique for suturing blood vessels called "triangulation", which he regarded as another important precondition for making organ transplantation a reality. Tissue culture, however, would also make it possible for Carrel to address broader ontological questions. The ability to grow small pieces of tissue in glass, he hoped, would make it possible to observe and manipulate the 'event' of life itself (Landecker 2007, pp. 13–15). Drawing on

[2] Albeit usually via ideas developed in the writings of Alfred North Whitehead, which have been influential on a group of natural scientists developing an organicist theoretical biology, including J.H. Woodger, but also Joseph Needham and Conrad Waddington, whose notion of epigenetics has recently been taken up again, for example in the field of stem cell research (see e.g. Dupré and Nicholson 2018; Peterson 2016).

[3] See for example Sprenger's (2019) recent work on the biopolitics of environmental control.

the Bergsonian idea of duration, Carrel wanted to show that temporality was the core distinguishing character of living things, and, moreover, that this 'physiological time' depended on the interrelations between the living organism and its milieu.

In 1909, Carrel sent his research associate Montrose T. Burrows to Harrison's laboratory to learn his "hanging drop" cell culture technique; and after Burrow's return they embarked on a number of experiments culturing different kinds of animal tissues (Reggiani 2007, p. 37). By 1912 they had developed a number of new techniques for culturing various different types of tissue in chicken plasma knots and had moved on to a series of experiments that would become famous as the "immortal chick heart" tissue culture. It is also in reference to this series of tissue culture experiments that Carrel first formulated his more philosophical claims about physiological time. Carrel described the "chick heart" experiments for the first time in a 1912 paper entitled "On the Permanent Life of Tissues Outside of the Organism". He opened the article by explaining his motivation for working on tissue culture techniques. The "purpose of experiments described in this article" he wrote "was to determine the conditions under which the active life of a tissue outside the organism could be prolonged indefinitely." (Carrel 1912, p. 516) In his opinion, it was possible for "the length of the life of a tissue outside of the organism" to "exceed greatly its normal duration in the body, because elemental death might be postponed indefinitely by a proper artificial nutrition" (Carrel 1912, p. 516). The paper goes on listing a number of experiments employing several techniques and using a variety of different types of tissue. All the protocols revolved around culturing tissue in mixtures of plasma, water, Ringer's solution and "a drop of embryonal or muscle extract" and repeatedly washing the tissue samples in Ringer's solution before placing them in new medium. The "embryo juice", as he would refer to it later, was Carrel's self-produced nutrient medium, which he made by grinding up embryonic tissue, adding saline solution, centrifuging the mixture and filtering the supernatant solution through paper (Landecker 2007, p. 77).

The specific goal of the embryonic chick heart culture was to "acertain whether tissues after a long period of life *in vitro* could retain their normal functions."(Carrel 1912, p. 525) Carrel described this experiment as following: "On January 17, 1912 a small fragment of the heart of an eighteen day old chick fetus was cultivated in hypotonic plasma. The fragment pulsated regularly for a few days and grew extensively. After the first washing and passage on January 24 the culture grew again very extensively, but there were no rhythmical contractions." After eleven more washings and passages the culture "became surrounded by fusiform cells and many dead cells. There was no pulsation. After the twelfth passage the culture did not grow at all. Then the tissue was dissected and the old plasma was completely extirpated. A small central fragment was removed, washed and put in a new medium. On March 1 it was pulsating at a rate that varied between 60 and 84 per minute." Pulsation stopped again after a few days, but reappeared on March 5 after a fourteenth passage (Carrel 1912, pp. 525–526). The result of the experiment, Carrel claimed, was that the embryonic chick heart culture remained pulsating for over one hundred days, and remained alive and growing after that period—even though pulsation had been by no means continuous.[4] After the publication of his first article on the embryonic chick heart culture, Carrel's claims about 'immortality' were reported enthusiastically by the press. On the same day the New York Times had reported on Carrel's article, the story was taken up by newspapers across the U.S. and it was also reported in France and Germany. Public interest was further excited when Carrel was awarded the Noble prize, and articles reporting this event tended to blur together the surgical techniques and the tissue culture work, writing about Carrel as the scientist who uses the dead to make immortal life. As Hannah Landecker writes: "In a beautiful but probably unintentional spelling mistake, the *Indianapolis News* called the story of Carrel's experiments 'grewsome', in reflecting that the story had all the 'creeping horror of the most morbid narrative of Edgar Allan Poe'"(Landecker 2007, p. 92).

By 1925 Carrel's laboratory had published over 140 articles on tissue culture. Even though Carrel was seen as the leading figure in the fast growing field of tissue culture, he was not uncontroversial. This is often attributed to his flair for the eccentric and to what some saw as his 'mystic' insistence on exact procedures and laboratory lay-out. Carrel claimed that his extraordinary, and as it turned out, hard to replicate, success with keeping tissue cultures alive was due to the meticulous care he had taken with the set-up of his laboratory space and the training of his staff. The dark walls of the laboratory and the black, floor-length hooded robes the lab workers wore, which Carrel deemed necessary to make dust visible and reduce glare, surely contributed to the vibe of the uncanny surrounding these experiments. Much of the aversion of biologists stemmed from the fact that Carrel insisted on techniques he had used as a surgeon to ensure asepsis, which they saw as unnecessarily complicating biological laboratory practices (Witkowski 1979, pp. 282–283).[5]

In 1923 Carrel designed a culture flask, in order to solve the "great technical difficulties" that "have so far prevented" the possibility to "maintain tissues in a condition of uninterrupted growth in a medium which does not deteriorate spontaneously". This new technical apparatus made it possible to "give the cells the necessary food material and removing the catabolic substances from the medium without disturbing the tissues and without bacterial contamination" (Carrel 1923, p. 407). The flasks would make tissue cultures much easier to handle and help alleviate the number one issue of bacterial contamination. The flasks Carrel designed were flat and round "with narrow, oblique necks through which tissues and media may be introduced and removed. The neck is 3 cm long and 1 cm wide,

[4] After this initial article was written, Carrel passed the care for the culture on to his associate Albert Eberling. Eberling pubished a second paper in 1913, "The Permanent Life of Connective Tissue outside of the Organism", which listed the sub-culturing and tissue growth conditions in detail, including records of the 129 passages. In a series of articles published in 1913 and 1914 Carrel and Eberling compared the ability of the embryonic chick heart tissue cells to divide indefinitely with the behavior of microorganisms and infusoria, (a term used at the time for tiny aquatic creatures such as ciliates, euglenoids, protozoa and unicellular algae). These papers also discussed in length the composition of the different media used and their effects on growth rate, the modifications growing cells make to the medium, and methods for measuring the volume of tissues in the culture.

[5] As Carrel wrote: "The culture must be made in a warm, humid operating room with the same care and rapidity as a delicate surgical operation … the perfect teamwork of well-trained assistants is necessary" (Carrel and Burrows 1911, p. 390).

and can be easily sterilized in a Bunsen flame" (Carrel 1923, p. 407). In the flask, the culture was kept in a nutrient medium composed of chicken plasma, chick embryonic juice, and a solution of salts and glucose. As Carrel described it "[t]he culture medium is composed of two parts, solid and fluid. The solid medium consists of a coagulum of fibrin obtained from plasma or fibrinogen" (Carrel 1923, p. 408). This medium was to be introduced into the flask first and the tissue sample was placed in it, before it could fully coagulate. With coagulation, a soft, uniform clot would form, which held the tissue fragments in place while furnishing an invisible, fibrinous network in which the cells could multiply. Then the second, liquid medium was added. The cultures were bathed by a salt and glucose solution, which could be withdrawn by suction. The culture was regularly fed with fresh diluted embryonic juice. The manipulations allowed enough air into the flask to renew the oxygen (Carrel 1923; Reggiani 2007, pp. 38–39, 55).

After Carrel had retired from the Rockefeller Institute in 1939, his associate Eberling took the cultures to his new post at the Lederle Laboratories of the American Cyanamid Company, in Pearl River, New York, where the cultures were used to test the toxicity of drugs and germicides. The last of the cultures was thrown away in 1946, two years after Carrel's death (Jiang 2012). In retrospect it is extremely doubtful that Carrel established an 'immortal' tissue culture. This only became clear, however, when in 1961 Leonard Hayflick showed that normal somatic cells in culture only divide for a set, species specific, number of times. Hayflick believed that the embryo extract Carrel used to 'feed' his 'immortal' embryo chicken heart culture provided new viable embryonic cells to the tissue culture, which replaced the original cells. Another explication could be that Carrel's cultures were contaminated by the Rous sarcoma virus, which was cultured in the laboratory at the same time. While the Rous sarcoma tissue samples in Carrel's laboratory did not survive long, the virus could have transformed the embryonic chick heart cells into cancerous cells, which would have made them truly 'immortal' (Landecker 2007, p. 167). Nevertheless, Carrel's work was deeply influential for the development of cell culture techniques. His understanding of the importance of asepsis, a specifically equipped laboratory and well-trained laboratory staff shaped the form of new laboratories that were able to work with cell cultures. Carrel developed a tissue culture apparatus, including glass-ware, film-equipment and complex protocols to avoid contamination, which was used well into the 1950s. Immortal or not, with his embryonic chicken heart culture, Carrel showed that tissue could be 'reactivated', if it was regularly washed in physiological solution, kept in fresh plasma and 'fed'. Similar protocols of washing tissue and feeding it with self-made nutrient media, including versions of 'embryo juice', would be used for the next decades. The figure of Alexis Carrel was not only important for the development of cell culture because of his emphasis on technique and the creation of a laboratory apparatus, however. As Hannah Landecker argues, "Carrel's focus on duration … left an enduring legacy" also "in terms of expectations and emphasis—tissue culture as a method to study the cell as a dynamic, temporal being" (Landecker 2007, p. 70).

Modernism, the 'engineering ethos', and medical holism

In many ways, Carrel's understanding that the spatial and temporal properties of living tissues are open to manipulation fits well with what historian Philip Pauly has described as the 'modernist experience' of early 20th century American biologists, when biology as a discipline moved towards an "interventionist rather than observational focus". In his book about developmental biologist, and Rockefeller Institute colleague of Carrel, Jacques Loeb, Pauly called this the 'engineering ethos' of modern biology. In the late 19th century, he argues, the development of experimental, laboratory-based biology started to re-define the fundamental purpose of this science as the control of organisms. In this narrative, biologists moved away from ontological and epistemological concerns in favor of an emphasis on technique. "Nature", Pauly states, was turned into the "raw material" that is "transformed by the power of the biologist" (Pauly 1987, p. 4). Loeb himself expressed his belief that it was "possible to get the life-phenomena under our control". Moreover, Loeb saw such "control and nothing else" as "the aim of biology" (Loeb quoted in Pauly 1987, p. 5). For Pauly, the "modernist experience" of early 20th century biological researchers was expressed in a turn to the "strategy and practices" of artifice where "serious biologists began to see themselves as designers and inventors of new things" (Pauly 1987, 286)[6].

One should be careful to note, however, that the interventionist spirit of the novel laboratory based experimental life sciences did not necessarily mean that scientists would adopt a 'mechanical engineering' outlook on the organism at the turn of the 20th century. Evelyn Fox Keller argues that throughout the 19th century and up until World War II the Kantian idea of a clear distinction between living organisms and humanly designed machines held fast. Only with the rise of cybernetics in the 1940s, she writes, was the idea that "organisms were machines, and at least some machines could be organisms" taken on (Keller 2008, p. 47). In the "ongoing struggle for methodological and epistemological supremacy" between the life sciences, the physical sciences, and engineering, in the late 19th and early 20th century, the question was not whether organisms were (or could be built like) machines, but whether they could be explained by the laws of physics, as we will see in more detail below (Keller 2008, p. 46). Moreover, as Robert Brain reminds us, this modernist moment in the life sciences was not one where intervention *replaced* observation, but where intervention and the development of new tools and techniques created new objects for observation, and new possibilities for recording it (Brain 2008).[7]

[6] This mindset, many argue, has perpetuated through the development of molecular biology in the second half of the 20th century and culminates in contemporary synthetic biology—a field that has attracted researchers trained in engineering or chemistry (Gelfert 2013, p. 142). Synthetic biology has appropriated the goals, language and practices of engineering disciplines, like design, modularity and standardization (Schyfter 2012, p. 45). As Calvert and Fujmura put it, synthetic biology "aspires to reduce the complexity of biological systems by developing discrete and substitutable parts" from which new, functional living things can be built (Calvert and Fujimura 2011, p. 160).

[7] Brain argues that experimental physiology and modernism as a movement in the arts were connected by their fascination with new methods of recording. He writes that graphical recording methods "spearheaded the laboratory revolution in nineteenth-century medicine" (Brain 2008, p. 399). Moreover "[f]

This emphasis on using technological tools to bring into view life processes which were previously hidden is an important aspect of Carrel's tissue culture work, for which he also developed a sophisticated apparatus for filming living cells, thus making their temporal properties recordable.

Carrel's writings, however, also testament to the ambivalence of modernism. There were growing concerns about the social upheaval increasing technization and industrialization seemed to cause. Progress and crisis appear, by the beginning of the 20th century, as already interwoven. Carrel's intellectual formation was influenced by French medical holism, even though his insistence on the importance of laboratory research made him an unusual figure in holist circles. As Lawrence and Weisz describe this movement, medical holists understood the human body in a "systemic fashion", where parts have "many intense and multidirectional interconnections", and "the whole is said to determine the action of the parts". Therefore "sickness is regarded as a general disorder of the body." Holistic approaches at times "operate at the level of systemic biological processes" or they "can attempt to incorporate emotions and the psyche into the study and cure of individuals" (Lawrence and Weisz 1998, p. 1). While also a distinct movement in the medical sciences, holism in the first half of the 20th century was closely connected to scientific, social and philosophical debates that extended beyond the discipline. Lawrence and Weisz point out that the "new physics of relativity and quanta served as a model for holistic doctors and antireductionist scientists in a wide variety of fields" (Lawrence and Weisz 1998, p. 6). Carrel shared with other French holists like Rene Biot, Auguste Lumière and Rene Leriche a strong interest in Christian medical humanism, where an engagement with the Catholic revival movement often had strong mystical leanings (Weisz 1998, pp. 71–73). Moreover, they also shared a fascination with the philosophy of Henri Bergson. Most French holists were conservative, and, like Carell, prone to ascribing to a "sociobiology of decline", as Andres Reggiani (2007) has fittingly called it. In his bestselling book *Man, the Unknown* (1935) published in Europe and the U.S. in the mid-1930s, Carrel wrote about the general crisis "corroding the very structure of Western civilization." (Reggiani 2007, p. 64) This crisis was caused, in Carrel's opinion, not only by the gap between material and scientific progress on the one hand, and spiritual progress on the other, as many holists bemoaned, but also by a decline of the white races, which previously had dominated the world "because they were endowed with 'exceptional' physical and psychological qualities" (Reggiani 2007, p. 65). Carrel blamed this decline on unhealthy environments, stemming

Footnote 7 (continued)

or many physiologists after 1879 the freestanding character of the graphical self-recording instrument offered a rich set of analogies for thinking about the physiological and psychological functions of organisms themselves." European physiologists "began to regard the animal body itself as a matrix of surfaces upon which impulses were received from the milieu and stored in tissues as organic memory. It was a prime case of turning an 'epistemic thing'—a scientific object that is brought into existence by the experimental set-up, in this case physiological graphics—into an object of the natural world" (Brain 2008, p. 402). Carrel's laboratory work and the Bergsonian ideas he drew on can be both seen as continuations of these early modernist notions and practices.

from “alien” hot and humid climates as well as from modern amenities, and on an “ill conceived education, feminism and a short-sighted selfishness” that turned modern women away from their reproductive and childrearing roles (Reggiani 2007, p. 66). While on the level of tissues or cells, then, building an artificial milieu made it possible to prolong cellular life, on the level of human population, Carrel worried about the influence of the changes modern culture and technology made to the environments in which humans lived, which he believed adversely affected the ‘natural’ properties of the human species (or, more particularly, the ‘white races’). Carrel, a vocal supporter of eugenics, endorsed more extremely right-wing positions than most of his French peers. In 1911, he gave expert advice on surgical matters to a committee on sterilization that had been set up by the eugenics section of the American Breeders Association. While in a healthy society, peasants and industrial workers would owe their inferior status to their “hereditary organic and psychological weakness”, this natural order, he argued, would have to be reestablished today by creating an ‘non-hereditary aristocracy’ with the offspring of exceptional personalities such as “imaginative criminals, great revolutionaries, and high-handed businessmen”, whose “ancestral qualities” of medieval warriors and the founders of civilization often lay hidden under the “cloak of degeneration” (Reggiani 2007, p. 69).[8] In the 1930s Carrel stated that fascism was a superior form of rule, because it “infused with life the products of our mind” and engendered “men burning with a passion to create” (Reggiani 2007, p. 67).

While, to my knowledge, Carrel makes no explicit mention of his social and religious beliefs in his writings about tissue culture, he frequently expresses his admiration for Bergson’s philosophy in these texts. To clarify how Carrel’s engagement with biological time overlaps and differs from Bergson’s the next section first turns to a very brief sketch of Bergson’s understanding of time. Given the scope and complexity of his work this discussion remains quite rudimentary. We then return to Carrel’s writings on tissue culture and physiological time. My aim is not to show that Carrel’s concept of ‘physiological time’ was as ‘Bergsonian’ as Carrel framed it. Nevertheless, I hope to show that Carrel and Bergson did ascribe to a similar understanding of life based on the importance of time.

Bergson on time as *durée*

Henri Bergson, a philosopher trained in mathematics and keenly interested in the natural sciences, constructed his impressively wide-ranging *oeuvre* around one core point of critique: the forgetting of time in modern scientific and philosophical thinking. In his famous work *Creative Evolution* Bergson considers the question of time by starting from a distinction he had already established in his earlier works: between abstract time *t* and experienced, lived time *durée* (duration). By abstract

[8] We should not forget, however, that eugenics was at the time of this writing not exclusively linked to right-wing positions, but also found followers among socialists and reform oriented liberals, like for example Julian Huxley, another avid reader of Bergson.

time Bergson means both clock time, as we refer to it in everyday life, and time as understood by modern (that is, pre-20th century) mathematics and physics. In both cases, time needs to be measureable, and therefore is represented as a series of discrete, and thus countable, units. This, however, means that time becomes 'spatial'. Numerical distinctness implies externality and juxtaposition—that is, classical geometrical properties, which (for time) only exist as abstraction. This abstract, spatial understanding of time, Bergson argued, ultimately allows for a model of the universe as lawful and determined; a view which enables humanity's extraordinary success in manipulating matter. But it dismisses the reality of time *as flow* which brings about real change. The picture of the universe abstract time carries ultimately has to remain static: in modern physics time is re-described in terms of the motion of matter and this reduces change to the reversible 'displacement' of parts, excluding the possibility for novelty.[9] As Bergson explained it:

> A group of elements which has gone through a state can … always find its way back to that state, if not by itself, at least by means of an external cause able to restore everything to its place. This amounts to saying that any state of the group may be repeated as often as desired, and consequently that the group does not grow old. It has no history. Thus, nothing is created therein, neither form nor matter. What the group will be is already present in what it is, provided 'what it is' includes all the points of the universe with which it is related. A superhuman intellect could calculate, for any moment of time, the position of any point of the system in space. And as there is nothing more in the form of the whole than the arrangement of its parts, the future forms of the system are theoretically visible in its present configuration. (Bergson 2011 [1910], p. 13)[10]

[9] The tendency to disregard time is already inherent in Newton's work—who by the way himself distinguished between measurable time and time as duration. As Newton writes "Absolute, true, and mathematical time, in and of itself and of its own nature, without reference to anything external, flows uniformly and by another name is called duration. Relative, apparent, and common time is any sensible and external measure (precise or imprecise) of duration by means of motion; such a measure—for example, an hour, a day, a month, a year—is commonly used instead of true time" (Newton 1999 [1687], p. 408). The full effect of a spatialized time, however, only becomes clear with the mathematical work of Lagrange. He introduced the concept of work as a principle for the measurement of the transfer of energy from one physical system to another, and with this physics gets rid of the notion of time, in its proper sense. As Isabelle Stengers writes, with Lagrange, to know "is to construct, and Lagrangian construction does not define change in terms of movement in space in the course of time," as envisioned by Galileo and Newton. Instead, change "is defined in terms of 'distances' measured by costs, by what we henceforth call work, the 'price' of the passage form one state to another. … With Lagrange, temporal evolution itself will be subjected to this logic of equivalence." (quoted in her own translation in Guerlac 2008, p. 19).

[10] The world-view Bergson here criticizes is epitomized by Laplace's 'demon', a famous passage Bergson quotes in *Creative Evolution*: "An intellect which at a given instant knew all the forces with which nature is animated, and the respective situations of the beings that compose nature—supposing the said intellect were vast enough to subject these dates to analysis—would embrace in the same formula the motions of the greatest bodies in the universe and those of the slightest atom: nothing would be uncertain for it, and the future, like the past, would be present to its eyes" (Laplace 1886 quoted in Bergson 2011 [1911], p. 27).

Against this ‘spatialized’ understanding of time, Bergson proposes the notion of time as *durée*, an idea of time as unidirectional, undividable flow, where the past does not disappear into nothingness, but accumulates. In his earlier work *Matter and Memory* Bergson explains what he means by the accumulation of the past by discussing memory. As he sums it up in the beginning of *Creative Evolution*, memory “is not a faculty of putting away recollections in a drawer, or of inscribing them in a register. … there is not even, properly speaking, a faculty, for a faculty works intermittently, when it will or when it can, whilst the piling up of the past upon the past goes on without relaxation.”(Bergson 2011 [1911], p. 11) For him,

> all that we have felt, thought and willed from our earliest infancy is there, leaning over the present which is about to join it, pressing against the portals of consciousness that would fain leave it outside. The cerebral mechanism is arranged just so as to drive back into the unconscious almost the whole of this past, and to admit beyond the threshold only that which can cast light on the present situation or further the action now being prepared—in short, only that which can give useful work. (Bergson 2011 [1910], p. 12)

This accumulation of ‘memory’ means that time is not reversible and that temporal events are not repeatable:

> From this survival of the past it follows that consciousness cannot go through the same state twice. The circumstances may still be the same, but they will act no longer on the same person, since they find him at a new moment of his history. Our personality which is being built up each instant with its accumulated experience, changes without ceasing. … That is why duration is irreversible. (Bergson 2011 [1911], p. 12)

In *Creative Evolution*, Bergson moves from a description of *durée* as rooted in human experience to a general description of the nature of time. As a first step, he broadens the applicability of *durée* from human existence in time to the time of living systems in general by discussing theories of evolution. Evolution, for Bergson, is duration as an accumulation of the past (visible in the development of the singular organism and the species), which entails a creative process that continually brings forth new properties, organisms and species. Bergson argues, however, that theories of evolution have arrived at an impasse, where the two prominent theoretical camps, mechanism and finalism, are equally unable to explain *how* new properties emerge (Bergson 2011 [1911], p. 28). Put simply, he argues that mechanistic theories of evolution like neo-Darwinism understand “the organism as an inert system in mechanical equilibrium, whose decomposable parts can be ‘selected’ piecemeal by the action of the environment” (DiFrisco 2015, p. 59), as James DiFrisco sums up Bergson’s critique:

> Since it calls upon natural selection as the sole explanatory principle for the organization and evolution of the living world, neo-Darwinism lacks a notion of the activity of life, of internally-generated organizational constraints and evolutionary directions. Most importantly for Bergson, however, because it is based on the classical mechanistic image of nature, time does not have any

> "efficacy" in the neo-Darwinian framework. Since present and future states are the necessary consequence of past states, "all is given" in advance, and it is impossible for any true evolution to take place (DiFrisco 2015, p. 59)

The second option runs into similar issues. While finalist theories of evolution might sound different at first, Bergson argues that they ultimately rely on corresponding ideas. Not only do they also regard the organism as an "aggregate of parts", they likewise disregard the importance of time. For finalists "everything is given in advance—no longer in the past state but in the future" (DiFrisco 2015, p. 59; see also Bergson 2011 [1911], p. 29).

> The doctrine of teleology, in its extreme form, as we find it in Leibnitz for example, implies that things and beings merely realize a program previously arranged. But if there is nothing unforeseen, no invention or creation in the universe, time is useless again. As in the mechanistic hypothesis, here again it is supposed that all is given. Finalism thus understood is only inverted mechanism. (Bergson 2011 [1911], p. 28)

For Bergson, both mechanism and finalism "are reluctant to see in the course of things generally, or even simply in the development of life, an unforeseeable creation of form" (Bergson 2011 [1911], p. 31).

Bergson introduces his idea of the *élan vital* as a way to bring time back into the picture. The *élan vital* is an impulsion that brings about the internal organization of living organisms, passed on from generation to generation. This impulsion, however, is not an inexplicable force or substance, as in vitalism (like for example Driesch's *entelechies*). Instead, it is an 'inner' organizational constraint of living systems that shapes their evolution in addition to external selective constraints. With the notion of the *élan vital* Bergson thus moves towards what DiFrisco calls a "thermodynamic definition of life" (DiFrisco 2015, p. 66).[11] This ultimately collapses the dualistic distinction between living systems and 'dead' matter into a differentiation of degree. Extremely simplified, and put into language closer to more contemporary systems theories, the *élan vital* is a tendency towards organization and differentiation that stands against the tendency of dissipation of energy and increased equilibrium which will ultimately leads to the heat death of the universe. In this understanding, inert matter and living matter differ from each other only in their

[11] Bergson's writing then in striking ways prefigures some of the core ideas of thermodynamics before they were established in physics, where the work of Ilya Prigogine led to the establishment of nonlinear nonequilibrium thermodynamics in the mid-20th century. This work describes the role of energy flows in producing macroscopically ordered states. As DiFrisco explains it: "The input of excess free energy into an open system forces it to adopt the configuration that dissipates the energy most effectively, and sometimes these are highly ordered configurations (the classic examples of such 'dissipative structures' include Bénard convection cells and oscillating chemical reactions such as the Belousov- Zhabotinsky reaction). As nonequilibrium thermodynamics continued to evolve in the latter half of the 20th century, theorists became increasingly interested in linking it to the phenomena of biological organization and evolution, since the variety of dissipative structures to be found in nature includes living systems. Starting in the 1970s and 1980s, a 'thermodynamic paradigm' began to take shape in theoretical biology." (DiFrisco 2015, p. 68).

relative state of organization. For Bergson, then, matter becomes “a flux rather than a thing” (DiFrisco 2015, p. 62). As DiFrisco points out, this conception of matter is a both “thermodynamic and energeticist” understanding of open-systems dynamics (DiFrisco 2015, p. 62). In other words, for Bergson the organizational complexity of living system allows them to differentiate from their environment. While this can never be fully successful, they strive towards systemic closure, which enables them to accumulate and store energy. The ‘higher up’ a living system is, the greater is its relative freedom, where freedom is defined as freely using stored energy. Through this tendency to organization living systems also reach a higher state of duration: they retain within themselves more history in the form of more complex systemic structure. A living system, then, “is able to ‘remember’ and incorporate the effects of past events. Its present is spread over a longer interval due to its more continuous rhythm of uptake and dissipation. Since the future pathways of its release of energy cannot be predetermined, finally, it is a site of ‘indetermination’ and even of creative activity in Bergson’s terms” (DiFrisco 2015, p. 66). For Bergson, then, the universe becomes ordered into more or less ‘living’ systems by two opposed tendencies: *mechanism* and the *élan vital.* The tendency of *mechanism* leads ultimately to the dissipation of energy—but the *élan vital* works to counteract this tendency. Bergson ultimately provides for an understanding of evolution as a process of *durée* that incorporates the whole universe. After the formation of organized matter (and thus life) has first taken place, the *élan vital* pushes into motion an evolutionary process that leads to ever more diverse, and internally differentiated, living beings, which become more and more independent of their environments, and thus also more autonomous and ‘free’. Human freedom, for Bergson, then is a result of evolutionary process that allowed the human species to become relatively independent of its environment. This separation of subject and object made it possible, in turn, to grasp the environment abstractly and thus also to manipulate it more effectively.

Carrel and physiological time

The question of time looms large in Carrel’s writings about tissue culture. In the 1930s he also integrated his understanding of the temporal processes involved in cell culture with a more general theory of physiological time, which draws heavily on Bergsonian terminology. With Bergson, Carrel argued that physical or ‘clock-time’ time “obviously differs from the time which we live.”(Carrel 1931b, p. 618) In difference to Bergson, however, he was not concerned with physical time as a mathematical, spatial abstraction, he just pointed out that physical time proceeds at a constant rate, while ‘lived time’ does not. Moreover, while Bergson’s concept of *durée* ultimately collapses immediate (human) time experience (i.e. psychological time) with the ‘biological time’ of living systems, and with the ‘cosmological time’ of the evolving universe as a whole, Carrel distinguished clearly between psychological and physiological duration. He understood physiological time as the substratum of psychological and social time experiences. Physiological duration, Carrel argued “is a certainty much more than the flux of our inner life. It comprehends the whole organism. Mind and body are two aspects of a single thing” (Carrel 1931b,

p. 618). Clearly "[b]ody and consciousness" were united into one "history", but the precise relationship between physiological and psychological time, he argued, was as of yet unknown. To understand the living organism, however, the study of physiological duration would be of utmost importance. "The living organism", he wrote "undergoes two classes of changes: rhythmical and reversible, or progressive and irreversible". These changes "are as indispensable a part of the body as the tissues and organs" anatomy studied. Anatomy could only grasp the organism "in timeless space". While this approach was "imposed by methodological necessity", it meant that the object of anatomy "is not the concrete body, but only an artefact". For Carrel, "[a]n organism deprived of duration is just as unthinkable as if deprived of spatial extension. Dead organs and histological sections are nothing but useful abstractions. The body really consists of a flux of structural and functional processes, that is, of an uninterrupted modification of tissues, humors and consciousness. Such is physiological duration" (Carrel 1931b, p. 619). Bergson, Carrel argued, had "clearly shown how the past persists in the present". This means that "[t]he present of a living organism does not pass into nothingness. It never ceases to be, because it remains in the memory and is entered in the tissues. … The body is obviously made up of the past. While the present glides into the past, it seems to assume spatial form". Time and space are thus "indissolubly united." Time, for Carrel, was "really the fourth dimension of living organisms. It enters as a part into the constitution of a tissue." This means that living things, from "cell colonies" to organs and whole organisms are better understood as "events which progressively unfold themselves" or as a "flux of structural and functional processes" (Carrel 1931a, p. 298). This was so obviously visible in living things, that for Carrel, biologists "should have conceived long before Einstein and Minkowsky that space and time are not separate entities but constituent elements of a four-dimensional continuum" (Carrel 1931b, p. 620).

The processes that make up physiological duration, Carrel's argued, could be made accessible to scientific analysis with tissue culture techniques. Within physiological time he seemed to distinguish between two temporal movements or tendencies, but failed to make this explicit: differentiation and growth on the one hand and 'aging' or decline leading to death, on the other. Carrel pointed out that cells from embryonic organisms grew better in culture than cells taken from an organism after birth. This slowing in growth rate with age could also be measured clearly in wound healing, which Carrel had the opportunity to study in France during World War I. Carrel led the Front Hospital No. 21, where he and his student Lecomte du Noüy started researching the treatment of infected wounds, with funding from the Rockefeller Institute. They claimed that the speed of healing of open wounds was directly correlated to the age of the patient (Carrel 1931b, p. 619; Canales 2015, pp. 299–300). While Carrel did not explain where the tendency for growth is located, he explained that aging, which over time diminishes the ability of tissues to grow, was a result of the metabolic interactions between organism and environment. He argued that Claude Bernard had already known that the life of an organism was the result of relationships among cells and between the organism and its environment (Landecker 2007, p. 78). Aging, then, was a result of the accumulation of certain metabolic products (which exactly, he wrote, was still unclear) in the *milieu interieur* of the organism. When aging is not determined by *fixed* physio-chemical properties of the cell itself, however, this means that the possibility to provide living tissue with an artificial environment also makes it possible to manipulate its temporality. Looking back on two decades of tissue experiments, Carrel wrote in 1931 "[t]ime is recorded by a cell community only when the metabolic products are allowed to remain around the tissue" (Carrel 1931b, p. 621). Therefore, in cultured cells the process of growth could be decoupled from the process of 'aging', by removing these metabolites. Then, "the cell colonies remain indefinitely in the same state of activity. They do not record time qualitatively. In fact, they are immortal" (Carrel 1931b, p. 621). That manipulation of the environment allows for manipulation of physiological time, Carrel argued, also holds for the whole organism: "[b]y drying a rotifer, one may temporarily stop the stream of duration. On the contrary, when Loeb increased the temperature of the environment of *Drosophila melanogaster*, these flies aged more rapidly" (Carrel 1931b, p. 620). This manipulability, however, has its practical limits. Tissue culture, Carrel made clear, is a simplified system, where dependence on an artificial environment is total. Rotifers and fruit flies are lower organisms, which depend heavily on their environment. "As the organism of the warm-blooded animals is comparatively independent of the outside world", however, "an artificial modification of the processes on which aging depends is a difficult undertaking". He was hopeful, nevertheless, that "it would certainly be possible to discover what physiological and psychological disciplines should be offered to human beings in order to increase the span of their life." (Carrel 1931b, p. 620) In his foreword to Du Noüy's book *Biological Time*, published in 1937, Carrel argued for the importance of studying human duration, because "[a] better knowledge of human duration will permit *a more effective application of the factors of our environment* to the development of our physiological and mental life." (Carrel 1937, vii; my emphasis)[12] However, the relationship to the environment, and the accumulation of the past also meant that no yet existing manipulation of the environment of an organism, or piece of living tissue, could *reverse* the flow of physiological time: "the problem of rejuvenation, if this word is taken with its full significance, appears to be insoluble. The reversion of physiological time would require a method capable of replacing tissues and humors in the structural and functional state of an earlier life period. Such a method has still to be discovered" (Carrel 1931b, p. 620). It wouldn't be until the development of induced pluripotent stem cells in 2006 that such a reversal of physiological time became an accepted technical possibility of cellular biology.

[12] Du Noüy dedicated the book to Carrel, as the "spiritual godfather of the book". Carrel wrote in the foreword, that "[t]o endure is an essential characteristic of all living organisms" and quotes from Bergson's "admirable" book *Creative Evolution* "'[w]herever anything lives, there is, open somewhere, a register in which time is being inscribed.'" (Carrel 1937, p. vii)

Conclusion

Carrel's experiments at the very beginnings of somatic cell culture are a good example for how, from the early 20th century till today, the development of new biotechnologies has been connected to societal and philosophical ideas about what life is. New techniques and tools have had, in turn, a strong influence on how the modern life sciences would be able to understand—and alter or produce—living things. These insights have led to the development of new medical applications which contribute to how humans think about their own biological existence (we might think here for example of the possibility to store gametes and embryos, or the repeated expectations raised by advances in stem cell research or genome editing to 'defeat' not only specific diseases, but aging itself). It cannot be denied that with the rise of molecular genetics in the 1950s reductionist explanations have eclipsed holistic and organicist approaches in cell biology. In the bioengineering or synthetic biology community today *understanding* biological systems is closely linked with one's ability to rebuild them, where the ability to make living things depends on one's understanding of the genome as an information medium. Nevertheless, in particular in light of the recent 'epigenetic turn' in molecular biology which brings environmental interactions back into play, it might be helpful to consider how holist and organicist ideas of life have contributed to shaping contemporary biotechnologies.

Carrel interpretation of Bergsonian ideas diverges from how philosophers would later read Bergson's work. At the time of Carrel's tissue culture experiments Bergson was a celebrity, and it might have been a result of his popular success that a multiplicity of 'Bergsonisms' sprang up, which often had very little resemblance with Bergson's own work. One should not forget, however, that the reading I offered above is colored by a language of systems theory that would only become developed later. Nevertheless, Bergson and Carrel do agree on some important points. Carrel seems to think similar to Bergson about the necessity to distinguish between artificially closed system models scientists create (and in which then mechanism becomes applicable and time can be made to disappear) and natural open systems. While there is something to learn from models, they cannot teach us everything about the complexity of living systems. As Bergson writes, natural systems strive towards closure and thus towards establishing autonomy; but, as Carrel stresses, they always rely for their maintenance on metabolic exchange with their environments. The environment, for both Carrel and Bergson, is understood as an external constraint on living systems—it delimits their possibilities of development and, in the course of evolution, takes part in establishing their form and function. However, living things also actively shape their environments. As Bergson points out, organisms experience their surrounding world selectively—an organism's 'world' is comprised only of those aspects of its surroundings which are necessary for it. This is true in spatial and temporal terms—one only 'sees' those parts of one's environment that one interacts with, and one only 'remembers' those parts of the past which one needs for action in the present (Bergson 2011 [1911], pp. 15–16, 24). A living system, in this way, creates its own milieu and its own history. In a more concrete sense, Carrel and Burrows thought that tissue cultures created an environment conductive of their own survival, because cells would excrete certain substances the cell community needed. Again close to Bergson, Carrel seems to have assumed that the nearer as system is to the 'artificially closed' model of scientific thought, where the system for him involves the living organism/tissue and a simplified milieu, the easier its temporal existence can be manipulated. While tissue culture had to account for the influence of the *milieu*, Carrel sought to make the environmental interactions as controllable as possible—as we have seen, with variable success. It was paradoxically his apparent failure in control (the unknown properties of the nutrient media, or viral infection) that probably got him the results he expected. With his understanding of physiological time, Carrel wanted to go beyond what he understood as the Bergsonian idea of duration. To do so, he distinguished different aspects of duration, and separated (albeit not clearly defined) the temporal phenomena of growth and differentiation from aging. Moreover, he turned physiological duration back into a spatial, measurable phenomenon. However, in Carrel's understanding of physiological time we also see what Hannah Landecker describes as the plasticity of living matter coming to the fore as a spatio-temporal concept. Cells and organisms are not only 'plastic' because they can survive interference with their 'spatial' boundaries or shape. Plasticity also has a temporal aspect when the lifespan of living things seems open to manipulation. Carrel and Bergson exemplify the equivocality of early 20th century modernism, where a strong belief in the ability of the natural sciences to change the world co-existed with nostalgia for spiritual wholeness and with growing political and social upheaval.

In closing, I want to note that one has to be careful in making too quick jumps from biological ontologies to normative theories. Bergson's work has been taken up by people from all over the political spectrum, and holistic and organicist ideas were popular with politically outspoken biologists from the right as well as from the left. Biologists who held similar views about the organism as Carrel were often ardent socialists, and, for example in the case of Joseph Needham, sought to show the concurrence of Marxist historical materialism and organicism (Needham 1943). Nevertheless, I do believe that a close engagement with different notions of 'biological' time like those offered by Carrel and Bergson would be enriching for debates about the ethical and socio-political implications of new biotechnologies and biomedical applications today, and could also provide some important insights for social and political theory more generally. The Bergsonian idea of the importance of the past that presses into the present and the future without predetermining it, can be read as stressing the importance to resume ethical and political obligations to address histories of injustice which structure our material present, while his insistence on creativity and the possibility for genuine novelty can be enriching for contemporary debates about transformation and change in political and social theory. Moreover, the idea of the *élan vital* and creative evolution could be a possible avenue to think about the normative issues with biotechnological interventions into living systems, where in a sense, innate evolutionary change, complex interaction and diversification is curtailed by planned intervention.

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Compliance with Ethical Standards

Conflict of interest I confirm that the manuscript is comprised of original material that is not under review elsewhere. As only literary sources were used ethical review was not necessary. I have no competing interests—intellectual or financial—in the research detailed in the manuscript.

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