Strategic roadmap for research in morphological freedom
Authored by the Freedom of Form Foundation Inc, a 501(c)(3) nonprofit organization
2018

Now that we have gone over our overall anatomical objectives, we can discuss some key technologies as they exist currently, elucidate their anticipated roles, and mention some research problems that still need solved. In other words, these are some of the specific areas of research that we want to pursue, in order to make the anatomical objectives of transformations possible.

We've put these research plans together for a couple reasons: first, to provide a tangible path towards transformation that inspires confidence, and direct action, by the scientific community; and second, to strategize for the optimal productivity of research that we fund. But, to be clear, we don't intend for these plans to be final or infallible. Other people may have better ideas, too! Assuming we have the resources, we'll fund any good research proposal we get, as long as it's relevant to morphological freedom. Scientists, engineers, doctors, and other professionals that propose research projects won't be required to limit themselves to the below plans.

Neuroprosthetics and neural interfaces

A "neuroprosthetic" is simply any prosthetic, a synthetic device on (or in) the body, that has a neural interface with the user, communicating with sensory and motor information, via nerves or the brain. Neuroprosthetics can take many forms, and provide a diversity of novel motor and sensory functions throughout the body.

At a glance
- Neuroprosthetics are active prosthetics that can be motorized, or provide sensory information, or both.
- Neuroprosthetics have been studied for decades, and are almost ready for prime time if we can solve a few remaining questions.
- These technologies may be particularly useful for attaining the tail and wings, especially in terms of mechanical performance. Secondarily, they may contribute to modifications of the head, skin, and external sex organs.

State of the art

Neural interfaces are the most important parts of neuroprosthetics to get right, since the interface is where artificial materials communicate and interact with biological tissues. Generally, we're most interested in interfaces for the peripheral nervous system (PNS) (e.g. Fig. 1.A), since the PNS is safer to access for surgery, can naturally regenerate after damage, and conveniently divides signaling functions into separate nerves, with further divisions into fascicles (Ghafoor et al., 2017; Jung et al., 2017). However, some interfaces may be more appropriate for the central nervous system (CNS), e.g. the spinal cord or cortex, for communicating with the tail or wings, since these are not naturally served by the PNS.

There's a gradient of different general types of neural interfaces, ranging from the most specific (but most invasive) contacting individual neuron cell bodies or axons, to the least-specific interfaces that communicate with thousands or millions of neurons at once at a population level, such as cuff electrode interfaces and EEG electrodes (Borton et al., 2013). We won't cover the least specific interfaces, because they can only partially recover lost signaling functions (Jung et al., 2017). They won't work well enough to justify an elective body modification. Of the interfaces that are at least moderately invasive, broad

classes include: intrafascicular electrodes, regenerative electrodes, neural dust, and optrodes (optical light interfaces).

Contemporary interfaces include the well-researched longitudinal intrafascicular electrodes (LIFEs). These have been used extensively in humans and other animals, and appear able to avoid tissue damage and signal degradation as long as specific engineering decisions are followed (Jung et al., 2017). These will offer improvements in both signaling quality and biocompatibility over more classical, rigid electrode arrays, even though even classic arrays have already met success in restoring aspects of image-forming vision at the visual cortex in human clinical trials (Dobelle and Mladejovsky, 1974; Dobelle et al., 1974; Lane et al., 2013; Lewis et al., 2016), and to a lesser extent in scientific studies and acute tests (Christensen et al., 2014; Ghafoor et al., 2017).

Figure 1: Neuroprosthetics

Ghafoor et al, Frontiers in Neurorobotics, 2017
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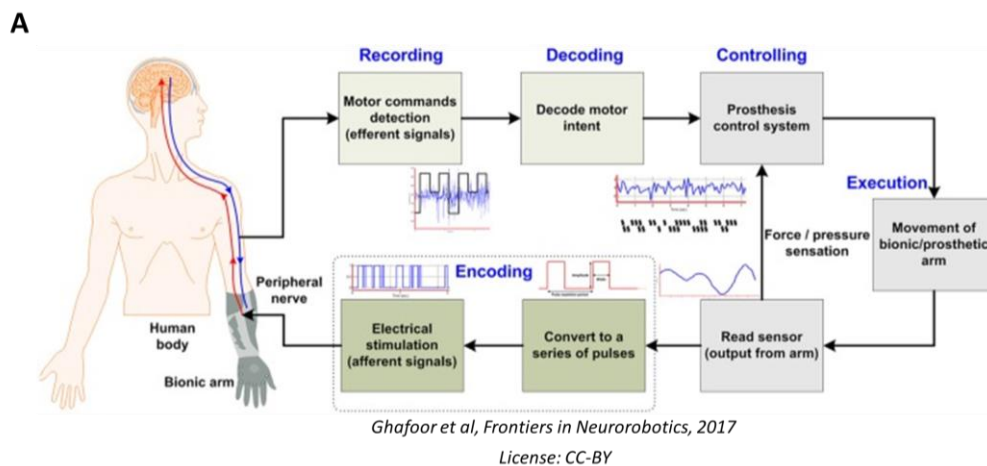
NIH NINDS, 2012
License: Standard YouTube License

Sharmander, 2016
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An example of regenerative electrodes includes a thin, flexible regenerative electrode design that was implanted into the tibial nerve of rats, where axons from the transected nerve were able to grow along the interface, resulting in reasonable biocompatibility and electrical recording quality (Clements et al., 2013). This may be more successful than the regenerative "sieve" electrode strategy (MacEwan et al., 2016; Navarro et al., 1998).

More radical designs include neural dust, which has been demonstrated to record neural activity in the peripheral nerves of rats (Seo et al., 2016). While neural dust currently has a lower resolution than some LINEs or regenerative electrodes, it has advantages in that individual electrodes are wireless, meaning that electrode-nerve mechanical interactions are more flexible, and eliminating the chronic penetration of tissue by wires.

Perhaps even more radical is the idea to use optics, rather than electrical charge, to interface with the neural system in humans. Optical techniques are experimental work-horses in neuroscience, relying on genetically encoded or chemically provided tools that link fluorescent light to neural depolarization, such as channelrhodopsin (Warden et al., 2014). While these are primarily research tools, they are being actively pursued with an eye to clinical translation (Aravanis et al., 2007; Cobb, 2010).

Some of the most striking demonstrations of the power of neuroprosthetics include neural interfaces for thought-controlled usage of motorized robotics in paralyzed individuals. These include clinical trials of BrainGate (Fig. 1.B), and the kick-off by a paralyzed individual of the 2014 World Cup led by the Nicolelis lab at Duke (NIH NINDS, 2012; Smith, 2014). Equally as important, recent developments in tactile perception and proprioceptive feedback suggest that fully functional neuroprosthetics are nearing reality (Graczyk et al., 2016; Marasco et al., 2018; Park et al., 2015; Tabot et al., 2013; Tee et al., 2015). Finally, the nervous system has flexibility to work with completely new motor controls, ranging from the on-screen control of a computer cursor by a paralyzed individual (Pollack, 2006) to the whimsical control of motorized ears (Fig. 1.C) (Isaacson, 2012; Sharmander, 2016). Clearly, neuroprosthetics present incredible opportunities for accomplishing morphological freedom.

Okay, so what's the hold up?

We think that an important technical challenge is the number of simultaneous channels for neural recording and stimulation. While long-term tissue biocompatibility is also a concern, it's already being well-handled in scientific literature (Fattahi et al., 2014; Green et al., 2008; Kim et al., 2008; Scaini and Ballerini, 2017).

The number of channels is limiting because electronics in current use generally rely on huge, special-built electrophysiology equipment, which amplifies nanoampere-scale electrical signals (Blair and Bean, 2002; Wikipedia, 2018a) to be communicated through a USB port, and then processed by a computer with nanoampere currents again (Prunty, 2008). Inspired by some ongoing efforts (Dai and Rosenstein, 2017; Ng et al., 2016), we suspect that specially produced microchips should reduce this awkward up-and-down conversion, making equipment more compact and amenable to thousands of parallel channels. Interestingly, CCD chips, used as light sensors in photography, can detect voltages on the order of microvolts with megapixel resolution and millisecond speed (QSI Imaging) – regardless of how CCDs work, this is on the same scale as neuron depolarization. Therefore, we'll keep our eyes out for research that might exploit consumer products and standard industry practices to create paradigm-changing neural interfaces.

Additionally, we'll encourage research that begins to assemble functional systems, such as demonstrating prosthetics integrating neural interfaces with motors and artificial sensor-embedded skin. We'll also emphasize platforms that make these technologies more modular, reliable, affordable, and customizable.

Basic research plan
- Design and test neural interface architecture using penetration or regenerative electrode strategies, for mixed motor and sensory peripheral nerves.
- Select and test biocompatible materials and micro-structures that produce a smooth, rather than abrupt, transition zone between artificial and natural tissue:
    - Neural interfaces (including electrodes and insulating/structural materials).
    - Bones, ligaments, and muscles (with hard or soft materials, as appropriate). Possibly avoid current approaches, like titanium, where the material is harder than surrounding tissue (creating an abrupt mechanical interface) and lacking microstructure (making the transition zone between prosthetic and natural tissue to be instantaneous).

- o Integration between synthetic membranes and natural skin, for strong, sterile, stretchy, and seamless connections.
- Catalog the electrical signals produced by specific motor neurons, and what signals should be given to specific sensory neurons.
- Design specific electrodes, amplifiers, and converters for the specific types of neurons we've characterized.

Practical / integrative research plan
- Engineer and test integrated actuator systems of motors, springs, transmissions, cables, etc that are appropriate for the prosthetic part in question. Prioritize 'soft robotics' approaches.
- Engineer and test integrated synthetic skin systems of durable, stretchy membranes that also contain temperature and touch sensory receptors.
- Develop a proprioceptive feedback system where mechanical forces detected by motors or springs are used to stimulate proprioceptive sensory neurons in the nerve.
- Optimize energy systems, including both mechanical energy recovery and electronic batteries.
- Miniaturize, and parallelize, the electrodes, amplifiers, and converters onto printed circuit boards.
- Ensure that neural interfaces and prosthetic devices are modular, interoperable, and replaceable.
- Standardize signaling protocols and communication ports between neural interfaces and prosthetic devices.
- Develop onboard software for the prosthetic to interpret and actively learn from raw communication with the neural interface.
- Integrate neuroprosthetics with other methods, e.g. genetic modifications, bioprinting/assembly, and remodeling.

Translational research plan
- Identify neural interface installation sites for a given prosthetic, with consideration for anatomical variation between patients.
- Optimize the efficient connection of several interfaces, to minimize the amount of surgery needed to install a neuroprosthetic.
- Develop and improve best practices for the manufacture and installation of neuroprosthetics, including safety, sterility, robustness, and continued resistance against infection.

Genetic modifications

Genetic modifications are some of the most frequent ideas mentioned in our discussions with people who want to bring about morphological freedom. And for good reason – there's tremendous potential even in current gene therapy strategies. With the broadening deployment of CRISPR and similar technologies, there's ample substance behind the excitement to say that genetic modifications may be useful for attaining morphological freedom.

At a glance
- Gene editing rewrites the instructions by which the body builds and maintains itself.
- Vectors are used to deliver genetic changes to target cells. These are mature technologies, but we see space to improve.

- Many genes affect multiple pathways, cell types, tissues and organs, making engineering tricky. We'll avoid this problem by designing systems that are orthogonal to existing ones, where needed.
- Further developments in genetic editing technologies are promising for accomplishing nearly all target objectives of morphological freedom, in a highly scalable and integrated way.

Figure 2: Genetic modifications

A   Virus-delivered reprogramming that induced the formation of new beta cells *in vivo*.

Induced beta cells (Insulin/Fluorescent reporter)
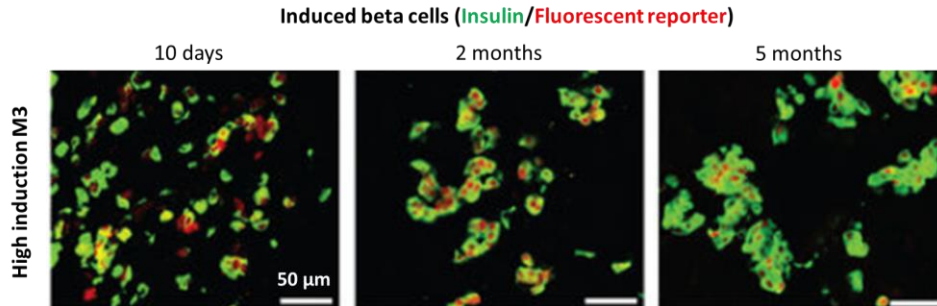
Li et al, Nature Biotechnology, 2014
© 2014 Springer Nature

B   Improvement in patients' visual light sensitivity with blindness from retinitis pigmentosa, given immediate or delayed Luxturna treatment (AAV-delivered genetic therapy).
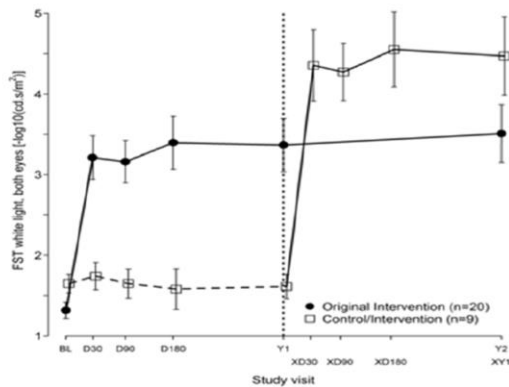
Spark Therapeutics Inc, clinical review for the FDA, 2017

C   Example of gene network modularity and conservation. Sea urchins and starfish diverged 500 million years ago.
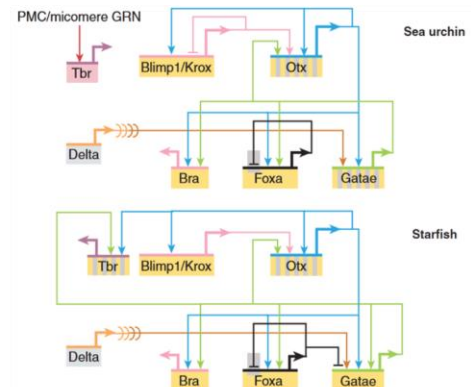
Davidson & Erwin, Science, 2006
© 2006 American Association for the Advancement of Science

State of the art

Gene therapy strategies involve the introduction of new, engineered DNA (or RNA) to cells, whether those cells are inside a patient, or outside the body with in vitro culture. A vector is used to deliver this new information. Commonly, the vector is derived from a virus. The viral capsid is taken, but not the rest of the virus – this takes advantage of the virus as a delivery vehicle, but doesn't allow it to produce more of itself. Instead, the desired genetic information is 'packaged' inside the viral capsid.

Moreover, it's possible to more-or-less target specific cells and tissues with genetic treatments. This can be accomplished through specificity in viral capsids or envelopes, localization in injection

(vectors tend to diffuse poorly if not injected into the blood stream or cerebrospinal fluid), and usage of conditional promoters (i.e., specific for cell type, signaling type, or inducible through specific drugs).

A specific example of vector technology is the AAV, or Adeno-Associated Virus. There are several AAV serotypes with differing specificities for infecting cell types in mice (Naso et al., 2017; Watanabe et al., 2013). There are also ongoing efforts to engineer new types of AAV with new specificities and dramatically improved efficiencies (Chan et al., 2017; Landegger et al., 2017). However, AAVs only have enough genetic space for about 1-2 genes, so AAV treatments using multiple genes would rely on mixtures of different viruses. Other current vector strategies for *in vivo* gene delivery include Adenoviruses (distinct from AAVs) and Lentiviruses, each with advantages and disadvantages.

There's countless examples of vector usage in literature, with exciting results in both basic science and clinical translation. For example, adenoviruses were used to reprogram pancreatic cells *in vivo* to become insulin-secreting cells (Fig. 2.A), using a mix of 3 carefully selected genes (Li et al., 2014). AAVs have been used to deliver payloads that restore hearing in mice (Pan et al., 2017), induce regeneration in the spinal cord (Geoffroy et al., 2015; Zukor et al., 2013), and partially regenerate and/or restore functions in mouse vision (Bei et al., 2016; Belin et al., 2015; Lima et al., 2012; Norsworthy et al., 2017). Lentiviruses have similarly been used in various aspects of nervous system repair and cellular reprogramming (Chen et al., 2017; Thomas et al., 2015; Zhang et al., 2017).

Early vector technologies used to be dangerous, exemplified by the tragic induction of leukemia by a retrovirus treatment for severe combined immunodeficiency in children in Paris (Check, 2002), but subsequently an ad-hoc committee made recommendations on how to avoid this from ever recurring (Kohn et al., 2003). But, vectors are reaching maturity as safe technologies. Many are now in the middle of human clinical trials (ClinicalTrials.gov, 2018) while approvals for clinical usage are starting to trickle in, including Luxturna (AAV) (Fig. 2.B), Glybera (AAV), and Strimvelis (a retrovirus) (FDA, 2017; Gallagher, 2012; Pollack, 2012; Regalado, 2016; Spark Therapeutics Inc, 2017).

As vector technologies improve, and as new gene vector technologies emerge, capabilities should increase while costs decrease. Viruses with larger genome capacities, such as multicomponent viruses (Ladner et al., 2016; de Lazaro, 2016), Cytomegalovirus/Herpesvirales (Borst and Messerle, 2003; Mahmood et al., 2005; de Silva and Bowers, 2009), and perhaps Megaviridae and other nucleocytoplasmic large DNA viruses (Yutin et al., 2013) present exciting possibilities for expanding gene delivery options to hundreds or thousands of genes simultaneously.

Okay, then what's the hold-up?

What might genetic modifications actually *do*? They might deliver regulators of metabolism and cell growth, they might manipulate developmental morphogen signaling, they might regulate cell adhesion or structural properties (e.g. through adhesion and cytoskeletal genes), or they might control transcription factor networks to manipulate the differentiation status of cells, just to name a few possibilities.

These possibilities are exciting, but also hard to narrow down into actionable genetic programs. We see these as the major limitation for accomplishing transformations through genetic modifications. Therefore, most of our research in this area will prioritize analysis, the buildup of databases and models, and the use of those models in increasingly predictive, CAD-like engineering tools. Since scientific literature already has discovered functions and relationships of thousands of genes, a lot of the effort will focus on integrating, rather than repeating, previous results. Furthermore, some of our cofounders have direct experience in designing and building highly integrative biological models (Davies et al., 2017; Norsworthy, 2017; Norsworthy and Immendorf, In preparation), so we're uniquely positioned to advise and guide these research efforts.

In parallel, we'll pursue research resulting in independent, modular components, such as a genetic modification resulting in the growth of fur. Modular gene programs are likely to be useful in the

bigger picture, even if some details need adjustment later. After all, modularity of gene programs is a strategy that naturally occurs in evolution (e.g. Fig. 2.C) (Davidson and Erwin, 2006), meaning that solutions can be developed and applied as (approximately) separate modules.

Basic research plan
- Look into ways to replicate large-payload vectors in-vivo to efficiently infect cells (≥1 vector per cell) and even vector distribution in all tissue types.
- Assess and plan development of options and methods for assembling artificial, custom designed multi-compartmental gene-editing vectors for serial deployment of stepwise DNA altering processes in synchronization with neighboring cells. Do so in a manner which overcomes or circumvents present vector capacity constraints.
- Catalog unique signatures of target tissues in humans – as well as their variability from person-to-person – to understand the best 'entry points' for activating a new genetic program:
    - Tissue selectivity and efficiency of vector infection.
    - Transcription factors and other regulators expressed by tissues, that can be used to initialize and modulate the effects of the delivered vector in specific cells.
- Compile lists of 'master regulator' genes and their relationships, in humans and other animals. Understand how differences in these regulators are relevant to species-specific traits, such as size, fur, etc.
- Catalog a more in-depth 'parts list' of RNA and protein sequences, as well as DNA sequences required for regulation of gene expression.
- Construct and evaluate models of genetic modifications needed in various target tissues.

Practical / integrative research plan
- Automate and standardize production of genetic vectors.
    - Simplification of methods of production through the combination of computation and user-friendliness to ensure the broadest usability.
- Assemble and optimize genetic models into deliverable vector systems:
    - Select vectors and injection strategies appropriate for the tissue.
    - Determine optimal dosages and timing.
    - Increase flexibility of vector systems for different patients' genetics and for customizability of desired results.
- Improve specificity and efficiency of *in-vivo* genetic modifications among cell types, and in 3D space:
    - Structured delivery of small vectors, such as via an array of micro-needles with microfluidics and piezoelectric controllers. *This would make individual vectors easier to design*.
    - Develop 3D- and cell-type-specific regulation of gene expression for large vectors, that are delivered systemically to the whole body. *This would make vectors easier to deliver, and will likely be less expensive in the long run*.
- Integrate genetic modifications with other methods, e.g. neuroprosthetics, bioprinting/assembly, and remodeling.

Translational research plan
- Ensure viral vectors are introduced safely and specifically, and that delivered genes and/or cells do not increase the risk of oncogenesis or immune rejection.

Bioprinting

Bioprinting is a massive new development in the capabilities of tissue engineering, involving the precise 3D arrangement of biological materials to form desired tissues for an organ. Further development and usage of this technology will let us construct new limbs, tails, organs, and any other new body part with exceptional precision and customizability while integrating seamlessly into the body.

At a glance

- Like other 3D printing, bioprinting takes designed and engineered tissues from a computer, and creates biological tissues through 3D printing-like processes.
- Bioprinting methods are varied, and are being pursued at scales ranging from multicellular tissue to single-cell deposition. Moreover, complementary methods open the door to the scale of organelles and molecules.
- A varied combination of approaches has been taken to improving the technology and its applications in organ regeneration and replacement procedures and in surgery.
- Bioprinting represents a complete sea-change for the relatively "old" field of tissue engineering. Its rapid advance has already solved basic conceptual issues, e.g. of reasonable cell survival and spatial resolution of cell placement. We see several places to improve, such as methods of cell production, and modular design and assembly of components.
- These technologies will be useful for the tail and wings, as well as internal or hormonally active sex organs. Bioprinting might also play roles in all other anatomical objectives we've mentioned.

State of the art

Generally, bioprinting technologies involve deposition of a scaffold and/or stem cells. Several examples exist of this working as a method to grow organs in vitro (Fig. 3.A) (Murphy and Atala, 2014) and in vivo (Pan et al., 2016). Scaffolds are typically made from decellularized collagen matrices or other biocompatible, 3D printable materials such as hydrogels (Hinton et al., 2015) and perhaps even silicone rubber composites (O'Bryan et al., 2017). Dental repair and regrowth using a dentin-derived hydrogel 'bio-ink' to make 'cell-laden scaffolds' now allows teeth to be regrown (Athirasala et al., 2018).

Bioprinting has been heavily influenced by the late Jemma Redmond. In Ireland in the early 2010s, she demonstrated her first 3D printed body part. Fittingly, it was a middle finger raised in a vehement gesture against those who had doubted the possibility of her work. She also bioprinted finger bones for her thesis (Bray, 2016; Redmond, 2012). Interestingly, a need for Freedom of Form shaped her life (Redmond, 2016a), and she had the goal of eventually bioprinting uteruses for intersex, infertile and transgender women (Carpenter, 2016). Her company, Ourobotics, proceeded to develop more advanced bioprinting technologies (e.g. Fig. 3.B) (Redmond, 2016b) would doubtlessly be a major player in biotechnology today were it not for Jemma Redmond's untimely death (Belton, 2016).

Meanwhile, Martine Rothblatt, an emblem of success in the LGBTQ community and a transhumanist (Rothblatt and Brackman, 2011; Wikipedia, 2018b), oversaw the development of lung bioprinting techniques leading to the ability to provide badly-needed replacement lungs to transplant patients (Jackson, 2017). Her company, United Therapeutics, was founded to enable the treatment of rare diseases including Pulmonary Hypertension.

Figure 3: Bioprinting

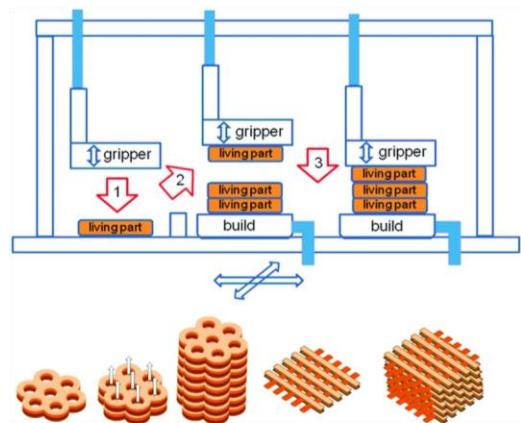**A** Examples of tissues bioprinted in vitro
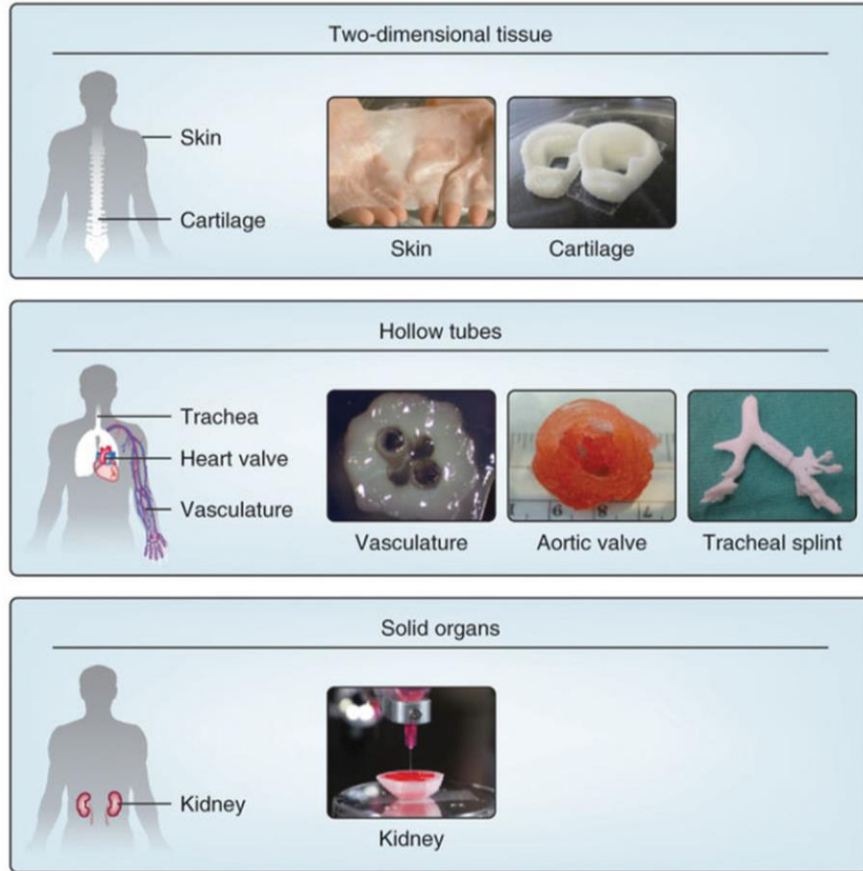
Murphy and Atala, Nature Biotechnology, 2014
© 2014 Springer Nature

B Ourobotics bioprinter

© 2015 Ourobotics

C Assembly of tissue-engineered components

Blakely et al, Tissue Eng Part C Methods, 2015
© 2015 Mary Ann Liebert, Inc.

In urology, surgeon Anthony Atala of the Wake Forest Institute for Regenerative Medicine has been working on stem cell scaffold and bioprinting based technologies for organ transplants since before 1994 and demonstrated bioprinting techniques publicly for the production of kidneys (Atala, 2011). He's also working on bioengineered reconstruction of the penis, bladder and vagina (Mohammadi, 2014).

One thing in common between these companies is they are approaching bioengineering from a stem cell reperfusion of collagen technique first, and 'true' bioprinting later. The idea of stripping a donor organ of its existing cells to fill its extracellular structure with new ones, has been around since the 90s, while bioprinting is more of a product of the more recent trend for 3D printing. However, printing may not need to provide a full complement of pre-made blood vessels (Flieser, 2017).

Around the world, companies like Organova, Biobots and Anyprint have been vying to bring down the costs and improve the capabilities of bioprinting devices and systems for all kinds of purposes from drug toxicity tests, to printing corneas, to cytoskeletal research (Hipolite, 2014). Some individuals are even looking past the cellular scale and look at the possibility of molecular bioprinting, depositing layers of specific molecules in fine enough resolutions to construct nanotechnological devices, or as was the case with Cambrian Genomics, a mixture of depositing, scanning and sorting of multiple strands of 'printed' DNA in genetic (Stein, 2015) or self-assembling DNA structures (Shih, 2014). Overall, bioprinting technologies have been advancing rapidly, and are attracting significant scientific commercial interest.

Anticipated solutions

It is expected that in the coming 5-10 years, just about all organs will be possible to bioprint. Organ bioprinting has started from the less complex tissues in terms of the number of cell types and arrangement of them in the organ, and how much perfusion is required post-printing to allow cells to grow to sufficient length. It is possible that molecular preparations and cell surface molecule adjustments – pharmacological, genetic or otherwise, will enable direct deposition of stem or other cells without the use of a scaffold. This might be done by printing extracellular matrix materials appropriate to the organs in question, at a fine resolution in between layers of cells.

The deposition of materials in 3D printing methods occurs at increasingly fine scales as the technology matures. In bioprinting, usually the deposition is of cellular or cell-clump resolutions. It is expected that methods of reliably depositing biomolecules in arbitrary locations and configurations will be developed and improved in the coming years. It may even be possible to combine micro-scale bioprinting with nano-scale fabrication and self-assembling DNA-templated systems. Further, bioprinted DNA may be useful for 4-dimensional control of dynamic shapes (Rieland, 2014).

We expect that bioprinting with multiple materials in mixed modes of deposition will allow the use of hormones, morphogens and axonal guidance patterns in a combination between stem cell bioprinting and a recapitulation of embryonic-style neuronal growth and vascularization. Control of cellular transdifferentiation including the capacity to generate neuro-progenitor cells from blood cells (Lee et al., 2015) will bring bioprinting and genetic modification together. Furthermore, the building of tissue components into ever-more complex assemblies (Fig. 3.C) (Blakely et al., 2015) will improve speed and versatility of organ bioprinting.

Okay, then what's the holdup?

Bioprinting is currently a very active area of research and development, with a plethora of startups rubbing shoulders with bigger players. However, the ground covered so far is small compared to the potential. Molecular bioprinting is almost unexplored, as is subcellular construction and axonal guidance factor deposition. These are areas we want to get into.

Strategic roadmap for research in morphological freedom

Basic research plan
- Production and placement of polarized and non-spherical cells.
    - Extrusion of long cells like neurons and muscle fibers that are cut-to-size.
- Printing of heterogenous and polymeric extracellular biomolecule structures like collagen and proteoglycans.
- Printing morphogens, axon guidance factors, and other signaling molecules:
    - Guide existing axons from the body into the bioprinted tissue.
    - Guide new axons within the tissue to connect to their targets appropriately.
    - Guide blood and lymph vessels into the tissue.
- Control of cell signaling states and differentiation
- Software to handle cell signaling, cell shapes, cell-cell signaling relationships, mechanical properties, and actual firmware/drivers for the printer.
- Develop multi-step or hierarchical printing where simpler structures are separately built as 'black boxed' components before higher-order assembly.
- Investigate nano-scale printing or assembly where individual cells can be built with desired mixtures of proteins, signaling molecules, and fine control of 3D structures.

Practical / integrative research plan
- Increase printing speed, precision, and reliability.
- Printing in non-isometric layers for more integrated / less laminated tissue.
- Progressively enhance and test assembled tissues *in vitro* and *in vivo*:
    - Survival and differentiation of bioprinted cells.
    - Check side-effects: assay survival and differentiation of existing, nearby cells.
    - Confirm that innervation and vascularization are intact.
    - Confirm functionality and performance, as appropriate to the organ's intended biological function.
    - Confirm long-term stability and safety.
- Increase the customizability and ease-of-use for the whole work-flow of conceptualizing and designing the tissue, surgical installation, and long-term functionality.
- Integrate bioprinting/assembly with other methods, e.g. neuroprosthetics, genetic modifications, and remodeling.

Translational research plan
- Optimize surgical integration of bioprinted tissue with existing tissues, e.g. expenses, invasiveness, scarring, recovery time, risks of infections, and other side-effects.
- Develop and improve best practices for manufacture and deposition of cells, biomolecules, tissue components, and fully assembled bioprinted tissues and organs.

Gradual remodeling
Biological tissue adapts to loads (and other environmental changes) placed upon it. Dental braces are a common example of a way to guide this remodeling process. Bones, and the soft tissues around them, grow and shrink as needed to equalize stress channeled through the teeth into the maxilla and mandible. We want to support the investigation and development of technology and surgical techniques that exploit these principles to yield desired morphological changes.

At a glance
- Place enough steady mechanical strain on a part of the body and it will adapt gradually.
- This approach already has widespread uses in limb length and dental correction, for example.
- Remodeling modifies the shape of existing tissues and organs, while preserving the *in-situ* functional systems like nerves and blood supply.
- This could be expanded upon to include morphological adjustments.

State of the art

Distraction osteogenesis (bone growth) is a surgical technique used to produce large morphological changes in bones (e.g., craniofacial bones and leg bones) and their surrounding soft tissues (Wikipedia, 2018c). The surgery is usually an outpatient procedure, and is associated with discomfort but generally not pain (Quitmeyer, 2018; Wikipedia, 2018c). Conceptually, it involves the partial or complete separation of bone into two parts, and gradual separation of those halves as new osteogenesis takes place. Gradual separation may involve steps, or continuous tension from a spring (Wikipedia, 2018c). Outcomes of distraction osteogenesis are at least on par with, and are likely superior to, those of conventional acute surgeries (Kloukos et al., 2016). For example, a patient with severe jaw damage due to cancer is having their tissues restored with good results already (at the time of this writing) (BBC, 2018) (Fig. 4.A). There is ongoing interest in improving the capabilities of distraction osteogenesis e.g. with multidirectional cranial distraction osteogenesis (Gomi et al., 2016) and using computers, medical imaging, and tangible 3-D printed models to improve predictability of outcomes (Shah et al., 2017).

Figure 4 - Remodeling

A   Patient receiving distraction osteogenesis treatment

© BBC, 2018

B   Extreme growth of axons and nerves in young whales

Weiss, 1941

C   Skin stretching device for foreskin restoration

DTR, 2018

Neural tissues are likewise adaptable to changing environments. This is seen in early embryonic development: Neurons connect to their targets, which in an embryo might be less than 1 centimeter away. As the organism grows, the neuron's cell body is gradually pulled away from the innervation target, such as the growing distance between the spinal cord and the feet. Axons and nerves can grow to extreme lengths over time if under continuous mild tension (Pfister et al., 2004; Smith, 2009; Smith et al., 2001; Suter and Miller, 2011). The axon growth in young whales is an extreme example (Smith, 2009; Weiss, 1941). Moreover, peripheral nerves (i.e., spinal nerves, and cranial nerves except for the optic nerves) can grow even after damage, as long as neural cell bodies are intact (Chandran et al., 2016; Lee et al., 2017; Mar et al., 2014). Cell bodies are present in ganglia, and ganglia are generally unaffected by our transformation plans. Therefore, even if our modifications damage or remove peripheral portions of nerves, they will self-repair with reasonable efficiency.
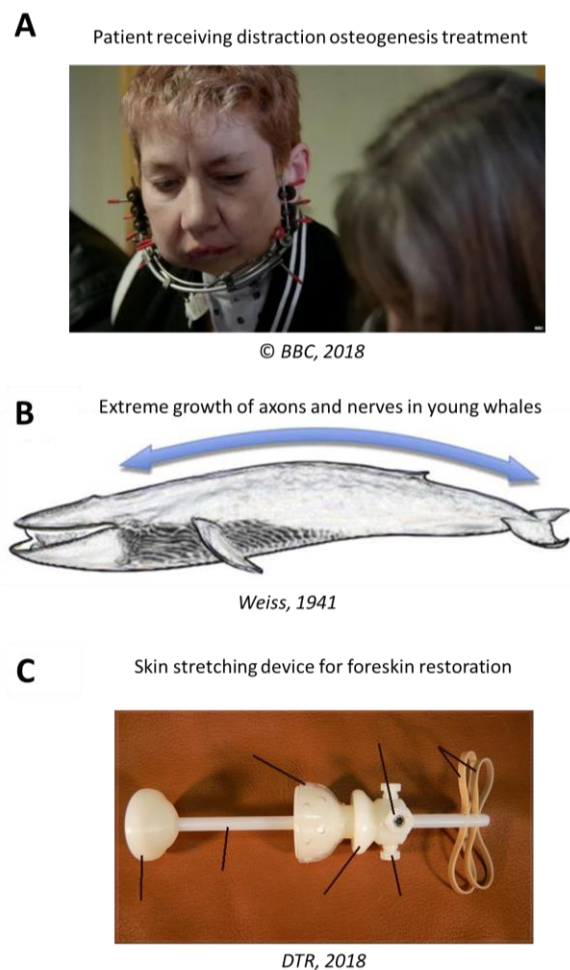
Strategic roadmap for research in morphological freedom

Male circumcision has been regarded by some of its recipients as a procedure with an overall negative outcome for their genital, sexual and mental health and wellbeing. For these biologically male individuals, it may be possible to restore a functional prepuce (foreskin), albeit with some differences in shape and sensitivity from the original, by means of stretching the skin around the circumcision scar regularly and keeping it under frequent sessions of tension in the desired direction of growth (Holslin, 2015). Simple devices have been made available to assist in this endeavor and have attracted an impassioned community (DTR, 2018; Elder, 2016; Tally, 2009) (Fig. 4.C). This model of consumer and community-driven devices may also be useful to copy for some other gradual remodeling procedures, as appropriate.

Okay, then what's the holdup?

Clearly, it's possible to substantially alter someone's tissues gradually, through self-regulating and self-limiting processes, while preserving their musculoskeletal, neurological, and other functions, as long as those structures and functions already exist in a similar form. We think the remaining limitations relate to the customizability and predictability of modifications.

For example, we think we can do better than a single-dimensional growth of bone from one expansion site, such as by controlling bone reshaping in three dimensions from multiple sites. We would also like to see integrated systems that combine bone growth with guided soft tissue growth, rather than simply leaving soft tissue to be secondarily affected. As well, we think there is room to improve computer modeling of current morphology and desired results.

Basic research plan
- Develop small motorized agents that can be implanted into tissues, and push, pull, inflate, or contract to change that tissue's shape over time.
- Precision control of the result of the change.
- Changes involving more than a simple, single-axis linear growth

Practical / integrative research plan
- Integrate these small motorized agents into a coordinated mechanical network for remodeling of tissues in 3D.
- Growing/shrinkage process that is self-contained, and won't require manual replacement of a series of orthotics over time.

Translational research plan
- Integration of modeling tools with the planning and performance of surgery, e.g. to specifically select optimal sites for the insertion of the tissue-modifying agents.

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