Title: **Not anytime soon: the clinical translation of nanorobots and its biocompatibility-interdisciplinarity critique**

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Introduction

Nanorobots encapsulate the entangled, complex and contingent conflation of *thinking* systems with *embodiments* at *nanoscales*[1]. They combine the hype, hope and discontents of the wider AI, biorobotics and nanotechnology domains discussed in previous chapters into a single artefact with the single overarching promise of revolutionising biomedicine and healthcare. By autonomously traveling to hard-to-access *in vivo* sites, nanorobots are expected to image and deliver drugs, zap cancer cells and even perform surgical incisions. This is the promise of nanorobots presciently cinematised in Hollywood's 1966 blockbuster *Fantastic Voyage* and demonised nearly forty years later in 2002 in Michael Crichton's thriller *Prey*. Yet, nanobots are neither the utopia of *Fantastic Voyage* where surgeons shrunk to microscopic scales to traverse the human bloodstream in a microscopic submarine, nor the dystopia of Crichton's parasitic nanobot swarms feeding off human preys. Indeed, a modified version of the utopia where autonomous nanorobots (instead of shrunken humans) deliver targeted therapies - is attainable, or at least that is the hope underpinning the millions that have been invested globally in the last three decades to realise it (WIPO, 2015). At the same time, that the realisation of this promise is unlikely without a well-defined consideration, characterisation and mitigation of the unprecedented risks that this conflation of the human, the biological and the digital brings is widely accepted. Thus, beyond the hype and hope of nanorobotics' promise for biomedicine and healthcare, the question as we explore here is what will it take to routinize these artefacts into clinical practice?

As many have shown, the pathway of translating technology into clinical practice is a difficult one and narratives of "nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability" are the norm than the exception (Greenhalgh et al., 2017). Even the ubiquitous humble stethoscope faced an uphill task of routinisation into general clinical practice at the time of its invention in the early 19th century. John Forbes, a medical practitioner, dismissed it at the time as,

> "That it will ever come into general use, notwithstanding its value, is extremely doubtful; because its beneficial application requires much time and gives a good bit of trouble both to the patient and the practitioner; because its hue and character are foreign and opposed to all our habits and associations" (Forbes, 1823).

Since then, Forbes' critique of routinizing technologies in patient care have presciently encapsulated much of the sociotechnical issues that ails clinical uptake of technologies today; from practitioner's time constraints (Liao & Mark, 2003) to trust deficits in the safety or efficacy of new technologies (Datta Burton, Mahfoud, Aicardi, & Rose, 2021a). Contemporary artificial intelligence (AI) based medical technologies such as clinical prediction models are no different and face similar challenges of routinization (Mann et al., 2011) with few adopted into clinical practice (Shah, Steyerberg, & Kent, 2018; Wessler et al., 2017).

However, efforts to improve clinical adoption have not been lacking with initiatives since at least the 70s aimed at professionalising 'implementation' of primarily information technology-

[1] "Nanotechnology is the understanding and control of matter at the nanoscale, at dimensions between approximately 1 and 100 nanometers"(https://www.nano.gov/nanotech-101/what); 1 nanometer(nm)=billionth of a meter (10^{-9}m).

related tools into practice settings (Pressman & Wildavsky, 1973; Fisher, 1983). These initiatives or what became eventually known as 'implementation science' were primarily 'technical fixes' such as developing 'technological' skills of clinicians and clinical staff (Gruber et al., 2009; Kellermann, & Jones, 2013) but had very limited success (Greenhalgh et al., 2017; Yang et al., 2016; Wessler et al., 2017). The enduring critique was the approach's failure to take into account the "broader social, cultural and institutional" contexts within which technology adoption is embedded (Liberati et al., 2017, 11) (see also Greenhalgh, Swinglehurst, & Stones, 2014; Kilsdonk, Peute, & Jaspers, 2017). Key among these was(is) lack of attention in technology development to its end-user's (i.e. the clinician's) tacit knowledge of individual patient histories, disease progression, diagnostics and prognoses (Allegaert, Smits, & van den Anker 2012; Datta Burton et al. 2021a).

In turn, meaningful integration of clinician's knowledge especially in the upstream phases of research and its conceptualisation was(is) viewed by clinicians as crucial for improving adoption (ibid; Wyatt & Altman, 1995) and increasingly finding agreement within traditional non-clinical 'engineering' disciplines like bioengineering (Yang et al., 2016) robotics (Michalec, O'Donovan, & Sobhani 2021; Patel et al., 2019) and nanotechnology (Contera, 2019). Notwithstanding, momentum towards meaningful interdisciplinarity have at best been gradual with (bio)engineering communities, atleast where emerging AI-based medical technologies are concerned (Datta Burton et al, 2021a). As this paper will show, this is also the case for bio-intelligent systems specifically nanorobotics where weak interdisciplinary engagement is easily the overarching critique of the domain's grand translatability aims.

Drawing on an exhaustive review of literature informed by discussions with basic scientists, policymakers, regulators and sociologists, the chapter begins with a discussion of the entangled 'technology-driven' search for higher intelligence though which nanorobotics emerged. This is followed by a critical analysis of *in vivo* (bio)compatibility issues in emerging nanorobotic research as the contentious space where various facets of the interdisciplinarity critique becomes visible. Understandings of what biocompatibility is or should be for ensuring patient safety and wellbeing (a key aim of translation-led research) is presented through the lens of existing regulatory frameworks for medical devices across USA and Europe. Finally, the chapter reflects on the domain's predominantly 'engineering' ontologies that inadequately adapts to the biological or *in vivo* as well as the wider social context within which nanorobots hope to be routinised. Notably, the ethical, social and legal implications of nanorobots in particular and the nanotechnology area more generally are substantial and explored elsewhere but beyond the remit of this article (see e.g., Allhoff, 2009; Allhof et al., 2007; Singh et al. 2019; Abidin, Hassan, & Zainol, 2020; Dupuy, 2007; Grunwald, 2010). Our concern here is with the issue of interdisciplinarity (rather its lack) that undermine the realizability of nanorobotics-led targeted therapeutics.

How we got here: the quest for higher AI

Before the 40s: The whimsical automata

Nanorobotics, as the term suggests, brings together the domains of nanotechnology with bioengineering in robotics (biorobotics) and are inextricably rooted in the histories and hopes of each. Contemporary robotics grew out of a rich history of efforts to design, build, operate and control autonomous mechanical devices. Whimsical automata, such as Al-Jazari's and Da Vinci's automatons in the 13th and 15th centuries to mechanised swans[2], 'digesting ducks'[3], 'draughtsmen

[2] Cox and Merlin, 17th century England (see https://themadmuseum.co.uk/history-of-automata/)
[3] Jacques de Vaucanson, 17th century, France (see https://themadmuseum.co.uk/history-of-automata/)

writers'[4], tea servers[5], and others, crowd the history of human ingenuity in creating mechanical representations after their own image or that of other organisms. However, it was (William) Grey Walter's electronic autonomous 'tortoises' built in the 1940s-50s that are now widely considered the first modern 'robots'. These had the basic design features that much of today's advanced micro- or nanorobotics architecture aspire to; namely: a sensing mechanism, a viable energy source for mobility (e.g., Grey Walter used rechargeable batteries) and circuitry for actuation[6] or locomotion (e.g., Grey Walter used analog electronic circuits).

50s - 70s: The rise of AI

Importantly, the more famous of Grey Walter's tortoises, the *Machina Speculatrix* or the 'thinking machine' as the name suggests, could *think* and *act upon it*; as Grey Walter wrote, "it explores its environment actively, persistently, systematically, as most animals do" (Grey Walter, 1963). *Thinking* systems, or *artificial intelligence* (AI) as Stanford University's Professor McCarthy called it in 1956, are a much more recent development than building automata. Indeed, what is now the 'AI domain' is widely considered to have begun with Alan Turing's famous inquiry into "Can machines think?" (Turing, 1950), followed by intensifying scientific interest in machine learning and AI during the early-50s until around the mid-60s. Notable achievements during the time (to name a few) were Arthur Samuel's 'temporal-difference-learning', McCarthy's and Minsky's *Dartmouth Summer Project*, Rosenblatt's early work on developing neural networks etc. However, reality failed to live up to the inflated hype of AI and research interest declined after the 70s with leading figures like McCarthy declaring that "AI is harder than we thought"[7]. The influential *Automatic Language Processing Advisory Committee's* (ALPAC) expressed similar discontent in its 1966 report to the US government; noting that "there has been no machine translation of general scientific text, and none is in immediate prospect" (ALPAC, 1966) (see also Taube 1961; Garvey 2021). Similarly damning was British mathematician James Lighthill's 1973 report to the British Science Research Council that "in no part of the field [of AI] have discoveries made so far produced the major impact that was then promised"[8]. A key outcome of these reports was that AI funding soon dried up and the domain entered into what has since been referred as 'AI winter' (Agar, 2020).

80s – 2000s: A shift towards embodied AI

Notwithstanding the funding pause during this time, research on various sub- and correlated domains of AI (e.g. robotics), at times under the guise of different names ('expert systems') to qualify for non-AI focused research funding, continued throughout the 80s and 90s. Robotics, in particular, benefited, as integration with AI rescued it from a narrowing focus on robotic-arms for industrial use (e.g., Unimate[9]) and the occasional prototype (e.g., Shakey, HILARE[10]) to eventually broaden into a domain of relevance with cross-sectoral applicability (Kuipers, Hart & Nilsson, 2017; Matarić, 2007; Moran, 2007). From the perspective of AI

[4] 19th century: Henri Maillardet, France; Pierre Jaquet-Droz, Switzerland (see https://themadmuseum.co.uk/history-of-automata/)
[5] Hisashige Tanaka, 18th century, Japan (Hornyak, 2006)
[6] Actuator is an electronic gearbox that converts energy to mechanical force to move and or control a device.
[7] https://sitn.hms.harvard.edu/flash/2017/history-artificial-intelligence/
[8] https://www.forbes.com/sites/gilpress/2016/12/30/a-very-short-history-of-artificial-intelligence-ai/
[9] `Unimate' the first industrial robot arm built by George Devol Jr. joined General Motors' assembly line at its Ewing, New Jersey plant in 1961 (http://www.robothalloffame.org/unimate.html) (Mickle 1961)
[10] Shakey was the first mobile robot developed at the Stanford Research Institute (now SRI Intl.) in 1966. Other prototypes in the 60s-70s were CART, HILARE, Freddy, Leachim, SCARA (see e.g., Matarić 2007; Moran 2007).

research(ers), the field had to broaden not only to access other non-AI funding sources in response to scarce AI-focused funding, but also to some extent to remain relevant alongside co-emerging competing technologies of high promissory value such as nanotechnology, bioengineering, industrial robotics etc.

Ironically, the integration of AI and robotics in many ways led to the disintegration of AI's holy grail of developing human-level intelligence (Artificial General Intelligence (AGI)) in traditionally disembodied forms or what is known as *strong-AI* (McCorduck, 2004). By the mid-80s, new thinking on a 'situated' approach to AI proposed a paradigmatic shift away from strong-AI towards AI interactions adaptive of its living environment (embodied or weak-AI) "whose coexistence and co-operation let more complex behaviors emerge" (Brooks, 1990, p. 4). Embodied intelligence proposed a narrower type of AI focused on specific and simpler tasks informed by a more modest, lower 'organismal' level (e.g., insect-level) intelligence (Brooks, 1991), at times borrowing heavily from child development (Di Nuovo & McClelland, 2019; Nehaniv, Morza & Olsson, 2007; Smith & Gasser, 2005; Turing, 1950). In turn, robotics inspired by living biological systems flourished throughout the 90s, intermingling with emerging knowledge across a wide spectrum of technological domains from neuromorphic engineering, evolutionary electronics to nanotechnologies. In particular, an emerging biological offshoot of AI or *biointelligence* using molecular programming (Adleman, 1994; 1998) and DNA nanoscience (Seeman, 1982) inspired an unprecedented integration of AI and robotics with another new area of knowledge that had started garnering immense interest and funding – nanotechnology.

2000s onwards: The rise of nanorobots (embodiments at nanoscales)

A relatively new disruptor compared to AI and robotics, the idea of 'nanotechnology' was born only in 1959 in a now famous address by Richard Feynman, a Caltech physicist and future Noble prize winner at the American Physical Society titled "There's Plenty of Room at the Bottom" (meaning, at the molecular level). Attention to molecular engineering at the time was sparse and it wasn't until 1974 that the term 'nanotechnology' was first used by Professor Norio Taniguchi (1974) at an address to the Japan Society of Precision Engineering to describe the "processing of separation, consolidation and deformation of materials by one atom or one molecule". In large part, nanotechnology took off after the scanning probe microscopy invented in 1981 provided the necessary tool for 'molecular engineering' (Drexler, 1981, 1988).

By the mid-80s, 'nanotechnology' had started attracting research interest globally including garnering immense corporate funding from the likes of Samsung Electronics, Nippon Steel, IBM, Toshiba etc. (WIPO, 2015, p. 12). Patent filing by corporations and academics also ramped up from the early-90s led by the US, Japan and Germany (WIPO 2015, 115). Public sector support too rose globally after 2000 when the Clinton administration - nudged by Richard E. Smalley's[11] dogged lobbying - recognised 'nanotechnology' as a focus area for USA research and development and launched its National Nanotechnology Initiative with the promise of substantive funding to follow (www.nano.gov). Soon after, 60 countries had launched their own nanotechnology strategies, including the European Union and United Kingdom in 2004[12]. Corporate spending on research and development, however, consistently exceeded public support. For example, according to one World Intellectual Property Office report, government funding for nanotechnology in 2012 was $7.9 billion USD compared to the $10billion received from corporate sources the same year

[11] Professor of Chemistry and joint-Nobel winner for the discovery of carbon-60 (popularly 'buckyballs').

[12] The EU's *Towards a European Strategy for Nanotechnology* and Britain's Royal Society and the Royal Academy of Engineering publishing *Nanoscience and Nanotechnologies: Opportunities and Uncertainties*

(WIPO 2015, 115). Throughout the decade, nanotechnology research advanced rapidly, forming new disciplines and coalescing with existing ones (for a detailed analysis of emerging sub-domains in nanotechnology between 1991-2012 see Chen et al. 2013, 16).

In particular, basic research in the biomedical applications of nanotechnology expanded rapidly, bolstered in large part by complementarities with several co-emerging areas of knowledge across various sub-domains of engineering such as tissue engineering, neural engineering, deoxyribonucleic acid (DNA) computing, biomimetics and biological microelectromechanical systems (BioMEMS). Resurgent interest in AI since around 2014 also helped the field of biointelligence (Hodjat, 2015; Morris, Schlenoff, & Srinivasan, 2017; Steels, 2007; Waters, 2015). Rapid advances in AI supported by billions in public and private investments (Waters, 2015) along with increases in computing capacity (cloud services, graphics processing units[13]) for analysing simultaneous increases in data generation worldwide (big data) also benefitted nanorobotics. For instance, various types of DNA sequencing using artificial neural networks (ANN – a set of algorithms for machine learning) provided the necessary 'nanoinformatics' (Adir et al., 2020; Afantitis, 2020) tools needed to realise nano-bioengineering's next frontier – targeted therapeutics.

This was the hope and hype of nanorobotics since its dawn in the mid-80s - that nanorobots would engender a paradigm shift in biomedicine and healthcare – from the traditional systemic treatments to targeted therapeutics. Autonomously propelled by organic (e.g., attached to sperms, blood cells, bacteria) or inorganic actuation (e.g., magnetic or chemical), nanorobots were (are) envisioned to 'get close to' remote areas of the human body to deliver *targeted therapeutics*. Traditional systemic (whole body) therapeutics that left the whole body to suffer from various debilitating side-effects such as in chemotherapy, were be replaced with targeted- surgery, drug delivery, gene editing, diagnostics and *in vivo* imaging. Recent prototypes of *nanorobots* propelled by autonomous navigation systems (Li, et al., 2017) and their more advanced cousins - the *connected nanorobot* with a (wireless) communication interface (Dressler & Fischer, 2015; Kuestner et al., 2020) - advance these hopeful visions at the biomedical frontier ever closer to realisation. In a sense, nanorobotics' holy grail of targeted therapeutics is thus not far from the fantasy of *Fantastic Voyage*. Only, in reality, surgeons would not need to shrink physically to travel inside the body, but instead conduct surgeries from outside the body via wirelessly connectivity to an intelligent nanorobot inside the body designed to perform specific tasks (ibid).

Where we are: the pursuit of strong-(bio)AI

The problem is that realising the promise of nano or microbot-led targeted therapies means grappling with issues of compatibility between *the biological* (the *in vivo* environment) and *the bio-intelligent device* designed using primarily 'engineering' ontologies and epistemologies. Consider *biointelligence* in nanorobots. It encapsulates advances in molecular programming, DNA computing (Adleman, 1994, 1998; Seeman, 1982) and stimuli-responsiveness that are very different than electronic computing. Nevertheless, the race among researchers is for biointelligence to reach electronic computing's levels of higher intelligence but mostly (as we shall see) at the expense of greater attention to its biological compatibility and therein its usability in clinical contexts. Even since its earliest days, starting with the earliest nanorobot prototype - a two-dimensional DNA surface (Gu et al., 2009; Benenson et al. 200; NNI 2009) - research and development of molecular programming as a key component of nanorobotic intelligence was almost wholly focused on achieving higher levels of intelligence inherent in the,

[13] for learning visual data.

> "hierarchical design strategies that were essential to the development of complex electronic systems. The central concept [was] to establish a hierarchy of abstractions that permit[ted] the programming of high-level dynamical [and autonomous] behavior separately from the design of low-level components" (Srinivas et al., 2017, p. 1).

Inherent within these aspirations towards strong-AI was an overwhelming attention to the 'design' calculus that has since dominated the logic of recent advances in DNA-nanoscience. Nanorobotics research(ers) have religiously followed in the footsteps of the path of discovery followed by early electronic systems. As in electronic computing, researchers have developed (to name a few) greater DNA data storage capacity to over 200MB with random information retrieval (Church et al., 2012; Goldman et al., 2013; Organick et al., 2018), DNA barcodes for cellular tagging and or fingerprinting (Shah, Dubey, & Reif, 2019), renewable DNA circuitry (Eshra et al., 2019; Garg et al., 2018) including the reverse applicability of DNA search algorithms in silicon computing (Jazayeri & Sajedi, 2020)[14]. Early machine learning (ML) attempts in AI are similarly reflected in recent work on 'pattern recognition' using "a simple training algorithm" on DNA-based neural networks and are even evaluated against the Modified National Institute of Standards and Technology (MNIST) database commonly used to evaluate ML algorithms (Cherry & Qian, 2018).

Similarly, 'design' goals for attaining higher intelligence levels dominate research on nanodevices using biointelligence derived from 'stimuli-responsiveness' to changes sensed in the acidity or temperature levels of its *in vivo* environment. Most of such stimuli-responsive prototypes are yet to advance beyond a low-level of intelligence essentially resembling "a navigation system for micro/nanoscale vehicles, relying on vision-based close-loop control and path planning" (Wang et al. 2021, 3). Nevertheless, the research driver is uncritically towards strong-AI.

At the same time, that these stimuli-responsive nanorobots are considered "highly promising for their autonomous operation in complex dynamic settings and unpredictable scenarios expected in a variety of realistic nanoscale scenarios [such as vascularised or highly viscous *in vivo* environments]" is important (ibid). For it shows somewhat of a turn in recent thinking around integrating *in vivo* contexts within the 'design' calculi that is crucial for realising nanorobotics-led targeted therapeutics. This is further evidenced by emerging nanorobot exoskeleton designs that combine state of the art stimuli-responsive intelligence with latest advances in molecular programming using 'framework nucleic acid' (FNA) structures - a group of DNA nanostructures of proven biocompatibility (Elmowafy, Tiboni & Solliman, 2019; Wu et al., 2012; Yuan et al., 2019). The 'nanobee' is one such biomimetic nanostructure encapsulating the bee's venom (melittin or MLT) within a tetrahedral FNA exoskeleton (Tian et al., 2021). In much the same way a bee responds with a venomous sting when it perceives a hazard, the 'nanobee' is molecularly programmed to decompose its venomous cargo in response to specific stimuli (e.g., a target cancer protein) in its environment (ibid).

Bio-AI and its biocompatibility problem

The problem is that although such emerging nanoconjugate are designed to deliver the technological state-of-the-art by combining multiple sources of intelligence including some with proven biocompatibility, they don't go far enough to consider the breadth of complexity that dynamic *in vivo* contexts involve. For one, even the latest nanorobotic conjugates leave unaddressed

[14] These are a few examples from the expanding domain of DNA computing and molecular programming.

the overarching challenge of 'how nanorobots will reach its target?' Will the nanorobot be propelled to its *in vivo* target? Or, will it rely on the bloodstream to get there?

The challenge is that very little (if any) research is currently devoted to approaching this 'propulsion problem' beyond a design and fabrication calculus focused on the choice of 'intelligent' or autonomous energy sources to get the nanorobot to its target. This is unsurprising as nanorobotics is dominated by engineering-based domains where realization of biomedical aims (e.g., drug delivery, gene therapies, neurosurgery) necessarily start with 'design' first and all others second including the biology of *in vivo* environment (Horejs, 2020; Van den Hoven, Lokhorst, & Van de Poel, 2012). Consider for instance, Soto and colleagues' (2020, 2) overwhelmingly design-driven choice of propulsion material when they explain that:

> micro/nanorobots relies on developing engines that are continuously "turn-on" and generate enough force to overcome the drag forces from the environment. Therefore, the design and fabrication of small-scale robots are driven by the need for active materials that can continuously convert diverse energy sources into locomotion.

Implicit within these design-driven approach to the 'propulsion problem' is also the methodological reliance on computational models of dynamic *in vivo* environments (like the bloodstream) to conduct *in vitro* or *in silico* simulations of *in vivo* navigation and interactions (Latour Jr & Black, 1993; Perez-Guagnelli et al., 2020). Models for *in silico* simulations are standard practice in bioengineering, biochemistry and related areas, although widely accepted that such oversimplified abstractions inadequately represent the dynamic complexity of *in vivo* environments that vary significantly across organs e.g., the brain environment differs significantly from say the liver, heart etc (Park et al., 2020; Saifi, Poduri & Godugu, 2020). Oversimplification not only tends to have a bias for the more formalizable and quantifiable variables of interest for modelling purposes (Edmonds & Moss, 2005; Lavé et al., 2007) but also disconnects research(ers) from the biological and the human (e.g., bloodstream is often referred as 'hostile environments' (Muresan et al., 2018)) while privileging design-based 'technical' approaches.

One outcome of this is that years have been spent studying a diverse range of organic (enzymes, sperms) and inorganic (magnetic, chemical) autonomous energy sources for nanorobotics propulsion with little or no biocompatibility profile. Chemical sources of self-propulsion are one such contentious bio/nanomaterials used in nanorobot fabrication despite having high oxidative toxicity incompatible with *in vivo* human tissue like hydrazine (N_2H_4) or hydrogen peroxide (H_2O_2). It is only recently that this strand of research has started to look for biocompatible variations such as catalysing H_2O_2 decomposition to release oxygen bubbles for propulsion (Li et al., 2017; Xiao et al., 2016) although with limited success (Chen et al., 2018, 3). Likewise, *in vivo* locomotion with external magnetic instrumentation applying heat probes to *in vivo* nanoparticles (with magnetic properties) although relatively better for locomotive control than chemical sources and minimally invasive, are incompatible due to the risks of heat-damage to tissue (Behkam & Sitti, 2006, 155). Recent use of hydrogel layers in soft micro/nanobots for external magnetic steering, especially the plant-derived hydrogel microstructures, are encouraging in terms of biocompatibility but carry the same risks of tissue damage from heat sensitivity especially when "near-infrared fluorescence" probes are used to excite magnetic locomotion (Chen et al. 2018, 7-8)(Martin-del-Campo et al. 2016, 968). Externally applied acoustic-based locomotion using resonance properties of trapped air bubbles in soft hydrogel-based robots are again, encouraging in terms of research attention to biocompatibility considerations, but unhelpful as bubbles become unstable after a few hours (Bertin et al., 2015, p. in ibid, 15-16). Various other nanomaterials

(including mechanisms for sensing and processing data) that subjectively integrate varying levels of biocompatibility considerations are currently underway and discussed exhaustively elsewhere (see e.g., Behkam & Sitti 2007; Wang et al., 2021; Soto et al., 2020; Singh et al., 2019).

Given these 'propulsion' issues, developing nanostructures like the 'nanobee' that depend on systemic circulation via subcutaneous injections or oral routes to get to target sites attract research attention. The problem is that such journeys via systemic biodistribution poses immense 'en-route' challenges. These include *off-target effects* whereby nanorobots may bind with other cells to form ever-larger aggregations by accretion with serious or fatal consequences (Lächelt & Wagner, 2015, p. 11048). Moreover, many target cancer sites have limited bio-accessibility via the bloodstream, such as the tight vascular networks in the brain "forming a blood-brain-barrier …[that] cannot be passed by passive processes" and thus inaccessible for nanorobots (ibid). Other issues such as retaining efficacy of drug payloads add to the challenges because nucleic acid polymers used for encapsulating payloads are typically made from biomaterials less likely to decompose en-route to the target (e.g., hydrophobic materials) but lack conclusively defined excretory or degradation strategy (see discussion in ibid, 11047-49; Spain et al. 2011).

To overcome these *design* challenges of propulsion, yet more *design* alternatives to systemic *in vivo* distribution have been proposed. One such, is the use of distributed AI based on insect-swarm behaviours whereby insect swarms achieve complex tasks unachievable by a single insect, such as attacking a much larger hazard (Beni, 2020; Mahapatra, 2020). In nanorobotics-led targeted therapeutics, deployment of 'swarm intelligence' require an external AI unit to control a swarm of *in vivo* self-propelled nanorobots that would "need to autonomously disperse in the capillary bed, take chemical sensor reading, mark the region where a positive signal is detected, and form a cluster in that region" (Amato et al., 2010, p. 412). Communication between *in vivo* swarms and its external control unit would use widely used existing short-range communication technologies over wireless (e.g., wi-fi, bluetooth, zigbee, or other radio technologies in the ISM - industrial, scientific and medical- band) or cellular bandwiths (e.g., GSM) (Alsuwaidi et al. 2020; Malan et al. 2004; Memon et al., 2020). However, such connectivity carries immense risks of exposure to the global cyberattack surface and the possibility of unauthorised access to *in vivo* data and algorithms with potentially detrimental or fatal consequences; as shown across a number of implantable medical devices (Mills 2011; Radcliff 2019; CBSNews 2018; see also Dressler and Fischer 2015). Thus, even if swarm intelligence solves the design problem of how a nanorobot can reach its target, it exacerbates the biocompatibility challenges now multiplied by 'swarms' while raising additional concerns around the privacy, safety and security of personal nanorobot networks *connected* to the global internet (Geyer et al., 2018; Kuestner et al., 2020).

Bio-AI and its translatability within a regulatory context

In a sense, this quest for ever-higher levels of bio-AI at the expense of its embodiment's (the nanorobot's) adaptiveness to its *in vivo* environment may be interpreted at best as a critique and at worst a rejection of translatability aims. For if clinical translatability is the end goal, nanorobotics must necessarily expand its focus beyond intelligent task-delivery to (a) its compatibility with the *in vivo* environment within which task delivery will take place, and (b) the external (*ex vivo*) context when nanorobots are also connected to the external world. Connectedness of nanorobots to the global internet pose considerable cybersecurity risks to patient safety and security but are currently anticipatory given that most nanorobotic research still remain in early research phases and have no appreciable implications for clinical translatability at the time of writing. Moreover, the nature and scope of these cybersecurity risks are no different

than those faced by connected medical devices in particular and internet-connected devices more generally; these are discussed exhaustively in 'cybersecurity' scholarship (see Datta Burton et al, 2021a; Dressler & Fischer, 2015). Our concern is with the enduring central question in medical nanorobotics - "will medical nanorobots be biocompatible?" (Freitas Jr., 2003).

According to the International Standard ISO 10993-1 on "Biological evaluation of medical devices" (BSI, 2020; USFDA, 2020b) 'biocompatibility' is defined as the "ability of a medical device or material to perform with an appropriate host response in a specific application". Traditionally, the risks to patient safety arising from issues of biocompatibility, toxicity etc. in innovative medical devices are governed by a risk-based classification system harmonised across existing regulatory frameworks in the USA, Europe and UK with some jurisdictional variability. Medical devices with the highest risks are classified on a scale of ascending risk based on its invasiveness into the human body. *Active Implantable Medical Devices* (AIMDs) and Class III devices are considered the riskiest, and Class I the least. Efforts in the last few years to update these frameworks in order to better capture the relatively less understood but increasingly salient emerging risks of innovative drug-biologic-device combinations have seen the introduction of a new classification of 'combination products' under the AIMD category across the **UK** (MHRA, 2021, pp. 27–28; UK Parliament, 2002), **Europe** (European Medicines Agency, 2019) and **USA** (US-FDA, 2020a)). Under harmonised USA-EU risk categories, combination products generally include further sub-categories such as 'Prefilled Drug or Biologic Delivery Device/System', 'Device Coated/Impregnated/Otherwise Combined with Drug/Biologic/Device' etc. (European Medicines Agency, 2019; US-FDA, 2020a). Nanorobots would fall within one or more of these categories (see Table 1) with some minor jurisdictional variability across the UK and Europe.

Table 1: Combinations Product Types and Common Examples.

Type	Combination Product Description	Common Examples
2, 3	Prefilled drug/biologic delivery systems	transdermal systems or microneedle path pre-loaded with biological product
4, 5	Device coated/impregnated with a drug/biologic	Drug pills embedded with sensors, drug-eluting stents, live cells seeded on or in a device scaffold
6	Drug/Biologic Combinations	Antibody-drug conjugates, progenitor cells combined with a drug to promote homing
7	Separate products requiring Cross Labeling	Light-activated drugs or biological products not co-packaged but labelled for use with a specific light source device
9	Combination product not otherwise described	Various combinations of 'types'

Source: Adapted from (21 CFR 3.2(e)(1) in US-FDA 2020a)*; for full list of types, descriptions and examples see US-FDA (2020).*

Within this regulatory context, clinical translation of nanorobots necessarily entails adherence to a risk-based evaluation of biocompatibility with the human *in vivo* environment. In stark contrast to the centrality of 'design' focus in upstream research, the regulatory view of nanomaterials in downstream medical use is overwhelmingly driven by biocompatibility and toxicity evaluations for ensuring patient safety, above all.

Moreover, recent updates for evaluating biocompatibility of combination and other products in the USA, UK and EU are informed by new proposals in ISO 10993's section 22 devoted to nanomaterials calling for a much more broader view of risk-based criteria than before (US-FDA 2020b; BSI, 2020). Section 22 extends regulatory oversight to emerging nanorobotic

specimens using a purposively broad risk evaluation remit extending over device life cycles (life cycle analysis or LCA) and including even non-nano medical devices with potential for releasing nanoparticles (ISO, 2017).

Yet, as studies show, even conventional LCA do not adequately capture or fully understand the profound implications of nano-particles on patients and society especially in its 'degradation' and systemic-excretion phases. For instance, the impact of a (potential) release of unknown nano-particles (as a micro/nanorobot degrades) on a foetus via the mother's blood has been shown to have highly concerning implications from "malignancies diagnosed during pregnancy, chromosomal abnormalities, abnormal metabolic development" to miscarriages and genetic abnormalities (Gatti et al., 2015, pp. 164–165) (see also Asare et al. 2012; Teng, Wang, & Yan, 2016). Even those nanoparticles evaluated as biocompatible may eventually be rejected by the human host often with fatal consequences in a phenomenon popularly known as 'foreign-body reaction' (FBR). However, as FBR is highly patient-specific and typically encountered post-translation, a discussion of this is beyond the remit of this article although discussed elsewhere (e.g., Anderson, Rodriguez, & Chang. 2008; Klopfleisch & Jung, 2017).

Similarly, regulatory efforts to update conventional toxicology studies' (another key step in clinical translation) to reflect key nanotoxicological considerations such as biopersistence and pharmacokinectics, remain in its early stages (Saifi, Poduri, & Godugu 2020). Adequate expansion of toxicology testing capacity to nanotoxicology are constrained by paucity of specialist expertise (ibid) and funding support (estimated to cost between $249million and 1.18billion USD, see Choi, Ramachandran, & Kandlikar, 2009). Yet this expansion is much needed as conventional toxicology studies not only "neglect [toxicity] at molecular levels …e.g. [nanoparticles] often produce sublethal toxicity which does not directly cause organ toxicity but alter physiological functions of the cells," but also that toxicity data conventionally derived in *in-vitro* testing inadequately mimics *in vivo* environments with inconclusive results (ibid, 410). In sum, generation of conclusive data on biocompatibility and toxicology characterisations of medical-use nanorobotics/particles, especially over device lifecycles and beyond, remains a long way off.

Where next: contextualising bio-AI within its environment

The central issue for the domain's translatability aims is thus the lack of meaningful engagement between design and biocompatibility aims; and reflected at the disciplinary level as weak engagement between (bio/nano)engineering, medical practice and regulatory domains. In the early years of medical nanorobotics, biocompatibility challenges received little or no attention within what was then considered the domain's 'grand challenges'. Mettin Sitti, founding member of the influential US-based Carnegie Mellon University's Nanorobotics Laboratory, and colleagues for example, summarised these in 2007 as "On-board chemical motion control, steering, wireless communication, sensing, and position detection [as the] few of the future challenges for this work" (Behkam & Sitti, 2007, 154). Recent scholarship are more acknowledging of biocompatibility as a key challenge. As Agrahari and colleagues conclude,

> "assembling these functions of nanosystems while remaining biocompatible and nontoxic, controllable, and degradable or eliminable, is a *formidable long-term technological and engineering challenge*" (Agrahari et al. 2020, *my emphasis*).

What is problematic here however, is the persistence of an uncritical and reductive interpretation of 'biocompatibility' as a technical challenge alone and resolved with a technical fix. This is challenging for translatability as it misses the salience of regulatory and medical practice

considerations without which translation is unlikely as "technical fixes do not address the real problem [of biocompatibility] but the problem in as far as it is amenable to technical solutions" (Van den Hoven et al., 2012, 152) (see also Datta Burton et al. 2021a; 2021b, 13-17). A key outcome of this is that after two decades of research and billions in funding, nanorobotics remains firmly in the early stages of testing (*in-silico*, *in-vitro*) with a handful being trialed on animal models, and some human trials planned.

As such, basic research articles in the field typically acknowledge the need for biocompatibility considerations in future research. However, they show little or no evidence of meaningful interdisciplinary involvement from downstream regulatory or user areas (such as regulatory specialists, clinicians) that have been shown to significantly improve technological translatability (Datta Burton et al., 2020a; Patel et al., 2019; Sollini et al., 2020). To borrow from Sharp and Langer (2011, p. 527), 'convergence' of disciplines "where engineers and physical scientists are equal partners with biologists and clinicians in addressing many of the new medical challenges" has been at best limited in nanorobotics as expertise have stayed within their disciplinary silos. For instance, a recent 296-page textbook on 'Engineering, Medicine and Science at the Nano-scale,' intended for "Students at universities the world over" (Fonash & Van de Voorde, 2018) mentions 'biocompatible' once (in pp 215) and stemmed variations of 'toxic/toxicity/toxicology' just five times (twice in page 202, and once each in pages 203, 2010, and 2011). In a similar vein, the basal ISO 13014 "Guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment [for nanotechnologies]" views its applicability for a limited downstream audience writing that,

> "This Technical Report will be of value to parties *(e.g. toxicologists, ecotoxicologists, regulators, health and safety professionals)* interested in assessing and interpreting the potential toxicological effect of manufactured NOAAs [nano-objects and their aggregates and agglomerates greater than 100 nm]" (ISO, 2012, *my emphasis*).

In many ways, disciplinary silos are the unintended consequences of specialisation that is at once necessary for developing emerging domains like nanorobotics, as it is problematic. For it risks insulating knowledge thus generated from its practical and societal context that is crucial for routinisation into practice where the overarching goal is that the innovative technology,

> "must give patients, users and other persons a high level of protection and achieve the intended level of performance when implanted in human beings; …relating both to the technical safety features and the inspection procedures for such devices" (Council, 1990).

Meaningful interdisciplinarity, especially in upstream research, has been shown to be helpful in mitigating the adverse impacts of disciplinary silos (Datta Burton et al., 2020b; Michalec et al., 2021; Patel et al., 2019; Wong et al., 2008) such as the disconnect between design and biocompatibility aims in medical nanorobotics. As Sonia Contera, Professor of Biological Physics at the University of Oxford has argued in her book *Nano Comes to Life* that "biology [will need to] become physics" for medical nanotechnology to be realizable (in Horejs 2020). I argue, perhaps even more provocatively than Contera, that until physics becomes biology and engages with a host of multidisciplinary expertise from cybersecurity, regulatory to medicine and healthcare, nanorobotics-led therapeutics is unlikely to be realizable.

Conclusion

This article presented weak interdisciplinary engagement as the overarching critique of the nanorobotics domain's grand clinical translatability aims. Through the historically entangled ambitions of technologists across multiple (bio)engineering and computational domains since the 40s, the article showed how an array of 'peak' technology nanorobots have been produced driven overwhelmingly by an uncritical 'technical' design ethos. Along the way, and especially in the last two decades of intensifying nanorobotics research, meaningful considerations of *in vivo* contexts have largely been neglected in favour of advancing 'technical' research for ever-higher levels of bio-AI with few if any qualitative commitment or contribution to medicine. The point, as some may argue, that technical knowledge production is for knowledge alone and do not need to have societal benefit considerations is a fair point. However, it does not hold in the case of nanorobotics given the founding clinical translatability ethos of the domain especially when medical applicability is the stated aim of a majority of basic research papers in the area.

To make translation realizable, safety and wellbeing of the human host should have driven research especially in its upstream conceptualisation phases by integrating translation-related regulatory and medical-use considerations such as biocompatibility, toxicity etc via meaningful inclusion of regulatory and medical expertise. Indeed, that research direction towards meaningful adaptiveness of nanorobots to its (*in vivo*) environment have so far been overwhelmingly ceded by the seemingly loftier design-driven race for attaining the holy grail of ever higher levels of bio-AI, may be interpreted as a rejection of embodied weak-AI in favour of abstract strong-AI. Likewise, that the meaningful inclusion of multidisciplinary translation-related voices is yet to happen after nearly decades of design-led research may also be reasonably interpreted as a critique of the nanorobotics domain's commitment to translation or its likelihood anytime soon.

Abidin, Z. H. F., Hassan, K. H., & Zainol, Z. A. (2020). Regulating Risk of Nanomaterials for Workers through Soft Law Approach. *NanoEthics*, *14*(2), 155–167.

Adir, O., Poley, M., Chen, G., Froim, S., Krinsky, N., Shklover, …& Schroeder, A. (2020). Integrating Artificial Intelligence and Nanotechnology for Precision Cancer Medicine. *Advanced Materials*, *32*(13).

Adleman, L. M. (1994). Molecular computation of solutions to combinatorial problems. *Science. 266* (5187), 1021–1024.

Adleman, L. M. (1998). Computing with DNA. *Scientific American*, *279*(2), 54–61.

Afantitis, A. (2020). Nanoinformatics: Artificial Intelligence and Nanotechnology in the New Decade. *Combinatorial Chemistry & High Throughput Screening*, *23*(1), 4–5.

Agar, J. (2020). What is science for? The Lighthill report on artificial intelligence reinterpreted. *The British Journal for the History of Science, 53*(3), 289-310.

Agrahari, V., Chou, M. L., Chew, C. H., Noll, J., & Burnouf, T. (2020). Intelligent micro-/nanorobots as drug and cell carrier devices for biomedical therapeutic advancement: Promising development opportunities and translational challenges. *Biomaterials*, *260*, 120163.

Allegaert, K., Smits, A., & van den Anker, J. N. (2012). Physiologically Based Pharmacokinetic Modeling in Pediatric Drug Development: A Clinician's Request for a More Integrated Approach. *Journal of Biomedicine and Biotechnology*, *2012*, 1–3.

Allhoff, F. (2009). The coming era of nanomedicine. *American Journal of Bioethics*, *9*(10), 3–11.

Allhoff, F., Lin, P., Moor, J. H., & Weckert, J. (2007). *Nanoethics: the ethical and social implications of nanotechnology.* John Wiley & Sons.

ALPAC. (1966). *Languages and machines: computers in translation and linguistics.* A report by the Automatic Language Processing Advisory Committee, Division of Behavioral Sciences, National Academy of Sciences, National Research Council. Washington, D.C.: National Academ.

Alsuwaidi, A., Hassan, A., Alkhatri, F., Ali, H., & Mohammad, Q. H., Alrabaee, S. (2020). Security Vulnerabilities Detected in Medical Devices. *IEEE. 2020 12th Annual Undergraduate Research Conference on Applied Computing (URC)*, 1-6.

Amato, P., Masserini, M., Mauri, G., & Cerofolini, G. (2010). Early-stage diagnosis of endogenous diseases by swarms of nanobots: an applicative scenario. In *International Conference on Swarm Intelligence,* 408-415. Berlin, Heidelberg: Springer.

Anderson, J. M., Rodriguez, A., & Chang., D. T. (2008). Foreign body reaction to biomaterials. In *Seminars in immunology, 20*(2), 86-100. Academic Press.

Asare, N., Instanes, C., Sandberg, W. J., Refsnes, M., & Schwarze, P., Kruszewski, M., Brunborg, G. (2012). Cytotoxic and genotoxic effects of silver nanoparticles in testicular cells. *Toxicology, 291*(1-3), 65-72.

Behkam, B, & Sitti, M. (2006). Toward Hybrid Swimming Microrobots: Propulsion by an Array of Bacteria. In *Proc. of the IEEE Int. Conf. of Engineering in Medicine and Biology.* 2421–2424.

Behkam, Bahareh, & Sitti, M. (2007). Bacteria Integrated Swimming Microrobots. NanoRobotics Laboratory, Department of Mechanical Engineering, Carnegie Mellon University, USA. Lecture Notes in Artificial Intelligence. In M. Lungarella et al. (Eds.) (Ed.), *50 Years of AI.: Vol. LNAI 4850* (pp. 154–163). Springer-Verlag, Berlin and Heidelberg.

Beni, G. (2020). Swarm intelligence. Complex Social and Behavioral Systems. *Game Theory and Agent-Based Models,* 791-818.

Benenson, Y., Paz-Elizur, T., Adar, R., Keinan, E., Livneh, Z., & Shapiro, E. (2001). Programmable and autonomous computing machine made of biomolecules. *Nature, 414*(6862), 430–434.

Bertin, N., A., T., Spelman, O. S., Gredy, L., Bouriau, M., Lauga, E., & Marmottant, P. (2015). Propulsion of bubble-based acoustic microswimmers. *Physical Review Applied 4(6), 064012.*

Brooks, R. A. (1990). Elephants Don't Play Chess. *Robotics and Autonomous Systems*, *6*, 3–15.

Brooks, R. A. (1991). New approaches to robotics. *Science 253,* 1227–1232.

BSI. (2020). Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process. *British Standards Institute.* Retrieved 12 March 2021 from https://www.bsigroup.com/en-GB/standards/bs-en-iso-10993-12020/.

CBSNews. (2018). How medical devices like pacemakers and insulin pumps can be hacked. *CBS News.* (November, 8). Retrieved 12 December 2020 from https://www.cbsnews.com/news/cybersecurity-researchers-show-medical-devices-hacking-vulnerabilities/.

Chen, H., Roco, M. C., Son, J., Jiang, S., Larson, C. A., & Gao, Q. (2013). Global nanotechnology development from 1991 to 2012: Patents, scientific publications, and effect of NSF funding. *Journal o Journal of nanoparticle research, 15(9),* 1-21.

Chen, X., Jang, B., Ahmed, D., Hu, C., Marco, C. De, Mushtaq, F., …& Mushtaq, F. (2018). Small-Scale Machines Driven by External Power Sources. *Advanced Materials*, *30*(15), 1–58.

Cherry, K. M., & Qian, L. (2018). Scaling up molecular pattern recognition with DNA-based winner-take-all neural networks. *Nature, 559*(7714), 370–388.

Choi, J.-Y., Ramachandran, G., & Kandlikar, M. (2009). The Impact of Toxicity Testing Costs on Nanomaterial Regulation. *Environmental Science & Technology*, *43*(9), 3030–3034.

Church, G. M., Gao, Y., & Kosuri, S. (2012). Next-generation digital information storage in DNA. *Science 337, 1628*.

Contera, S. (2019). *Nano comes to life: How nanotechnology is transforming medicine and the future of biology*. Princeton University Press.

Council. (1990). Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. *Official Journal L 189*, 0017-0036.

Datta Burton, S., Mahfoud, T., Aicardi, C. C. R., & Rose, N. (2021a). Clinical translation of computational brain models: understanding the salience of trust in clinician-researcher relationships. In Special Issue 'AI and its Discontents'. *Interdisciplinary Science Reviews 46*(1), 138-157.

Burton, S. D., Kieslich, K., Paul, K. T., Samuel, G., & Prainsack, B. (2021b). Rethinking value construction in biomedicine and healthcare. *BioSocieties,* 1-24.

Di Nuovo, A., & McClelland, J. L. (2019). Developing the knowledge of number digits in a child-like robot. *Nature Machine Intelligence, 1(12),* 594-605.

Dressler, F., & Fischer, S. (2015). Connecting in-body nano communication with body area networks: Challenges and opportunities of the Internet of Nano Things. *Nano Communication Networks*, *6*(2), 29–38.

Drexler, K. E. (1981). Molecular engineering: An approach to the development of general capabilities for molecular manipulation. *Proceedings of the National Academy of Sciences, 78*(9), 5275-5278.

Drexler, K. E. (1988). *Engines of Creation: The Coming Era of Nanotechnology*. Anchor Library of Science.

Dupuy, J. P. (2007). Some pitfalls in the philosophical foundations of nanoethics. *The Journal of medicine and philosophy, 32*(3), 237-261.

Edmonds, B., & Moss, S. (2005). From KISS to KIDS–an 'anti-simplistic'modelling approach. Manchester Metropolitan University Business School Working Paper Series. In *International workshop on multi-agent systems and agent-based simulation, 130-144*. Berlin, Heidelberg: Springer.

Elmowafy, E. M., Tiboni, M., & Soliman, M. E. (2019). Biocompatibility, biodegradation and biomedical applications of poly(lactic acid)/poly(lactic-co-glycolic acid) micro and nanoparticles. *Journal of Pharmaceutical Investigation*, *49*(4), 347–380.

Eshra, A., Shah, S., Song, T., & Reif, J. (2019). Renewable DNA Hairpin-Based Logic Circuits. *IEEE Transactions on Nanotechnology*, *18*, 252–259.

European Medicines Agency. (2019). Draft Guideline on the quality requirements for drug-device combinations. *EMA/CHMP/QWP/BWP/259165/2019 Committee for Medicinal Products for Human Use (CHMP)*, *EMA/CHMP/Q*(May), 1–26. Retrieved 13 March 2021

from https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-requirements-drug-device-combinations_en.pdf

Fisher, D. (1983). The going gets tough when we descend from the ivory tower. *Analysis and Intervention in Developmental Disabilities, 3*, 249–255.

Fonash, S. J., & Van de Voorde, M. (2018). *Engineering, medicine and science at the nano-scale*. John Wiley & Sons.

Forbes, J. (1823). *A Treatise on the Diseases of the Chest by R.T.H. Laennec [René-Théophile-Hyacinthe Laënnec]*. Translated from French to English by John Forbes, Translator's Preface by John Forbes, 13-14, [First American Edition], James Webster, P. Retrieved on 12 January 2021 from https://archive.org/details/65340230R.nlm.nih.gov

Freitas Jr., R. A. (2003). Nanomedicine, Volume IIA: Biocompatibility. *Landes Bioscience, Georgetown, TX*. Retrieved 19 January 2021 from *http://www.nanomedicine.com/NMIIA.htm*. https://www.kurzweilai.net/will-medical-nanorobots-be-biocompatible

Garg, S., Shah, S., Bui, H., Song, T., Mokhtar, R., & Reif, J. (2018). Renewable Time-Responsive DNA Circuits. *Small*, *14*(33), 1801470.

Garvey, C. S. (2021). The "General Problem Solver" Does Not Exist: Mortimer Taube and the Art of AI Criticism. *IEEE Annals of the History of Computing, 43*(1), 60-73

Gatti, A. ., Montanari, M., & Vaseashta, A. (2015). Nanopathology - Risk Assessment of Mysterious Cryptogenic Diseases. In A. Vaseashta (Ed.), *Life cycle analysis of nanoparticles: reducing risk and liability. DEStech Publications, Inc.*, 143–171.

Geyer, R., Stelzner, M., Büther, F., & Ebers, S. (2018). BloodVoyagerS. *Proceedings of the 5th ACM International Conference on Nanoscale Computing and Communication*, 1–6.

Goldman, N., Bertone, P., Chen, S., Dessimoz, C., LeProust, E. M., Sipos, B., & Birney, E. (2013). Towards practical, high-capacity, low-maintenance information storage in synthesized DNA. *Nature, 494*(7435), 77-80.

Greenhalgh, T., Swinglehurst, D., & Stones, R. (2014). Rethinking resistance to 'big IT': a sociological study of why and when healthcare staff do not use nationally mandated information and communication technologies. *Health Services and Delivery Res.*, *2*(39), 1–86.

Greenhalgh, T., Wherton, J., Papoutsi, C., Lynch, J., Hughes, G., A'Court, C., …& Shaw, S. (2017). Beyond Adoption: A New Framework for Theorizing and Evaluating Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies. *Journal of Medical Internet Research*, *19*(11), e367.

Grey Walter, W. (1963). *The Living Brain*. New York: W.W. Norton & Co.

Gruber, D., Cummings, G. G., Leblanc, L., & Smith, D. L. (2009). Factors influencing outcomes of clinical information systems implementation: a systematic review. *CIN: Computers, Informatics, Nursing, 27*(3), 151-163.

Grunwald, A. (2010). From Speculative Nanoethics to Explorative Philosophy of Nanotechnology. *NanoEthics*, *4*(2), 91–101.

Gu, H., Chao, J., Xiao, S.-J., & Seeman., N. C. (2009). Dynamic patterning programmed by DNA tiles captured on a DNA origami substrate. *Nature Nanotechnology*, 15 February.

Hodjat, B. (2015). The AI Resurgence: Why Now? *WIRED*. Retrieved 18 December 2020 from https://www.wired.com/insights/2015/03/ai-resurgence-now/

Horejs, C.-M. (2020). I, nanorobot. Review of `Nano Comes to Life' (By Contera, Sonia, 2019, Princeton University Press). *Nature Physics*, *16*(3), 239–239.

Hornyak, T. N. (2006). *Loving the Machine: The Art and Science of Japanese Robots. Kodansha International.*

ISO. (2012). ISO/TR 13014:2012(en). Nanotechnologies — Guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment. *International Standards Oorganisation (ISO).* Retrieved 13 March 2021 from https://www.iso.org/obp/ui/#iso:std:iso:tr:13014:ed-1:v1:en

Jazayeri, N., & Sajedi, H. (2020). DNAVS: an algorithm based on DNA-computing and vortex search algorithm for task scheduling problem. *Evolutionary Intelligence*, 1-11.

Kellermann, A. L., & Jones, S. S. (2013). What It Will Take To Achieve The As-Yet-Unfulfilled Promises Of Health Information Technology. *Health Affairs, 32*(1), 63–68.

Kilsdonk, E., Peute, L. W., & Jaspers, M. W. (2017). Factors influencing implementation success of guideline-based clinical decision support systems: a systematic review and gaps analysis. *International journal of medical informatics, 98,* 56-64.

Klopfleisch, R., & Jung, F. (2017). The pathology of the foreign body reaction against biomaterials. *Journal of Biomedical Materials Research Part*, *105*(3), 927-940.

Kuestner, A., Stratmann, L., Wendt, R., Fischer, S., & Dressler, F. (2020). A simulation framework for connecting in-body nano communication with out-of-body devices. *Proceedings of the 7th ACM International Conference on Nanoscale Computing and Communication, NanoCom 2020*, 9–10.

Kuipers, B. F., Hart, P. E., & Nilsson, N. J. (2017). Shakey: from conception to history. *AI Magazine 38,* 88-103.

Lächelt, U., & Wagner, E. (2015). Nucleic Acid Therapeutics Using Polyplexes: A Journey of 50 Years (and Beyond). *Chemical Reviews*, *115*(19), 11043–11078.

Latour Jr, R. A., & Black, J. (1993). Development of FRP composite structural biomaterials: fatigue strength of the fiber/matrix interfacial bond in simulated in vivo environments. *Journal of biomedical materials research, 27*(10), 1281-1291.

Lavé, T., Parrott, N., Grimm, H. P., Fleury, A., & Reddy, M. (2007). Challenges and opportunities with modelling and simulation in drug discovery and drug development. *Xenobiotica*, *37*(10–11), 1295–1310.

Li, T., Chang, X., Wu, Z., Li, J., Shao, G., Deng, X., …& Wang, J. (2017). Autonomous Collision-Free Navigation of Microvehicles in Complex and Dynamically Changing Environments. *ACS Nano*, *11*(9), 9268–9275.

Liao, L., & Mark, D. B. (2003). Clinical Prediction Models: Are We Building Better Mousetraps? *Journal of the American College of Cardiology, 42*(5), 851–853.

Liberati, E. G., Ruggiero, F., Galuppo, L., Gorli, M., González-Lorenzo, M., Maraldi, M., …& Moja, L. (2017). What hinders the uptake of computerized decision support systems in hospitals? A qualitative study and framework for implementation. *Implementation Science*, *12*(1), 1-13.

Mahapatra, S. (2020). Simulation of Artificial Bio-Nanobots for Cell Repair. Protection Using Swarm of Kilobots. *KU Leuven,* 1–32.

Malan, D., Fulford-Jones, T., Welsh, M., & Moulton, S. (2004). Codeblue: an ad hoc sensor network infrastructure for emergency medical care. *Proceedings of the International Workshop on Wearable and Implantable Body Sensor Networks 5* (April).

Mann, D. M., Kannry, J. L., Edonyabo, D., Li, A. C., Arciniega, J., Stulman, J., …& McGinn, T. G. (2011). Rationale, design, and implementation protocol of an electronic health record integrated clinical prediction rule (iCPR) randomized trial in primary care. *Implementation Science*, *6*(1), 109.

Martin-del-Campo, M., Rosales-Ibanez, R., Alvarado, K., Sampedro, J. G., Garcia-Sepulveda, C. A., Deb, S., …& Rojo, L. (2016). Strontium folate loaded biohybrid scaffolds seeded with dental pulp stem cells induce in vivo bone regeneration in critical sized defects. *Biomaterials Science*, *4*(11), 1596–1604.

Matarić, M. J. (2007). *The robotics primer*. Mit Press.

McCorduck, P. (2004). *Machines Who Think*. (2nd ed.), Natick, MA: A. K. Peters, Ltd.

Memon, M. H., Memon, M. H., Marium, S. M., & Khan, J. (2020). Security and Privacy Issues of Medical Systems in Wireless Sensor Networks: A Survey. *Asian Journal For Convergence In Technology 5*(3): 08-12.

MHRA. (2021). Human Factors and Usability Engineering – Guidance on the regulation of Medical Devices Including Drug-device Combination Products in Great Britain. *The Medicines and Healthcare products Regulatory Agency*. Retrieved 12 March 2021 from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/970563/Human-Factors_Medical-Devices_v2.0.pdf.

Michalec, O., O'Donovan, C., & Sobhani, M. (2021). What is robotics made of? The interdisciplinary politics of robotics research. *Humanities and Social Sciences Communications*, *8*(1), 1-15.

Mickle, P. (1961). *A peep into the automated future*. The Trentonian.

Mills, E. (2011). Researcher battles insulin pump maker over security flaw. *CNET*. (August, 26). Retrieved 13 December 2020 from https://www.cnet.com/news/researcher-battles-insulin-pump-maker-over-security-flaw/.

Moran, M. E. (2007). Evolution of robotic arms. *Journal of Robot Surgery 1,* 103-111.

Morris, K. C., Schlenoff, C., & Srinivasan, V. (2017). Guest Editorial A Remarkable Resurgence of Artificial Intelligence and Its Impact on Automation and Autonomy. *IEEE Transactions on Automation Science and Engineering*, *14*(2), 407–409.

Muresan, C. I., Birs, I. R., Folea, S., & Ionescu, C. (2018). Fractional order based velocity control system for a nanorobot in non-Newtonian fluids. *Bulletin of the Polish Academy of Sciences: Technical Sciences*, *66*(6), 991–997.

Nehaniv, C. L., Mirza, N. A., & Olsson, L. (2007). Development via information self-structuring of sensorimotor experience and interaction. *Lecture Notes in Computer Science, 4850*. Springer, Heidelberg.

NNI. (2009). NNI Scientific Accomplishments 2009. US *National Nanotechnology Initiative*. Retrieved 23 January 2021 from https://doi.org/10.1038/nnano.2009.5

Organick, L., Ang, S. D., Chen, Y.-J., Lopez, R., Yekhanin, S., Makarychev, …& Strauss, K. (2018). Random access in large-scale DNA data storage. *Nature Biotechnology*, *36*(3), 242–248.

Park, D. Y., Lee, J., Chung, J. J., Jung, Y., & Kim, S. H. (2020). Integrating Organs-on-Chips: Multiplexing, Scaling, Vascularization, and Innervation. *Trends in Biotechnology*, *38*(1), 99–112.

Patel, M., Webb, H., Jirotka, M., Davoust, A., Gales, R., Rovatsos, M., & Koene, A. (2019). Harnessing interdisciplinarity to promote the ethical design of AI systems. *In ECIAIR 2019, European Conference on the Impact of Artificial Intelligence and Robotics, Oxford: UK 246*.

Perez-Guagnelli, E., Jones, J., Tokel, A. H., Herzig, N., Jones, B., Miyashita, S., & Damian, D. D. (2020). Characterization, simulation and control of a soft helical pneumatic implantable robot for tissue regeneration. *IEEE Transactions on Medical Robotics and Bionics, 2(1),* 94-103.

Pressman, J. L., & Wildavsky, A. (1973). *Implementation.* Berkeley, CA: University of California Press.

Radcliff, J. (2019). PEAC Presentation: Patient turned Hacker. *FDA.gov.* (July, 13). Retrieved 12 December 2020 from https://www.fda.gov/media/130719/download.

Saifi, M. A., Poduri, R., & Godugu, C. (2020). Nanomedicine: Implications of nanotechnology. In M. A. Saifi, R. Poduri, & C. Godugu (Eds.), *Nanomedicine: Implications of Nanotoxicology. Drug Discovery and Development: From Targets and Molecules to Medicines.* (pp. 393–415).

Seeman, N. C. (1982). Nucleic acid junctions and lattices. *Journal of Theoretical Biology, 99*(2): 237–247.

Shah, N. D., Steyerberg, E. W. & Kent, D. M. (2018). Big Data and Predictive Analytics Recalibrating Expectations. *Jama 320*(1), 27-28.

Shah, S., Dubey, A. K., & Reif, J. (2019). Programming Temporal DNA Barcodes for Single-Molecule Fingerprinting. *Nano letters, 19*(4), 2668-2673.

Sharp, P., & Langer, R. (2011). Promoting convergence in biomedical science. *Science 333:527*.

Singh, A. V., Ansari, M. H. D., Laux, P., & Luch, A. (2019). Micro-nanorobots: important considerations when developing novel drug delivery platforms. *Expert Opinion on Drug Delivery*, *16*(11), 1259–1275.

Smith, L., & Gasser, M. (2005). The development of embodied cognition: Six lessons from babies. *Artificial life, 11(1-2),* 13-29.

Sollini, M., Gelardi, F., Matassa, G., Delgado Bolton, R. C., Chiti, A., & Kirienko, M. (2020). Interdisciplinaridad: un requerimiento esencial para la traslación de investigación en radiómica a la práctica clínica. *Revista Española de Medicina Nuclear e Imagen Molecular*, *39*(3), 146–156.

Soto, F., Wang, J., Ahmed, R., & Demirci, U. (2020). Medical Micro/Nanorobots in Precision Medicine. *Advanced Science*, *7*(21), 1–34.

Spain, S. G., Yaşayan, G., Soliman, M., Heath, F., Saeed, A. O., & Alexander, C. (2011). Nanoparticles for Nucleic Acid Delivery. In *Comprehensive Biomaterials*, 389–410.

Srinivas, N., Parkin, J., Seelig, G., Winfree, E., & Soloveichik, D. (2017). Enzyme-free nucleic acid dynamical systems. *Science*, *358*(6369), eaal2052.

Steels, L. (2007). Fifty years of AI: from symbols to embodiment – and back. *Lecture Notes in Computer Science, v4850.* Springer, Heidelberg.

Taniguchi, N. (1974). On the Basic Concept of "Nano-Technology". *Proceedings International Conference on Production Engineering,* Tokyo, Part II, Japan Society of Precision Engineering.

Taube, M. (1961). *Computers and Common Sense. The Myth of Thinking Machines.* Columbia University Press.

Teng, C., Wang, Z., & Yan, B. (2016). Fine particle-induced birth defects: Impacts of size, payload, and beyond. Birth Defects Research. *Part C, Embryo Today: Reviews, 108*(3), 196-206.

Tian, T., Xiao, D., Zhang, T., Li, Y., Shi, S., Zhong, W., …& Lin, Y. (2021). A Framework Nucleic Acid Based Robotic Nanobee for Active Targeting Therapy. *Advanced Functional Materials*, *31*(5), 1–9.

Turing, A. M. (1950). Computing machinery and intelligence. *Oxford University Press on behalf of MIND (the Journal of the Mind Association)*, 433–460.

UK Parliament. (2002). *Medical Devices Regulations 2002 (SI 2002 No 618, as amended). 618*, 1–6. Retrieved 13 March 2021 from https://www.legislation.gov.uk/uksi/2002/618/contents/made

US-FDA. (2020a). *Combination Product. Definition Combination Product Types. 21 CFR 3.2(e).* Retrieved 13 March 2021 from https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types

_____(2020b). Use of International Standard ISO 10993-1, "Biological evaluation of medical devices-Part 1: evaluation and testing within a risk management process" guidance for industry and Food and Drug Administration staff. *U.S. Department of Health and Human Services Food and Drug Administration*, *301*, 1–68. Retrieved 13 March 2021 from https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-%0Ahttp://www.fda.gov.proxy1.library.jhu.edu/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

Van den Hoven, J., Lokhorst, G.-J., & Van de Poel, I. (2012). Engineering and the Problem of Moral Overload. *Science and Engineering Ethics*, *18*(1), 143–155.

Wang, X., Hu, C., Pane, S., & Nelson, B. J. (2021). Dynamic Modeling of Magnetic Helical Microrobots. *IEEE Robotics and Automation Letters*, 1–1.

Waters, R. (2015). Investor rush to artificial intelligence is real deal. *The Financial Times.* Retrieved on 22 February 2021 from https://www.ft.com/content/019b3702-92a2-11e4-a1fd-00144feabdc0#axzz3Ny5kj89q

Wessler, B. S., Paulus, J., Lundquist, C. M., Ajlan, M., Natto, Z., Janes, W. A., …& Kent, D. M. (2017). Tufts PACE Clinical Predictive Model Registry: update 1990 through 2015. *Diagnostic and Prognostic Research*, *1*(1), 1-8.

WIPO. (2015). Breakthrough Innovation and Economic Growth. *Economics & Statistics Series*, 1–144. World Intellectual Property Office. Retrieved 19 December 2020 from http://www.wipo.int/edocs/pubdocs/en/wipo_pub_944_2015.pdf

Wong, M. C., Turner, P., & Yee., K. C. (2008). Involving Clinicians in the Development of an Electronic Clinical Handover System-Thinking Systems not Just Technology. *Studies in Health Technology and Informatics 136*, 490–495.

Wu, Y., Wu, Z., Lin, X., He, Q., & Li, J. (2012). Autonomous movement of controllable assembled Janus capsule motors. *ACS nano, (12),* 10910-10916. 6.

Wyatt, J. C., & Altman, D. G. (1995). Commentary: Prognostic models: Clinically useful or quickly forgotten? *BMJ*, *311*(7019), 1539.

Xiao, M., Wang, L., Ji, F., & Shi, F. (2016). Converting chemical energy to electricity through a three-jaw mini generator driven by the decomposition of hydrogen peroxide. *ACS applied materials & interfaces, 8(18),* 11403-11411.

Yang, Q., Zimmerman, J., Steinfeld, A., Carey, L., & Antaki, J. F. (2016). Investigating the Heart Pump Implant Decision Process. *Proceedings of the 2016 CHI Conference on Human Factors in Computing Systems*, 4477–4488.

Yuan, Y., Gu, Z., Yao, C., Luo, D., & Yang, D. (2019). Nucleic Acid–Based Functional Nanomaterials as Advanced Cancer Therapeutics. *Small*, *15*(26), 1900172.
