Perspective

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The biote-bot hybrid. The ultimate biothreat merging nanobots, AI-enabled cybernetics and synthetic biology

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The paper intends to warn stakeholders, by using open sources, of the possibility of extremely small, nano-/pico-aerial vehicles controlled locally or remotely by artificial intelligence mindsets to deliver, on specific hosts and tissues, either diverse bioagents produced by conventional and synthetic (micro)biology, including xenobiota or bionic microbiota or existing microbiota selected from natural reservoirs. The accuracy in delivery would leverage minute quantities of pathogens to cause mass-scale bioevents. Such hybrids (biote-bots) would increase the effectiveness of unfit but virulent pathogens, preserve the carried biota for the trip and contain bioagents' weaponization footprint to levels below the detection threshold of current regimes, while complicating immune response and denying pre-infection detection and identification. To respond, we suggest that novel diagnostics and surveillance amenities are needed, prompting cooperation of experts from Medicine, medical instruments/diagnostics, artificial Intelligence and from disciplines tackling cybernetics, remote sensing, surveying and tracking.

Tweetable abstract: Nano/picodrones may load and deliver select/engineered bioagents and place them to specific biocompartments of targeted hosts, evading usual surveillance methods. AI-enhanced diagnostics leveraging advances from fields as aeronautics could detect and identify such threats.

First draft submitted: 2 June 2023; Accepted for publication: 11 August 2023; Published online: 29 August 2023

Keywords: biodrones • bionic agents • cybernetics • engineered bioagents • technosignature • technosynthetic entities • UAV-unmanned aerial vehicles • xenoorganisms

The state of the art

Although the malevolent use of bioagents is a well-established fact of the human history in both ancient and modern times and includes events of different scales and with different kinds of perpetrators, state, state-sponsored or non-state ones [1], a number of bioevents taking place in the last 15 years have raised the alarm in the medical sector of the biosecurity establishments. These events included, without being limited to the Ebola [2] and the CoViD-19 [3] outbreaks, although in both cases no perpetrated origin has been firmly established to date. The bioagents in general were identified in the early 2000s as a major threat for the USA [4] and were included in the rationale for staging the 2003 invasion and regime change in Iraq [5]. The issue was taken to new dimensions in the second half of the 2010s, when the GCBR-Global Catastrophic Biological Risk was coined as a cognitive entity [6–8]. In-between, discouraging developments had been published legitimately, including the synthesis of a viral genome from scratch [9] and the development of a hyper-lethal pox virus, endowed with genes that could switch off functional areas of the immune response of the target organism/host animal species [10]. The latter was

Table 1. Generations of cellular and acellular, reproducible bioagents.

Generation	Description	Incident	Epidemic	Ref.
Gen 0	Infected material/carcass	Caffa, 1343 AD; Fort Pitt, 1763 AD	The black death (plague); smallpox	[15]
Gen 1	Isolated and cultured microbiota	Unit 731, WW II	Bubonic plague; (para) typhoid fever; cholera	[15]
Gen 2	Optimized microbiota	Anthrax letters, 2001	Inhalational anthrax	[11]
Gen 3	Engineered microbiota/gain-of-function	SARS-CoV-2, 2019	COVID-19	[3,15]
Gen 4	Genomic attack factors	mRNA/DNA vaccines; malevolent gene therapy applications	Range of deregulation, autoimmune and neoplastic diseases	[15]
Gen 5	Xenomicrobiota			
Gen 6	Hybrid microbiota/Cyb(micr)org			

to be the first case of the notorious gain-of-function (GoF) concept of GCBR-related proactive, if not preventive, research.

The issue of Iraq, coming to build upon the – overstated – disruptive effect of the 2001 Anthrax letters in the USA [11,12] was focal, for it brought back into discussion the dimension of state-operated, massive production facilities, even if in mobile, self-contained and relocatable units. The size and footprint of such equipment, even if much smaller than the usual setting of permanent, protected facilities, showcased a possible concept of stealth development and production of bioagents, not as shadow projects hidden within legitimate institutions, but as fully illegitimate and clandestine operations. These would be using spatiotemporal uncertainty, masking/camouflage, deception and relatively small weaponization footprint (understood as the sum of processes and materiel/personnel necessary for weaponization that may be identified and tracked by other interested parties) to evade detection and location.

The next iteration was the two allegations within 3 years for offensive bioweapons/bioagents being used on purpose or released accidentally; or, at least, being prone to be deployed in any of the two formats. This was similar an intent to the one that led to the 2003 invasion of Iraq. The first case refers to the SARS-CoV-2. This case is conceptually similar to the GoF experiments of 2003 [10], as it allegedly referred to the result of one such study (GoF), outsourced to facilities in countries with rather lax regulative regimens. The product, to be classified as the SARS-CoV 2, either accidentally escaped or was maliciously released [13,14]. Should this have been the case, it would refer to a third generation bioagent according to the classification presented herein (Table 1).

The other case is the allegations made by Russian authorities in early March 2022, regarding a series of facilities in Ukraine engaged into dual-purpose research on bioagents [16]. The proofs were anything but conclusive – which may be due to the inaccuracy of the said allegations, or to a successful implementation of containment/deniability measures. What is of interest is the categories of agents reported by the Russians, which showcase, irrespective of actuality, the current standard and state-of-the-art of bioagents and dispersion approaches; or at least one such combination. The allegations referred to naturally existing pathogens (Gen 1–2), although engineered strains (Gen 3) cannot be excluded. In any case, what has been reported was nothing exotic or revolutionary regarding the pathogens, nothing remotely approaching the theoretical level of the state-of-the-art [15].

Contrary to the technological level of the prospective bioagents in this alleged scheme, the transmission/delivery methodology is of interest. Animal vectoring by birds, reptiles and bats that cover significant distances and/or are very hard to control, track and contain or intercept were supposedly combined with the careful selection of native, naturally occurring pathogens so as to mask a perpetrated event as naturally occurring outbreak – possibly using selected (Gen 1–2) or engineered (Gen 3) strains of the native pathogen for increased morbidity and resistance to medical countermeasures.

The delivery approach above is much more subtle, although less controllable and accurate than the rather high-profile spraying methods or the use of any kind of missiles and other delivery vehicles [17]. The revealed intent of spraying biowarfare, or chemical warfare agents by tactical UAVs (Turkish TB-2) modified with suitable tanks and sprayers [18] is nothing more than the translation of a mainstream, if not obsolete, delivery method to the vogue of unmanned platforms delegated to the conduct of multiple, highly distributed operations. More elaborate solutions may become available, as a patented biosprayer designed for the release of selected breeds of toxic mosquitos from an UAV under remote control [19], while the substantiated use of agrowarfare practices against drug plantations in Central America [20] may be applicable against human populations. Still, massive, powered dispersion, operating through pyrotechnic, pneumatic, mechanic, hydraulic/spraying principles [17], is undeniably obsolete. Much more elaborate, if simple in conception, is the use of fomites or vectors – the latter for vectorborne diseases (VBD) [21] and the ages-old injection [17,22]. The latter is actually preferable as it optimizes agent delivery on-target and thus causes neither environmental contamination and pollution (both of which allow easier detection by biosurveillance formats) nor uncontrollable transmission. Furthermore, the delivery by injection spares the agent from possible degradation due to environmental exposure and various, mostly biological, interactions.

On the other side, the bitter experience of COVID-19 primed the widespread application of distributed surveillance [23], meaning numerous small groups deployed in checkpoints, fixed or movable, to cover wide and/or remote areas. These small units operate basic equipment and conduct point-of-need (PoN) tests. In this case the technology used was based to immunodiagnostics, requiring zero infrastructure, utilities and basing or storing facilities and thus has been very flexible in massive implementation, and relatively easy to use. Actually, in the relevant complexity level (CL) scoring system of the United States Clinical Laboratory Improvement Amendments (CLIA) such tests are graded *Low* [24,25].

Still, the metagenomics seem to be the next standard – mostly as nucleic acid amplification tests (NAAT) but not exclusively as such (non-amplification formats have their merits as well). This is so due to their compatibility with agent-agnostic setups, which is the most operationally relevant concept [26]. The iconic such tests are based on the consensus sequence amplification principle and usually come in the form of conventional reagents to be used and mixed just prior to the implementation of the test(s) rather than in a ready-made platform, thus lowering waste disposal and transportation volume and needs. Their results may be uploaded to decision hubs and further analyzed, combined, fused and mined for the compilation of differential picture in almost real time so as to project predictions and enable comparisons with both similar and dissimilar events [24,27–29]. The COVID-19 prompted the mass development and production of portable instrumentation for massive, intense and continuous implementation of screening in resource-limited settings (RLS); that is, in severe environment or/and austere conditions [23,30]. Thanks to these industrial, operational and cognitive developments, the Metagenomics/NAAT are expected to become the PoN method of choice. Especially so, since the decoding of a genome and the design and massive synthesis of PCR primers and other oligonucleotides for the consensus sequence amplification assays is much faster than the development of monoclonal and even polyclonal antibodies necessary for immunodiagnostic PoN assays [29].

At the same time, medicine has been revolutionized as well. The personalized medicine and selective medicine approaches [7] use the state-of-the-art to adapt therapeutic interventions and diverse regimens to the particular occasions, trying to diminish the error and delay of empiricism and the uncertainty in diagnostics and therapy implementation. An explosively evolving sector produces medical robots to diagnose and intervene directly and with exceptional precision [31] while Artificial Intelligence already predicts and assists drug development [32]. Thus, some tools to counter novel, plausible biothreats seem to be already available, but in need of retasking, reorientation and optimization.

This work intends first and foremost to provide an initial assessment of a new technology that may be pursued by prospective perpetrators and its potential operational ends. It is approached from the aspects of biology and drone use and technology. The above assessments are expected to prime discussion, promote consideration and vigilance, especially within the medical community, for unexpected and unexplained mass outbreaks or isolated but high-profile bioevents of exceptional impact. A second intention is to provide a basis for deliberation on surveillance and diagnostic amenities, so as to prioritize evolution of the most promising existing ones for near-term response and also initiate concept definition and development of novel ones that are to address needs the former may not satisfy even prospectively.

The cybernetic dimension (*bot*)

The late 60s witnessed the advent of what was to be described as 'uninhabited or pilotless aircraft', actually small, unmanned air vehicles. The difference with the missiles was that these were normally returning and reused. They were classified in two broad categories, the drones and the RPVs. The former were programmed beforehand to execute a flight and a mission. The latter were under the control of an operator located in a ground control center (which could be placed on a floating platform, a fixed or mobile ground platform or an airborne one). The operator was supervising the mission by using the flying vehicle's sensors and was sending orders by remote control through radiowaves. Later, in the 1990s the two categories were unified as the unmanned aerial vehicles (UAV), partly because the technology allowed the coexistence of both options: remote control and, should that fail, reverting

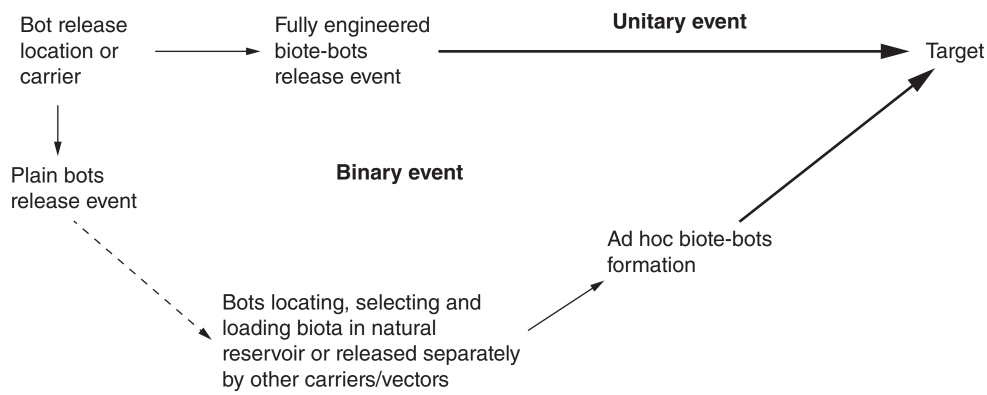

Figure 1. The unitary and the binary delivery methods.

to a programmable routine – a combination further elaborated later by swarming and artificial intelligence (AI) options. Additionally, there were counterparts of the UAVs for use in every element: USV – unmanned surface vessels for the surface of water masses, UUV – unmanned underwater vessels for submerged missions, and UGVs – unmanned ground vehicles for land applications.

Enter the 21st century, and the cost for UAV development, purchase and use has diminished so much that they are a commercial commodity and most affordable at that; the technology progressed and now there are some such amenities, rebranded 'drones' as it sound playfully, for all tastes. Among these there are very small ones, the micro-/nano/pico-drones [33]. The picodrones are too small to see with naked eye, much less with the usual sensors and seekers (EM-radar, EO-electrooptics, IR-Infra-Red) hitherto developed to detect sizeable drones of any kind, especially military ones. The picodrones could be the basis of a novel category of bioagent delivery platforms, a hybrid infectious mechanism made from two different and separate entities: one being a technomechanic (the picodrone proper, which would be the platform and henceforward called 'bot') and another, the 'biote', being a living entity (hence the name 'biote-bot'). Each of the two, in principle, may exist and partly functional without the other. The picodrone is to be custom-designed to load specific cells (biota), perhaps even a single one (biote) picked among thousands of similar ones and to deliver them with high precision to a designated target location, usually a selected biocompartment of some host organism. One option for coupling the bot to a specific biote is by procedures implemented in controllable space such as – indicatively and not exclusively – in a lab, although that is restrictive as a process. The other option would be for the bot to detect such cells by itself, using some biosignature, and then load one or more cells of the correct population by using some purely technomechanical, or some biochemically assisted mechanical process.

Once loaded, such picodrones may be unleashed to find live targets and deliver their load by some means, including, but not limited to, microinjection to the selected biocompartment for the maximization of the infection/disease onset or for any other specified mission parameter. If this process is not achieved for any reason in a given temporal window, machine and microbe may 'self-destruct' to leave no trace; the same would occur if environmental indices suggest collection and/or processing of the biote-bot by any means of sampling surveillance, such as the chemical conditions used for DNA extraction. This would be a necessary precaution in order to deny any kind of forensics to the surveying authority [34–36]. The self-destruction mechanism would negate traceable signals. In principle such a provision may be based on a mechanism tasked with the conservation/life support of the loaded cell for the duration of the transportation, target detection and inoculation phases, so as to remain viable during transit and with the highest possible virulence upon delivery.

In this way, relatively very few cells would be needed to cause a disease of epidemic proportions in some population. But the idea may be used for individual or very few infections at a time; the concept of the biote-bot is ideally suited for biocrime and targeted assassinations [1,34,37–39]. In both cases it uses a small fraction of the pathogens population/bioeffectors required by usual delivery/dispersion schemes of bioagents in all three plausible operational cases, that is biowarfare, bioterrorism and biocrime [1,40]. It must be also remembered that the bioeffector may be no microbe, viruses included: cancerous cells may well transmit their routine in heterologous metastasis [41].

As a result there are two main operational concepts (Figure 1): the unitary and the binary delivery methods. In the unitary delivery method the bioagent is selected from available pure cultures/preparations, which allows also the selection of the growth phase. Examples of such optimization may be the exponential phase, for fast establishment of the infection; or the plateau phase for maximum production of secondary metabolites, including but not limited to biotoxins, either individual or within the context of venomous or poisonous secretions [42]. Selected cells would be used to load bots, and these cells (or virions, actually) may well be manufactured, engineered or anything else from the iterations included in the generations 1–6 (Table 1).

The binary method refers to two distinct dispersion/release events, one for the bots, one for the pathogens, and their spatiotemporal coincidence, so as the former may search for, detect, bind and load the latter. This method is more difficult as the bot must scan space and biosignatures, detect the one pre-defined or approved in real-time by its operator, approach and bind the entity of interest (cellular or acellular). Once loaded, the bot potentially, but not necessarily, connects with the biote to conserve/support it, and then transits to the target area, scans it to detect and track the target, and upon target acquisition (a step uniquely suited to safety features for mission abortion) it executes the final approach and delivery/inoculation. The binary method makes away with the need for a selected, possibly engineered agent, and the existing microbiomes, especially local ones in areas where reservoirs of dangerous pathogens abound, may be used instead, thus allowing zero footprint – and related direct and indirect costs – in terms of facilities for the production, processing and storage of bioagents. Mother Nature provides amply. But it is obvious that the bot should be AI-enabled, as the two different phases, that is, the scans of biosignatures for biote selection and the executive steps for target contamination/infection are very complicated and perhaps incompatible with step-by-step control by remotely based operators. An AI element, hosted locally – or remotely and conveyed by signals – seems necessary (or, at least, highly preferable) to implement the binary method.

A separate case is the biodrones [33], where mechanic parts (actually 'technomechanic' may be a better term) are inserted in a preferably dead, but possibly alive, organism, especially an animal, to keep it operating. The 'operating' clause usually refers to the appearances of movement. The live biodrones refer to bionic implants bridging telecoms, cybernetics and neurophysiology so as to control the functions of a live animal over and beyond its own will, decisions and control [33].

In the former case, mechanical parts may be inserted in a taxidermy mount to endow it with motion and effectors, or to artificially operate the physiology of the dead animal (in here referred to as the 'necrobot'). To classify this case, exemplified by the concept of dead insects injecting parasites thanks to technomechanic parts powered by artificial sources, in here we propose the 'necrobiote' term. It refers to a cadaveric host, meaning a clinically dead host organism that supplies the environmental support necessary to a symbiont ('necrobiont'). The necrobiosis is a transitional condition between symbiosis and symbiont failure (demise or expulsion or transition to saprobiosis) and it is evidently time-sensitive and of a rather limited temporal window, which depends on the symbiontand host tissues' rate of corruption.

This 'zombie technology', which includes the abovementioned live biodrones and necrobots, has two objectives: the obvious is the concealment of the signatures of the technomechanical part, such as sensors and telecommunications/control equipment, but also terminal effectors, like miniature ammunition or injection. A flock of birds does not trigger air defense responses, with the possible exception of the – intimidating rather than destructive – falconry missions of trained hawks kept around airbases to secure flight safety by crossing flocks of birds. If the necrobot or biodrone flock does not break formation and keeps on, possibly a bit off-course to quell suspicion, only to turn at the last minute – even if this needs to be against the wind – and release miniature explosive warheads, or any bioagent (in some dehydrated/airborne preparation) the perfect surprise scenario would be implemented.

The other, less obvious objective refers to the plane of biothreat proper. The dead (and much more so the alive) biodrones are perfect vectors for communicating vectorborne diseases in a targeted and, at the same time, biologically optimal manner, as some obligate pathogens (especially engineered ones) may have low environmental resilience and tolerance and their integrity may be augmented by necrobiotic transportation.

The microbiotic aspect (*biote*)

The anthrax letters of 2001 delivered small quantities of a decently processed – to say the least – strain of a bioagent *Bacillus anthracis* [11,12,43]. That this bioagent was produced, processed and stockpiled in one or more US facilities, the latter being one of the most ardent signatories and supporters of the Biological Weapons Convention of 1972 (BWC), suggests that such endeavors were in line with the conception of the BWC. As a result, anyone, especially a signatory, could be found in possession of weapons-grade bioagents and associated equipment and still not violate the BWC, as made clear by the answer of Turkiye to the BWC after a Russian notification in 2022 [18].

Table 2. Generations of molecular, non-reproducible bioagents (biotoxins and bioregulators).

Generation	Description	Ref.
0	Naturally occurring venoms and poisons, unprocessed or minimally processed from hunted/collected source organisms (frog poison or snake venom spiked on edged weapons)	[42]
1	Purified, brewed and extensively processed agents from bred/cultured source organisms (poisonous mix used by the Scythian nomads; ricin biotoxin used in assassinations, as in Markov incident, 1978; production of medical use Botulinum toxin)	[48–50]
2	Biotechnological products or bioequivalents, produced synthetically or by genetic engineering (chemical synthesis of HCN, biotoxins, heterologous translation)	[51,52]
3	Molecules subjected to genetic recombination/editing of the coding gene; OR by biomodification of the end product (protein engineering)	[53]
4	Fully synthetic molecules (designed and bioengineered following the genetic code)	[53]
5	Xenobiological products; non-standard monomers or different classes of monomers (xenogenetic codes)	[54]
6	Hybrids: molecular constructs of biomolecules and technosynthetic molecules	[49,55]

The main issue here is that legitimate purposes under the provisions of the BWC refer unmistakably to small quantities, definitely incompatible with warfare use and possibly inadequate for large-scale bioterrorism. Small-scale bioterrorism by targeted assassinations and similarly performed biocrime, of course, require small quantities. But once the accuracy of targeted delivery is increased exponentially, as for example by a picodrone carrier, such limited quantities may be leveraged to critical mass for massively destructive (and disruptive) bioevents.

A pathogen is expected to pack more destructive qualities as the level of engineering invested for its development increases. In nature the virulence of a given, novel pathogen tends to decrease, to allow the improvement of the fitness needed for the survival of the said pathogen in the long term, according to the Evolutionary Theory of Virulence [44]. Thus, the co-existence, in one strain, of several threat qualities, especially if these are dissimilar and cover a wide spectrum of virulence characteristics, insinuates development by engineering and not by spontaneous evolutionary events. As differences in the level of technology represent quantum leaps in threat potential, a rough classification of the evolutionary status of bioagents available for perpetrated events has been proposed previously [40] and is now reappraised and updated (Table 1). A second one could be proposed for molecular/biochemical agents (Table 2), again based on previous publication [39]. This differentiation of biothreats by the agents' nature rather than the more integrative common scale for cellular, acellular and molecular agents that has been proposed as well [45] allows, as claimed by the authors, better flexibility at the cost of ease in apprehension and standardization. In both cases [40,45], there are some levels fairly similar if not common: (1) the virtually unprocessed, rudimentary preparations without isolated/purified agents; (2) the optimized agents of none to some biological enhancement; (3) the xenobiologic concept of synthetic agents using natural processes but unnatural compounds/molecules of chemical compatibility but biological incompatibility with the existing biome (i.e., xenobiota [15,46,47]); and (4) the hybrid techno-bioentities, such as bionic microbiota [15].

The latter category is taken as one, but more subcategories may evolve under the inclusive concept of biohybrids. One spinoff is the bionics, another is the cyborgs, irrespective of size and complexity. A rough discrimination would be that the bionics refer principally to bioorganisms with functional technomechanical parts. Not a simple prosthetic as a nail, a tooth, a plate or a titanium surrogate of the bone, but a functioning, non-energy neutral part, limb or organ. The non-energy neutrality clause means that the item requires energy to operate or produces energy for the hybrid or some of its parts, the example being hearing enhancements, synthetic vision, microchips and conductors for bypassing degenerate neuronic circuitry and other 'updates'/'enhancements' [56].

In the cellular level, which is applicable to microorganisms in pathogenic or any other capacity, there are steps in the developmental procedure that may be taken either together, be it concomitantly or successively; or exclusively. For example, the cellular engineering, being much less celebrated than its relative, the genetic engineering, may implement the manufacture of artificial cells. The latter term includes, indicatively and not exclusively, either synthetic/technomechanic prosthetics/bionics [57] or heterologous organelles. The latter may be natural ones or some artificial spinoff, but of organic, biological constitution (biomechanics). The natural heterologous organelles include plastids as additional source of energy in low-resource settings [58–60], thus imitating some protozoa, as are *Euglena* spp, that carry plastids and use them conditionally [61,62]. Heterologous centrosomes is another possibility, recasting the organization and function profile of a given cell [63], while transplanting heterologous mitochondria [64] may increase the pace of metabolism and thus endow a given cell with increased potential, something like the superpowers in Comics' characters.

On the other hand, the cyborgs (CYBernetic ORGanisms) are synthetic, mechanical devices with non-biological energy source, with living tissues or biomechanical parts and socioeconomic interfaces intended to integrate AI into intelligent life standards. Tissue/microtissue additives, in a benign setting, may make mini/nanobots immunologically compatible so as to ingress the inner tissues and reach the bloodstream in order to treat lesions and injuries or to monitor health, as in the case of Medical Robots [28]. But the principle is applicable to any sinister purpose [65].

Lately the concept of the cyborg seems to become less mechanistic and more oriented to the use of decision logic, with or without AI provisions: thus cells, provided with some kind of externally controlled steering system so as to guide at a given space/target to implement actively or passively a routine, are considered cyborgs, without the need for structural and active technomechanical parts [66].

Given that the biote, the live element of the hybrid infectious mechanism may – or may not – be life-supported by the bot element but does not affect it in any way (positive, negative, neutral) their functional co-existence, irrespective of its time span, is not a symbiosis. As a result, the term 'biote' has been preferred for the biote-bot rather than the term 'biont', which implies a symbiosis event, of any nature.

Defying (bio)surveillance & diagnostics

Biosurveillance may be implemented in the environment, before a pathobiont (re)hosts itself, or within the bioenvironment of the host. The first option requires methodology upgrades to tackle environmental samples, inherently contaminated with various biosignals and homologous and heterologous noise hiding the presence of the analyte. The advent of metagenomics revolutionized the research output in this area, while making turn around time (TAT) relatively predictable and compatible to the operational prerogatives [25,26]. Unfortunately, when precise analysis is required to dictate or inform policymaking, and especially if a hostile Intelligence is, or may be, implicated, the reliability of such methods may be doubted as they assemble metagenomes from all available amplified sequences, they do not identify organisms at the cellular level. Still, this surveillance option gives a clear picture and a temporal window of opportunity, actually a heads-up, to initiate protective and pre-emptive measures [36].

The second option is more dependable, as it is informed by the fraction of the pathobionts that actually achieve hosting onto a host population and thus more accurate threat estimates may be projected. A method is seeking one among a finite number of organisms, which lowers as the symptomatology and epidemiology gradually supply new data, inclusive and exclusive. But in many a case, when the pathogen has achieved establishment in the host, it is somewhat late to contain the wider event and the responders have rather to manage the damage and casualties, hoping to curtail their extent and impact. Additionally, the host environment is not very permissive for analyses, as the biosignals of the host create high levels of noise shadowing the ones of the pathobiont, especially where low numbers of the latter are enough to initiate colonization and/or disease (pathogens of high virulence and morbidity). Recently, quantifying SARS-CoV-2 in wastewater has been used to predict actual presence in the community and disease dynamics [67]; the approach is neither universally applicable nor necessarily correct. It was followed because it was feasible [28,67–70]. If the environmental residue of the released agent is significantly diminished by using smart, or rather intelligent, targeted delivery, the part of the surveillance effort regarding the use of air and liquid sampling traps will come to naught. Similarly, the approach of quantifying the presence of the agent by its environmental footprint and thus projecting disease dynamics, as with the quantification of the load in wastewater, would become irrelevant.

Upon the first uses of the biote-bot, if they ever occur, screening schemes after infection/hosting would not be directly affected. But these procedures need to be informed by pure samples that would provide the standard for biosignal detection/identification and analysis, whatever the said biosignal may be. If an agnostic, imaging method of surveillance and screening cannot detect an unknown agent so as to direct its retrieval, analysis and study [26], no seeking-oriented diagnostic routines (may they be differential or binary) may be developed and tested.

At a higher level, producing very limited quantities of pathogenic bioagents that may still cause massive events due to accurately targeted delivery implies a far more affordable production and processing setup, the observable parts of which make up the weaponization footprint. This limited setup may be easily funded and even more easily concealed within the urban or the suburban environment, as supplies, infrastructure, equipment, manning and energy consumption (especially for freezers and other conservation and containment equipment) would be minimal. It is a different, rebooted version (redux) of the infamous Black Biology concept that caused nightmares during the 90s [40,71,72].

With the depreciation of current and envisaged therapeutics that is bound to occur due to the possible fielding of thoroughly engineered agents, the culmination of which would be the generations 5/6 (Table 1), the infectious biote–bot hybrid approach would also capitalize on intelligence denial. The self-destruct provision, especially of seppuku type (see below), is meant to keep proprietary the bio- and techno-signals and the codes (principally the genetic/xenogenetic [47,73,74] but possibly other ones, too) of the biote so as not to inform diagnostics/therapeutics. This operates at the level of NAAT, at the level of immunodiagnostics, and at the level of complex electromagnetic and other signatures, including but not limited to visuals under microscope; and of course at the level of any intelligence produced by tracking the operating and communications systems of the bot.

Discussion

The sealed or even the hibernating biote may be carried by the bot in such a way so as not to present any exploitable biosignal; for example, internally into some version of the cockpit arrangement of aircraft. This possibility perplexes diagnosis, surveillance and intervention vastly. By being covered within the bot, the biote exposes no immunogenic moieties. At the same time, the synthetic (plastic, ceramic) or metallic structures of the bot present no active moieties for epitope–paratope recognition and thus immune response triggering or antibody-based detection are not expected to function. The solution to detecting such entities lies in deciding over two operational issues. First, the location: whether the biote–bots are to be tackled within an internal, organic (bio)environment, as befits a medical problem and possibly contitures another layer of immunity, a techno-immunity of sorts; or before their ingress into their targets, which is compatible rather with an expanded public health/agrohealth setup.

Second comes the technology. The biosignals are expected to be degraded or null, but there are the technosignals which may collectively form a technosignature, despite the bot being practically invisible, due to its size, to existing infra-red, radiosignal (radar) and electrooptics-based sensors and thus evading detection from current such technoamenities. The bot needs energy, thus emits residual EM signal and possibly IR signal different than that of the biota. It is made up from metal and/or technosynthetic materials, such as polymers/plastics, ceramics, etc. All these have tell-tale properties in reflecting EM radiation/waves, including IR, UV and radar (microwave) wavelengths, very differently from one another and from biota. The finish of the product is expected to be very fine in skin and edge, in sharp contrast to biostructures, which tend to be rugged. All these may create differential technosignals that may become interpretable by AI-driven signal processing software to apprehend, assess and track such entities upon contact.

The infectious biote–bot, contrary to cyborgs, does not need AI to operate. It may be programmed or remotely controlled, although AI (locally or remotely hosted) exploits its potential further. Swarming modes, with low or high numbers of units operating in coordinated manner and communicating with each other and adapting their approach may be applicable in some occasions, but not universally so; nor are they essential in all cases and mission scenarios. Also, the bot part is fully operational even in the absence of the biote part. The biote is interfaced but is actually the load or, rather, the effector of the mission module, in military parlance.

To counter the biote–bot, there are two approaches in theory: the blanket approach, where a signal or other effect covers an area and destroys or incapacitates all copies of the target entity (in here biote–bot) present therein. This is the ‘area coverage’ or ’area defense’ concept and possible solutions would include pressure waves but, most importantly, electromagnetic emissions to jam or even melt the sensitive electronics of the biote–bot. Sonication by ultrasounds, on the other hand, may increase shear and tear of delicate connections, from circuitry to tubing of microhydraulics and microinjection effectors and disrupt quorum-sensing/orientation amenities [21,75].

The other option seems to be to seek, track and attack individually each unit/biote–bot. This is the interception approach and the interceptive entities are expected to be drones as well (hunter-bots), most probably AI-enabled, that may damage their target by direct contact or by distant effects. The former may be through direct crashing, reminiscent of galleys ramming each other; or by using movable limbs, such as hooks and cranes, to dismember the less robust parts of the biote-bot, such as joints, rudder or other instrumentation, such as – indicatively but not exclusively – guidance, seeker, propulsion.

And then there are the issues of ethics and regulation. Although these would require a separate study effort, the former may be digested to a simple determination regarding the biote–bot – which is a speculative entity proposed herein. There is absolutely no such dimension. The ’assault’ biote–bot is intended to be an assault device, to effect mass casualties either directly, by initiating epidemic spirals, or indirectly, by allowing the targeted assassinations of key individuals whose demise, especially if concerted, would cause chaos, damage and casualties (actual or prospective) by disruption [1,7,40,76]. The assault biote–bot has no beneficial applications; destructive ones with beneficial outcome, as is the case with agrowarfare practices used against extensive drug plantations [20], would be a very precarious road once more, as the 'beneficial' is a matter of interest, posture, values and, in two words, utterly subjective. Other kinds of biote–bots may well be beneficial, but this does not infringe with the ethics of the assault version discussed herein.

The issue of regulation, on the other hand, may apply to the biote–bot as a concept and as a whole, integrated system; or separately to the enabling technologies. The AI is an enabler, but the biote-bot concept might work without it, thus possibly – and partly – circumventing regulatory provisions focused on AI. After all, the basic idea is similar to the AI-enabled operation of legitimate micro/nano-robots in medicine or industry [77–79]; thus it is extremely hard and possibly least rewording to try to regulate the development of AI amenities. Killer robots are a fact, with the invention of the Israeli 'Tikad' sniper/killer drones and their cousins, the Turkish 'Songar' [80]. Even if at present there are safety features with man-in-the-(decision) loop, these are inserts and added limitations that may easily be forsaken, bypassed or disabled.

The total failure of the BWC, in that it has been either directly violated, as by the Soviet Union and its gigantic bioweapons development effort, the 'Biopreparat' [81], or skillfully circumvented, as by the GoF and other experiments vested under the (not so plausible) allegations of 'build to learn' and 'create to study' [10] is ominous. It allows no optimism for any regulation regime, especially through conventions. The US select agents list [82,83] attempted to regulate the transfer of plausible agents, but this was applicable to Generations 1 and 2 of Table 1. No matter how many tampered agents are included in the list, from Generation 3 and beyond, the regime is ineffective [26,45]. The spill of the technology makes such efforts to be spend in vain, but for the sole purpose of discouraging the most naive of possible perpetrators – the number of which might be large, to be sure.

The authors are no experts in international affairs, nor in legal science, but plainly see such efforts as doomed from the very onset: the history shows them failed, as detailed above, and ignoring the verdict of history is ignoring data of an experiment for preconceived, possibly wishful, thinking – not one step too far from outright prejudice. Conventions are used mainly to safeguard the supremacy of the most powerful parties against new players, and no ambitious state (not to mention non-state players) would ever be contributory or signatory to any, especially after the –unspoken of – failure of any regime for the control of the nuclear weapons, such as the Treaty on the Non-Proliferation of Nuclear Weapons (NPT) [84]. The agreements were prohibiting new entries into the club of owners of nuclear weapons (which did not happen, either due to tacit acceptance by the powerful parties, as is the case of Israel [85,86]; or despite their best intentions, as happened with Pakistan [87,88]) but with the stated condition that the already nuclear powers would disarm themselves eventually, by dismantling their nuclear weapons [84,89]. This did not happen under numerous pretexts during the 1990s and will most probably never will. All the nuclear powers are modernizing their arsenals, for different reasons/pretexts [89]. So, such conventions are weighted and thus counterproductive and would not be widely accepted, except if the minor, potentially revisionist contributing parties wish to secure some temporal allowance to catch up, if their research and knowledge basis accelerates faster than that of the established leaders in the regulated field(s) [90].

Conclusion

The biote-bot is a technological entity that, at least in theory, may well be developed legitimately for the targeted delivery of cells to restore injuries, lesions and other damage, or of biologicals to either mend damage as mentioned previously or to restructure microbiomes and/or suppress aggressive colonizers [91–93]. Other beneficial uses may include the targeted delivery of molecular agents (medicaments, toxins or bioregulators to suppress tumors) [94], but prospective usefulness is only limited by the engineers' imagination. To generalize, they are expected to thrive for therapeutic purposes as is the case with medical robots [31], but also for biotechnological purposes, or even in the context of synthetic biology and agrotechnology. Thus it qualifies as a dual-use technology, very likely to be funded and developed for benign uses and then fine-tuned for sinister purposes. As it introduces a technomechanic dimension in the disease causality, very different in materials and signatures from the biomechanic one suggested in the synthetic biology context, it defies usual detection. Thus both bioresilience [28] and diagnostics [27–29] are bypassed in one step: the bot part may present no biosignature and use no biomaterials if it is entirely technosynthetic, while the biote presents a very low biosignature, in a high-clutter environment. This makes detection and, even more so, analysis and identification, a herculean feat and probably an impossible task, even if the self-destruct routine is not applicable or malfunctions. An entirely different awareness and surveillance approach is needed, and at the point it is difficult to define even its principles. The technomechanic part (the bot) is too small in size for the usual technosignatures (visual, IR, EM) to be used for detection, tracking and analysis.

On the other end, it may be possible at the very least to track the results of a massive biote–bot incident and thus to understand the nature and extent of an event, taking some kind of action, from retaliatory to relief. The BAS/Bioagent-Agnostic Signatures principle [26] may allow the apprehension of a centrally occurring, and possibly perpetrated, event. In any case, an anticipatory approach is sought for, requiring (pro)active, cognitive horizon scanning to stay ahead of the innovation curve [95] and thus create the temporal windows of opportunity to contemplate on assets, liabilities and responses.

The technological scenarios described herein are not acknowledged as existing (under wraps of secrecy), nor as imminent, but merely as possible; they may come to being, or not. At present the authors have no solution to suggest to stop such eventualities; this review is simply identifying a risk area and hope to cause other scientists to ponder upon the issue and perhaps come up with a solution, preferably not worse than the problem it is supposed to tackle. Adjacent to this admission, it is also underlined that this work is not concerned with ethics, and never intended to be. A discussion on the subject would be essential if not vital, but due to its capital importance it should materialize in the context of relevant studies and carried out by scholars and scientists with some expertise on the issue.

Future perspective

The interwined parameters of operational range and cost constitute the main limitation of the biote–bot. The operational range clearly segregates the most ambitious assault biote–bots from possible benign, legitimate and profitable versions, which would operate in close range, very near their control facility and probably in a tightly controlled environment, to avoid any kind of technomechanic complications, such as loss of control due to background noise. The assault biote-bots need to cover immense distances in proportion to their size, in order to reach their targets – not to mention if the bots need to independently load biota from natural reservoirs, if a binary scenario is pursued. This implies the need for highly miniaturized and efficient energy sources, and very accurate navigation. Practically, a robust mid-course navigation system for the transit to the target area and a very accurate terminal guidance sensor system to guide the biote–bot to the target point are essentials.

The cost is important as it pertains all the issues mentioned above and one more: the massiveness of production and use. This is necessary for causing massive events, even when using extremely virulent agents spreading epidemics from only one initially infected individual/'Patient 0' to multiple secondary hosts, as a high failure rate is to be expected even for the best designed and manufactured biote–bots. Deploying for use large numbers presupposes low manufacturing, fielding and handling costs (not only in monetary terms) while the detection becomes, due to the collective, aggregate footprint size, more probable. Isolated uses, which are probable whe using very high-cost devices for individual attacks against extremely important targets (thus causing important 'disruptive' effects) retain stealth and undetectability, but cannot cause massive 'destructive' effects.

The origin of suitable counter-technologies is obviously the wide arsenal of similar ones used in the military and security establishments, in the civil aviation and seafaring sectors and in transportation and transition networks in general. The size of relevant contacts in terms of signal cross-section for the different sensor technologies and the respective equipment should be adapted drastically and rendered safe for use near or within living organisms; this may trigger a high demand for transforming such technologies; it could be viewed as a more advanced iteration of the translational research, qualifying perhaps as 'meta-translational' (a term proposed by the authors herein), as the transformation includes a transition from a completely different sector of applications.

And in here comes the issue of the location: outside of the host/target bioenvironment, the spatial distances and the volume to survey and control are, by comparison to the biote–bot size, huge; but it is much easier and entails much fewer expected adverse reactions (for the prospective hosts) to use scanning technologies in such formats than to scan their bodies with massive doses of highly focused EM radiation. Still, if one takes into consideration the miniaturization progress that seems unstoppable, spinoffs of current scanning medical instruments may be improvised for biote–bot detection within the hosts' bioenvironments. These would ideally be combined with much more basic and affordable, portable models that would be used regularly for hundreds of subjects at a time.

The intervention is a problem; there are more or less innovative proposals, some verging on the Sci-Fi. This is not necessarily something extraordinary; if one sees the degradation of some of the Sci-Fi of decades past to mundane reality, it takes a lapse of 30–10 years. But the disabled biote–bots, if accumulated within a target organism, could well present, due to their structure, a direct risk factor, especially for puncturing blood vessels and causing hemorrhage or other injuries. And this is according to the best-case scenario, where they remain neutralized. If they have any provisions for self-destruction, the prospects become bleak to the extreme for in-host clearance and disposal. Self-destruction logic and mechanisms is hereby proposed to be considered as either seppuku-type [96] (intended for simply making the remains unusable for accountability and reverse-engineering or study purposes), or kamikaze-type [97] (intended to cause maximum damage to an environment/target/host while self-destructing). Both cases may be developed based on experience with recent suicide drones [98]. The Kamikaze-type would ensure a terminal effect on the target, which, though, would be highly visible, negating prospects of deniability.

As a result, the destruction of the biote-bot before entry into the host, at the free roaming phase of its mission ('off-host'), will be given precedence as an operational priority. Volume effect approaches would be sought for, first due to the sheer volume of space to be surveyed [36] and second, due to one inherent operational antithesis or zero-sum condition: few biote-bots make detection improbable, a multitude of them makes incapacitation almost impossible. In such a context, some of the amenities in (slow-paced) development for electrostimulation, electrotherapy and other similar interventions would gain traction; especially so the dynamic fields-based and the wave-based ones [21,99]. Although the in-host interception is unattractive as an option, if small numbers, perhaps even individual biote–bots are assigned to each target, then the issue of disposal of the debris may be handled somehow and in-host interception/incapacitation would be plausible. This would suit perfectly conductive electrostimulation modalities, routing current through the target [99–102].

Executive summary

- The alleged clandestine use of bioagents, or the purpose of such use appears intermittently in the 21st century in global context.
- Dispersion options generally include elaborate use of fomites or vectors and old-school injection and spraying; the latter occasionally by unmanned air vehicles.
- The counter is by immunodiagnostics, with minimal footprint and low complexity level and by metagenomics, more elaborate and adaptable but more complex and demanding.
- Personalized and selective medicine use the state-of-the-art to adapt therapeutic interventions and diverse regimens to the particular occasions.

The cybernetic dimension (bot)

- Nano- and pico-drones, of the airborne (nano-/pico-UAV) category would be the vehicle (bot) to carry a pathogenic element (biote).
- Such biotic elements may be collected from the environment during the mission by the bot using sensors tuned to biosignatures artificial intelligence (AI)-criteria; or be loaded before releasing the bot, in a lab/base context.
- Remote guidance, local or remotely hosted AI and swarming formats are the main guidance options.
- A troubling prospect is the biodrones, with technomechanic parts inserted in a dead or alive macroorganism, usually an animal, to turn it to a vehicle for natively hosted symbionts/pathobionts to be transmitted to other hosts.

The microbiote (biote)

- Different breeds and kinds of microbiota may be used as the biote element; they may be collected from the environment, selected in the lab, modified or wholly synthesized.
- Biotoxins and bioregulators are not actually bioagents, but may be loaded on picodrones/picobots for targeted delivery.
- The novel element would be the biohybrid microbiota: either techno-enhanced ones (bionic germs) or purely technomechanical ones with some semblance of bioentity/ use of biomaterials (microbial cyborgs).

Defying surveillance & diagnostics

- Biosurveillance may be implemented in the environment, before a pathobiont hosts itself, or within the context/bioenvironment of the host.
- Low environmental residue of the agent through targeted delivery nullifies surveillance by air and liquid sampling traps.
- Diagnostics after infection would remain practicable; but the need of pure reference samples for acquisition of the respective biosignature shall undermine their practicability.
- The minute quantity of bioagent required for targeted biote-bot delivery may be produced clandestinely, with minimal footprint in terms of supplies, infrastructure, equipment, workforce and energy consumption.

Discussion

- The infectious biote-bot, contrary to cyborgs, does not need artificial intelligence to operate but may profit from it.
- The biote, as carried by the bot, may present no exploitable biosignal for detection and identification.
- Technosignatures may be a possible solution for detection, but existing instrumentation needs drastic adaptation to be used in relative sizes and environments.

- For incapacitating the biote-bot, off-host interception would be easier and safer and doable by modifying existing effects-generating solutions, from sonication by ultrasounds and sonic waves to electromagnetic pulses (waves or currents).
- Ethics do not apply to an inherently aggressive technology clearly violating the Biological Weapons Convention of 1972 (BWC).
- Regulating regimes have failed and would do so again given the similarity of all three constituents of the biote-bot concept to legitimate, benign applications.

Conclusions

- The bot may be developed legitimately for therapeutic purposes as with medical robots. It is a dual-use technology, likely to be funded and developed for benign uses and possibly diverted and fine-tuned for sinister purposes.
- The limitation of the biote–bot concept stems from their possible costs as a function of the distance the vehicles and their sensors and communications should cover.
- The technomechanic part of the disease causality differs in materials and signatures from the biomechanic one of the synthetic biology context. So it defies usual detection and bypasses bioresilience and diagnostics in a single step.
- The bot part may present no biosignature and use no biomaterials if it is entirely technosynthetic, while the biote presents a very low biosignature, in a high-clutter environment.
- It may be possible to track the results of a massive biote–bot incident by the Bioagent-Agnostic Signatures principle.
- The ethical and regulatory aspects of the above are not within the context of this work, which does not provide possible solutions of any scale. It is hoped that future studies with encompass both these issues.

Future perspective

- Technosignals interpretable by AI-driven signal processing software may be the solution for surveillance/diagnostics.
- The respective technologies would be meta-translations of existing ones in the military, the civil aviation and seafaring and in the transportation sectors, but adapted for massive, dense use in very low volumes and intensities.
- Self-destruction mechanisms of the biote–bot, either seppuku-type or kamikaze-type perplex interception and countering within the host.
- Volume-effect procedures, especially electromagnetism in the form of waves and fields from electrotherapy spinoffs may be used for off-host biote–bot interference and incapacitation.
- In select in-host cases, conductive electrical modalities could be applicable to disable infecting biote–bots before they release their load.

Author contributions

ME Kambouris: conceptualization; investigation; writing - original draft. Y Manoussopoulos: investigation, writing - original draft. A Velegraki: investigation, writing - review & editing. GP Patrinos: conceptualization; supervision, writing - review & editing.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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