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The Analogies between Human Development and Additive Manufacture: Expanding the Definition of Design

L. E. J. Thomas-Seale[1*], J. C. Kirkman-Brown[2], S. Kanagalingam[1], M. M. Attallah[3], D. M. Espino[1] and D. E. T. Shepherd[1]

[1]*Department of Mechanical Engineering, School of Engineering, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK*

[2]*Centre for Human Reproductive Science, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK*

[3]*School of Metallurgy and Materials, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK*

* *Corresponding Author*

Email: Email: l.e.j.thomas-seale@bham.ac.uk

Phone: (+44) 0121 4143622

Abstract

Design techniques represent a huge economic barrier to the progression of Additive Manufacture (AM) to more industrial applications. The aim of this research is to use biological analogies, taken from human development to offer a new perspective on what the definition of additive design and manufacturing could encompass in the future.

Efficient design for additive manufacture requires increased creativity, something that is currently constrained by the psychological inertia imposed by a history of subtractive manufacturing. The development of the human, i.e. the differentiation and proliferation of cells to form tissues and organs, creates an organism that develops and functions in synergy. This may be considered the epitome of sophisticated AM. In this study a novel methodology, utilising the Theory of Inventive Problem Solving, was applied to develop bottom-up analogies between the two systems. A detailed biological discussion of human development is presented, offering a vision of how AM could begin to reflect the synergy displayed during the growth of the foetal form. The results propose a series of developments to current design methods and manufacturing systems for AM. *In-situ* design for AM is projected as an innovative methodology of expanding design freedom to incorporate temporal stimuli and material response through space and scale across the build envelope. Manufacturing technologies under the themes of Hybrid, Suspended, Perfusion and Diffusion Manufacture are proposed from insight taken from the development of the foetal bones, amniotic fluid, cardiovascular system and the function of the placenta and fast block polyspermy.

About the Author

Dr Lauren Elizabeth Jane Thomas-Seale is a Lecturer in the School of Engineering, University of Birmingham. Lauren has interdisciplinary research interests including Design for Additive Manufacture, Human Development and Cardiovascular Imaging, Modelling and Biomaterials.

Public Interest Statement

Design for Additive Manufacture (AM) is an area of high research interest, due to the barrier it presents to the progression of AM to more industrial products. Novel perspectives are required to progress the technique and break the psychological inertia (the difficulty in changing a process) imposed on design by a history of subtractive manufacturing. This paper utilises a novel methodology, applying the Theory of Inventive Problem Solving, to develop detailed biological analogies between the development of the foetus and AM. The discussion draws comparisons between the two systems, and results in a series of proposed developments to the current design methods and manufacturing systems for AM.

Keywords

Additive Manufacture; Design; Developmental Biology; Foetal Development; Materials; Manufacturing;

1) Introduction

Additive manufacture (AM) has seen a huge acceleration in its application over the past decade. By 2025, the global AM market is expected to reach $0.2-0.65 trillion (1). All additive techniques may be encompassed by the ISO/ASTM 52900:2015(E) standard definition "process of joining material to make parts from 3D model data, usually layer upon layer" (2). Additive manufacture offers benefits in terms of weight reduction, geometric flexibility and customisation, however, there are also a number of barriers, preventing wider industrial adoption. Amongst these, the design framework is repeatedly acknowledged as a limitation across technologies, materials and industrial applications (3, 4). This study questions whether the definition of AM and design for AM (DfAM) has been be expanded sufficiently to fully exploit the advantages of the technological concept and overcome the industrial barriers.

A unique characteristic of AM is that the material is created in tandem with the form (3). Whilst there has long been a drive to increase the scope of design to encompass the entire product lifecycle (5), AM has further widened this perspective. There is much less distinction between the isolated selection of materials, design of the geometry and manufacture of the form in the DfAM process, all the variable parameters within the framework intrinsically impact each other. This phenomena has been highlighted in previous studies. Rosen (2007) defines DfAM as "Synthesis of shapes, sizes, geometric mesostructures, and material compositions and microstructures to best utilize manufacturing process capabilities to achieve desired performance and other life-cycle objectives" (6). A comprehensive study by Pradel et al. (2018) maps all DfAM knowledge onto a framework for AM (7). In doing so, this research visually demonstrates the interconnectivity between outcomes of each stage of the design process on subsequent or proceeding development phases (7). In essence DfAM now requires the designer to have a detailed knowledge of the two-way impact of manufacturing variables on material and geometric design in the context of optimising a design variable for a specified function.

Design for AM also requires a balance between the creativity required to exploit the increased freedom in topology, based on a foundation of understanding the opportunities and limitations of each technique (3). Yet, comprehensive knowledge of DfAM is far from being widespread. Whilst a basic, technique specific overview can be gained from research or industrial literature (8, 9), predominately the knowledge required to effectively DfAM is gained through hands-on experience. However, the acceleration in the development and breadth of AM across machines and materials means that knowledge can become experience specific, leading to its pocketed nature and the high value of the intellectual property in industry (3). Whilst software development and topology optimisation frameworks gain strides in the automated optimisation of DfAM, the conceptual design phase demands a more creative approach. Design education and the majority of established experience is routed in subtractive and forming techniques, a problem which is compounded by design software which remains entrenched in Boolean operations. Although generic frameworks exist to increase the creativity and innovation in design (10) only a limited amount of literature is specifically aimed at expanding creativity in DfAM (11, 12). Therefore, DfAM remains heavily constrained by both the inclination of the engineer to spatially reason in terms of traditional manufacture techniques and compounded by software primarily developed to satisfy design in terms of extrusion and subtractive functions.

The concept of using biological inspiration to inform and solve engineering problems has been well documented (13), but the application of bioinspired design to manufacturing is rare in the research literature. Byrne et al. (2018) define 'Biologicalisation' as "The use and integration of biological and bio-inspired principles, materials, functions, structures and resources for intelligent and sustainable manufacturing technologies" (14). This research explores biologicalisation broadly in the context of Industry 4.0, and provides an overview of how the hierarchical intricacies of bioinspired design intersect with the hierarchical system of advanced manufacturing from materials through to supply

chain, and concludes that it represents a ground-breaking frontier, with strong market potential (14). Whilst there are many examples of using advanced fabrication techniques to create bioinspired materials (15), more specific applications of bioinspired design to physical manufacturing systems is limited to biomimetic machine tools, for example (16). It can be concluded that there is economically important gap in the research to both break the psychological inertia of DfAM and widen the perception of AM systems through bioinspired design. This paper achieves this through a radically different approach; the comparison of AM to the development of the human form i.e. the growth of the foetus *in-utero*.

Human life starts from just a single cell. Cells proliferate, differentiate, lay down extracellular matrix which eventually forms tissues and organs, which all grow and function in synergy. This incremental growth in the size and the function of the foetus *in-utero*, one which fundamentally increases cell by cell, is analogous to certain types of AM such as powder bed fusion. Powder based techniques increase the part size through incremental fusion of the grains of the material. Yet, there are many more AM techniques which adopt a layer by layer approach, one which still incremental, but less comparable to the growth of the human form. In essence, human growth can be considered as very advanced and sophisticated AM process, far beyond what can be conceived of the technology today. In the context of *in-utero* growth, the concept of materials, design and manufacture of the form are intrinsically intertwined. Yet this interlinked development and interdependency between manufacture of the form and function displayed in human development is not yet reflected in AM, from a top-level concept through to individual manufacturing platforms. The aim of this research is use detailed exploration of the biological processes during foetal development to challenge the current perception of design and AM systems. In turn this research will question whether the definition of AM as it stands, truly encompasses all the technique could offer. This research utilises a bottom-up approach, through the analysis of nature (14) and adopts analogical reasoning (17) combined with the Theory of Inventive Problem Solving (TRIZ) to transfer this knowledge to the domain of AM.

2) Background

To expand the definition of design and how additive as a manufacturing technique achieves the requirements of a design problem, a current definition of design and DfAM is required. The spectrum of current AM techniques, materials and applications are extremely well documented in the literature. This information will not be repeated here. The formal definition of engineering design "is a systematic, intelligent process in which designers generate, evaluate, and specify design for devices, systems of processes whose forms(s) and function(s) achieve clients objectives and users' needs while satisfying a specified sets of constraints" (18). From this definition, there are three pertinent points to take forward; the client's objectives/needs, the constraints, and the designer's generation and evaluation of a system that may satisfy these needs within the bounds of the constraints. Engineering literature approaches the analysis of customer requirements through different methods but with similar objectives, they all effectively take a problem and break it down into a series of design requirements (18, 19). Constraints in design are not solely client defined, and the process dependent limitations of DfAM are well documented (8, 20-22). The subjective part of the definition of engineering design lies in the designer's interpretation of a system which could satisfy the client's objectives; this is open to the interpretation of the designer and is constrained or achieved by their inherent creativity.

As discussed in Section 1, DfAM raises the question of interdependency between materials, design and manufacture. In the literature this is often denoted as a variation on the concept of "process-structure-property behaviour", originally developed in the context of design for materials (6). Rosen (2007) develops this framework for cellular structures by combining Manufacturable Elements, to

represent the manufacturing and process planning considerations (6). Doubrovski et al. (2011) proposes another framework based on the "process-structure-property behaviour" relationship; routing from performance to processing, this framework embodies a design process instigated from a 'desired' performance to a manufacturing process (12).

Yet, the issue of giving the designer full control of all additive parameters, from the conceptual design stage remains a long-standing problem; the development of AM platforms is progressing at such a speed that supporting these new methodologies with encompassing design frameworks and software is invariably lagging. At the time of publication, build constraints are only just beginning to be incorporated into computer aided design (CAD) and optimisation or generative design software (23, 24). The concept of incorporating spatial variation of materials into design has been addressed by two groups at the Massachusetts Institute of Technology. Monolith approaches the issue of spatially varying composition using bitmaps, where changes in discrete voxels represents different material compositions, combined into a 3D image, this allows variation of the material through the part, demonstrated using Stratasys MJP technology (25). Conversely, Foundry applies different functions describing material characterisation within discretized volumes (26). What all these DfAM software have in common, either broadly or specifically, is the emphasis on "design for X".

One of the most fruitful applications of using biological inspiration to increase the impact of AM has been in the development of advanced materials. "Living organisms are examples of design strictly for function" where evolutionary forces have resulted in elegant designs exceeding those of engineering (27). The boundary between materials and design has become so intertwined, that essentially advanced material development can be known as design for materials. This concept, described as "material ecology", is framed eloquently by Oxman (28, 29). Murphy and Atala (2014) review the application of "Biomimcry" to 3D bioprinting to facilitate the manufacture of cellular and extracellular constituents of tissues (30). The temporal activation of responsive 3D printed materials, known as 4D printing, is another example of inspiration founded on the inherent responsive nature of naturally occurring systems. This is demonstrated particularly elegantly, when applied to bioprinting (31).

3) Method

Boden (1994) pronounces "How is analogical thinking possible? An analogy links two previously unrelated concepts" in her text "What is Creativity?, The Dimensions of Creativity" (32). Knowledge is often embedded in context, and failure to problem solve has been shown to often lie, not in the absence of knowledge but the inability to recognize transferable knowledge (33, 34). The application of analogies have been an accepted tool for decades, however they are predominately applied in an impromptu manner and recognised retrospectively (also described as top-down application). An analogy may be defined as drawing references or comparisons between two different things, often these things are inherently different but a certain aspect of them, reflects each other. Thus, the use of analogies, forces the innovator outside of the constraining boundaries of psychological inertia.

An analogy can be explanatory, drawing parallels between a new and familiar situation to promote reasoning and learning, and/or inventive, problem solving by transferring knowledge from one field to another (35). Kalogerakis et al. (2010) categorise analogies in terms of the transfer of content (type of knowledge) and distance (similarity of the source and target of information) (35). Using the same framework, this study transferred design arrangements between non-product knowledge domains i.e. the source and target of the information are highly dissimilar systems. Kalogerakis et al. (2010) deduced through case study analysis, that this combination of transfer content and large transfer distance can lead to "radically new" solutions (35). The structured use of analogies to aid innovation as a tool in research is a relatively rare but powerful technique (33, 35, 36). The application of

bottom-up analogies was proposed by Byrne et al. (2018) as a method of applying biologicalisation to manufacturing (14).

To structure the derivation of the analogies in this study the Theory of Inventive Problem Solving (TRIZ) analysis technique entitled “Thinking in Time and Scale” (10) was employed. TRIZ employs various tools to analyse a system and each tool is utilised to extract a different type of information. Thomas-Seale et al. (2018) have previously utilised an in-depth functional analysis to analytically discuss the barriers to the industrial progress of the technique (3). In this study, the “Thinking in Time and Scale” spatiotemporal system analysis was used to decompose the system into the past, present and future and the super-system, system and sub-system. The tool can be used to map out systems, solutions, needs and causes/effects, where thinking in time offers insight to trends, causes and the future, and thinking in scale offers visualisation of context and detail (10). This tool was chosen specifically to analyse AM and human development over distinct time periods, and explore the changes with time across the hierarchal levels.

This research considers AM broadly as the fusion of material point by point and layer by layer, incorporating all processes including powder bed and extrusion AM. To clarify the focus of this research the boundaries of the systems were constrained and are outlined with reference to the spatiotemporal analysis displayed in Figure 1. In this and the subsequent analyses the sub-systems of the foetus are the cells, tissues and organs. The sub-systems in AM is the form of the material. The super-system during the time frame of pregnancy is the mother, and during manufacture is the AM platform. Analogies will be drawn across all the scales shown in Figure 1, however they will be limited to a defined period of time (highlighted). In foetal development this is the behaviour of the gametes, just prior to fertilisation, through embryogenesis and foetal development, during AM this is the finite build time.

The method utilised in this research is novel and thus the external validity of the two components, analogical reasoning and spatiotemporal decomposition, must be assessed. The utilisation of analogies, through a top-down or bottom-up approach, have been reported in engineering research literature as a method to stimulate innovation (17, 35, 37, 38). The validity of the application of analogies to AM, is demonstrated by Byrne et al. (2018) who review the wide application to advanced manufacturing of materials and surfaces yet highlight a lack of literature in the application to manufacturing systems (14). The spatiotemporal decomposition, known “9-boxes” or “9-windows”, is primarily used to understand the system in terms of the environment and components and how it changes over time (39). Ilevbare et al. (2013) report moderate application of this technique from TRIZ professionals and enthusiasts and detail survey responses that associate the benefits of this analysis type with forecasting (39). The TRIZ toolkit itself is largely underpinned by the transference of engineering knowledge from one domain to another, for example the Inventive Principles (10). Knowledge transference between domains is also the definition of an analogy (35), thus validating the relevance of applying the TRIZ spatiotemporal decomposition to analogical reasoning.

4) Results

Figure 1 frames the top-level analogy of this research. The system in Figure 1a, is the AM part, the system in Figure 1b is the developing human. Analogical reasoning is drawn between each matrix entry corresponding to a similarly positioned entry in the other system. This is expanded in much greater depth in Figure 2 and through the discussion. The highlighted central column (C) defines the time envelope of interest in this study. In this time period, the part is being manufactured and the foetus is developing: both systems are spatially and temporally encapsulated within the AM volume for the built time and the uterus for the duration of pregnancy. Within this time frame the super-system (i.e. the environment in which the system is hosted) is the AM machine and expectant mother,

and the sub-system (i.e. the components of the system) is the fusion of material and growth of cells, tissues and organs respectively. Analogical reasoning between the fusion of material and the proliferation of cells in the growth of tissues and organs, varies between AM platforms in terms of transfer distance. In AM techniques that utilise powdered raw material, the analogy between grain fusion is stronger than between layer based manufacturing. However the incremental nature of growth in the foetus and manufacture in AM, remains across all AM platforms. Figure 1 also represents the preliminary research of this study and was presented at the 8th World Congress of Biomechanics 2018 (40). It is replicated here for completeness and to frame the context of this study, permission has been granted by Oxford Abstracts.

The highlighted central columns of the temporal axes in Figure 1, are expanded into the 4 temporal columns of the images in Figure 2. Figure 2 (a) the AM build from the unfused material to the completion of the build, prior to part removal is analogous to Figure 2 (b) just prior to fertilisation, through to just prior to birth. It should be noted, in Figure 2 (b), that the completion of embryogenesis (C3) and commencement of foetal development (C4) is at the beginning of week 9. Similarly, the spatial scales of Figure 1 have been expanded to create a distinction in the material and biological composition in Figure 2. The bottom two rows (R) denoted “Part / Material” and “Organism / Cells, Tissues and Organs” in Figure 1(a) and 1(b) respectively have been expanded into the three bottom rows of Figure 2(a) and 2(b) respectively.

Figure 2 and 3 are coded as follows. Where the material is active chemically, thermally and/or mechanically, the matrix entry is highlighted in green. In AM, Figure 2(a), this is the “fusion” temporal column. This column represents where the designer has the most control of the system. At a super-system level during fusion, the material (powder/liquid/filament) is physically active to locate at the X/Y/Z position for fusion. At the system level the material is fused via thermal, photo or chemical means. At the sub-system material level thermal, chemical and/or mechanical interactions happen between the materials and fusion source. In human development, Figure 2(b), the system is continuously active and responsive, and hence highlighted fully in green. The yellow matrix entries signify where a component of the system is active but in a passive sense i.e. it may have chemical or mechanical activity to set up the system prior to component activation, or residual from component activation. The orange matrix entries represent where the material is predominately dormant. In AM this corresponds to before and after fusion yet within the timeframe of the build. The orange highlighted sections represent the greatest opportunity to exert additional design control over the process. Figure 2 highlights that the state of the material whether active or dormant does not map directly between AM (a) and human development (b). This is primarily because of the dormant nature of the materials pre and post-manufacture compared to the continuously active nature of biological mediums. The spatiotemporal analyses of Figure 2 and how they reflect each other, have been expanded in further depth in Section 5.1.

Figure 3 maps human development analogies, back onto the spatiotemporal analysis of Figure 2(a). These are discussed in full throughout Section 5. The green demonstrates that *In-situ* DfAM and Tertiary Material Responses have expanded the active nature of the material and hence design freedom within the build envelope of AM. The proposed developments to AM as a manufacturing system, discussed in Section 5.2, are also denoted within the matrix column and row where they present an opportunity to control the design parameters.

5) Discussion

5.1) *In-Situ* DfAM

Human development enables the creation of complex multiscale materials. Organs, tissues, cells, their micro, biological and chemical structures seamlessly interact during the process of growth; over time through their scalar levels and also between distinctive systems, to create the synergy of the human form. Human design is not constrained to geometry of any scale but encompasses the simultaneous development of tissue, its geometry and functionality through the levels of the cell through to the organ. The functionality of cells, tissues and organs operate both across scales and also combine to address overarching functions at a higher level. The essence of human development is the synergism of responsive growth across multiple scales that combine in a hierarchal arrangement to address functions throughout the system.

The development of the cells, tissues and organs of the foetus demonstrates both local spatial and temporal responsiveness i.e. they respond to stimuli that vary by position and time. The point of fertilisation, where the discrete time frame outlined in Figure 1 commences, poses the first analogy. The remote attraction of a sperm towards an egg cell, is facilitated by rheotaxis and chemotaxis, the response to fluid velocity and chemical gradients (41). The response to these stimuli varies in space. The egg also controls the time at which the chemical signal gradient, is released (42). The response to this stimulus varies in time. Moving forward through the time frame, *in-utero* foetal growth, repair and remodelling are also controlled both by the spatial variation of receptor cells and time-varying chemical, biological or mechanical stimuli.

These concepts translate into two analogies for the design of materials; the spatial and temporal stimulus of materials during manufacture. Where the temporal stimulus of materials during manufacture is distinct to the temporal stimulus of an AM part after manufacture, i.e. 4D printing. Research into 4D printing, is summarised in the review by Khoo et al. (2015) (43). Another distinction that needs to be drawn is the responsiveness of materials at the point of fusion. An example of manipulating the parameters which exist in C2 of Figure 2(a), the fusion column, and the design freedom that this facilitates, is the variation in the heterogeneous deposition rates of polyjet and wire arc AM extrusion nozzles. These techniques have led to the manufacture of functionally graded materials (25, 44). Composite materials can also be created through spatial variation of the type of deposited material, for example fibre reinforcement (45). In Figure 3 these techniques exert design freedom within C2R1 and C2R2. Whilst these examples, demonstrates the variation of material composition within the build envelope, they are not strictly examples of temporal or spatial responsiveness, since these techniques are varying deposition not a stimulus. However, some AM materials already present an inherent responsiveness during manufacture (46, 47) and this offers the opportunity to exert design freedom in C2R3 and C2R4 of Figure 3.

The term “design” in the context of AM, needs to be expanded to incorporate the manipulation of the material and part through the time, space and scale parameters of the whole AM build envelope. This research proposes methods to increase the capacity of AM to exploit stimuli and responsive materials and defines this additional design freedom as “*In-situ* DfAM”.

5.1.1) Temporal Stimuli

The growth of biological systems within the foetus are not linear with time; different organs develop at different rates, and these rates change through gestational age (48). At the macro level of the organism, foetal growth is affected by maternal, placental and by its own parameters. Whilst growth is pre-programmed in the genome, it is also affected by environmental factors such as size, nutrition and substances ingested by the mother (48). Genetics, i.e. pre-programmed data from the sperm and ovum, are analogous to the pre-programmed data within the CAD model. The plethora of manufacturing

variables are analogous to variable *in-utero* and environmental factors. This is shown by comparing row (R) 1 of Figure 2(a) and Figure 2(b).

Mechanotransduction during foetal development is utilised to explore this concept in more-depth. Mechanotransduction is defined as the impact of forces on the biochemical interactions of molecules inside and outside the living cell (49); it is analogous to a temporally varying stimuli acting on a responsive medium. Mechanical forces as stimuli in the human body, affect the growth of almost every tissue and organ (50) and mechanotransduction is integral to the development of the foetus. As such, it presents a reoccurring theme in this research. In embryogenesis, cells are influenced by mechanical stress in two ways, through the environment and the presence of other cells (51). The foetal heart, develops from a rhythmically contracting tube to the driving organ for transporting blood through the developing vasculature, and demonstrates a stiffness which changes daily (52, 53). The cardiovascular system demonstrates a complex feedback loop which is responsive to its own mechanical stimulus as it varies over time. Whilst there is substantial evidence to suggest that it is the endothelium that senses and discriminates between and responds differently to different types of hemodynamic forces, the translation of this phenomena to the physiological changes remains unclear (54). Whilst the process at one scale, the cellular level, is well explained, the translation of the phenomena through to morphogenesis at the macro scale, i.e. the organ, is not.

The description of how mechanotransduction influences growth on a cell, tissue and organ level poses the innovation of integrating time-varying stimuli across the whole timeframe of the AM build shown in Figure 2 (a). Essentially, increasing the responsiveness of materials from just the point of fusion, back to the unfused material and forward to the material post fusion.

5.1.2) Responsiveness through Space and Scale

Stem cells, can be classified by their ability to differentiate into different classes of cells. All cells are derived from the totipotent cells of the cleaving embryo. Totipotent cells give rise to pluripotent cells which in turn differentiate into one of the three germ lines (ectoderm, endoderm and mesoderm), these multipotent cells are able to differentiate into cells from a number lineages of which unipotent cells are limited to one cell type (55). Yet, the DNA embedded in a cell does not contain information about the location of a cell (55). Therefore, it is not the DNA of the cell which fully controls the derivation of the cell through to its final type. The differentiation of cells are also spatially dependent, i.e. they are governed by external factors. This provides an interesting analogy to explore the concept of spatial stimuli.

In vertebrates, environmental cues are integral to the establishment of the coordinate system of the embryo; these include the entry point of the sperm, gravity and maternal cytoplasmic determinations (55). Mechanotransduction, is present even in cleaving of the embryo. Spatial variation of the forces in which the developing embryo is exposed to, occurs internally through cell polarization (56). Cells become polarized when they are in contact and in tension against another cell or substrate (56-58). Hence, the 8-cell embryo experiences a variations in the forces on each side of each cell, depending on whether the surface is in contact with another cell (56). At the tissue scale, the main process behind the differentiation of adjacent but different tissues is cell interaction; where the cell either acts as the inducer of the signal or the responder to the signal (42, 55). Not all cells respond to all induction signals, and the ability to do so is known as competence (42). Induction is a highly complex sequential process, which requires multiple factors to combine and facilitate induction of a certain cell; it can be classified into either instructive or permissive, depending on whether either an inducing cell is essential or a specific environment is required (42).

Across the scale of cells and tissues, in the developing human, responsiveness varies spatially in terms of both the stimuli and the substrate. To translate this analogy to AM, rather than hierarchy of cells, tissues and organs, we can consider variation of the response through the scales of the materials i.e.

the nano, micro, meso and macro composition. This analogy represents the variation of the stimuli/response through scale and with spatial location throughout the entire AM build.

5.1.3) Tertiary Material Responses

Finally, the tertiary material response (TMR) analogy, is developed from a perspective drawn from the interaction of primordial germ cells (PGCs) and genital ridges in the development of gonads. The PGCs eventually develop into the gametes; they may be identified in the 4th week of gestation in the umbilical vesicle (59, 60). The PCGs are motile cells, and during development they change their spatial location, which is described as 'migration'. The migration of the PCG's from the umbilical vesicle, into the embryo and to the genital ridges, shown in Figure 4, leads to the development of the gonads in male and female vertebrates. Godin et al. (1990) demonstrated that it is the genital ridges that stimulate the PCGs to both proliferate and migrate towards them (61). In turn, upon arrival, the PCG's then stimulate the development of the gonads. In the first instance, the PGCs stimulate the proliferation of the somatic support cells, which nourish and regulate the development of the maturing gametes (62).

The migration of the PCGs are triggered by a time dependent chemical signal during the development of the foetus. The cellular response is three-fold; the genital ridges exert a chemotropic effect on the PCG's leading to a change in spatial location, this results in localised contact between the PCGs and genital ridges, triggering responses in both cells to develop the gonads. If the process of self-healing composites, could be classified as a secondary material response, i.e. damage triggers a change in the material, which subsequently leads to repair. Then the analogy posed here represents a TMR; the initial stimuli triggers change and movement of the receptor cells, which upon contact with the origin of the stimuli, leads to a third level of material activation in both the receptor and the origin of the stimuli. *In-situ* DfAM is underpinned by the theory that design and manufacture can incorporate temporal variation of a stimulus and variation of the response in terms of space or scale. This final analogy takes both dimensions one step further. The level of material activation proposed is beyond the initial stimuli/receptor response, thus as the analogy is mapped on to AM, TMR proposes additional material activation post-fusion and beyond.

5.1.4) Summary

Implementing the analogies of 5.1.1 through 5.1.3 would enable expansion of the responsiveness of the material currently highlighted in green in C2 of Figure 2 (a), through the entire system, to represent the continuous responsiveness of the components of the developing foetus in Figure 2 (b). Implementation of such an innovation would require significant develop to current AM platforms. Whilst responsive (smart) materials may be manufactured through AM (4D printing) (43), they are not activated during manufacture. Similarly, whilst some materials display responsive to manufacturing parameters (46, 47), this is limited to the point of fusion (C2 of Figure 2 (a)). The concept of *In-situ* DfAM presents an opportunity to integrate new stimuli; before, during and after manufacturing, and in doing so, vastly expand the repertoire of responsive materials. Receptors that vary spatially and through scale would allow activation of material through all rows of Figure 2 (a), and combining this with temporally varying stimuli would the activation across all the columns of time. Finally a TMR would allow activation of material specifically after the initial stimulus of the material. If the initial stimuli is assumed to be fusion, TMR would allow activation of material in C4 of Figure 2 (a) and beyond the temporal boundaries of the analysis. These analogies, and the potential impact to the systems analysis of AM, are summarised in Figure 3.

5.2) Future Perspectives on Additive Manufacturing

In-situ DfAM proposes to control the design of the material, composition and form through an expanded design envelope during manufacture. Section 5.2, progresses the discussion to explore how analogies may be further utilised to inspire manufacturing systems. The current definition of AM constrains the technique to the fusion of material point by point or layer by layer. In the context of the discussion so far, that definition begins to seem highly primitive. Therefore, the second half of this research applies analogies that focus on the processes that govern growth during human development and compares these to AM as a physical technique. The purpose of this section is to challenge the definition of AM by exploring how matter is bonded, with far more complexity than point by point and layer by layer, in the development of the human system.

5.2.1) Hybrid Manufacture

Hybrid Manufacture, is currently perceived as the combination of both additive and subtractive manufacture. Hybrid techniques offer a full manufacturing solution within one automated process, which has implications for remote manufacture and repair. A recent review by Flynn et al. (2016) outlines research and industrial developments, concluding that the field is predominately, though not exclusively, focussed on the combination of direct energy deposition (DED) with computer numerical control (CNC) machining (63). Yet, foetal growth is far from limited to one or two distinct methods. This is demonstrated by the distinct difference in the physiology of bone growth relative to its spatial location; intramembranous ossification in the skull, and endochondral ossification in the limbs.

Bone is a highly dynamic tissue; bone modelling during growth and remodelling upon maturity results in the constant regeneration of the skeleton (64). Bone remodelling is the renewal of bone to maintain strength and homeostasis, it is not limited to the mature adult, but begins in the foetus and continues until death (65). Remodelling has four distinct stages: activation, resorption, reversal and formation (65). The cellular contributors to these processes are osteoblasts, osteoclasts and osteocytes. Osteoblasts are differentiated from mesenchymal stem cells and contribute to the formation of bone matrix, whereas osteoclasts differentiated from the monocyte/macrophage lineage, reabsorb the bone (64, 66). The osteocyte is differentiated from the osteoblast and becomes embedded in the bone matrix. Osteocytes, which make up 90-95% of all adult bone cells, have many functions, one of which is as a mechanosensitive cell (67). Effectively osteoclasts, osteoblasts and osteocytes coordinate, at a cellular level, the tissue response to the external environment. This process not only operates across scales, but also differs between spatial locations.

Intramembranous ossification which forms the skull bones is initiated by the proliferation of neural crest-derived mesenchymal cells; some form vessels and some differentiate into osteoblasts (42). The osteoblasts secrete an unmineralised osteoid matrix, into which calcium is deposited to form the calcified matrix, in which the osteocytes, become embedded (60). Conversely, endochondral ossification, which forms the long bones, demonstrates an intermediate step where tissue is transformed from cartilage to bone. The mesenchymal cells, condense into nodules and differentiate into chondrocytes which secrete the molecules required for the extracellular matrix of cartilage (62). The subsequent hypertrophy of the chondrocytes, has two key functions, firstly they secrete vesicles into the extracellular matrix, the enzymes of which initiate the mineralisation process (42) and secondly they lengthen the bone (68).

All additive techniques have strengths and weakness, hence their use is very much application specific. This analogy demonstrates the combination of multiple additive and subtractive techniques within the manufacture of different sub-components of one overarching system. In doing so, a particular additive technique, in this instance endochondral ossification, exploits its strength, the enlargement of bone, where is it specifically required, in the long bones. The analogy of endochondral and intramembranous ossification, to create distinct organs of the foetus, proposes combining

different methods of fusion (H1), and hence increases design freedom at the part level and the scales below i.e. R2C2, R3C2 and R4C2 of Figure 3. The discussion of endochondral ossification demonstrates the transformation of materials in the generation of the system. Whilst a supporting structure that can be removed via chemical or mechanical means, is commonplace in AM, this is strictly after the build. This analogy raises a second proposal of transforming material during the build envelope (H2), but after fusion and maps onto R2C4, R3C4 and R4C4 of Figure 3.

The H1 and H2 analogies, both introduce the concept of changing the perception of AM from one single fusion method to multiple additive techniques (and subtractive) and/or the integration of a transformation process of the material after fusion but during the build time. The key challenge to develop such a platform is the combination of different types of materials, within the system itself, and fusion, removal or transformation of the material in a multi-material system. In the first instance, this will require extending research beyond the fusion or interaction of materials within the same classification, for example metals or polymers.

5.2.2) Suspended Manufacture

The development of the foetus, does not incorporate any voids that would require a support structure, it is encased in amniotic fluid. The concept of supporting initial growth by a surrounding fluid applies to the development of all other land vertebrates (55) and extends to the embryogenesis of plant seeds (42). Up until an organism is self-supporting, growth does not occur in a gas, it is supported by a weight bearing medium. This simple analogy has the potential to relieve a huge amount of the geometric constraints faced by AM. In the instance of powder bed techniques, the inherent supporting nature of powder, offers some relaxation of the geometric constraints seen by other techniques, however, this is in part offset by the requirement of supports to alleviate thermomechanical warping (69). There are also examples of hydrogel based techniques where the material is extruded into a tank of pre-existing polymer, which inherently providing a support for increased topology freedom (70, 71). Suspended Manufacture (S) is one of the simpler analogies to visualise being expanded to more additive techniques. In doing so it would allow relaxation of the geometric design constraints; R2C1, R2C2, R2C3 and R2C4 of Figure 3.

The S analogy introduces the concept of dynamics into a build or supporting material i.e. the material is responsive to the changing geometry of the part which is being manufactured. In powder bed techniques, the ability of the build material to support the topology is due to its unfused powder based nature. Of course, there are limitations to the weight that an unfused powder or liquid can support. Therefore a challenge in expanding the development of such platforms, or expanding the use into other materials, is how to control the weight bearing capacity of the supporting material. This could be achieved through active control of the dynamics of the supporting material. Raising this avenue of research also combines with the concept of Perfusion Manufacture discussed in Section 5.2.3.

5.2.3) Perfusion Manufacture

Perfusion Manufacture is derived from an analogy of the motion of fluids in the circulatory system. The growth of tissue in the foetus happens simultaneously with the growth of the vasculature (48). Similar to the complex feedback loop seen in the morphogenesis of the heart, Section 5.1.1, the perfused fluid in the developing circulatory system, is also carrying the nutrients for growth. The development of the cardiovascular system occurs through vasculogenesis and angiogenesis. Vasculogenesis, the development of new vessels, beginning in the third week of embrogenesis, in response to the requirement for nutrients from the maternal circulation (60). Its physiology is summarized as follows: angioblasts (differentiated from mesenchymal cells) group into clusters called blood islands, the confluence of intercellular clefts result in small cavities in these blood islands, which become lined with angioblasts flattened to form the endothelium, finally these endothelium lined cavities then fuse to form the endothelial channels (60). Angiogenesis, the growth of new

vessels from pre-existing vessels, expands the vascular network. Angiogenesis of vessels occurs by budding and sprouting of existing vessels or the intussusception, i.e. the separation or fusion of vessels (62).

The essence of the development of the cardiovascular system in tandem with development of foetal tissue, is the perfusion of a medium which contains the nutrients for growth, flowing through a constantly evolving network of vasculature. In the foetus the medium of growth is highly dynamic, in vast contrast to the preconceived notion of a static build material which is predominant in most AM platforms. If the concept of AM materials being static prior to manufacture were to be abandoned, then it is actually far easier to conceive that a build material could be responsive to stimuli during manufacture i.e. *In-situ* DfAM. A dynamic build material (P1) would enable design freedom of the unfused material in R1C1, R2C1 and R3C1 of Figure 3. Additive manufacture already offers many benefits in the optimisation of topology for flow efficiency (72), including applications to tissue scaffolds, in which it is desirable to have intrinsic, interconnected vasculature (73). A second analogy is drawn from the observation that the development of the human form occurs in tandem with the vascular network, i.e. the growth medium is perfused through the structure. This is again is in contrast to AM where build material is distinctly added to the form from the outside. The perfusion of build material through the incrementally developing structure (P2) would allow increased control of the unfused material and maps onto R1C1, R2C1 and R3C1 of Figure 3.

The P1 and P2 analogies, in the context of their origin in cardiovascular growth, are specific to the control of a build material in a fluid state. As such the main challenges would be the integration of a system which controls the dynamics of the fluid in terms of direction, velocity and pressure. The control of the pressure of a build material, also offers as alleviation to the weight bearing capacity of the build material, identified as a limitation of Suspended Manufacture. From the perspective of P2, there is the additional complication of the interaction of the fluid with the topology of the part during manufacture, raising the question of designing fluid networks which are fit for function during and after manufacture.

5.2.4) Diffusion Manufacture

Diffusion Manufacture draws an analogy from the placenta as the interface for growth and waste mediums between the foetus and mother. Exchange between the foetal and maternal circulation, occurs across the interface between the arteriocapillary venous system, which branches from the umbilical artery, which is immersed in the intervillous space containing the circulating maternal blood supply (74). Where Perfusion Manufacture proposes the use of the perfused fluid as the build material, Diffusion Manufacture proposes the control of the composition of the build material. Manufacturing the circulation of a build material into the developing structure (P2), would facilitate the diffusion of molecules across a permeable boundary by manipulating concentration gradients, the porosity of the boundary or active transport. Thus the part itself would become a conduit for the variable composition of the build material.

A final analogy is required to complete the discussion of diffusion during manufacture, one to signal a local or global end point to the transport of molecules. The fastest biological process in the human body, fast block polyspermy, occurs at the point of conception. The spermatozoa must penetrate through the cumulus cell barrier, the zona pellucida and perivitelline space to reach the plasma membrane of the oocyte (75), shown in Figure 5. At the moment of membrane fusion between the spermatozoa and oocyte, the zona pellucida changes its properties to become impenetrable to other sperm (60). The sperm receptor molecules in the zona pellucida are altered by a calcium wave and the release of cortical granules into the perivitelline space, thus preventing fertilisation by more than one sperm (62).

Diffusion Manufacture, the manipulation of the composition of the build material (D), increases design freedom in terms of the composition of the material pre-manufacture, and the permeability of the fused material post-manufacture, thus mapping onto R4C1 and R3C4 of Figure 3. Diffusion manufacture displays a strong synergy to Perfusion Manufacture, just on a different scale. To progress the D analogy, would require significant developments to the composition of AM materials, to create materials that demonstrate responsiveness to diffusion gradients at a different scale to the bulk properties of the material. This development would also be required to progress the design control of receptors which vary through space and scale in *In-Situ* DFAM.

5.3) Critical Reflections

Section 3 outlined how the combination of transfer content (design arrangements) and transfer distance (across non-product knowledge domains) can lead to high novelty analogies. The general trend reported by the research of Kalogerakis et al. (2010) is that increasing transfer distance, increases the novelty of the solution (35). However, what defines innovativeness, is highly dependent on perspective, whether that be from a 'macro' i.e. the market or industrial viewpoint or 'micro' i.e. the consumer viewpoint (76). This study has presented design and manufacturing system innovations that vary in their degree of novelty. To assess their novelty, the macro perspective will be adopted, that is the industrial viewpoint and whether any such similar system exists applicable to any application. From this vantage point the innovativeness of the analogies used to define *In-Situ* DfAM, P1, P2, D, H2, TMR which do not currently exist in the AM market are of higher novelty than S and H1, which do exist, albeit only for a subset of consumers. The analogies posed in this research all have a substantial transfer distances between knowledge domains and this also impacts the efficiency of implementation. Whilst these analogies offer inspiration in the direction of a new solution space, because they are outside of the product knowledge category, they do not directly map onto the concept development (35).

Whilst the analogies between the confined time envelope of AM and foetal development have been discussed in detail, the pre/post manufacture and pre/post pregnancy time periods have been neglected. The scope of this paper was restricted to human development *in-utero.* Exploring the time frame after manufacture where the comparison between the final geometry and function of the part, is in contrast to the continued growth of the human, may have the potential to offer yet more inspiration to the design of AM parts. The advanced topological capabilities of AM, offer methods of design that can lead to adaptable products that have not yet reached their final geometry and function after manufacture. This concept was recently explored by Kanagalingam et al. (2019) in the context of conceptual design for fracture fixation devices that have different functional requirements at different time frames of the healing process (77). In addition, details of the technical product requirements have been omitted from the results of this manuscript, such as the topology specific post-processing requirements, because it was beyond the scope of the paper to consider every variant of AM platform, product, and indeed the potential difference in the human form.

Whilst the future perspectives on DfAM and AM that are posed here, can be envisaged in the physical domain, their integration into the software domain is an additional level of complication. The development of software to support such changes to design and AM was beyond the scope of this paper. Referring back to Section 2, current design techniques are predominately orientated around the concept of "design for X", where "X" is a singular variable. However as has been discussed extensively, human development does not demonstrate "design for X" but "design for X, Y, Z and ∑XYZ etc…". Therefore, further research into how the synergy of human development can be applied to design software is required.

6) Conclusions

This research has used analogical reasoning to extract the biological processes that govern the development of the human form to challenge the current definition of DfAM and AM. One underpinning analogy that has been extracted in this research is that AM, like human development, intrinsically intertwines function and form, across time, space and scale, it is an inherently synergistic process. Whilst AM offers significantly more design freedom than traditional manufacturing techniques, these freedoms can only be fully exploited if DfAM and AM itself evolves to reflect the synergy, which in part already exists, between the design and manufacture of the material, form and function. The results of this study proposes innovation in DfAM and the future development of AM systems.

- *In-situ* DfAM:
    - Time-varying material stimuli
    - Material response at different scales and spatial locations
    - Tertiary material responses
- Hybrid Manufacture
    - Combining different methods of fusion
    - The transformation of materials during manufacture
- Suspended Manufacture
    - Manufacture within a supporting medium
- Perfusion Manufacture
    - A dynamic build material
    - The perfusion of the build material through the part during manufacture
- Diffusion Manufacture
    - Manipulation of material composition
    - Signalling a finite end to molecule transport

Figures

(a)

Spatial Scale			Temporal Scale: Before	Temporal Scale: *During*	Temporal Scale: After
			Pre-Manufacture	***Build Envelope***	**Post-Manufacture**
Spatial Scale	Super-System	External Environment	Process supply chain	***AM machine***	Functional interactions of part
Spatial Scale	System	Part	Geometric design	***Fusion***	Geometry of part
Spatial Scale	Sub-System	Material	Unfused material characterisation	***Material-fusion interactions***	Material and mechanical characterisation

(b)

Spatial Scale			Temporal Scale: Before	Temporal Scale: *During*	Temporal Scale: After
			Before Fertilisation	***During Pregnancy***	**After Birth**
Spatial Scale	Super-System	External Environment	Man / woman	***Expectant mother***	Environment
Spatial Scale	System	Organism	Reproductive organs/ parental genetics	***Embryogenesis and foetal development***	Human
Spatial Scale	Sub-System	Cells, Tissues Organs	Sperm and egg	***Cell, tissue and organ growth***	Cells, tissues and organs

Figure 1: Overhead spatiotemporal analysis of (a) AM and (b) human development. The highlighted columns are expanded upon in Figure 2. Replicated and adapted from an abstract and presentation by the authors at the 8th World Congress of Biomechanics 2018 (40); permissions granted by Oxford Abstracts.

(a)			Temporal Scale, Column (C)			
			Unfused Material	Fusion	Fused and Active Material	Fused and Dormant Material
			1	2	3	4
Spatial Scale, Row (R)	Build Platform	1	Design information (STL) and deposition system	Location/parameters of fusion source and material	Displacement perpendicular to the build platform	Displacement perpendicular to the build platform
	Part: Geometry	2	G-code	Material fusion	Global geometric form which may continue to deform due to the residual effects of fusion	Dormant part
	Part: Material	3	Unfused material	Interaction between material and fusion source	Material which may continue to deform locally due to the residual effects of fusion	Fused material
	Part: Material Composition	4	Unfused material composition	Interaction between material composition and fusion source	Residual interactions between material composition and the fusion source	Fused material composition

(b)			Temporal Scale, Column (C)			
			Gametes	Fertilisation	Embryogenesis	Foetal Development
			1	2	3	4
Spatial Scale, Row (R)	Expectant Mother	1	Genetics and *in-utero* environment	Genetics and *in-utero* environment	Genetics, *in-utero* environment and environmental factors	Genetics, *in-utero* environment and environmental factors
	Organism: Organ	2	Ovary/ testicle	Fallopian tube/ uterus	Organogenesis	Morphogenesis of foetal organs
	Organism: Tissue	3	Ovary/ testicular tissue	Wall of fallopian tube/ uterine wall	Cell differentiation	Cell differentiation
	Organism: Cells	4	Ovum and sperm	Ovum and sperm	Cell proliferation	Cell proliferation

Figure 2: Expanded spatiotemporal analysis of (a) additive manufacture and (b) human development. The figure is coded as follows, corresponding to the state of the material; green: physically, chemically or thermally active; yellow: passively active; orange: predominately dormant.

				Temporal Scale, Column (C)			
				Unfused Material	Fusion	Material Immediately After Fusion	Material Post-Fusion
				1	2	3	4
Spatial Scale, Row (R)	Build Platform		1	*In-situ* DfAM, P1, P2	*In-situ* DfAM	*In-situ* DfAM	*In-situ* DfAM, TMR
	Part	Geometry	2	*In-situ* DfAM, S, P1, P2	*In-situ* DfAM, H1, S	*In-situ* DfAM, S	*In-situ* DfAM, TMR, H2, S
		Material	3	*In-situ* DfAM, P1, P2	*In-situ* DfAM, H1	*In-situ* DfAM	*In-situ* DfAM, TMR, H2, D
		Material Composition	4	*In-situ* DfAM, D	*In-situ* DfAM, H1	*In-situ* DfAM	*In-situ* DfAM, TMR, H2

Figure 3: The analogies mapped onto Figure 2(a), to demonstrate where and how they have increased the design control over the material and form. Hybrid Manufacture (ossification) - H1; Hybrid Manufacture (endochondral ossification) - H2; Suspended manufacture - S; Perfusion Manufacture (dynamic nature of blood in the developing cardiovascular system) - P1; Perfusion Manufacture, (perfused nature of blood in the developing cardiovascular system) - P2; Diffusion Manufacture – D. The physically, chemically and/or thermally active nature of the material realised through *In-situ* DfAM and/or Tertiary Material Responses (TMR), is coded as green.

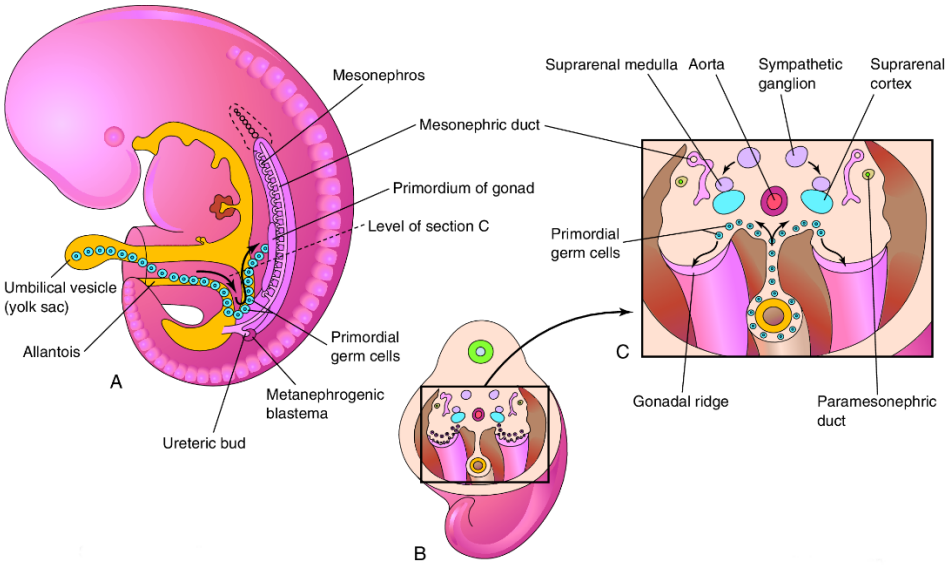

Figure 4: The primordial germ cells migrate from the umbilical vesicle into the embryo to colonise the gonadal ridges. Analogous to Tertiary Material Responses. Replicated from The Developing Human (60) Figure 12-29 (A, B, C); permissions granted by Elsevier Ltd.

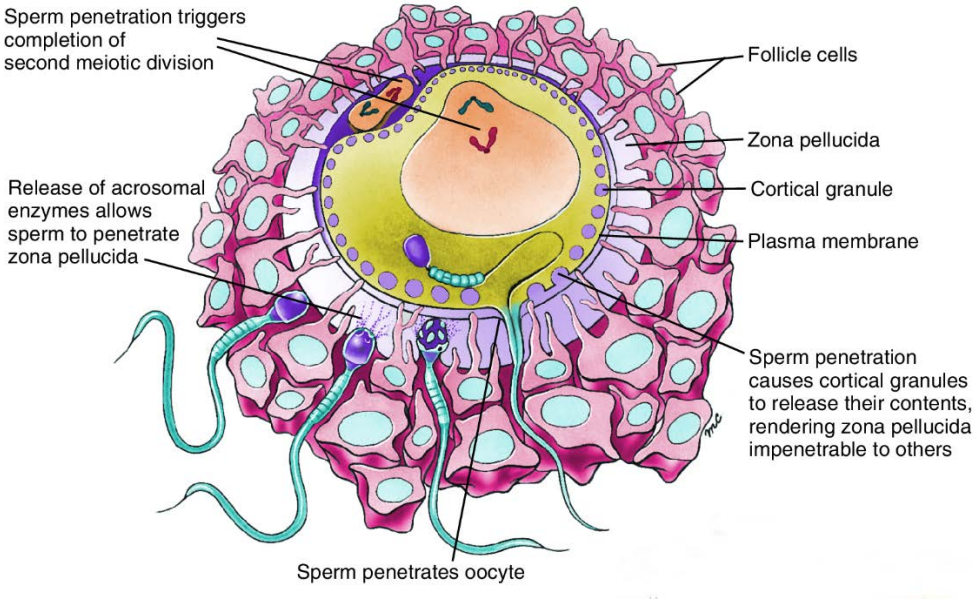

Figure 5: Mechanisms of fertilisation including fast block polyspermy; upon fusion of the sperm and oocyte membranes, cortical granules are released which make the zona pellucida impenetrable. Analogous to signalling a finite end point to molecule transport in Diffusion Manufacture. Replicated from Larson's Human Embryology (62) Figure 1-14 (A); permissions granted by Elsevier Ltd.

Research Ethics

Research ethical approval was not required for this study.

Data Accessibility

This research uses design and innovation tools to create new concepts, thus the data is summarised in the results section (displaced as spatiotemporal analysis matrices) and expanded upon on in the discussion. All the data that is summarised in the results, was drawn from references that appear in the discussion; primarily but not limited to (42, 48, 55, 56, 60, 62, 64, 74).

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