What is an organism?

Thomas Pradeu (IHPST, Paris 1 Sorbonne-University, 13 rue du Four 75006 Paris, France)

Email: thomas.pradeu@gmail.com.

Abstract

The question 'What is an organism?', formerly considered as essential in biology, has now been increasingly replaced by a larger question, 'What is a biological individual?'. On the grounds that i) individuation is theory-dependent, and ii) physiology does not offer a theory, biologists and philosophers of biology have claimed that it is the theory of evolution by natural selection which tells us what counts as a biological individual. Here I show that one physiological field, immunology, offers a theory, which makes possible a physiological theory of individuation. I give a new answer to the question 'What is an organism?', and try to link together the evolutionary and immunological individuations.

1. Introduction

The question 'What is an organism?', formerly considered as essential in biology (Huxley 1852, Haeckel 1866, Loeb 1916, Goldstein 1939, Medawar 1957, Wolvekamp 1966, Lewontin 1983, etc.), has now been increasingly replaced by a larger question, 'What is a biological individual?' (Hull 1978, 1992; Buss 1987; Wilson 1999; Sober 2000; Gould 2002). This problem of how one should individuate biological entities is critical both for the life

sciences and for philosophy, especially metaphysics (Hull 1981). An individual is any separable, countable entity. More precisely, following Hull, we can say that an individual is 'any spatiotemporally localized entity that develops continuously through time, exhibits internal cohesiveness at any one time, and is reasonably discrete in both space and time'.[1] The word 'individual' can refer to natural objects (rocks, plants, etc.), as well as to artifacts (tables, cars, etc.). The problem of individuation is certainly very general (Strawson 1959), but it has taken a particular importance in biology.

We can think of three ways to individuate biological entities:

i) A phenomenal way, according to which we can easily 'see' biological individuals. In the same way as a table is considered as a good example of an artificial individual, a mouse will be considered as a good example of a biological individual. People who adopt this conception follow a commonsense view of biological individuals.

ii) A physiological way, according to which the biological world is made of organisms, which are described as functionally integrated units, undergoing continuous change, and made of causally interconnected elements (Sober 2000). The underlying assumption is that other entities can naturally be studied by biologists, whether at a lower (genes, proteins, tissues, etc.) or at a higher level (groups, species, etc.), but the fundamental biological individual is the organism, which is conceived of as the only truly unified, autonomous entity in the living world. This view, exemplified by Kant ([1790] 2007), dominates functional biology.[2] Physiological individuation may, but does not necessarily, amount to phenomenal individuation.

iii) An evolutionary way, according to which it is the theory of evolution by natural selection (TENS) which tells us what a biological individual is. A biological individual is any

[1] Here, 'develops' has to be understood in a broad sense: any entity which changes through time, a stone for instance, 'develops'.

[2] As I show in section 3, I consider that the terms 'physiology' and 'functional biology' are synonymous, and that they comprise all biological fields which try to answer '*how?*' questions. Examples include morphology, embryology, immunology, etc.

entity on which natural selection acts. It can be a portion of the genome, a cell, an organism, a species, etc. (Lewontin 1970).

In the vast literature devoted to this subject, strong arguments have been made in favor of evolutionary individuation. The main argument is that individuation in science is always theory-dependent (Hull 1992): it is our scientific theories that, in physics as well as in biology, tell us what our entities (atoms, fields, genes, etc.) are. The next step in the reasoning is that the only true biological theory is the theory of evolution by natural selection (Hull 1992). Therefore, a biological individual is seen as any entity on which natural selection acts. It is defined by the following characteristics, derived from the structure of evolutionary theory: variation, heredity, differential fitness (Lewontin 1970). The consequence of saying that it is the TESN which tells us what a biological individual is is that the organism is, at best, one individual within the rich hierarchy of biological individuals (Buss 1987[3], Gould and Lloyd 1999, Gould 2002). Indeed, in this view, a gene, a molecule, a cell, an organism, a group, a species, etc. can all be biological individuals. Furthermore, what is particularly interesting is that this way to individuate biological entities often leads to an *ontological revision*: for instance, where phenomenal and physiological individuations apparently tell us that a dandelion is that green thing in our garden, evolutionary individuation tells us that, in real fact, it is the extended, long-lived clone of dandelions which constitutes the biological individual, because it exhibits 'reproductive fitness' (Janzen 1977).

Hull and others emphasize that physiology, morphology and other fields within functional biology would be very useful to determine what a biological individual is, *if only* they were grounded in a theory. Unfortunately, the argument goes, there is no such thing as a physiological or morphological theory, and therefore we are supposedly left only with the TENS to individuate biological entities:

[3] By 'individual' Buss means 'a physiologically discrete organism'. With Gould (2002) and many others, we reject this equation: once again, we define an individual as any separable, countable entity. An organism may be a biological individual, but all biological individuals are not necessarily organisms.

> The trouble with Haeckel's solution to the problem of biological individuals is that morphology and physiology do not provide sufficiently well articulated theoretical contexts. Biologists have been engaged in the study of anatomy and physiology for centuries, but no 'theories' of morphology and physiology have materialized in the same sense that evolutionary theory is a 'theory'. In order to see the dependence of individuality on theories, one must investigate more highly articulated areas such as evolutionary biology. (Hull 1992: 184).

Recently, very interesting attempts have been made to show that the organism is a very important, or even unique, entity in biology (e.g. Bateson 2000, Laubichler and Wagner 2000). Nevertheless, these attempts do not answer Hull's problem, which is crucial: is there anything like a physiological theory? Here I show that, if properly understood, one field of contemporary functional biology, immunology, offers a theory of biological individuality. Hence, I address Hull's problem by demonstrating that a *physiological theory* of biological individuation is possible. Naturally, once made clear, this physiological individuation needs to be articulated with evolutionary individuation. Thus, I argue that:

i) a physiological theory of individuation is possible, using immunology.

ii) the two theoretical individuations (evolutionary and physiological) of biological entities must be articulated.

iii) the organism is the best instance of a biological individual.

2. Individuation by the theory of evolution by natural selection

If individuation is always theory-dependent and if the TENS is the main, or sole, biological theory, then the best way to individuate biological entities is to determine what an *evolutionary* individual is. Therefore, in the massive literature on this subject, determining what a biological individual is amounts most of the time to determining what an evolutionary individual is.

So, what is an evolutionary individual? The answer is given by the structure of the TENS. A biological individual is an evolutionary individual, that is, any entity on which natural selection acts. More precisely, though, one can follow Gould (2002: 602-611), who suggests seven criteria of an evolutionary individual:

1. A beginning
2. An ending
3. Sufficient stability
    - 3.1. Progressive (*i.e.* gradual) change
    - 3.2. Discreteness and cohesion
    - 3.3. Continuity
    - 3.4. Functionality, or organization
4. Reproduction
5. Inheritance
6. Variation
7. Interaction with the environment

The first three criteria are general criteria of vernacular individuality, while criteria 4 to 7 are specific to evolutionary individuals; it is the sum of the seven criteria which tells us what an evolutionary individual is.

Now, what counts, in the real world, as a biological individual? When dealing with evolutionary individuals, one radical possibility is to choose one level of individuality and to argue that it is the only 'real' biological level. Genic selectionism, for instance, argues that the gene is the proper level of biological understanding, because it persists through evolutionary time. This view can lead to the idea that the living world is, from a scientific point of view, made of genes, and not of organisms (Dawkins 1982). Such an idea that 'there is no such thing as an organism' is discussed by Sterelny and Griffiths (1999: 70).

Nonetheless, the most common attitude when defining biological individuals as evolutionary individuals is to hold a hierarchical conception of evolution (Buss 1987, Gould and Lloyd 1999, Michod 1999, Gould 2002). In this view, the organism is only one biological individual among many others. A cell, or a cell lineage, can be perfectly legitimate biological individuals. A good example is that of adaptive immune cells like B lymphocytes, which are selected when they face an antigen (Burnet 1959; Buss 1987; Michod 1999). Thus, evolutionary individuation warns biologists: contrary to what commensense suggests, the organism is not the only biological individual in the world.

But the hierarchical view of biological individuality goes further. It leads to a revision of the biologist's ontology. We thought that the biological world was made of organisms as we see them, but this is simply not true, and it is individuation by natural selection which brings this to light. Janzen (1977) typically illustrates this attitude. He argues that while phenomenal and physiological individuations apparently tell us that a dandelion is that green thing in our garden, evolutionary individuation tells us that, in real fact, it is the extended, long-lived clone of dandelions which constitutes the biological individual, because it exhibits 'reproductive fitness'. The consequence is that 'there may be as few as four individual dandelions competing with each other for the territory of the whole of North America' (Dawkins 1982: 254). Equally, the aphid evolutionary individual is the set of insects originating from the same egg and 'growing' by parthenogenesis. Because they share the same genome, they cannot be said to compete with each other, and they constitute the 'parts' of the same individual.

Thus, evolutionary individuation often conflicts with the commonsense view of biological individuation, and leads to a revision of our biological ontology. It is probably a good argument in its favor, since this is precisely one of the main things science does: to change the way we see the world.

3. Physiological individuation

Some authors emphasize that physiology (and morphology) could be of great assistance in definng biological individuality (Hull 1992). Indeed, if successful, physiology could give us a scientifically precise definition of what an organism is, the organism being its main object of study. Here, in order to show how physiology can be useful to define biological individuality, we use a broad definition of 'physiology', so the first thing we need to do is to make clear how the term is being used here.

3.1. What do we call 'physiology'?

Here physiology is broadly defined as all the biological fields which deal mainly with '*how?*' questions (in contrast with '*why?*' questions, dealt with by *evolutionary* fields). It includes anatomy, morphology, most of molecular biology (including molecular genetics), most of developmental biology, etc. Gathering all these fields under the term 'physiology' should not seem surprising (Boron 2005). In any case, the term is not important, whereas the idea is. What we call physiology here is sometimes referred to as 'functional biology' (Mayr 1961). Furthermore, it is akin to systemic views of biological functions (Cummins 1975), and to at least some aspects of mechanistic biology (Machamer, Darden and Craver 2001).

Why use physiology to define biological individuality? According to Hull (1974: 75), physiology deals with the continued maintenance of organisms. My aim is to elaborate on his view, using the broad definition of physiology I have just suggested. Hull distinguishes physiology ('continued maintenance'), and embryology ('initial development of the organisms from the fertilized ovum to the adult'). By contrast, we gather all these fields, which aim at explaining the construction and the maintenance of an organism, that is,

organismic identity through time.[4] Let us call this problem, following Reichenbach (1956), organismic *genidentity*.

3.2. Two inappropriate physiological individuations: approximate functional integration and genetic homogeneity

At first glance, individuals can be defined as 'spatiotemporally localized material bodies that either remain unchanged through time or else undergo relatively continuous change' (Hull 1992). Especially when one insists on continuous change, as (Hull 1981) does[5], organisms as we know them seem to be very good instances of individuals. Indeed, if we think of organisms as different as a plant, a fly, or a rhinoceros, what they all have in common is that each of them constitutes a coherent, functionally integrated, 'whole' (Wolvekamp 1977). According to Sober (2000), functional integration is probably the best criterion we have for individuating biological entities. In this case, 'natural boundaries', like the skin or membranes, are very important. The individual is all that lies 'within the skin' and remains functionally integrated.

The problem is that the concept of functional integration is too vague to offer a *criterion* of individuation. It is too close to the phenomenal individuation: we simply trust our impression that the organism is a coherent 'whole', which we cut into functional pieces. Sober describes counterexamples, but says that individuation by functional integration is enough, that we do not have, and do not need, a more precise definition (Sober 2000: 155). The problem is that 'commonsense is strongly biased by our relative size, duration, and perceptual abilities' (Hull 1992; see also Lewontin 2000: 76-77). I agree with Hull that 'inherent in the scientific enterprise is the need to go beyond ordinary usage and common conceptions' (Hull 1981).

[4] Both terms 'identity' and 'individuality' are used to refer to biological beings. To be perfectly rigorous from a metaphysical point of view, one must consider 'identity' as the most inclusive term: 'identity' refers both to the individuality (spatiotemporal localization and continuous existence) of a being and to its uniqueness (it is the only one to be as it is). For instance, two identical tables are not unique, but they are still two individuals.

[5] Recall the quotation above: an individual is 'any spatiotemporally localized entity that develops continuously through time, exhibits internal cohesiveness at any one time, and is reasonably discrete in both space and time'.

For example, what are the 'natural boundaries' of the colonial organism *Botryllus schlosseri*? Each zooid has a membrane, and is, at least to some extent, an integrated whole, but one could say that the 'true' functional integration happens at the level of the colony, which has a common vascular network. What, then, is the proper physiological individual? In organisms like ourselves, a cell is spatiotemporally localized and functionally integrated: what are the criteria which lead us to say that the organism is the 'true' biological individual in this case? Functional integration is certainly a good principle, but it needs a more precise account, based on a *criterion* of individuation.

Building on metaphors of genetic and developmental programs, a second inappropriate way to understand biological individuals in physiology has been to claim that the organism is the set of constituents originating from the egg cell. This conception of the organism as a genetically homogenous entity is simply wrong, as I show in section 5.

I agree with Hull (1992): a proper individuation needs a theory. We must therefore figure out if a criterion of individuality based on a physiological *theory* is possible. In the next section, I show that, if properly understood, one field of contemporary functional biology, immunology, offers a theory of biological individuality.

4. Individuation by a physiological theory: immunity and the biological individual

As we saw, in the usual physiological definition, the organism is a functionally integrated whole, which is made up of interconnected elements, and which undergoes continuous change. If biochemistry is used to make this definition more precise, it is a useful one (see next section). Nonetheless, what is needed is a convincing *criterion of individuality*. Our claim is that immunology, which is one of the best examples of a physiological field, offers such a criterion.

4.1. What is the relation between immunology and individuation?

Since its inception as both a theoretical and an experimental field, immunology has been considered as a key domain for the definition of biological individuality (Metchnikoff 1907; Loeb 1937; Medawar 1957; Burnet 1969). Yet what one should understand by this notion of 'individuality' remains unclear. Here I use the notion of a *criterion of immunogenicity* to precisely define the contribution of immunology to the problem of biological individuation.

Immunology aims at finding a criterion of immunogenicity, that is, at determining why and when an effective immune response is triggered. An immune *reaction* is a biochemical interaction between immune receptors and antigenic patterns. In certain conditions, an immune reaction can lead to an immune *response*, that is, to the activation of effector mechanisms, which leads either to the destruction of the target (lytic activity), or to the prevention of such a destruction (downregulatory activity). The immune system, in every organism, exerts a permanent surveillance of the molecular patterns expressed by the entities present in this organism (Burnet 1970; Khush, Leulier and Lemaitre 2002). Any entity expressing strongly abnormal patterns will be rejected by the immune system. A criterion of immunogenicity is precisely an attempt to say what exactly this 'abnormality' is. Hence, the immune system, by its surveillance activity, defines what will be accepted, and what will be rejected, by the organism, and therefore a criterion of immunogenicity constitutes a *criterion of inclusion* for the organism: the distinction between the entities which will stick together as constituents of the organism, and those which will be rejected from the organism, is made by the immune system[6]. As a consequence, the immune system is certainly not the same thing as the organism, but it is a sub-system of the organism, the activity of which leads to the

[6] Of course, other biological activities lead to the *rejection* of some entities. We can think of metabolic activities: nutrition (rejection of fecal matter) and breathing (rejection of CO_2). Nevertheless, by these metabolic activities, the organism *assimilates* something, and rejects the by-product of its own assimilation activity. By contrast, the immune system accepts or rejects living entities (organs, tissues, bacteria, parasites, even viruses – which we consider as living entities) themselves as parts of its identity.

discrimination between what is a part of the organism, and what is not. This discrimination happens through time (*i.e.*, it is diachronic): for instance, a proper criterion of immunogenicity must explain why an organism with one kidney at time 1 can have a second, perfectly tolerated kidney, coming from its twin brother, at time 2. Immunity offers a *criterion of diachronic inclusion*, that is, a criterion for what makes the organism a *unit* constituted of different entities through time.

The problem of biological individuality is stated very clearly by Sober: individuality asks 'what it takes for two things to be part of the same individual organism' (2000: 153), and two forms of individuality can be distinguished: synchronic ('given that two parts exist during *the same period of time*, what makes them parts of the same organism?'; emphasis in the original) and diachronic ('When two parts exist during *different periods of time*, when will they be parts of the same organism?'; emphasis in the original) individuality. In my view, immunology makes a critical contribution to the problem of diachronic individuality, by saying what the constituents of an organism through time are. Moreover, individuality being one of the two aspects of identity (along with uniqueness), immunology also helps to answer Hull's request for a definition of biological genidentity (Hull 1992)[7]. The idea that the immune system can explain what the constituents (parts) of the organism are has been intuitively expressed many times (e.g., Gould and Lloyd 1999: 11906). In order to make a critical contribution to the problem of biological individuation, however, we need to move from the intuition that immunity may help to define biological individuality to the definition of a precise criterion, grounded in a well-defined immunological hypothesis. So the question we want to ask now is: what can we consider as a good criterion of immunogenicity?

[7] Naturally, other biological fields may help to understand the organismic genidentity of the organism (developmental biology, studies of metabolism, studies of phenotypic plasticity, etc.), but unfortunately they do not offer a *criterion of individuation*. If they do in the future, it will constitute a very useful contribution to the definition of biological individuality.

For sixty years now, immunologists have suggested that the proper criterion of immunogenicity consists in the discrimination between 'self' and 'nonself', and that this discrimination tells us what a biological individual is (Burnet and Fenner 1949, Burnet 1969, Langman and Cohn 2000). I agree that immunology offers a physiological theory of individuation, but I do not consider that this theory can be grounded in the discrimination between self and nonself. In section 4.3, I ask which immunological theory can constitute a proper basis for a physiological theory of individuation. Before that, however, I shall examine a possible objection: aren't there very few organisms in nature which possess an immune system? If this is indeed the case, then how can I claim to build on immunology a general physiological theory of biological individuation, supposed to hold for all organisms?

4.2. The domain of an immunological theory of individuation

My answer is that this is simply not true that only very few organisms (*i.e.*, higher vertebrates) have an immune system. For several decades, immunologists have believed that immunity was limited to jawed vertebrates, because of an illegitimate focus on lymphocytes, seen as the only 'true' immune actors. Nevertheless, it is now clear to all immunologists that immunity is ubiquitous (Kurtz and Armitage 2006): in all organisms in which immunologists have looked for an immune system, they have found one, and most of the time a very complex one.

What, then, is immunity? One can talk of an immune system each time one finds specific interactions between receptors and ligands which can lead to the destruction (lysis) of the target. With such a definition in mind, one finds immunity in all organisms. Let us examine two cases, the well-known insect *Drosophila*, and plants. The *Drosophila* possesses an immune surveillance system, especially thanks to its 'Toll' receptors, with which it can sense pathogens (Khush, Leulier and Lemaitre 2002). Interestingly, an equivalent of these receptors

exists in mammals, where they are called 'Toll-like receptors', and play a key role in initiating immune responses (Medzhitov 2007).

Plants have several immune mechanisms, which can be classified according to two lines of defense. The first one is the direct recognition of *pathogen-associated molecular patterns* by plant transmembrane receptors. The second one, called the 'indirect' pathway, is the recognition of specific effector molecules produced by the pathogen. It consists, like mammalian adaptive immunity, in a highly specific recognition of pathogen products. It is mostly triggered by NBS-LRR proteins, that is, proteins encoded by resistance (R) genes and containing a nucleotide-binding site (NBS) and leucine-rich repeats (LRR) (DeYoung and Innes 2006). The architecture of these proteins, some of which are encoded by the newly discovered CATERPILLER gene family, is conserved in plants and vertebrates (Ting and Davis 2005).

Here lies what is probably one of the most important immunological revolutions of the last decade. The clear-cut separation between 'adaptive' immunity (sometimes equated with 'specific immunity') and 'innate' immunity has vanished (Vivier and Malissen 2005). Adaptive immunity was attributed to jawed vertebrates only. Innate immunity was considered to be non-specific, but in fact, it proved to be very specific (DeYoung and Innes 2006). Organisms with innate immunity were also said to have no immune 'memory', *i.e.* no capacity to mount a more rapid and more efficient immune response in case of a second contact with the same antigen. Yet, here again, many organisms with 'innate' immunity have been found to have this capacity (Kurtz and Franz 2003). The consequence is that today's immunologists admit that the old clear-cut boundary between innate and adaptive immunity is blurred, or even non-existent.

According to an emerging consensus, even unicellular organisms possess an immune system that is, a system of receptors recognizing abnormal patterns. It is a genome's

immunity, which can be based on CRISPR (*clustered regularly interspaced short palindromic repeats*) (Barrangou *et al*. 2007), or on similar mechanisms, probably analogous to ARN interference, found in eukaryotes (Plasterk 2002).

Thus, we can conclude that immunity is ubiquitous both in multicellular and in unicellular organisms, and hence that it can be the basis of a general physiological theory of organismic individuation. With these very important precisions in mind, we can now go back to our main question: what criterion of immunogenicity should we adopt, and how can it be the basis of a physiological theory of individuation?

4.3. Which criterion of immunogenicity should we adopt?

The self-nonself criterion of immunogenicity, which has been very influential in immunology for sixty years, is now increasingly regarded with suspicion (Tauber 1994; Anderson and Matzinger 2000; Pradeu and Carosella 2006a; Greenspan 2007). According to this criterion, an organism does not trigger an immune response against its own constituents, whereas it triggers an immune response against every foreign entity (except, of course, in cases defined as pathological). Nonetheless, recent discoveries in two critical areas, immune autoreactivity and immune tolerance, prove that this criterion is inadequate.

First, it is now clear that lymphocytes which do not react *at all* with 'self' constituents of the body simply die. To be selected, both in primary organs (Ashton-Rickardt et al. 1994) and at the periphery (Freitas and Rocha 1999), lymphocytes must be continuously stimulated by endogenous antigenic patterns. Furthermore, this normal autoreactivity concerns not only immune interactions, but also immune *effector* mechanisms: for instance, macrophages react to dying 'self' cells of the body and eat them (they are the 'scavengers' of the body) (Taylor et al. 2005), and regulatory T cells are 'self' cells which respond to other 'self' cells by downregulating their activity (Sakaguchi 2006).

Second, recent research has shown that immune tolerance is very common. *Immune tolerance* refers to the absence of immune response to foreign entities even if immune interactions with them occur. In particular, all known multicellular organisms are hosts of many bacteria, parasites, and viruses. For instance, in a human being, commensal and symbiotic bacteria outnumber eukaryotic cells by at least one order of magnitude (Xu and Gordon 2003). Though these foreign entities are sometimes deleterious and can even kill their host, in many cases they are beneficial to the host, and play a functional role (see below). Another example is that the mother does not reject the fetus, though it is genetically different from her.

Instead ot the self-nonself criterion, I prefer the recently suggested 'continuity criterion' (Pradeu and Carosella 2006b). According to this criterion, every strong molecular discontinuity in the antigenic patterns (whether endogenous or exogenous) with which immune receptors interact induces an immune response. The receptors involved are those of macrophages, dendritic cells, lymphocytes, etc. There is a discontinuity if there is a strong modification of molecular patterns with which immune cells interact: to put it very simply, the immune system responds to strongly 'unusual' patterns. The criterion is molecular difference, as stated in the self-nonself theory, but not the *origin* of the molecular pattern (*i.e.* endogenous or exogenous?), contrary to what is stated in the self-nonself theory.

Immune habituation works both ways: when the immune system responds to an unusual antigen (whether endogenous or exogenous), the second response is usually more rapid and more efficient; but, according to the continuity criterion, when the immune system reacts but does not respond to a usual antigen (whether endogenous or exogenous), the second response is likely to be weaker. This is called induction of tolerance by induction of continuity. Therefore, the repeated presentation of an antigen in non-immunogenic conditions leads to a subsequent tolerance of this antigen (Grossman et al. 2004). Non-immunogenic conditions

are: small quantities of antigen, antigen introduced progressively, and with no proinflammatory signals. Tolerance of microorganisms, feto-maternal tolerance, chimerism, some cases of graft tolerance could all be examples of induction of tolerance by induction of continuity.

The continuity criterion accounts for immune autoreactivity, because it states that immune receptors interact with normal constituents of the body with a medium strength (which is measurable very precisely by its specificity, affinity, and avidity). Interactions are very strong when immune receptors meet unusual patterns. The continuity criterion also accounts for immune tolerance, with the concept of induction of continuity.

Thus, the criterion of immunogenicity we are looking for cannot be the self-nonself criterion, which is grounded in a wrong idea, the preservation of endogenous elements by the immune system of the organism. By contrast, the continuity criterion integrates autoreactivity and tolerance; it offers an experimentally adequate account of immune phenomena, and therefore it can be the criterion of inclusion we are looking for.

This criterion of inclusion is derived from a true physiological *theory* of individuation, because i) it is composed of several, hierarchically organized, hypotheses, ii) it applies to all organisms, and iii) it makes predictions possible. Within scholars studying immunology, the idea that it produces theories is uncontroversial (Burnet 1959, Schaffner 1993, Darden 2006); however, the question of which theory is best suited is actively discussed in the current literature (Anderson and Matzinger 2000, Pradeu and Carosella 2006b, Greenspan 2007).

The next question is: what does this physiological theory of individuation tell us about the definition of the organism?

5. The organism, a set of interconnected heterogeneous constituents, interacting with immune receptors

5.1. Definition of the organism

Let us start with the usual physiological definition of an organism: the organism is a functionally integrated whole, which undergoes continuous change, and which is made of interconnected elements, characterized by causal dependence (e.g. Sober 2000). The constituents of John may causally interact with the constituents of Tim, but not with the same intensity, timing, and scale as John's constituents interact with each other. This definition is certainly correct, but it is too general. Biochemistry can help us to make it more precise. Indeed, though functional integration can be observed at many levels in the organism, the finest level is that of proteins: the parts of an organism (organs, tissues, cells, and even constituents with cells) are indeed interconnected by strong biochemical interactions, involving mainly proteins-proteins interactions (Lesk 2004). In plants, regulation and coordination of metabolism, growth, and morphogenesis often depend on a network of chemical signals (Taiz and Zeiger 2006). In many instances, in multicellular organisms, a cell which does not receive signals from its local environment and which does not send signals to it rapidly dies. This is true of immune cells (Freitas and Rocha 1999), neurons, cells involved in developmental processes (Artavanis-Tsakonas, Matsuno and Fortini 1995), etc. The elucidation of protein-protein interactions is a very active field in contemporary biology. It will probably be in the near future the best level to understand functional integration within an organism, because, again, the strength, timing and extension of 'inner' biochemical interactions are very different from those occurring between two different organisms (Lesk 2004)

The problem is that, even at a biochemical level, functional integration is *local*. In other words, two sub-systems in an organism can be quasi-independent (Lewontin 2000: 94). At

this point, the contribution of immunology is critical: immune interactions are fundamentally *organismic* (*i.e.* they concern the whole organism), because they are *systemic*, for the lymphatic system (or its equivalent) is an extensive system, collecting extracellular fluid (lymph) from all tissues of the organism. All the tissues and cells of the organism are therefore under the influence and control of the immune system.

Thus, immune interactions are a sub-set of biochemical interactions, but: i) they are *systemic* (as opposed to local), ii) they offer a *criterion* of inclusion, because they are responsible for the acceptance or rejection of constituents in the organism. Now we reach the heart of the argument. When we link together the general biochemical point of view and the specific but systemic immunological point of view, we obtain the following definition of an organism:

> *An organism is a functionally integrated whole, made up of heterogenous constituents that are locally interconnected by strong biochemical interactions and controlled by systemic immune interactions that repeat constantly at the same medium intensity*.

It should be clear that the immune interactions are critical in this conception and that they constitute the basis of our physiological individuation of the organism. First, whereas biochemical interactions are most of the time local, immune interactions are systemic. Second, while the strength of biochemical interactions is not always easy to define (because of their diversity), immune interactions are receptor-ligand interactions, the strength of which is very clearly defined in terms of specificity, affinity and avidity. Immune cells interact in a medium, but not too strong, way with the antigenic patterns of organism's constituents: if these interactions are very weak, the target (whether endogenous or exogenous) dies; if they are very strong, it means than an immune response, leading to a possible rejection of the target, has been triggered[8]; it is only if they remain at the same intermediate intensity that we

[8] Indeed, very strong interactions in an organism usually mean a pathological state (Lewontin 2000: 94). The development of a tumor is a good example.

observe a normal homeostatic state in the organism. These interactions must also be repeated continuously (constantly), which means regularly, and not, of course, without any interruption.

My definition does not imply that everything which does not trigger an immune response from an organism belongs to this organism: for instance, two identical twins can tolerate each other's organs in case of transplantation, but it does not entail that they are one and the *same* organism. Instead, my criterion requires both presence and inclusion (absence of rejection).

I also believe that my definition sheds some light on the frequently made assertion that every organism is 'heterogenous' (Lewontin 2000).

5.2. The heterogenity of the organism

According to my definition, the constituents of an organism are *heterogeneous*. The word 'heterogeneous' is not synonymous with 'different', it etymologically means 'coming from the other', that is, in this context, coming from what is initially the 'outside' of the organism. My discussion of immune tolerance has shown the importance of this heterogeneity: an organism is made of constituents which do not need at all to have originated *in* it. In other words, an organism is made of many foreign things, it is never endogenously constructed. I can illustrate this heterogeneity by an examination of the *functional* role of indigenous symbiotic bacteria in mammals (Hooper and Gordon 2001). For example, each human being is constituted of indigenous symbiotic bacteria which clearly outnumber his or her 'own' cells, originating from the egg cell. The majority of these bacteria live in our intestine. Most of them are obligatory symbionts, meaning that they cannot survive outside the host, and the host cannot survive in their absence. They play indispensable physiological (functional) roles: in particular, gut bacteria are needed for digestion. Strikingly, these symbiotic bacteria, far from being foreign enemies that our immune system should fight, also play an indispensable

immune role in our bodies (Noverr and Huffnagle 2004). These bacteria have permanent and constitutive biochemical interactions with other parts of the host. In particular, there is no difference between, on the one hand, interactions of the host's immune receptors with these symbiotic bacteria, and, on the other hand, interactions of the host's immune receptors with its 'own' (endogenous) cells. That is the key point: these endosymbiotic bacteria are not just 'here' in the organism, they are *parts* of the organism (O'Hara and Shanahan 2006; Xu et al. 2007; Gilbert 2002). An objection could be that the gut is an interface of the organism, not a true 'internal' part of it. Nevertheless, of the ten mammalian organ systems, eight (integumentary, digestive, respiratory, excretory, reproductive, immune, endocrine, circulatory) have persistent associations with normal bacteria (the exceptions being, so far, the musculoskeletal and nervous systems) (McFall-Ngai 2002). The organism is a local concentration of interfaces (Patrick Blandin, personal communication).

Obligate indigenous bacteria are in no way limited to mammals, we find them in arthropods, plants, colonial organisms, etc. For example, *Wolbachia* bacteria, which are present in many multicellular organisms, have been proved to be indispensable for the development of a parasitic wasp, *Asobara tabida* (Dedeine et al. 2001). In many plants, too, some bacteria are indispensable for nutrition, as illustrated by the symbiosis between the host plant and the bacteria *Rhizobium* (Kiers et al. 2003).

Thus, every organism is a heterogeneous entity, made of different constituents from different origins, but unified by common interactions with immune receptors. As a consequence, a proper criterion of immunogenicity tells us first that the organism is a unified whole (its unity is grounded in biochemical and above all in immunological interactions), and second that it is heterogeneous. It offers therefore a dialectical understanding of the 'inside' of the organism (Lewontin 1994): some entities usually considered as parts of the environment are in fact constituents of the organism's identity.

5.3. Biological genidentity defined thanks to immune interactions

My definition of the organism, grounded in immunological continuity hypothesis suggested by (Pradeu and Carosella 2006b), gives a precise content to the notion of genidentity as applied to biological entities (Locke ([1975] 1690); Lewin 1922; Reichenbach 1956; Hull 1992). The genidentity thesis asserts that individuality through time is insured by the spatiotemporally continuous interactions among the constituents of a being. A classical objection is that it is impossible to speak of interactions among constituents without saying *to what* these interactions must be attributed, and hence without considering that a 'core' (substratum) underlying these interactions must exist. Nevertheless, this objection can be rejected on the basis of my definition of the organism: the immunogenicity criterion allows us to single out the biochemical interactions which are constitutive of the organism as a whole. The (constantly repeating at the same medium intensity) immune interactions single out continuous biochemical interactions, which themselves single out the organism.

My definition does not start with the constituents of an organism, and then asks what the interactions between them are. It states that every entity bearing molecular patterns which continuously trigger immune interactions of medium intensity is a constituent of the organism. What is fundamental, therefore, is the strength of the immune interactions, which tells us what the constituents of the organism are (e.g., endobacteria).

5.4. Difference with other physiological ways to individuate biological entities

The immunological-physiological individuation I suggest differs from both commonsense physiological individuation, and endogenous physiological individuation.

First, my conception is grounded in the usual physiological definition of the organism (functional integration), but it certainly does not amount to the commonsense physiological

individuation, which states that the organism is what is behind the skin (or any membrane). Let us go back, for instance, to the colonial organism *Botryllus schlosseri*. In this case, as we saw, commonsense individuation cannot say what the proper biological individual is, between the zooid and the colony. My criterion of individuality tells us that the organism in this case is not each zooid, but the colony characterized both by strong biochemical interactions and by a one and the same immune system, based on one histocompatibility system (maintained from the larva stage to the colony stage) (De Tomaso et al. 2005). Sometimes, my criterion gives the same result as the commonsense view, but it offers a scientific ground for this result: for instance, my criterion tells us that a mouse as we see it is indeed an individual organism, but, contrary to the commonsense view, it also states precisely what counts as a *part* of the mouse. Counterintuitively, gut bacteria, bacteria situated on the skin, long-tolerated parasites, etc. are parts of the mouse. Thus, again, I offer a proper theory, leading to ontological revisions or confirmations.

Second, my criterion shows that the usual conception of the organism as an endogenous entity is wrong. The idea that the organism is the set of constituents originating from the egg cell, *i.e.* a genetically homogenous entity, is often expressed (e.g. Hull 1978). Immunological individuation shows, however, that the organism is heterogeneous. Again, there is no difference between, on the one hand, interactions of the host's immune receptors with indigenous symbiotic bacteria, and, on the other hand, interactions of the host's immune receptors with its 'own' (endogenous) cells.

In the last section, I try to articulate the two theoretical criteria (the immunological-physiological one and the evolutionary one), and to show what the consequences of this articulation are.

6. Articulating the physiological and the evolutionary individuations

We now have two theories with which to individuate biological entities. According to the evolutionary criterion, there exists a hierarchy of individuals, the organism being simply one of them. By contrast, my physiological criterion shows that the organism is the best instance of a biological individual, for the three following reasons.

6.1. The boundaries of the 'heterogenous organism' are clearly defined

Part of Hull's argument is that the organism does not possess clear-cut boundaries (Hull 1992). It is true with the phenomenal definition of an organism, but not with ours. Our criterion of individuation allows us to take decisions, as in the case of *Botryllus*. I do not pretend that my criterion of individuation eliminates all contentious cases, but I do claim that the organism as I define it has more clear-cut boundaries than the other levels in the evolutionary hierarchy, in particular a gene (see Griffiths and Stotz 2006) or a group.

6.2. The 'heterogenous organism' is sometimes the proper evolutionary individual

Let us go back to clonal organisms, and especially to Janzen's aphids (Janzen 1977). His point is that, during the parthogenesis phase, the aphid organism (the observable insect) is not an evolutionary individual. Instead, the evolutionary individual is the set of all the insects originating from the same egg, because they all have the same genome, and cannot be said to compete with each other. The underlying idea, more or less inherited from Weismann, is that genetic homogeneity is the key to evolutionary individuality.

The immunological-physiological criterion, however, suggests something else. Each immunological-physiological aphid[9] contains intracellular symbionts, whose presence is required for the survival of the host. These symbionts are vertically transmitted (each aphid

[9] Following our definition, an immunological-physiological aphid is a small aphid insect, including its indigenous bacteria, fungi, etc.

transmits its symbionts to its offspring). They are different in different aphids. They can mutate during the aphid lifetime, modify its fitness, and that of its offspring (O'Neill et al. 1997). For example, Dunbar et al. (2007) show that a point mutation in *Buchnera aphidicola*, hosted by *Acyrthosiphon pisum* aphid, modifies the host response to heat stress, 'dramatically affecting host fitness in a manner dependent on thermal environment'. It means that physiological aphids born by parthenogenesis do in fact compete with each other: they contain endosymbionts which vary, whose variation is inheritable, and modifies host fitness. The aphid case shows that the argument of genetic homogeneity can lead to wrong conclusions about what the evolutionary individual is. I defend an extended replicator view, stating that genes are not the only replicators in nature (Sterelny et al. 1996). Indeed, vertically-transmitted bacteria can be excellent replicators, too.

My argument concerning aphids probably holds for most clonal organisms, especially plants, which massively host obligate symbiotic bacteria (Kiers et al. 2003) or fungi (van der Heijden et al. 1998), though the mode of transmission (vertical or horizontal) makes a difference. For instance, it is likely that my argument can be made for dandelions. If this is true, it would revise Janzen's revision of the ontology of living entities: in many clonal organisms, the evolutionary individual would not be the clone, but the immunological-physiological organism. Hence, what counts as an evolutionary individual should not be determined by resorting to the sole criterion of genetic homogeneity. A precise observation of physiological, and especially immunological, mechanisms is needed. I do not claim that the organism as I define it is *always* the proper evolutionary individual, but that it is often necessary to start with the heterogenous organism to determine what the evolutionary individual is, especially in all cases where endobacteria are vertically transmitted.

I think that this conclusion extends (Buss 1987). Buss used a physiological domain, developmental biology, to show that the conception of the organism as a genetically

homogenous entity was (approximately) correct only in a very limited number of species. He showed that many organisms are heterogenous in the sense that, contrary to Weismann's main idea, their somatic cells can mutate and subsequently give rise to germ cells. Here I use another physiological domain, immunology, to show that many organisms are heterogenous in the sense that some of their consistuents do not come from the egg cell and can be transmitted to their offspring and influence their fitness. Even organisms Buss considers as 'homogenous', e.g. arthropods, are in fact heterogenous, because they are constituted of entities of different origins, which can influence their evolution.

6.3. The 'heterogenous organism' controls the variations of lower-level constituents, especially cell lineages

The emergence of the pluricellular organism in evolution presupposed the existence of mechanisms controlling the appearance of lower-level variants, especially at the level of cell lineages (Buss 1987). The immune system plays a critical role in this control (Buss 1987; Michod 1999), which is exerted on cell lineages, but also on endobacteria (Frank 1996). Naturally, it is possible that natural selection at a higher level (e.g. group or species) presupposes that variations at the organismic level should be restricted, but this control is not as regular and as efficient as in the case of the organism controlling its lower-level constituents.

7. Conclusion

Immunology makes a physiological theory of individuality possible. A proper criterion of immunogenicity, based on the continuity theory, offers an account of what the parts of an organism throughout its life are. An organism can be defined as a functionally integrated whole, made up of heterogenous constituents that are locally interconnected by strong biochemical interactions and controlled by systemic immune interactions that repeat constantly at the same medium intensity. When articulated with the evolutionary criterion of individuation, this physiological criterion shows that the heterogenous organism is not simply one level in a rich hierarchy of biological individuals, but the best biological individual one can possibly define.

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