Technical and ethical challenges associated with the creation of sapient human-animal hybrids

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Abstract

Creating sapient human-animal hybrids through technological means is a staple of speculative fiction since the novel "The island of Dr. Moreau" was published in 1896. Such a process of increasing the cognitive abilities of non-human animals, eventually up to the levels of human beings, is still theoretical. But rapid advances in relevant fields of bio-engineering could make it a reality far sooner than usually expected.

This article aims to review first the philosophical arguments regarding the creation of such hybrids, then the technical aspects of a potential protocol and their ethical implications.

Since technical progress is often faster than the relevant ethical and legal discussion, this can create suspicion and backlash from the public. Given the broad societal impacts and potential for abuse associated with this emerging technology, it is necessary to identify, analyze and address the ethical and regulatory issues regarding the creation of sapient hybrids before it comes to fruition. Ethically sound methods should be developed, reviewed and sanctioned before any protocol is implemented.

1 Introduction

The creation of sapient human-animal hybrids through technological means is a recurrent trope of speculative fiction since the publication of "The island of Dr. Moreau" in 1896. The creation process is often called 'uplift' since the popularization of the term by David Brin's "Uplift" novel series in the 1980s. Its subjects are often termed uplifts, provolves (from provolution or 'proactive evolution') or CMOs (cognitively modified organisms). An illustration of a possible human-animal hybrid is presented in figure 1. In the rest of this article, the term hybrids will be used for the cognitively enhanced animals and uplift for the associated process to create them.

The possibility of a successful uplift process is based on several assumptions :

1. Improvement of intelligence capabilities can be considered as beneficial to the target species
2. Intelligence can be quantified, at least through relative comparison
3. Intelligence is linked to causal factors (genes, hormones, etc.) that can be understood
4. These factors can be transferred or replicated across species
5. Such a transfer leads to the excepted outcome of increased intelligence

Here the term intelligence is taken as the ensemble of cognitive processes from a living being that allows it to understand, learn about and adapt to novel situations.

Hybrids are still confined to science-fiction, but rapid advances in the fields of comparative neurology, non-human linguistics and genetic engineering could unlock the techniques needed to start an uplift program. Factors like the emergence of open-source synthetic biology and the democratization of relevant equipment increase the feasibility of such a program. It is now possible to build a basic molecular biology lab with 1000$ of materials (Brunstein 2011-12).

Given the societal risks and potential for abuse towards hybrids, it is necessary to start an ethical and philosophical debate on this emerging technology before it comes to fruition. This article aims to provide a few leads in the matter. First, the philosophical arguments regarding the creation of hybrids will be reviewed. Then the technical aspects for a potential protocol and their ethical implications will be detailed.

2 Philosophical foundations

Given the scarcity of philosophical discussion about uplift in the peer-reviewed literature, most of the arguments presented in the following sections are taken from a debate about the creation of human-animal chimeras started in 2008 after scientific research on the subject was approved in the UK (Bobrow et al. 2011). Such a parallel can be justified because the characteristics ascribed to these hypothetical fully-grown chimeras are similar to that of sufficiently uplifted hybrids. A comprehensive review of these arguments can be found in (Huther 2009).

Figure 1: Example of a canine hybrid with an appearance mixing human and non-human attributes.
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2.1 Arguments in favor of uplift

While originating from various philosophical systems that are not always compatible with each other, most of these arguments listed above are based on the same premise : that a human-centered civilization could find beneficial to integrate other species into itself as partners rather than keeping them as subjects or legal objects.

2.1.1 Act-based utilitarianism (Savulescu 2003)

An utilitarian framework can be used to justify uplift, with the following reasoning :

1. One condition of humanity is its capacity to display practical rationality.
2. To act based on normative reasons is a way to express our humanity.
3. Uplift can be beneficial to humankind for various reasons : the scientific spin-offs from the program itself, the specialized workforce generated from it, the affective reinforcement provided by the hybrids, etc.
4. In conclusion, uplift is justified if it promotes and expresses our rationality.

It is important to note that this argumentation is incompatible with suffering-avoidance variants of utilitarianism. Also, the uplift process would be morally just only if the lives of hybrids are worth living, with the advantages from increased intelligence outweighing the pain and hardship caused by it (Cooley 2008). However, the benefits from an uplift program could be too limited in comparison to conventional research methods to justify the risks involved (Tarkowski 1998) and there is a risk of the hybrids outliving their usefulness.

2.1.2 Rawlsian theory of justice (Dvorsky 2008)

This argument uses two concepts from John Rawls' theory of justice : the primary good (an attribute that a rational person would not refuse if given the choice to have it) and the veil of ignorance (policy makers deciding the shape of a society without knowing their future position in it will tend to adopt a strategy maximizing the position of the least well off).

1. Animals are least-advantaged in our current human-centered society.
2. Animal rights' goal is to include higher animals in the human moral circle.
3. General intelligence is a necessity for integration in our society and can be defined as a primary good.
4. Enhancements can be moral if they augment primary goods (Allhoff 2008).
5. For society to be fair, it is morally just to enhance animals into equal social partners.

This reasoning constitutes a rather anthropocentric perspective on uplift which hinges on the importance of intelligence in our current society. However, there is nothing obviously unfair about a chicken being born a chicken as long as it is treated without cruelty.

2.1.3 Legal personhood of animals (Fuller 2014)

The debate on the possibility to granting legal personhood to animals has been used to justify uplift :

1. Granting legal personhood to animals confers to them additional rights and protections.
2. Being a legal person means having both rights and obligations towards others.

3. To be responsible for its actions requires the ability to scrutinize its own motivations critically.
4. Most animals do not seem to have such ability for introspection.
5. Uplifting animals endows them with the requisite cognitive skills to participate effectively in society.

It is important to note that additional rights can be granted without obligations, like in the case of protected classes of humans. However, the refusal to grant rights to animals is often based on their incapacity to understand their obligations in the first place, which generates a catch-22 situation. In addition, defending an animal in court could be done by humans alone, based on observation and indirect inference, without necessitating the defendant to be uplifted beforehand.

2.1.4 Plurality of umwelts (Brin 2014)

This argument is centered on the concept of the umwelt (the personal world-view of an sentient individual based on its senses and perception of the world) from the semiotic theories of Jakob von Uexküll.

1. Other species have a different understanding of the environment stemming from their umwelts.
2. Accessing their umwelts can be a positive addition for our society, leading to a better knowledge and stewardship of the environment surrounding humans.
3. To enable the sharing of umwelts, the inter-specific communication channels must be widened.
4. Uplift can be used to realize this objective.
5. Uplift is justified by the benefits of the plurality of umwelts.

In this case, the hybrids would act as ambassadors for their species and the entire animal population does not need to be uplifted. The uplift protocol used must be self-limiting since significant modification of an animal's sensory abilities might cause the scrambling or erasing of its unique umwelt. Another limitation is that information from species with non-overlapping umwelts (humans and dolphins for example) would be difficult to extract and exchange.

2.1.5 Prevention of species extinction (Rohwer 2018)

This argument is centered on the idea that biodiversity has intrinsic value and must be protected :

1. Some species are threatened by extinction because of human actions.
2. Said species lack the cognitive flexibility to deal with these actions.
3. Humans performed a wrong action by threatening these species with extinction.
4. This gives us an obligation to intervene to prevent this loss of biodiversity.
5. Traditional conservation practices are insufficient in this domain.
6. Using cognitive enhancement on threatened species is justified.

In this case the uplift process must be applied to most or all animals of the target species, but also be self-limiting to reduce the risks of lowering the evolutionary fitness of the species from side effects. However, this intends to fix the symptoms of the biodiversity loss rather than its causes.

2.2 Arguments against uplift

The rational criticisms against uplift are centered on the possible negative consequences for the hybrids whatever their cause. They also suppose that said consequences cannot be mitigated enough to tip the scales in favor of uplift.

2.2.1 Wisdom of repugnance (Kass 1998)

This inherently irrational argument is sometimes used to judgd the validity of a controversial technical innovation :

1. A technical innovation can generate disgust.
2. Repugnance incorporates an unconscious evaluation of the moral value of the innovation.
3. Morally dubious actions must not be pursued.
4. A technical innovation deemed repugnant is morally wrong.

This allows for a quick and instinctive response but is an unreliable mechanism. Emotions are a questionable basis for moral decision making and repulsion can be triggered by morally neutral or non-moral actions, like fecal transplants. Legitimate but disgusting procedures could be rejected without a proper consideration of their merits.

In addition, the human response to increasingly human-like beings is highly non-linear and only notably negative when said being is almost entirely but not quite human, a phenomenon known as the "Uncanny Valley" (Borody 2013). So it is possible that hybrids with a mostly unmodified appearance will not reliably trigger repulsion.

2.2.2 Hubris and playing God (Midgley 2000)

Quasi-religious objections to uplift are often centered on hubris (taken as the combination of ignorance, arrogance and exaggerated pride) and the injunction to not play God :

1. Some types of action are reserved for higher beings, called god or nature.
2. Nature is viewed in a teleological way, where animals fits in specific evolutionary niches ("Nature Knows Best").
3. Creating beings that have no place in nature is morally wrong.

4. Uplift is morally wrong because it goes against God or Nature.

This fundamentally non-rational argument is based of a flawed understanding of ecology (nature is not fixed or perfect, so that mankind must not interfere with it) and evolutionary biology (Nature has no purpose or aim). It is also only persuasive for persons sharing the same religion or teleology as the author of the argument.

2.2.3 Moral boundaries between species (Robert and Baylis 2003)

Another argument is based on the boundary between species and the moral confusion resulting from its weakening :

1. There is a fundamental division between species.
2. This boundary between species has a moral significance.
3. Creating hybrids adds moral confusion from mixing categories.
4. The mixed nature of hybrids makes their moral status difficult or impossible to determine.
5. This uncertainty leads society into questioning its ways to assign moral status (Glenn 2003).
6. Creating hybrids is not worth the moral hazards of this situation.

This type of reasoning tends to equate 'unnatural' with 'unethical', which constitutes a naturalistic fallacy. In addition, elevating a barrier between humans and animals generally leads to speciesism, where human beings are viewed as morally superior to animals in a fundamental and unchanging way. This wa y of thinking often has negative consequences for non-humans (Ankeny 2003).

Also, classifying chimeras is not especially problematic in moral systems like Kantianism and utilitarianism (Siegel 2003) while viewing hybrids as a collection of morally-different parts rather than organisms in their own right means committing a fallacy of composition (Castle 2003).

2.2.4 Anthropocentric imperialism (Raven 2011)

This argument was generated in response to the Rawlsian reasoning in 2.1.2.

1. Humans view themselves as the pinnacle of cognitive evolution.
2. Human culture is assumed to be superior to an animal's natural culture.
3. We cannot know what is good for an animal better than itself.
4. Bringing civilization to 'backwards' natives is a an imperialist notion.
5. Uplift would be an unacceptable human domination of other species.

It is true that anthropocentrism is prevalent in comparative neurobiology studies because it is easier to compare humans with each animal species rather than study all the possible combinations between each pair of non-human species. Also it is difficult to conceptualize a non-human perspective while avoiding anthropomorphism. But this reasoning commits a "Noble Savage" fallacy by assuming that animals as more innocent than humans because they do not exhibit a moral behavior as complex as those of humans.

2.2.5 Consequentialism

In this approach, uplift could be unjustifiable if the reasons for its occurrence are morally wrong, like if :

- Hybrids suffer from intrinsic defects in the uplift protocol, like side effects of brain modifications (Wei 2001) or enhanced emphatic abilities (Coors et al. 2010).
- Caretakers involuntarily mistreat hybrids because they have difficulties to adjust to their extraordinary nature (Stapledon 1944).
- Hybrids have difficulties to adapt to their in-between state, where they are significantly dissimilar to their wild-type counterparts but not completely human.
- Scientific experimenters treat hybrids like baseline animals despite their potentially higher moral status (Robert 2006).
- Hybrids are created specifically to do demeaning or dangerous jobs (Fletcher 1988).

The last point is how most works of fiction present the negative consequences of uplift, with hybrids revolting against their creators because they were created for abuse or enslavement. The proposition by Joseph Fletcher to create a race of "para-humans" slaves shows that such an unethical path could be chosen despite its obvious problems. This kind of issue can arise with utilitarianism, which does not always respect the Kantian moral imperative of treating any subject as an end in itself, so hybrids would not be morally protected against abandonment or euthanasia if they outlive their usefulness.

3 Technical foundations

If uplifting animals is deemed useful and morally justifiable, then it has to be realized in a practical manner. Given the important modifications needed to the brain and skeletal structure, it is useful to harnessing the transformation powers of embryogenesis by starting with genetically-modified gametes. But this strategy requires a multi-generation iterative process acting on the germ line of the animals, which means modifying permanently their genome with the associated ethical objections.

The broad outlines for such a project are recapitulated below, with the techniques to be employed detailed in the following sections.

1. Selection of the candidate species to be uplifted depending on project goals
2. Choice of the genetic sequences pertinent for the final result to be achieved
3. Iterative portion of the protocol, repeated until desired outcome is obtained :
   (a) Selection of breeding pairs
   (b) Elaboration of the trans-gene and insertion into the animal genome
   (c) Sorting of the gene-expressing gametes and artificial insemination
   (d) If needed, hormonal and cellular treatments during gestation
   (e) Post-natal assessment of physiological condition
   (f) Cultural and linguistic uplift of the offspring until maturity
   (g) Testing of their cognitive abilities
4. Integration of the uplifted hybrids into the human society or release into the wild

3.1 Selection of candidate species

Choosing a species to uplift is based on several subjective and relative criteria, among which the practicality of uplifting this species and the characteristics of their brain in terms of size and amount of cortical convolutions. The following list is non-exhaustive and presented with no order of preference.

Chimpanzees
They are the closest species to humans in general morphology. Their brain is similar to ours in terms of cell composition and distribution (Herculano-Houzel et al. 2007) with a simple scaling model accounting for the difference in size (Azevedo et al. 2009). This might make uplift relatively easy, but they are an endangered wild species whose physical strength and aggressive behavior make handling difficult.

Bottlenose Dolphins
They possess sophisticated social learning abilities, spontaneously understand gazing and pointing cues (Herzing, Delfour, and Pack 2012). There is also evidence of local cultures and examples of hunting cooperation with humans (Rendell and Whitehead 2001). Their echolocation-based perception and interest in observing human responses to their behavior makes them attractive for an ümwelt-justified uplifting, but their wild nature and the vast difference in habitat between humans and dolphins render the task daunting.

Crows and Parrots
Crows appear to possess a domain-general cognitive "tool-kit" that includes causal reasoning, flexibility, imagination, and prospective (Emery and Clayton 2004) allowing them to create tools and solve problems with insight (Bird and Emery 2009). African Grey Parrots are known for complex vocal communication and imitation of human languages. They can acquire a large vocabulary and use it in a sophisticated way, with the ability to differentiate meaning and grasp features of syntax(Pepperberg 2006). Their potential for physical manipulation is limited as long as the formation of a thumb-claw cannot be induced (like for *Opisthocomus hoazin*) but such modification of the wing structure could impair flight.

Domestic Dogs
They are already domesticated and well integrated into human society, they can follow human cues and pointing gestures spontaneously (Kubinyi, Virányi, and Miklósi 2007) and are able to learn an adapted form of sign language (Senechal 2009). In addition, humans and dogs share functionally analogous auditory brain regions and show sensitivity to vocal emotional cues (Andics et al. 2014), which is an encouraging step for the acquisition of complex language.

Kangaroos
This group of species may not be an obvious choice for an uplift program but they have several factors in their favor :

1. A brain size similar to that of mammals in the same size/mass range (Ashwell 2008)
2. Neurogenesis occurs mainly after birth, so brain growth is not as constrained by the dimensions of the birth canal as it can be for placentals. However, the early ossification of facial bones required for suckling constitute an evolutionary constraint on cranium size in marsupials (Bennett and Goswami 2013).
3. Their metabolism rate during prolonged breastfeeding is favorable compared to placental nutrient transfer (Weisbecker and Goswami 2010) (Watson, Provis, and Herculano-Houzel 2012)
4. Their semi-upright position makes their hands partially prehensile, limiting the amount of modifications needed for full dexterity.

Spotted Hyenas
They exhibit a complex social structures similar in size, structure, and patterns to those of cercopithecine primates, with cooperative hunting and problem-solving (Holekamp, Sakai, and Lundrigan 2007) . The matriarchal hierarchy within their society is driven by disparity in social support in favor of females (Vullioud et al. 2019) while deceptive behaviors points to the possibility for a theory of mind. Also, the fossil record demonstrates a long, shared evolutionary history with coexistence in Eurasia until the end of the Pleistocene (Baynes-Rock 2015). However, this is a wild species with aggressive behavior which requires careful handling. The species also

suffers from a high newborn mortality due to their pseudo-penis, which can only be worsened during the uplift process by the increasing brain case size unless obstretical surgery is performed.

In each case, a thorough cost/benefit analysis must be conducted. It is likely that domesticated species will be subjected to uplift before tame or wild species, even if their ultimate potential is lower, because their integration into the human society will be easier.

3.2 Selection of genetic sequences of interest

Since intelligence and related cognitive abilities are emergent properties of the brain, this organ is the most relevant target for an uplift program. Following the human neural template is not mandatory but more convenient, because the majority of comparative neurogenetics studies has Homo Sapiens as the benchmark in the domain of general intelligence.

These studies have helped uncover genetic changes that potentially underlie human brain evolution (Dorus et al. 2004) (Vallender, Mekel-Bobrov, and Lahn 2008). Such discoveries can be classified as either positive evidence (presence of human variant in genetically-modified animals causes enhancement) vs. negative evidence (absence of human variant in humans cause problems). The first category yields the most useful data in regard to animal uplift. The kind of phenotypes researched are a greater number of neurons, an increased connectivity between neurons, larger cortical structures, a larger skull, more agile hands, etc.

Instead of the human neural template, one could also start from avian brains, since they present a significantly higher neuron density and number of neurons in the fore-brain (Olkowicz et al. 2016). They also include unusual neural structures like the Wulst (isocortex homolog) which is made up of extremely densely packed and highly interconnected neurons and is probably a flight adaptation, as it reduces the overall size of the brain.

Table 1 gives a non-exhaustive list of human genes relevant for an uplift program.

3.3 Selective breeding

The selection of breeding pairs from an existing animal population, according to behavioral or performance criteria, is necessary in three cases :

- To domesticate a wild species deemed worthy of uplift, before committing to the program itself.
- To isolate physical or cognitive features useful for the next generation of hybrids. As a note of interest, a domestic cat breeding program focused on intelligence and problem-solving behaviors has been started by author Leslie Fish in 1970 (Fish 1992).
- To stabilize a lineage after a round of genetic engineering.

Domestication has a profound impact on the final phenotype, which has to be taken into account in the initial planning. As an example, repeated selection of silver foxes for tameness towards humans leads to a reduced production of stress hormones in the adrenal system, coupled to neoteny (the retention of juvenile morphology) and physical features similar to that of dogs (Trut, Plyusnina, and Oskina 2004). This 'domestication syndrome' has a potential origin in a slight cell deficit in the cranial neural crest during embryonic development (Wilkins, Wrangham, and Fitch 2014) : since these neural crest cells are precursor for cell populations in the head, they have an indirect role in the formation of the adrenal system. Domestication also induce variation in the expression level of genes associated with brain development (Albert et al. 2012) (Li et al. 2013), which could lead to interference with the genetic modifications applied.

Another way to obtain potentially useful features is to release the cryptic variation present in a population : inhibiting HSP90 (a heat shock protein which assists in the folding of gene transcription factors) with Radicicol results in an increase of low-prevalence phenotypes that remain active in the offspring (Rohner et al. 2013). However, most of these phenotypes are not obviously adaptive and either not viable or transient, posing ethical issues for the affected animals expressing them.

After a phase of gene therapy, the modified animals are generally heterozygous for the trans-gene inserted into their genome. This requires at least two generations of back-crossing to obtain a population of homozygous animals. This step can be accelerated with two techniques :

- The sorting of sperm with flux cytometry coupled to gene-specific fluorescent probes (Johnson, Welch, and Rens 1999) allows to select only the sperm cell expressing the trans-gene for artificial insemination.
- The use of the gene drive method, based on site-specific selfish genes (Burt 2003) and auto-catalytic mutations (Gantz and Bier 2015), induces the conversion of heterozygous mutations to homozygous ones in one generation. But this technique increases the risk of transgene proliferation in the wild population, unless the daisy quorum system described in section 3.10 is employed.

Selective breeding is a necessary counterpoint to genetic engineering, but will significantly lengthen the uplift process and leave a large proportion of each generation deemed unfit for reproduction. Their subsequent treatment and quality of life will be important to keep the process ethically justified.

Name	Type	Strategy	Effects of the strategy
FOXp2	G	S	Proliferation of cortico-basal ganglia (Enard et al. 2009) leading to humanized mice with enhanced learning (Scharff and Petri 2011).
HACNS1	G	S	Activation in thumbs, wrists and ankles, opening the possibility for occasional upright stance (Prabhakar et al. 2008).
hCONDEL332	D	D	Inhibition of regulatory gene GADD45G leading to increased neuron production (McLean et al. 2011).
SRgap2	PG	D	Emergence of human-specific features in the neocortex, including neoteny during neuron spine maturation and increased density of longer spines (Charrier et al. 2012; Dennis et al. 2012).
beta-catenin	G	A	Shortens the mitosis cycle of neuron progenitor stem cells causing a doubling of brain cell count (Chenn and Walsh 2002) but results in generally deleterious modifications of brain structure (Chenn and Walsh 2003).
MYH16	PG	D	Weakening of jaw muscles may leads to increased cranium size due to lesser constraints on bone growth (Stedman et al. 2001). Possible role in evolution of human brain (Daegling 2012) but causality is disputed (Perry, Verrelli, and Stone 2005).
miRNA-941	E	A	Regulation of the hedgehog-signaling pathway, involved in the maintenance of stem cell populations in adults and linked to increased longevity (Hu et al. 2012).
LAMC3	G	S	Role in formation of cortical structures, such that mutations cause malformations of occipital cortical development (Barak et al. 2011).
GPR56	G	A	Affects neuronal progenitors in the embryonic brain and causes an increase in the number of convolutions in the cortex (Rakic 2004).
LHX2	G	S	Helps expressing the cortical identity in neuron precursors at the edges of the developing cortex (Mangale et al. 2008).
EDAR	G	S	Human variant in mouse models results in an increase of both hair thickness and number of eccrine glands (Kamberov et al. 2013).
Dickkopf-1	G	D	Has a role in the maintenance of neurogenesis during lifetime (Niehrs 2006) with improvement in memory and learning abilities in old age (Seib et al. 2013).

Table 1: List of some genetic sequences of interest for an animal uplift program. Type = gene (G) pseudo-gene (PG) enhancer (E) deletion (D). Strategy = deactivation of animal sequence (D) substitution of animal sequence by human equivalent (S) addition of human sequence to animal genome (A).

3.4 Genetic engineering

This step constitutes the mainstay of any uplift project, since it permits the kind of morphological modifications necessary for its success and can apply them to the animal's entire organism. Large-scale modifications may be achieved if the genes of interest are active during embryogenesis, which requires to work on gametes and imply that they will be transmitted to the offspring.

The first step is the construction of a chimeric trans-gene (animal promoters + human sequence of interest) in order to integrate the substitution genes in the transcription network of the target animal as much as possible. Several methods of single-step DNA assembly are available (Stemmer et al. 1995) (Shao, Zhao, and Zhao 2009). When necessary, inhibition of an animal gene can be obtained with translational blocking via gene-specific RNA interferons (Ceroni et al. 2009).

Then the trans-gene can be delivered inside the target cells via different vectors, each with its advantages and limitations. They can be adenoviruses and retroviruses, non-viral episomal vectors (Manzini et al. 2006) or non-pathogenic bacteria in a process called bactofection (Pálffy et al. 2006). Delivering the transgene into the germinal cell line can be done with three techniques (SCNT, SMGT, TMGT) detailed in the following subsections.

Once delivered, several techniques can be used to precisely insert the trans-gene into the animal's genome and increase its retention across generations. One can employ zing-finger nucleases for which open-source variants have been developed (Maeder et al. 2008), transcription-activator-like effector nucleases (TALEN) (Jinek et al. 2012) or the promising CRISPR-Cas9 system (Cong et al. 2013) (Jinek et al. 2013).

The choice of methods for the construction, delivery and insertion of the sequences of interest will depend of program goals and available budget/timeline. Given their synergy, combining the TMGT method with bactofection as delivery vector and either zing-finger nucleases or CRISPR-Cas9 cassettes for targeted insertion will allow to transfer several genes of interest at once into an artificial chromosome with a limited risk for the animal genome and minimal manipulation of the animal.

3.4.1 SCNT

Somatic Cell Nuclear Transfer, commonly called cloning, consists in extracting the nucleus from an ovocyte then transferring the nucleus of a somatic cell into the ovocyte and implanting the embryo obtained in the uterus of a surrogate mother. The somatic cell can be genetically modified beforehand and the modifications are present in the germinal cells of the resulting clone, thus they are transmitted to its offspring.

SCNT is a mature technology that benefited from numerous advances since its inception in 1984 :

- improved methodologies and simplified instruments, that allows the task to be performed by a small team of 7-9 researchers and technicians (Vajta and Callesen 2012) (Jakobsen et al. 2013)
- extraction of adequate somatic cells from a single drop of blood, without the need of biopsies (Kamimura et al. 2013)
- the use of a histone deacetylase inhibitor to repair epigenetic damages before implantation, allowing reliable re-cloning over several generations without decrease of the overall efficiency. (Wakayama et al. 2013)

However, the overall success rate for mammals is still only 2 to 5% and requires the extraction of 20 to 50 ovocytes for each viable embryo born to term. In addition, some species present additional difficulties to overcome because of particularities of their reproductive system, like the domestic dog (Jang, Kim, and Lee 2010).

3.4.2 SMGT

Sperm-Mediated Gene Transfer consists in transferring a genetic sequence into sperm cells then using the modified sperms for artificial insemination. Various techniques can be used for transfection (DNA incubation, electroporation, liposomes) with an overall success rate of 50 to 80 %. SMGT does not require embryo handling or expensive equipment, resulting in a cost per session lower than US$1000 (Lavitrano et al. 2006), but the length of the trans-gene is limited (30 kilobases maximum) and the operation must be repeated for each sperm sample.

An important limitation of this technique is that most transfection methods result in the trans-gene being an extra-chromosomal structure not integrated in the host genome. This leads to mosaicism (presence of two different genotypes in the same organism) and a probability of transmission to progeny of only 25% (Smith and Spadafora 2005). The use of restriction enzyme-mediated integration (REMI) and linker-based SMGT (Epperly 2009) allows integration of the trans-gene in the sperm's genome, but the insertion is partially random with the risk of accidentally deactivating an essential gene.

3.4.3 TMGT

Testis-Mediated Gene Transfer is a variant of SMGT where the transfection occurs in the testicles of the target animal, so that the sperm cells produced directly integrate the sequence of interest in their genome. Between 10 and 25 % of sperm cells express the trans-gene (Chang et al. 1999) (Hibbitt et al. 2006), but the use of flux cytometry coupled with gene-specific fluorescent probes (Johnson, Welch, and Rens 1999) allows to keep only the transfected sperm cells.

Combined use of the Type IV secretion system (T4SS) bactofection method (Llosa, Schröder, and Dehio 2012) with a refined Human Artificial Chromosome (HAC) (Kazuki et al. 2011) permits to transfer a large amount of foreign DNA (0.3 - 3.0 megabases) while controlling the insertion site in the target genome. The procedure needs only to be applied once per animal, but precautions must be taken afterwards to avoid accidental dissemination of the exogenous genes into the wild population.

3.5 Cellular and hormonal engineering

The human brain differs significantly from that of other primates on three points : a higher total number of neurons (Herculano-Houzel 2009) (Azevedo et al. 2009), more developed cortical convolutions with a greater surface area (Toro et al. 2008) and a greater proportion of unusual neural cells like astrocytes and Von Economou neurons (Allman et al. 2010). In parallel to genetic engineering, the administration of hormones and specialized cells into animal brains may be another way to induce notable modifications of the cerebral structure and neuron distribution, leading to a potential increase in cognitive abilities.

Human cortical astrocytes, which are larger and more complex than those of rodents, may be a factor in the increased functional competence of the human brain (Oberheim et al. 2009). Injecting human glial cells into the brain of newborn mice leads to a proliferation of human glial astrocytes which retain their size and pleomorphism while systematically replacing the murine glial cells (Windrem et al. 2014). A resulting boost in learning abilities for object-location memory and contextual conditioning is also observed (Han et al. 2013). The main limitations of this method (as it exists) are that immunodeficient animals must be used to avoid rejection of the human cells, and that human glial cells come from aborted fetuses with the associated ethical objections. A way to overcome the first difficulty would be to use advanced genetic engineering techniques to perform in-situ substitution of human immunoglobin genes with their animal analogs, as the inverse of the procedure detailed in (Macdonald et al. 2014).

On the hormonal front, Lysophosphatidic acid (LPA) is a phospholipid with extracellular signaling properties expressed in the embryonic cerebral cortex. Its supplementary injection into mouse brain leads to an increase of cortex thickness and the production of cortical folds resembling gyri present in the primate brain (Kingsbury et al. 2003). The mechanism behind this effect could be a decreased apoptosis (receptor-dependent cell death) in the population of neurons precursors, inducing an increase in the final number of cortical neurons and the generation of circonvolutions to accommodate this larger population of cells (Price 2004). The need for targeted administration of LPA into the brain of embryos severely limits the application of these results to an uplift project. However, a way to bypass the intrauterine cranial injection could be to couple LPA with bi-specific antibodies tailored to traverse the placental and brain-blood barriers (Byrne et al. 2013) (Stanimirovic et al. 2014), allowing a simple injection into the mother's bloodstream to be realized instead.

Finally, administration of choline supplements to pregnant rats improved the performance of their offspring, with links to changes in neural development and associated gene expression (Mellott et al. 2004).

Contrary to genetic engineering targeting the germinal cell line, the methods described in this section must be reapplied for each generation and may not give enough benefits to offset their operating costs, especially if they require complex surgery or cell modification.

3.6 Complementary enhancements

In addition to genetic and cellular enhancements focused on cognitive abilities, other modifications are necessary to ensure satisfactory health and lifespan for the population of hybrids.

Increased metabolism

The energy needs of a mammalian brain are roughly proportional to the number of neurons, with a mean metabolic cost of 6 kcal per day and per billion of neurons (Herculano-Houzel 2011). This implies that building a larger brain will entail a change in diet, with more nutrients overall and more proteins in particular to support the formation of additional neurons. Using genetic or hormonal therapy to increase the efficiency of nutrient uptake by the digestive system and energy storage in adipose cells is a possible longer-term strategy.

Efficient brain cooling

A larger brain also outputs more waste heat which needs to be dissipated efficiently to avoid hyperthermia. Most mammals and non-human primates have thick fur and apocrine glands in their skin which limit their capability to evacuate body heat. Two human features offer a template to alleviate this issue :

- The human skin includes more than 1.5 million eccrine glands that emits a water-based sweat, whose evaporation is a much more efficient cooling process compared to the non-evaporating oily sweat secreted by apocrine glands (Ibraimov 2007). Using the human variant of genes implicated in the structure of the dermis could help to increase the cooling capabilities of the animal skin. An example is EDARV370A, whose substitution notably increased the number of eccrine glands in the mouse (Kamberov et al. 2013).
- The lower density and smaller diameter of human hair compared to its animal analogs also help with sweat evaporation and thus body cooling (Wheeler 1992). The same category of genes as mentioned before should be used to achieve the wanted phenotype.

Lifespan extension

The relatively low lifespan of several candidate species (like the domestic dog) is problematic with respect to their enrollment in an uplift program, since the hybrids may not be able to make use of their enhanced intellect before facing senescence. Research on aging reversal is a trending topic and a large amount of animal experimentation has been conducted (Kenyon 2010). Existing methods, developed mainly on mouse models, show an increase in life expectancy between 5 and 40 % compared to controls subjects.

They consist of the restriction of caloric input (Sun et al. 2009) the administering of metformine (Anisimov et al. 2005) the inhibition of metabolic enzymes (Yan et al. 2007) or the over-expression of genes linked to mitochondria (Schriner et al. 2005). Some of these methods have beneficial side effects, like PEPCK-C over-expression which leads to a greater physical endurance. However most anti-aging strategies run counter to other modifications, like caloric restriction and the enhanced metabolism needed for a bigger brain, and thus require trade-offs between the two domains.

Improved learning

In addition to lifespan expansion, the lengthening of the period during which cognitive capabilities are optimal would allow deeper education and learning. This can be achieved by focused gene therapy or the administering of appropriate drugs. For example, Valproate increases the length of the critical period during which sensory-association learning can occur (Gervain et al. 2013) while Montelukast leads to functional rejuvenation of brain tissues with improvements in learning and memory tasks in old animals (Marschallinger et al. 2015). The latter drug acts by inhibiting leukotriene receptors present in brain cells, reducing neuro-inflammation and boosting the proliferation of neural progenitor cells (Huber et al. 2011). In complement, silencing the Wnt antagonist gene Dickkopf-1 help maintain neurogenesis during the animal's lifetime and slows down aging-related cognitive decline (Seib et al. 2013).

Figure 2: Chimpanzees Panbinisha (L) and Kanzi (R) working on a portable 'keyboard' featuring lexigrams. Photo by William H. Calvin PhD, used under the CC-BY-SA 4.0 license.

The list above shows that a complete uplift program is much more that just cognitive enhancement and will require a holistic approach to the physiological, psychological and social bases of increased intelligence.

3.7 Cultural and linguistic uplift

Cultural uplift can be defined as sharing elements from human cultures with animals so that they may learn more complex notions and make full use of their cognitive abilities. In one study, the development of symbolic play in chimpanzees was accelerated by interaction with humans and a linguistic system for interspecies communication was necessary to achieve the highest level of symbolical play and pretense (Lyn, Greenfield, and Savage-Rumbaugh 2006).

In order for two species to exchange knowledge with each other, an efficient two-way communication channel must be present. It may already exist, like with vocalization for parrots, or be created with preliminary training or specially-build instruments. Examples of such developments are :

- a sono-visual communication interface to study human-dolphin cooperative play behavior (Herzing, Delfour, and Pack 2012)
- a system of whole-body sign language for dogs (Senechal 2009)
- a set of arbitrary visual symbols called lexigrams for use with chimpanzees, as illustrated in figure 2
- the use of constructed minimal-complexity languages similar to Toki Pona (Lang 2014), which is composed of only 120 base words with associated ideograms and a simple grammar.

Also important are the methods used to teach animals, since the gain of knowledge from others depends on the context and the social identity of both the learner and the teacher, the latter having to adjust their display to the skill level of the former (Nicol 2006). The Model/Rival training system, where two humans act as teacher and student while the animal watches their interaction, can be used to teach object-label correspondence along with more abstract concepts of same/different, absence and number (Pepperberg 2006).

Lastly, the environment where uplift is likely to take place will have an influence on the cognitive abilities of the hybrids. On one hand, human-centered urban areas generate a strong selective pressure for species migrating into it which favors individuals with significantly greater cranial capacity and behavioral plasticity (Snell-Rood and Wick 2013) and induces evolutionary changes in genes involved in xenobiotic metabolism, innate immune response, demethylation activity (Harris et al. 2013). On the other hand, captive environments designed by humans may be insufficiently stimulating for the animals placed in them. Inadequate handling partially determines their mental development and therefore limits the demonstration of autonomous culture. In apes, the recourse to lexigrams can help humans researchers to assess the welfare of their non-vocal charges before improving their environment to suit their cognitive potential (Savage-Rumbaugh et al. 2007).

3.8 Assessment of cognitive abilities

While seemingly secondary to the various methods of cognitive enhancement detailed above, the capacity to accurately measure the cognitive abilities of animals subject to uplift is indispensable in order to judge if the program is progressing as planned. A comprehensive summary of available techniques can be found in (Le Neindre et al. 2017, chap. 3).

When assessing the level of general intelligence for an animal, it is critical to avoid anthropomorphic bias. A multi-faceted approach like the COMPLEX framework can be useful to mitigate it (Herzing 2014). Within this multi-disciplinary method, several axes are investigated including encephalization quotient, communication signal complexity, individual complexity, social complexity and interspecies interaction .

In matter of physical measurements, the isotropic fractionator is a simple technique to obtain the number of neuronal and non-neuronal cells in a given brain (Herculano-Houzel and Lent 2005). However, this method necessitates a necropsy and cannot reveal fine morphological details since brain tissue is homogenized.

When studying the variation in language complexity that occur during uplift, the use of conditional entropy estimates from Shannon's information theory allows to estimate the total repertoire size in a communication channel without having to know the meaning of the symbols exchanged (Smith 2014).

Measuring the quality of life of animals requires studying their feelings, which can be quantified with various tests measuring preference, motivation and aversion. These tests have each their own strengths, limitations and methodological problems as listed in (Kirkden and Pajor 2006). In the same domain of animal welfare, apparatuses has been developed to assess judgment bias in animals like dogs. This kind of cognitive bias, where a subject shows a higher expectation for a given outcome that available information would infer, can be used to measure the animal's affective state and categorize it as either optimistic or pessimistic (Starling et al. 2014).

As shown above, available cognitive assessment methodologies are mostly indirect and inferential while requiring efficient cooperation between specialists in the fields of ethology, neurology and semiology. They are likely to represent one of the largest hidden sources of complexity for any uplift program.

3.9 Example of an uplift protocol

The following summary, based on the information detailed in the previous sections, is only one possibility among other.

Justification
: Mix of utilitarianism and Rawlsianism

Species
: Working breeds of domestic dog, with at least 50 to 500 animals during each 6+ generations.

Genes
: FOXp2, hCD332, SRgap2, miRNA-941, GPR56, LHX2 (brain) HACNS1, EDARV370A, Dickkopf-1, PEPCK-C (other organs)

Vector
: Bactofection using *Bartonella henselae* with Type IV secretion system, combined with a Human Artificial Chromosome including T-REX sequences.

Transfer
: Testis-Mediated Gene Transfer coupled with flux cytometry and DNA-specific fluorescent probes.

Drugs
: Administration of choline during pregnancy and valproate during childhood.

Culture
: Use of sign language for short term and a Toki Pona variant at long term.

Personnel
: At least 10 scientists and technicians for R&D plus 1 handler or vet per 10 animals.

Budget
: At least 5 million $/year, mainly in salaries, food and kennel.

3.10 Ethical concerns

Even if an uplift program can be morally justified and technically viable, there remains the question on how can it be implemented in an ethical manner.

Concerns about the proper management of a uplift program are very diverse. Identifying problems, understanding them and designing countermeasures is essential, but finite resources will lead to prioritization and trade-offs while leaving some potential consequences unanswered. It is important to implicate institutional reviews boards in the process to check for goal deviations. It is also possible to use existing social ethic models as guidelines, but they can enter in conflict with the goals of the uplift program.

3.10.1 Project-centered concerns

The first concern is the impossibility to obtain informed consent from animals prior to their uplift, since they do net possess the mental processes needed to understand the implications of the process. In addition, the uplift process being multi-generational means that a given animal cannot compare its own mental states before and after uplift in order to determine the validity of the program applied to it, because each generation will shift the baseline as it incorporates small incremental modifications.

A partial analogy can be made with a non-relativistic interstellar spaceship, where consent can be obtained from the original astronauts at the start of the mission but their descendants have their destination locked-in. In this case, consent could be propagated forward if the current situation is judged acceptable at each generation. For uplift, consent could be obtained retroactively from the hybrids after the program on at least two conditions :

- Global positive derivative : within the philosophy system chosen to justify it, the entire process can be judged beneficial to the last generation as compared to the first generation.
- Local positive derivative : members of each generation has lives worth living, as both observed empirically and defined in the philosophical framework of the program.

After that, the most frequent concern is the accidental dissemination of genetic material from the GM population into a wild one (Collective 2000). This is an issue primarily with mobile wild populations, except when uplift is performed for extinction prevention. It also constitutes a long-term issue for the recognition of reproductive rights of hybrids with a human level of intelligence.

Typical mitigating methods will be either neutering after gamete collection or the use of reversible contraceptive implants. These procedures are simple and well understood, al least on domestic animals, and only need to be done once or a few times per year. But they may be difficult to implement in wild species and cause additional suffering from surgery and handling.

A more elaborate solution is to incorporate a control system at the gene level, with two possible systems :

- A master translation switch based on a two-component signaling pathway (Hansen et al. 2014) is described in figure 3. The hybrids can still reproduce but only breed true if they receive the control substance (a man-made or non-food molecule) regularly. The insect molting hormone ecdysone could be used as the switch since it has been efficiently used to control gene expression in mammalian cells (No, Yao, and Evans 1996). However, this method will hamper the reproductive rights and bodily autonomy of the hybrid population as long as they do not have control of the switch substance's supply.
- The daisy quorum drive is a gene drive based technique which combines the daisy chain drive method and the genetic quorum effect to control the gene flow between populations (Min et al. 2017). It serves to both limit the number of generations during which the uplifting gene is dominant and to make the mixing between populations deleterious in an evolutionary point of view. Hybrids incorporating this system will be able to reproduce freely but mixed coupling will result in half the offspring being non-viable, an event that can generate psychological trauma.

Captivity and temporary confinement are also an issue. They are generally necessary during the uplift process, but not after its completion. Two methods can be used to alleviate the effects of captivity :

- Enriched habitats aims to reduce boredom and its deleterious effects by providing enough diversity in the environment (Chelone et al. 2014). They are based on the notion of the comfort horizon, which is the amount of a element (like space or food) needed to live comfortably. The psychological suffering of animals can be minimized through enrichment, but respecting all comfort horizons simultaneously can become cost prohibitive.
- Progressive freedom is a process similar to the socialization steps done with pets : they are first kept indoors, then allowed in the garden, then outdoors in lease, and finally left out of the lease. This process would make integration into the human society easier and gentler, but is limited to domesticated or tamed animals and requires handlers in sufficient quantity.

The possibility of a genetic modification having deleterious effects (Buchanan et al. 2013) or leading to awareness of inadequate conditions of care and psychological suffering (Coors et al. 2010) should not be neglected. To be effective, an uplift project must be operated in an incremental manner following a Plan-Do-Check-Act methodology : each modification to the animal's physiology must be observed and tested for innocuousness in the following generations before committing to another modification. Another possible hurdle is the considerable psychological suffering of humans following the death of their uplifted companions, if their respective lifespans are significantly different. This can be avoided by finding ways to increase the lifespan of hybrids and propose better palliative treatments for their end of life, as detailed in section 3.6

3.10.2 Society-centered concerns

Issues of intellectual property rights and gene patenting are likely to arise, given the highly technical aspects of the endeavor and the for-profit nature of some genetic engineering techniques. The potential benefits and harms of patents on human-animal hybrids must be carefully weighted, since they would be similar to patents on human genes and might pose a significant threat to human dignity (Resnik 2003). Otherwise, hybrids could have their autonomy and reproductive rights curtailed by the company or laboratory having undertaken the uplift program because they constitute a valuable property. One possible response is to use open-source variants of genetic engineering tools and employ the "Creative Commons" model for non-profit oriented patenting (Rai and Boyle 2007).

Correlated to those concerns is the problem of the legal status of hybrids. Instead of the current binary model with subjects and objects, person-hood could be treated as a continuum where a certain amount of rights and obligations are granted depending on demonstrated abilities. Two models of continuum have been proposed, one with two axis for higher-level cognition capacity and percentage of human genes/tissue (Bennett 2006) and one as a four-step pyramid where the rights obtained are cumulative (Wise 2011).

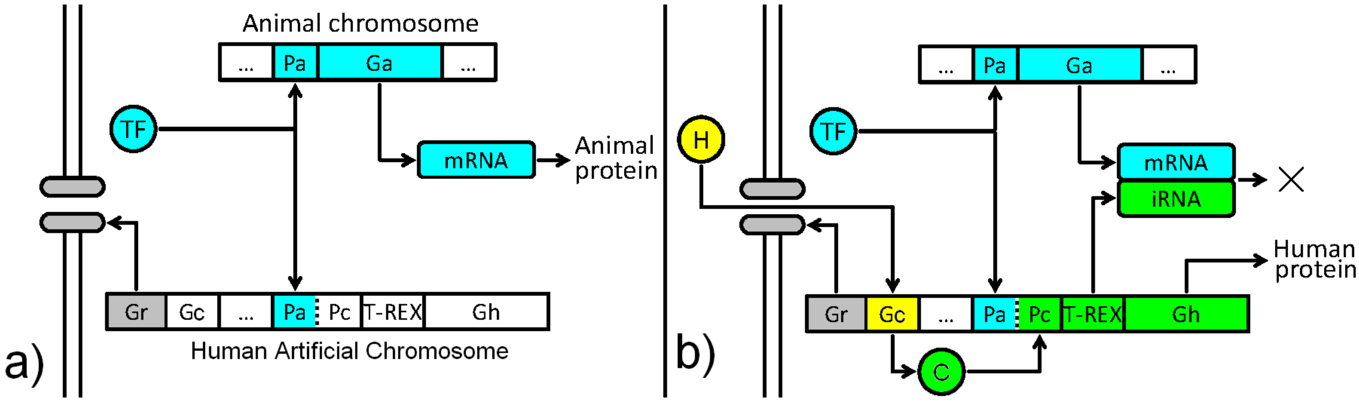

Figure 3: Schematic work-flow of the externally-triggered translation control scheme. In the inactive state (a) the HAC is dormant and the animal genes are expressed normally because the human genes do not receive the two transcription factors needed for activation. In the active state (b) an externally-supplied hormone H interacts with the activation gene Gc to produce a complementary factor C, which combines with the internal transcription factor TF to express the human gene Gh. If the output of the human gene needs to replace that of the animal gene, a T-REX (Trans-Repression of Expression) sequence is used to inhibit the transduction of the animal RNA generated (Ceroni et al. 2009).

4 Conclusion

The creation of sapient human-animal hybrids is a still theoretical process with potentially broad impacts on human society in general and animal welfare in particular. The timing of its emergence is difficult to guess : rapid advances in genetic engineering would accelerate it, but completion is dependent on the support of the public and political bodies. Since cognitive enhancement technologies for humans are likely to be tested first on animals, it is probable that methods relevant to uplift will be perfected before human enhancement is possible.

In addition, the assumptions about the uplift process listed in the introduction are mostly justified :

1. Several arguments has been advanced to justify the enhancement of intelligence capabilities in animals.
2. Assessing frameworks like COMPLEX can be used to quantify intelligence along several axis.
3. Genes and drugs have been found to have impacts on cognitive abilities.
4. Several methods of efficient gene transfer have been developed.
5. Experiments with animal models containing humans genes has lead to enhanced learning abilities.

Progress in biotechnology is often faster than the relevant ethical and legal discussion, which can create suspicion and backlash from the public. Politicians can then use this public outrage to propose overly-broad regulation, like the Human Chimera Prohibition Act of 2005 proposed after research on interspecies chimeras intensified in the US (Sherringham 2008). But prohibition would inhibit intellectual and scientific freedom, and would prevent any possible benefits from the targeted technology from being realized. Given the societal risks and potential for abuse associated with uplift, the probability of such a scenario is high.

To avoid this scenario, it is imperative that the ethical and regulatory issues concerning uplift are identified, analyzed and addressed early on. Education and awareness, both within the scientific community and in the public sphere, could also help to prevent a backlash (Samuel, Selgelid, and Kerridge 2009). Ethically sound methods should be developed, reviewed and sanctioned before any uplift protocol is implemented.

Existing social ethic models and guidelines for the treatment of animals in research (Buchanan et al. 2013) may be used as a template, although they can enter in conflict with the goals of uplift. For example, Bernard Rollin's social ethic model posits that "That the telos of an animal (its inherent nature, physically and psychologically expressed, which determine how they live in their environments) not be violated" (Glenn 2002).

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