New Blackfriars

DOI:10.1111/nbfr.12028

The Specification of Sex/Gender in the Human Species: A Thomistic Analysis

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Abstract

To develop a philosophical framework to address the specification of sex/gender in humans, I will begin by summarizing what we know about the biology of sex determination in human beings. Basically, sex/gender is specified by several networks of genes anchored in the genetic interaction between the two genes, *Sry* and *Sox9*. Next, I will propose that this biological mechanism is best understood within a philosophical anthropology that embraces insights taken from systems biology to articulate a hylomorphism that explains the integrity, dynamism, and teleology of the human organism. The systems perspective described here represents one attempt to reformulate the received philosophical framework of classical Aristotelian-Thomistic hylomorphism so that it incorporates the insights of modern biology. Finally, I will use the systems perspective and key principles articulated by St. Thomas Aquinas in his philosophy of nature to identify criteria that could be used to specify the sex/gender of a particular human being: The most certain criterion for maleness would be the capacity to produce sperm while the most certain criterion for femaleness would be the complementary capacity to produce eggs. Deviations from this criterion would decrease the certitude of our judgment regarding the sex/gender of the individual.

Keywords

sex/gender specification, systems perspective, hylomorphism, sex determination, gender identity disorder

Introduction

Mokgadi Caster Semenya is a South African middle-distance runner and world champion who won gold in the women's 800 meters at the 2009 world championships in Berlin. However, following her victory, an international controversy erupted when questions were raised about her sex/gender. Several of Semenya's competitors believed that she had too many male characteristics to compete as a woman, and track and field's governing body ordered sex testing. The results of those tests have not been released.

How do we specify sex/gender in the human species? For most of human history, the sex/gender of an individual was determined by the anatomy of his or her external genitalia. A boy has a penis and a scrotum, while a girl has a clitoris and labia. Since the discoveries, both of the human sex chromosomes in 1923 and of the sex determining gene, *Sry*, in 1991, however, the modern scientific consensus has linked an individual's sex/gender to his or her chromosomes: A male has a Y chromosome with the *Sry* gene that triggers the development of his testicles, while a female has neither, triggering the development of her ovaries. These gonads then direct sexual differentiation and maturation via the activity of the sex-specific hormones that they produce. However, a recent medical report describing an individual who developed as a normal woman, and was capable of conceiving and giving birth to a daughter, despite having a Y chromosome and a normal *Sry* gene has now complicated this consensus.[1] How are we to specify this person's sex/gender?

To answer this question specifically and to develop a philosophical framework to address the specification of sex/gender in humans more generally, I will begin by summarizing what we know about the biology of sex determination in human beings. Basically, sex/gender is specified, not by one gene, but by several networks of genes anchored in the genetic interaction between the two genes, *Sry* and *Sox9*. Next, I will propose that this biological mechanism is best understood within a philosophical anthropology that embraces insights taken from systems biology to articulate a hylomorphism that explains the integrity, dynamism, and teleology of the human organism. The systems perspective described here represents one attempt to reformulate the received philosophical framework of classical Aristotelian-Thomistic hylomorphism so that it incorporates the insights of modern biology. Finally, I will use the systems perspective and key principles articulated by St. Thomas Aquinas in his philosophy of nature to identify criteria that could be used to specify the sex/gender of a particular human being.

The Biology of Sex Determination in the Human Species

Contemporary research in the biology of human sex determination can be traced to the seminal discovery, in 1959, that the presence

[1] M. Dumic, K. Lin-Su, N.I. Leibel, et al., "Report of Fertility in a Woman with a Predominantly 46, XY Karyotype in a Family with Multiple Disorders of Sexual Development," *J Clin Endocrinol Metab* 93 (2008): 182–189; and M. Dumic, M. I. New, K. Lin-Su, K. McElreavey, N. I. Leibel, S. Ciglar, S. Nimkarn, et al. "Report of Fertility in a Woman with a Predominantly 46,XY Karyotype in a Family with Multiple Disorders of Sexual Development." *Adv Exp Med Biol* 707 (2011): 169–170.

https://doi.org/10.1111/nbfr.12028 Published online by Cambridge University Press

of the Y chromosome is the main factor that specifies maleness in our species.[2] In the years that followed, it became increasingly clear that the development of testes is associated with the presence of a single gene on the Y chromosome, which was called *TDF* for testis determining factor. This gene was eventually identified and cloned in 1990 and called *Sry* for sex determining region of the Y chromosome.[3] In a groundbreaking experiment, a British research team then showed that introducing *Sry* into a mouse with two X chromosomes was sufficient to induce the development of testes in that animal.[4] Furthermore, loss of function mutations in this gene give rise to XY females with dysfunctional gonads, and translocations of this gene to the X chromosome causes XX male syndrome.[5] *In toto*, this data suggests that *Sry* is an important and critical determinant in the specification of sex/gender in our species.

How does *Sry* work? It appears that the early gonads in the developing fetus are bipotential.[6] In other words, they are poised to become either testes or ovaries, where the presence of the *Sry* gene tips the molecular balance in favor of the male pathway. *Sry* does this by elevating the expression of a single target gene called *Sox9* above a certain threshold level. The activity of *Sox9* is sufficient to regulate several hundred downstream target genes that are important for the development and differentiation of the Sertoli cells in the testes. These cells then secrete the male sex hormones that drive the sexual differentiation and maturation of other tissues in the developing organism. For instance, if testosterone is present, the external genitalia of the fetus differentiate into a penis and a scrotum. If *Sry* is absent or fails to act in time, *Sox9* is silenced, and the development of the

[2] C.E. Ford, et al., "A Sex-Chromosome Anomaly in a Case of Gonadal Dysgenesis (Turner's Syndrome)," *Lancet* 1 (1959): 711–713.

[3] A.H. Sinclair, et al., "A Gene from the Human Sex-Determining Region Encodes a Protein with Homology to a Conserved DNA-binding Motif," *Nature* 346 (1990): 240–244; J. Gubbay et al., "A Gene Mapping to the Sex-Determining Region of the Mouse Y Chromosome is a Member of a Novel Family of Embryonically Expressed Genes," *Nature* 346 (1990): 245–250.

[4] P. Koopman et al., "Male Development of Chromosomally Female Mice Transgenic for Sry," *Nature* 351 (1991): 117–121.

[5] P. Berta et al., "Genetic Evidence Equating *SRY* and the Male Sex-Determining Gene," *Nature* 348 (1990): 448–450; J. Jager et al., "A Human XY Female with a Frame Shift Mutation in the Candidate Testis-Determining Gene Sry." *Nature* 348 (1990): 452–454; B. Van der Auwera et al., "Molecular Cytogenetic Analysis of XX Males Using Y-Specific DNA Sequences, Including Sry." *Hum Genet* 89 (1992): 23–28.

[6] The summary of sex determination that follows is based upon the following reviews: A. Quinn and Peter Koopman, "The molecular genetics of sex determination and sex reversal in mammals," *Semin Reprod Med*. 30 (2012): 351–363; Ryohei Sekido and Robin Lovell-Badge, "Sex Determination and SRY: Down to a Wink and a Nudge?" *Trends Genet* 25 (2008): 19–29; and Dagmar Wilhelm, Stephen Palmer, and Peter Koopman, "Sex Determination and Gonadal Development in Mammals," *Physiol Rev* 87 (2007): 1–28. Relevant citations to the scientific literature can be found in these reviews.

https://doi.org/10.1111/nbfr.12028 Published online by Cambridge University Press

ovaries takes place. The absence of the male specific hormones then leads to the differentiation of the clitoris and labia.

Clearly, the activity of both *Sry* and *Sox9* are essential for development of the testes, and therefore, for male sex determination. However, both these genes work within a particular genetic context. Thus, several genes including *Lhx9*, *Sf1, Wt1, Gata4*, and *Fog2*, are all required for the development of the early gonads. Animals lacking any one of these genes fail to develop either testes or ovaries. Furthermore, other genes are required for the development of the Sertoli cells. Finally, other genes like the *AR* gene that encodes the androgen receptor are required for target tissues to respond to circulating sex hormones. XY human individuals bearing a mutation in the *AR* gene are born with female-appearing external genitalia.

In the end, all the data suggests that the specification of sex/gender in mammals is a story not of the dominating influence of one gene but of opposing and collaborating genetic forces within networks of genes that function at different levels of tissue organization within the organism. One genetic network specifies the presence or absence of sex-specific gonads, which then regulates another genetic network that specifies the presence or absence of sex-specific hormones, which then regulates another genetic network that are responsible for the maturation of the sex-specific tissues throughout the organism. Together, these genes and the molecules they encode determine maleness and femaleness in our species.

A Systems View of Life

How are we to integrate this multi-level molecular process into a unified and coherent picture that would allow us to articulate criteria for the specification of sex/gender in the human species? I propose that this is best done within a philosophical anthropology that uses insights taken from systems biology to articulate an Aristotelian-Thomistic hylomorphism that explains the integrity, dynamism, and teleology of the human organism.

A product of the post-genomic explosion in biological information, systems biology is an emerging field of research that seeks to understand the living whole as a dynamic network of integrated parts.[7] Its

[7] For concise overviews of systems biology, see both L. Hartwell, J.J. Hopfield, S. Leibler, and A.W. Murray, "From Molecular to Modular Cell Biology," *Nature* 402 (1999): C47–52; and H. Kitam, "Systems Biology: A Brief Overview," *Science* 295 (2002): 1662–1664. For examples of how the systems perspective is changing the way biologists understand biological processes, see A. Kicheva, M. Cohen, and J. Briscoe, "Developmental Pattern Formation: Insights from Physics and Biology," *Science* 338 (2012): 210–2012; and C. Furusawa and K. Kaneko, "A Dynamical-Systems View of Stem Cell Biology," *Science* 338 (2012): 215–217. A good introduction to systems theory written for the non-scientist can be found in Stuart Kauffman, *At Home in the Universe* (New York: Oxford University Press, 1995); and in Albert-Laszlo Barabesi, *Linked: How Everything is*

https://doi.org/10.1111/nbfr.12028 Published online by Cambridge University Press

goal is to uncover the fundamental design principles of living systems by looking at what system theorists call a system's structure and its dynamics. An analysis of a system's structure identifies all the parts of the system and describes their interactions. In biology, this would involve cataloging all the molecules that go into assembling a living organism and then determining which ones interact with each other. An analysis of a system's dynamics focuses on the behavior of these interacting molecules over time. In biology, this would involve questions regarding growth, development, and maintenance of the living organism. As we will discuss below, the structure and the dynamics of a living system are inseparably inter-dependent. A living system consists of biological molecules in motion. Thus, the most important question for the systems biologist is how both the structure and dynamics of a living system together give rise to the physical properties and visible behavior of the organism.

The two insights of systems biology that are of particular interest to us here as we develop a systems-based philosophical account of the human organism and his sexual development are its emphases on the holism of the living organism and the determinism of animal development.

First, the emphasis on holism: Consider the human body. The most common view is to see the human being as a collection of organs working together under the sway of the central nervous system. Another approach is to see the body as an organized collection of different kinds of cells – nerve cells, heart cells, or skin cells, just to name a few of the approximately 210 cell types in the human body – all working together in the organic whole. However, the more radical perspective offered by systems biology is to see the human organism as a dynamic, complex, and seamlessly integrated network not of organs nor of cells but of *molecules,* including DNA, RNA, lipids, and proteins, connected by reaction pathways which generate shape, mass, energy, and information transfer over the course of a human lifetime. In contrast to the prevailing reductionist and mechanistic view, the organism is seen here as a single, unified whole, a complex and dynamic network of interacting molecules that appear and then disappear in time. It is an embodied process that has both spatial and temporal manifestations.

To illustrate the holistic perspective, we turn to a symphonic orchestra. One way to view a classical orchestra would be to say that it is made up of four groups of musicians playing a type of instrument, woodwind, brass, percussion or string. Another is to say that

Connected to Everything Else and What It Means (New York: Plume, 2003). This discussion of systems biology is based, in the most part, on my essays, 'On Static Eggs and Dynamic Embryos: A Systems Perspective', *National Catholic Bioethics Quarterly* 2 (2002), pp. 659–83; and 'Immediate Hominization from the Systems Perspective', *National Catholic Bioethics Quarterly* 24 (2004), pp. 719–38.

https://doi.org/10.1111/nbfr.12028 Published online by Cambridge University Press

it is made up of approximately ninety musicians. The systems view would be to see it as a single dynamic network of interacting parts where the whole is greater than the sum of the parts. Since each musician has an instrument and a score, the orchestra at a minimum has 300 parts all organized and seamlessly integrated into a single unity that produces music. In fact, from the systems perspective, an orchestra is not truly an orchestra until its parts begin to interact with one another, i.e., when it is performing a symphony. Therefore, to see the living organism as a dynamic system is to see it as a symphonic whole where DNA, RNA, lipid, and protein molecules, like musicians and their instruments, appear and then disappear on stage in the choreographed performance called life.

As noted above, systems biology, in addition to emphasizing the holism of the organism, also underscores the deterministic nature of animal development. In this, there is a crucial difference between an orchestra and an organism. One orchestra can play many symphonies because the musical score determines how and when the different parts will interact. In other words, the same structure can give rise to different dynamics – the same parts of one orchestra can interact in different ways to produce either Beethoven's Ninth Symphony or Mozart's Symphony No. 40. Thus, one cannot predict the future performance of an orchestra from simply studying its parts. It is an indeterminate system. An organism, on the other hand, is a deterministic system that follows a particular developmental trajectory, all things being equal. In other words, there is a causal relationship between the past, present and future states of a living system because the molecular composition of the organism constrains the possible sequence of ordered transformations through which the system can advance. A puppy cannot grow into an ostrich.

To illustrate the deterministic nature of development, our orchestra analogy will not suffice. Instead, take a hypothetical living network, say the simple organism of ten molecules at time, $t = 0$. When these ten molecules are in close proximity, they interact. Some of these interactions result in transformative reactions that generate new molecules, and the living system becomes the network of eight molecules at time, $t = T_1$. This system is deterministic because the system can only change in this one way – the identity of the molecules in the initial state of the organism at time, $t = 0$, determines the kind of change possible. Molecule A and molecule B because they are what they are, interact and produce molecule D. Molecule D is then able to interact in a subsequent reaction with molecule C to produce more of A and E driving the organism to change into the network of nine molecules diagrammed at $t = T_{2.}$ Thus, as this example illustrates, an organism changes and progresses through a sequence of ordered molecular changes precisely because each subsequent step in a reaction pathway is driven by the products

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of the previous step. Furthermore, it demonstrates that there is an intimate link between the structure and the dynamics in living systems. To change the composition of a living system, by changing either the kinds of or the relative abundance of the molecules in the system, is to necessarily change the dynamics and behavior of that same system. A corollary to this is that the only way to change the behavior of a living system is to change its molecular composition. Consequently, from the systems perspective, every developmental change, including the teething of an infant or the sexual maturation of a teenager, can be traced to transformations in the molecular composition of that particular human individual. In the end, animal development is like a falling chain of molecular dominoes that manifests itself as outward physical changes in the organism. Once the process begins, it is a self-driven, self-perpetuating chain reaction of molecular transformations that continues throughout the lifespan of the animal.

Finally, the determinism of the biological process that drives development does not rule out the very real effects of the environment on the living organism. From the systems perspective, at any given point in time, the development of an organism is determined because at that point in time its molecular network can only change in one way. However, not all the molecules in the network are derived from the genome. In fact, most of are derived from the environment. Approximately 66% of the human body, for instance, is made up of water molecules that have to be replenished every day. Thus, it should be no surprise to anyone that an individual raised in the calorically-restricted environment of Somalia would look different from the individual's identical twin raised in the calorically-affluent United States. Nurture influences nature.[8] Nevertheless, the genetic constitution of the organism still does constrain its developmental possibilities in a fixed and species-specific manner. Regardless of their childhood homes, the physical resemblance between the African and his American twin would still be striking.

To summarize, the challenge of the systems perspective is to move beyond the hierarchical and static model of the living organism. Rather, the living system is seen as a unified whole, an embodied process of interacting molecules which has both a past and a determined future.

Systems Hylomorphism: The Soul from the Systems Perspective

With an overview of the systems perspective in mind, we can now begin constructing a systems-based description of the human organism. The primary challenge for this task will be to explain the stable

[8] For a popular and insightful discussion of the interrelationship between nature and nurture, see Matt Ridley, *Nature Via Nurture: Genes, Experience, and What Makes Us Human* (San Francisco: Harper Collins, 2003).

https://doi.org/10.1111/nbfr.12028 Published online by Cambridge University Press

dynamism of a being that is able to maintain its integrity and its identity over a period that can last up to a century. This is a real stability despite the numerous kinetic and metabolic studies using a variety of experimental techniques that have shown that 98% of the atoms of the adult human body, including those found in the brain and nervous system, are replaced in about two years.[9] How are we to reconcile both these observations? To put it another way, the human organism is a being that has an origin, undergoes biological development, and then dies. It is always changing but still remains the same. How is this so? An adequate philosophical anthropology would have to explain this stable dynamism.

As a growing number of contemporary philosophers have acknowledged, a coherent and compelling philosophical solution to the challenge of describing the human being already exists in the hylomorphic theory of Aristotle and St. Thomas Aquinas.[10] Hylomorphism is already able to adequately explain the stability and the change found in living things. There is no need to re-invent the wheel. The theory simply needs to be updated in light of recent scientific advances. Thus, in constructing a scientifically informed description of the human being, the approach I will use here will be to weave together the basic principles of Aristotelian-Thomistic hylomorphism and the insights of the systems perspective.[11]

Before turning to a systems-based hylomorphic analysis of the human being, I begin with a basic review of hylomorphism.[12] First proposed by Aristotle and developed by his disciples especially St. Thomas Aquinas, hylomorphic theory sought to explain the nature of things and the nature of their changes. In brief, for the Aristotelian tradition, all things – especially all living things – are substances composed of both a formal and a material principle. The formal principle, also called the substantial form or, in living things, the soul, constitutes every being as a specific kind of thing with specific causal powers. In the biological realm, it gives the creature its stability, its unity, and its identity. It structures the organism, determines

[9] For calculations in support of this claim, see my essay, "The Pre-implantation Embryo Revisited: Two-celled Individual or Two Individual Cells?" *Linacre Quarterly* 70 (2003): 121–126.

[10] For example, see David S. Oderberg, *Real Essentialism* (New York: Routledge, 2009); and Christopher M. Brown, *Aquinas and the Ship of Theseus: Solving Puzzles About Material Objects* (New York: Continuum, 2005).

[11] This approach is particularly attractive to the Catholic tradition, which committed itself to Aristotelian-Thomistic language in 1312 when the Council of Vienne defined *de fide* that the human soul is the form of the body (Denzinger-Schonmetzer no. 902; cf. *Catechism of the Catholic Church*, no. 365.)

[12] For a good summary of classical hylomorphic theory, see William A. Wallace, OP, *The Elements of Philosophy* (New York: Alba House, 1977), pp. 41–84; and Jeffrey E. Brower, "Matter, Form, and Individuation," in *The Oxford Handbook of Aquinas*, ed. Brian Davies and Eleonore Stump (Oxford: Oxford University Press, 2012), pp. 85–103.

https://doi.org/10.1111/nbfr.12028 Published online by Cambridge University Press

its nature, and specifies its end. The matter, on the other hand, is the corresponding principle of potency that the form determines or actualizes. According to the hylomorphic theory, both matter and form are inseparable.[13] Together both constitute a stable substance.

Stable substances, however, often change. For the Aristotelians, change involved the replacement of a form. This process happens in two ways corresponding to the two types of change evident in the world. First, there is substantial change, which radically alters the identity of the thing. Substantial changes involve the replacement of one substantial form with another in matter that is properly disposed to receive the new form. The classic example of this type of change involves the death of an organism where say, the form of a living dog, is replaced by the individual forms of the elements in the dog's carcass. Next, there is accidental change, which only modifies a thing without changing its nature. This kind of change involves the replacement of one accidental form with another, again, in matter that is properly disposed to receive the new form. An example of this type of change involves the growth in size of an organism. Thus, according to hylomorphism, all change observable in nature can be accounted for by invoking the replacement of forms in properly disposed matter. Note that during accidental changes, the substantial form or soul remains, ensuring the integrity and identity of the organism. This explains well the stable dynamism of the human being. A man is stable because of his substantial form, yet he is dynamic because he is capable of changing his accidental forms.

We now turn to the systems perspective. How are we to talk about a human "soul," human "nature," or the "disposition of matter" in a scientifically informed manner? In other words, how are we to translate classical hylomorphism into a modern idiom? To begin, we should note that the systems perspective, like the hylomorphic perspective, is a substantial perspective.[14] The organism is seen here as a single, unified network of interacting molecules which is organized in a species-specific manner. Here, the whole is greater than the sum of the parts. A typical 70-kg man is made up primarily of oxygen (43-kg), carbon (16-kg), hydrogen (7-kg), nitrogen (1.8-kg), and

[13] The human form or soul is an exception to this rule since it can exist apart from the material principle. However, as so existing, the soul is not a complete person. For discussion, see Anton Pegis, St. Thomas and the Problem of the Soul in the Thirteenth Century (Toronto: Pontifical Institute of Mediaeval Studies, 1934).

[14] As noted earlier, the systems perspective presented here presupposes the metaphysical framework put forward by classical hylomorphic theory. Given the dynamic nature of the human body which is continually undergoing molecular change, anyone who rejects the distinction between living substances and non-living aggregates would have to conclude that he or she can only exist and be identified as a distinct and unique human individual for a maximum of two years. This, I believe, is obviously ludicrous. For a modern defense of the substantiality of the human person, see J.P. Moreland and John Mitchell, "Is the Human Person a Substance or a Property-thing?" Ethics & Medicine 11 (1995): 50–55.

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calcium (1-kg).[15] However, what makes this reference man radically different from a 68.8-kg random pile of these five elements is that in his case, the elements are organized and interact in a particular way, a species-specific way. Indeed, a snapshot of the human body at any point in time would reveal an intricate net of molecular interactions distributed in three-dimensional space. From the systems perspective, this particular pattern, this organization of the molecules of the human being, would be a manifestation of his soul, his immaterial soul.[16]

To see how the network of molecular interactions can be said to reflect and manifest the soul, note the parallels between three functions associated with this network and the three functions traditionally associated with the formal principle of an organism. First, the soul makes an organism what it is and determines its end. From a physiological perspective, the net of molecular interactions makes the man what he is and distinguishes him from a lion or a lima bean plant or some other living thing. Furthermore, since life is a predominantly deterministic process of molecular transformations, these molecular interactions also define his developmental trajectory and determine his biological end. Second, the soul unifies and integrates an organism maintaining its identity through changes. As noted above, the human body is in a constant state of molecular flux. Every two years, nearly all of its atoms are replaced. However, the pattern of the molecular interactions remains the same, providing a ground for the substantial unity and identity of an individual with a lifespan of eighty or more years.

Finally, to the ancients, the soul is the source for the powers and capacities of the organism. It is the principle of the being's nature. Analogously, the net of molecular interactions can also be said to ground the human being's physiological capacities. To illustrate this, everyone knows that a man is able to see because he has eyes. However, from the systems perspective a man only has eyes because there are molecules in his body that interact to form these eyes. Thus, in the terminology of systems theory, vision is a capacity that emerges from the network of molecular interactions that define the man as a human being.[17] In the same way, one can say that an individual's

[15] Body composition data was obtained from Report of the Task Group on Reference Man, International Commission on Radiological Protection (New York: Oxford University Press, 1975).

[16] Again, systems hylomorphism presupposes the classical conviction that the human soul is immaterial and subsistent. For a clear summary of the arguments for this view, see Brian J. Shanley, O.P., *The Thomist Tradition* (Dordrecht: Kluwer Academic Publishers, 2002), pp. 153–166. Also see the paper by Gyula Klima, "Aquinas on the Materiality of the Human Soul and the Immateriality of the Human Intellect," *Philosophical Investigations* 32 (2009): 163–182.

[17] For a popular discussion of emergence and the emergent properties of different systems, see Steven Johnson, *Emergence: The Connected Lives of Ants, Brains, Cities, and Software* (New York: Scribner, 2001). For philosophical analysis, see Timothy O'Conner, "Emergent Properties," *Amer. Phil. Quart.* 31 (1994): 91–105.

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sexual abilities also emerge from this network of molecular interactions that interact to form the sexual organs. Ultimately, both capacities – the capacity to see and the capacity to procreate – are rooted in the soul. With all this in mind, it should be easy to see how the systems perspective can envision a human being as a substance consisting of informed matter, here seen as a single dynamic system of molecules organized in a species-specific configuration.

However, how then do we account for change? If all change simply involves the rearrangement of atoms, does this mean that change can only be of the accidental variety? Not quite. To see how the system perspective understands hylomorphic substantial and accidentally change, we have to first discuss several aspects of the structure of living systems.

As a dynamic system, the living organism is a robust system. In other words, it is able to maintain its function in spite of the loss or breakdown of one or even many of its individual components. For example, it is not uncommon to find persons who live normal lives with several mutated genes. Systems theorists have discovered that this robustness, this high tolerance for error, arises from the particular topology or structure of natural systems.[18] These systems are organized in such a way that the molecules are related to each other in a hub-spoke network analogous to the route network of any airline. A few molecules are highly connected to other molecules – they are the hubs of the living network like the major airports in Chicago or Atlanta are the hubs for several U.S. airline route systems – while the rest of the molecules are only peripherally connected to a few other molecules – these are equivalent to the smaller airports often found in less populated states.

In this type of hub-spoke system,[19] two types of change are possible. First, there are changes that involve the addition or the removal of molecules that lead to alterations in the behavior of the network without changing its overall shape or trajectory. These involve the loss or addition of peripheral molecules in the network, and would be equivalent to shutting down a small and relatively isolated airport in Fargo, ND, or opening a new one in Statesboro, GA, two small

[18] For two studies on the robustness of biological systems, see A. Wagner, "Robustness against mutations in genetic networks of yeast," *Nature Genetics* 24 (2000): 355–361; Z. Gu et al., "Role of duplicate genes in genetic robustness against null mutations," Nature 421 (2003): 63–66; and H. El-Samad et al., "Surviving heat shock: Control strategies for robustness and performance," *Proc. Natl. Acad. Sci. USA* 102 (2005): 2736–2741.

[19] In the jargon of systems theory, the hub-spoke system is called a scale-free network. For a review, see Z. N. Oltvai and A. Barabasi, "Systems Biology: Life's Complexity Pyramid," *Science* 298 (2002): 763–4. For studies involving scale-free networks in living systems, see H. Jeong et al., "Centrality and Lethality of Protein Networks," *Nature* 411 (2001): 41–42; E. Ravasz et al., "Hierarchical organization of modularity in metabolic networks," *Science* 297 (2002): 1551–5; and J. J. Han et al., "Evidence for dynamically organized modularity in the yeast protein-protein interaction network," *Nature* 430 (2004): 88–93.

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communities in the United States. These changes do not affect the overall network of air traffic in the country. Indeed, even the loss or addition of several small nodes would not change the overall pattern of the system. Similarly, in a living system, one could lose or add different kinds of peripheral molecules to the network without changing its fundamental structure. In common parlance, one could lose or gain weight. Despite these molecular changes, however, the basic framework of the organism and its developmental trajectory remain intact. This type of molecular change would be the systems analog to Aristotelian-Thomistic accidental change.

In contrast, there are changes that involve the addition or removal of molecules that lead to system collapse. This would involve the loss or addition of well connected molecules and would be equivalent either to shutting down an airport like Washington's Dulles Airport or the sudden opening of a new hub in Boston's Logan Airport. Both would lead to chaotic conditions that could even lead to the collapse of the entire national air traffic system. Similarly, in a living system, the loss of a hub molecule either by genetic mutation or inactivation by a poison like cyanide would lead to a loss of the integrity of the network. Losing these molecules would be equivalent to generating gaps in a row of toppling dominoes. The chain reaction would stop, the network collapses, and the organism dies. This type of molecular change that changes the very nature of the being would be the systems analog to Aristotelian-Thomistic substantial change.

To summarize, the systems perspective described here represents one attempt to reformulate the received philosophical framework of classical hylomorphism so that it incorporates the insights of modern biology. Here, the human organism is a substantial being, a dynamic network of molecules now existing not as independent molecules *per se* but as different parts of one human organism. This species-specific network, which is distributed in three dimensional space and which is able to interact over time in the deterministic process which we call human development, is a manifestation of the human being's formal principle, his immaterial soul, as it informs his matter. It is the soul that makes a man a human being by organizing his matter, by determining his identity, and by specifying his biological end. Further, all change observable during development, both substantial and accidental, can be accounted for by invoking the replacement of forms manifested as changes in the molecular interactions within dynamic systems.

Sex/Gender Determination in the Human Species: A Systems Perspective

With the systems perspective in hand, we can now integrate the multi-level molecular processes involved in the specification of sex/gender

https://doi.org/10.1111/nbfr.12028 Published online by Cambridge University Press

into a unified and coherent picture. From this perspective, the sexual development of an organism cannot be readily divorced from its overall developmental trajectory. Early in embryonic development – the very first six weeks in the human species – the trajectory of the living system of molecules is the same for both male and female members of the species. Part of the overall network is regulated and shaped by those genes and molecules important for the development of the bi-potential gonad. However, at the sixth week of human embryological development, the presence and activity of both the *Sry* and *Sox9* genes and the master regulators they encode would modify the overall network of molecules in such a way that the organism now moves along the male-specific developmental trajectory. These male-specific molecules would do this by triggering the appearance of other downstream target molecules like *Fgf9* and *Ptgds*, which in themselves are important for the transformation of sub-network we call the bipotential gonad into testes. In this view, sexual development, like the overall process of animal development I described earlier, can be compared to a falling chain of molecular dominoes, which manifests itself as outward physical changes in the organism, in this case, the appearance of the tissues associated with the sexual identity of the organism. Thus, from the systems perspective, the specification of sex/gender and the maturation of the sexual organism is the result not of the activity of a single gene but of the interactions among numerous genes and the molecules that they encode. Together these molecules determine the shape and overall trajectory of human sexual development.

From the system perspective, it is not helpful to link the specification of sex/gender to any one gene or set of genes. In other words, from the systems perspective, it is not important if an individual has the *Sry* gene on the Y chromosome. This is not enough to specify maleness in the human being. Rather, sex/gender is a manifestation of the behavior of the entire network of molecules that drives and shapes the overall development of the organism. Therefore, to articulate adequate criteria for the specification of sex/gender in the human species, we will need to ground our analysis in a holistic view of the human being.

In his philosophy of nature, St. Thomas Aquinas provides helpful philosophical principles to guide us as we undertake this analysis. Most importantly, he taught that acts follow from nature. In other words, he pointed out that we know what a being is from looking at what it does. Thus, to determine the identity and structure of the living system, we need to see what it does. A male-specific developmental trajectory would manifest itself with the appearance of the capacity to perform male-specific acts. Biologically, this would be the capacity to make the male-specific gametes or sperm. On the other hand, a female-specific developmental trajectory would manifest

https://doi.org/10.1111/nbfr.12028 Published online by Cambridge University Press

itself with the appearance of the capacity to perform female-specific acts, in this case, the capacity to make female-specific gametes or eggs. Therefore, the most certain criterion for maleness would be the capacity to produce sperm while the most certain criterion for femaleness would be the complementary capacity to produce eggs. Deviations from this criterion would decrease the certitude of our judgment regarding the sex/gender of the individual. Human beings with testes that are unable to produce sperm are male but this affirmation would be less certain than our judgment that a human being with testes that able to produce functional sperm is a man. In the same way, a judgment that human beings with ovaries unable to produce fully functional eggs are female would not be as certain as our judgment that a human being with functional ovaries is a woman. If acts reveal nature then imperfect acts reveal nature only imperfectly.

Note that this analysis provides for scenarios of ambiguity and indeterminacy with regards to the specification of sex/gender. Biologically, these are individuals without gonads or with gonads that produce neither sperm nor eggs. These are individuals with disorders of sexual development, individuals who in the past were characterized as intersex. We simply have to conclude that we cannot make an accurate judgment regarding these individuals' sex/gender. I also need to emphasize that the presence of these intersex individuals with an incidence of approximately 1 per 4000 births does not undermine our analysis of species-typical sex/gender in the same way that the presence of Down's syndrome individuals with 47 chromosomes with an incidence of approximately 1 per 750 births does not undermine the biological claim that human beings have a species-typical karyotype of 46 chromosomes.

At the outset of this paper, I highlighted a recent scientific paper that described an individual who developed as a normal woman, and was capable of conceiving and giving birth to a daughter, despite having a Y chromosome and a normal *Sry* gene. What is this person's sex/gender? Genetic criteria would have us conclude counter-intuitively that this individual is a man. Using the system's perspective, however, we can say that she is a woman, because she is able to conceive and carry a child to term.

Post-Script: What about Individuals with Gender Identity Disorder?

Finally, I need to say something about individuals with gender identity disorder or gender dysphoria. These are persons whose gender identity, their sense of self as being male or female, diverges from their biological sex. There is currently little direct evidence for a biological explanation for this phenomenon. In fact, there are reports that

https://doi.org/10.1111/nbfr.12028 Published online by Cambridge University Press

suggest that core gender identity is consistent with assigned sex in most cases across a wide range of hormonal abnormalities, seemingly regardless of whether sex assignment is as a male or as a female. For instance, a follow up of 18 XY individuals, born with penises so small as to be given the diagnosis, micropenis, found at all were satisfied with their sex of rearing, including the 13 reared as males and the 5 reared as females.[20] Similarly, among 39 XY individuals with other causes of intersex appearance at birth, including 14 with partial androgen insensitivity syndrome, 77% were satisfied with the sex of rearing assigned to them by their parents or physicians.[21] The 23% who were dissatisfied were split approximately equally by gender of rearing. These are only two studies, but they are representative of a series of studies that reveal that it is not clear how biology influences the core gender identity of a human being.[22] Finally, there is data that suggests that sex reassignment surgery does not address the psychiatric burdens associated with gender identity disorder and transsexualism.[23] In the end, our systems criterion can still be used to assign a person's sex/gender even if the individual disagrees with that assignation.[24]

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[20] A.B. Wisniewski et al., "Congenital Micropenis: Long-term Medical, Surgical, and Psychosexual Follow-up of Individuals Raised Male or Female," *Horm Res* 56 (2001): 3–11.

[21] C.J. Migeon et al., "Ambiguous Genitalia With Perineoscrotal Hypospadias in 46,XY Individuals: Long-term Medical, Surgical, and Psychosexual Outcome," *Pediatrics* 110 (2002): e31.

[22] D.C. Rettew, "Apples to committee consensus: the challenge of gender identity classification," *J Homosex* 59 (2012): 450–459.

[23] C. Dhejne et al., "Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden," *PLoS ONE* 6 (2011): e16885. The study concluded the following: "This study found substantially higher rates of overall mortality, death from cardiovascular disease and suicide, suicide attempts, and psychiatric hospitalisations in sex-reassigned transsexual individuals compared to a healthy control population. This highlights that post surgical transsexuals are a risk group that need long-term psychiatric and somatic follow-up. Even though surgery and hormonal therapy alleviates gender dysphoria, it is apparently not sufficient to remedy the high rates of morbidity and mortality found among transsexual persons."

[24] This paper was first read at the Aquinas Seminar hosted by the Aquinas Institute of Blackfriars Hall, Oxford, on March 4, 2010. I thank William Carroll and the Dominican friars at Blackfriars for their kind invitation to visit the United Kingdom, and to the participants at the seminar for stimulating discussion.