Regenerative Technologies for Long Duration Interstellar Flight

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Introduction

Before I can write about this topic, I cannot help but address people's tendency of viewing an apocalyptic future. My theory is that people look at the future as bleak because the present is actually bleak. You cannot see a news broadcast or read the print of a newspaper without seeing some kind of disaster. War, disease, famine, pollution, and crime seem a constant backdrop to our daily lives. However, I believe that it is only the present that is bleak, the future defined as pragmatic transcendent. The idea of pragmatic transcendence is the combination of the definitions pragmatism and transcendence. Pragmatic is defined as an adjective by the Merriam-Webster dictionary as *"dealing with the problems that exist in a specific situation in a reasonable and logical way instead of depending on ideas and theories.*[1]*"* Transcendent is defined as a noun by the same source as *"The quality or state of being far better or greater than what is usual.*[1]*"*

Humanity will always strive to continue living and progressing despite the adversity it faces. This has been shown to be true even in the past. The black plague during the dark ages was believed to be god's judgment upon a sinful world. The University of Florida documented these cultural effects,

> *"The black death had religious implications as well. The people of the 14th century struggled with the failure of their religion. The church could not save people from the disease, leading many Europeans to question their beliefs. In that time doctors did not understand the origin of disease and how it was transmitted, so it was common for people to believe that supernatural powers were in control. They saw the plague as divine punishment. Flagellation, the act of self-mutilation through whipping became common and many people began to be beat themselves in the hope of atoning for their supposed sins*.[2]*"*

The Cuban missile crisis heralded nuclear winter that could strike at any moment. During this thirteen day political standoff, disaster was imminent but avoided due to the world following the unknown need for pragmatic transcendence. The history channel described the events that occurred,

> *"President John Kennedy (1917-63) notified Americans about the presence of the missiles, explained his decision to enact a naval blockade around Cuba and made it clear the U.S. was prepared to use military force if necessary to neutralize this perceived threat to national security. Following this news, many people feared the world was on the brink of nuclear war. However, disaster was avoided when the U.S. agreed to Soviet leader Nikita Khrushchev's (1894-1971) offer to remove the Cuban missiles in exchange for the U.S. promising not to invade Cuba.*[3]*"*

Despite these ill-omened events, humanity continued to strive forward. Even though most Americans want to believe in a post-apocalyptic world, they still believe they will survive it. Every college student I ever knew has a plan to deal with the zombie apocalypse.

I do not see the future as doom and gloom. I see that it is full of new opportunities for humanity to soar. Usually we make our mark with small deeds. Every once in a while, we achieve milestones in technology that make legends. Though skeptics state that these milestones take sacrifice to achieve, no one can deny their significance. Magellan sailed around the world proving its round. The Wright Brothers flew the first airplane proving the skies were not beyond our reach. Breaching the barrier of the earth's gravitational pull has been one of the most recent milestones. Though we have also built space stations, we are just in the beginning

of the unimaginable adventure of interstellar flight. However, this milestone will take advances in sustainable technology to make this possible. The way to do this is using a method I call "Regenerative Technologies".

My interest in the subject has been inspired by both my past and recent events. Ever since I was a child, my father has shown me the constellations of the night sky. Combined with a love for Star Trek, this has permanently instilled the wonder of space. However, my parents had their own agenda when it came to my upbringing. They were flower children who wanted to safeguard the earth itself. As such, they have bought movies such as "Ferngully" as part of our permanent VCR collection to mold me into a EPA official. Despite this, my father knew that I probably wouldn't fit their mold perfectly. He told me a message that resounded deeply within his idealist soul "Find something you love to do and devote yourself to it". It is a philosophy that I still carry with me to this day.

I recently found my true passion in life when I joined Pacific Spaceflight a year ago. This research project, headed by Professor Cameron Smith, is designing an affordable space suit. This project is one of many private industries which are pushing for the great expanse of space. I never had the chance to share my success with my father. He passed away a few weeks back after a short battle with cancer, but I know that he would have been proud to see me in such a vocation. Everyone on the team are very driven and have powerful personalities. One of the former members of the team enjoyed having me as an intellectual sparring partner. One of these sparring sessions actually led to the creation of the topic for this publication.

He had a contrasting skeptical personality to my optimism. He didn't like that I was hoping for an unrealistic star trek future and challenged me to a debate. This debate was about what it would take for humanity to engage in large scale interstellar flight. He believed that the earth did not possess the resources to house such a large crew for any length of time. The only method that humanity could make this work is by creating computerized harvesters. These harvesters would be able to travel to the distant asteroids and mine the necessary minerals for space travel. However, he believed that one harvester was not enough. As such, the harvesters would have the programming to self-replicate from the materials they gathered. Once the harvesters would become numerous enough and collect enough minerals, they would return to earth and be disassembled. From these resources, he reasoned that humanity could begin mass interstellar flight. However, he believed this would take hundreds of years to come into fruition.

At the time, I was upset by this argument. I could not accept a future that Skynet was the only possibility. I believed that with the recent interest in spaceflight generated by private industries, mass interstellar flight was becoming a reality. I argued that manned spaceflight was very possible if we embraced the idea of total sustainability.

The concept of total sustainability embraces three ideas:

1. All resources must be generated within the vessel
2. No resources generated within the vessel can go to waste
3. The waste that is created must generated into another resource

Despite my loss in the debate, it started my interest in life support technology. The group member did bring up an excellent point. With humanity's current level of technology, the crew is a large hindrance. Microgravity and ambient radiation are serious health hazards for the passengers. Sustaining the crew is also has large technology requirements and the waste generated by the crew is likewise a problem. Even the living quarters of the shuttles and space stations treat the crew as cargo. In order for total sustainability to work, the role of crew must be changed from cargo to components. The life support technology must also be changed to maximize the resources to the crew. Though there are some devices on space vessels that reclaim resources, most of the supplies are shipped with scheduled rendezvous.

The only real life example of a total sustainability system is our planet's ecosystem. Every animal, plant, and mineral is balanced perfectly to work in conjunction with one another. Laura Klappenbach, an ecologist who writes for about.com speaks about the balance of the ecosystem. *"An ecosystem can be defined as all the interacting components of the physical and biological world*.[4]" If humanity can create a living ecosystem through technology, the total sustainability needed for interstellar flight would be achievable. This is the basic concept of regenerative technologies. To make a successful life support system using this method, these technologies need to provide the basic human needs. These needs are the same essentials that survival experts preach to their audiences. These needs are food, water, and shelter.

Food

Food is something that every human being needs to live. We can only survive 10 to 14 days without food. Currently, shuttles bring all the food they will ever have from Earth. Space Stations require routine shipments of food to continue operation. These methods are impractical for long term space flight for obvious reasons. Preservation increases the storage time of food but it is not infinite. The only method that can provide food for a near infinite time is agriculture. Robert Zimmerman, author of "Leaving Earth", also stated this need.

> *"Unlike the Spanish and Portuguese sailors of the fifteenth century, who could trade or hunt for food as they went, deep space explorers will have no place in the outer reaches beyond low earth orbit to restock their food supplies. While it might be possible to carry enough food for a journey to Mars doing so on a journey to Jupiter or Pluto is probably impractical. Not only would growing some of the required food on the interplanetary ship reduce the weight of supplies but the plant life would also help recycle the ship's atmosphere*.[5]"

There has been extensive research done by the Russian Cosmonauts to grow food in microgravity. It was not an easy process and they have encountered various boundaries. During their trials of various updates to their Oasis greenhouse system, they encountered the same failed result. The plants they cultivated would grow extremely fast and wither just as quickly. One example is during a mission to the Salyut 6 with Cosmonauts Valery Ryumin and Vladimir Lyakhov. Not matter how many redesigns they have done, the results were the same. Ryumin wrote in his diary that *"the plants that got off to such a good start growing have begun to wither.*[5]" He also started to lose hope that growing plants was possible in microgravity. Ryumin told *"television viewers the same week that "...it is an established fact that plants won't grow in weightlessness*.[5]" However, there has been recent research in Canada which has determined the variable that caused the failed experiments is ethylene gas.

Ethylene gas is an organic compound that causes plants to ripen. Washington State University documented the effects of ethylene gas in their "Postharvest Information Network".

> *"Ethylene is a small hydrocarbon gas. It is naturally occurring, but it can also occur as a result of combustion and other processes. You can't see or smell it. Some fruit will produce ethylene as ripening begins. Apples and pears are examples of fruit that produce ethylene with ripening. Ethylene is responsible for the changes in texture, softening, color, and other processes involved in ripening*.[6]"

It is essential for their development but too much causes them to rot. Some plants generate more ethylene gas than others. It is why supermarkets store their bananas away from their other fruits and vegetables. Normally during growth, the open atmosphere removes the excess ethylene gas generated by crops. However, shuttles and space stations are a closed system. Any ethylene gas is trapped in the vessel's atmosphere. However, we can make changes to the ventilation system to store the ethylene gas. With this stored gas, the crew can make controlled

puffs of ethylene gas to ripen them in a controlled method. Ethylene gas is used *"commercially to ripen tomatoes, bananas, pears and other fruits postharvest*.[6]"

There is still the need for nutrients to allow plants to grow. Normally on earth, there is soil and fertilizer that is widely available. However, soil would float in microgravity, which would cause various problems. The best method of growth is by creating aeroponic systems that could use water vapor to control root growth. NASA has been heavily involved in research into aeroponic systems and documented their evidence in their article "Progressive Plant Growing is a Blooming Business". Aeroponic growing systems

> *"Provide clean, efficient, and rapid food production. Crops can be planted and harvested in the system year round without interruption, and without contamination from soil, pesticides, and residue. Since the growing environment is clean and sterile, it greatly reduces the chances of spreading plant disease and infection commonly found in soil and other growing media*.[7]"

The water vapor can generated from purified urine. Composted human feces and plant biomass can provide the nutrients and also turn a waste into a resource.

Water

Water is another essential for human survival. A human being can only survive 3 to 5 days without water. This is one of the few resources that today's space programs are actively using regenerative technologies to preserve the resource. Currently the ISS has systems that are sable to reclaim water from the condensation in the air, sweat, and urine; making the safe to drink. Water Environment Federation (WEF) author Jennifer Fulcher documents the water-recycling systems on the ISS.

> *"Since 2009, the ISS has had a water-recycling system with approximately 85% water recovery. The system, which uses distillation technology, an absorption bed, and a catalytic oxidation reactor, treat both urine and condensate water to generate potable water.*[8]"

However, many of these systems are very technology intensive and require significant electrical power resources. I believe we can do better by using plant biomass. The White Water Lily is able to filter water and purify it of pollutants. On Earth, we are hesitant to use them because they are considered an invasive species. This invasive species status could be an advantage in space, where it kills most organisms. Though it does take energy to as well to utilize these systems, it is energy we can provide from a waste resource vs an essential resource. The White Water Lily can be the first step to remove the harmful contaminants from our composted waste, making it safer for us to consume the water and use it to feed the other plants.

There is a significant disadvantage to this system. A large volume of water is needed to feed all the plant biomass, the crew, and various other systems (spoken about later). While the system is designed to reclaim the water for later use, it cannot last forever. There will be percentage loss of water converted into biomass which cannot be reclaimed. Since water is extremely precious, there must a method to store water for later use. There are plants that can store water that can be harvested as a fresh drinking source. The two most useful plants for this purpose are grapevines and bamboo.

Grapevines are able store more water than any other plant on earth with biomass to water ratio. The other advantage of grapevine is that it can produce edible grapes, which also hold a significant volume of water. The cut material can be composted for more nutrients. Bamboo's fast growth rate could be a hindrance while growing in space but it could also provide water quicker than grapevine. The plants also provided many more uses. The shoots are edible and can be eaten in dire circumstances. The adult plants are very durable and used in many

building materials. One of Professor Smith's future goals for Pacific Spaceflight is to use bamboo as sustainable material for the spacesuit. If this works, the crew could use bamboo to make and repair their own spacesuits.

Shelter

Shelter is another key component in survival. In space, it also presents its own unique and difficult requirements to make an adequate shelter. One of the most immediate and essential requirements is generation of pressurized breathable air. Vacuum is the most significant hazard that can kill the crew. Scientific American writes about the effects of Vacuum on the human body.

> *"Vacuums are indeed lethal: Under extremely low pressure air trapped in the lungs expands, tearing the tender gas-exchange tissues. This is especially grave if you are holding your breath or inhaling deeply when the pressure drops. Water in the soft tissues of your body vaporizes, causing gross swelling, though the tight seal of your skin would prevent you from actually bursting apart. Your eyes, likewise, would refrain from exploding, but continued escape of gas and water vapor leads to rapid cooling fo the mouth and airways. Water and dissolved gas in the blood forms bubbles in the major veins, which travel throughout the circulatory system and block blood flow. After about one minute circulation effectively stops. The lack of oxygen to the brain renders you unconscious in less than 15 seconds, eventually killing you*.[9]"

For this reason, liquid oxygen and nitrogen are essential to obtain the needed air. However, we can extend the duration of those tanks if we are able to reclaim the O_2 from the CO_2. This is the only other regenerative technology that space programs actively use. However, current methods are problematic. The Carbon Dioxide Removal Assembly is extremely mechanically complex and takes up space. The NASA report on the "Overview of Carbon Dioxide Control Issues during International Space Station/Space Shuttle Joint Docked Operations" indicates the complexity of the CO_2 removal procedure.

> *"The CDRA is the primary CO2 removal system for the ISS USOS. It operates as a dual-bed, zeolite-based CO2 removal system that uses an alternating cycle. The two beds, in this case known as desiccant-absorbent beds, operate on a cycle with one adsorbing CO2 from the cabin air while the other desorbs previously accumulated CO2 to space vacuum*.[10]"

The other method uses Lithium Hydroxide canisters, which are toxic and have a temporary operating life. We can do better by using plant biomass because their CO_2 scrubbing ability is a passive system and it is inherently non-toxic. Plants need CO_2 for cultivation, and they also naturally give off O_2 which we can breathe. Since the system I am proposing uses so much plant biomass, it would scrub a significant percentage of that CO_2. However, each plant scrubs different volumes of CO_2. There is a simple plant we can use to scrub a large amount of CO_2.

In order of these plants to use photosynthesis and live, an active light source must be provided. In a system that is restrictive on energy use, this can be a significant problem. However, there are "green" technologies that can reduce electrical requirements for illumination. Julia Layton from howstuffworks.com describes the performance capabilities of LED lights, *"An LED replacement light bulb called Geobulb emits 60-watt equivalent light using 7.5 watts of power.*[11]" Nearly every color in the visual spectrum can be replicated. The two colors needed for growth is blue and red as documented by Colorado State University.

> *"Red and blue have the greatest impact on plant growth. Green light is least effective (the reflection of green light gives the green color to plants). Blue light is primarily responsible for vegetative leaf growth. Red light, when combined with blue light,*

encourages flowering.[12]"

These colors can be combined, forming a purple light. Most of the plants in the system can be sustained with purple light but the use of the red algae requires orange light as well. The only significant disadvantage is that purple and orange LEDs are the most expensive colors.

To power these lights and the mechanical systems, electricity is required. Currently, electricity is generated from solar panels that are placed outside the shuttle. Solar technology has improved drastically with increased efficiency. Forbes writer Peter Kelly-Detwiler documents the improvements to solar panel efficiencies.

> *"But there is another piece of the equation that is improving the economics of the solar industry and that is the steady and relentless increase in panel efficiencies themselves. In other words, how well the PV cells convert sunlight into electrical power. Since the average conventional panel currently possesses a conversion efficiency rate of between 15% and 16%, a very small improvement in that number can represent a significant increase in total output*.[13]"

We can also gather more solar energy since we do not have the atmosphere blocking a large portion of the light spectrum. However, the position of the sun is crucial for optimal operation. As we travel farther away from the sun, the power generation becomes more limited. In order for long duration interstellar flight to be possible, other power generation systems must be available.

There are two other practical methods that the crew can use to generate electricity. One method is applying water-driven microturbines to generate electricity. The system already uses extensive amounts of water. However, the water we reclaim can be pressurized and run through the microturbines to spin them. Since this water won't be lost, we can reclaim it and use it for other systems. These microturbines can be strategically placed throughout the interstellar ship for maximum power generation. Even a pico-hydro turbine is able to generate *"from a few hundred watts up to 5kW*.[14]"

Another method actually uses human power. The last obstacle that must be conquered for long duration interstellar flight is bone density loss. This is not a problem on earth because gravity puts stress on our bones, forcing them to maintain density. Since microgravity does not put the necessary strain on the bones, this becomes a large factor. Many astronauts after their missions have to be carried once they land on earth because their bones became so thin that they are unable to stand. It takes months of physical therapy for them to be able to walk again. Since artificial gravity generation is still theoretical, there are certain exercises the crew can do to reduce the rate of this bone density loss. The Russians have developed a method of using a garment they dubbed the "chibis Suit", which forces blood down to the legs. While they are wearing the chibis suit, they ride strapped down to an exercise bike. This method has been successful to slow bone density loss. Russian cosmonaut Valeri Polyakov used this method on the Space Station Muir for his 438 day spaceflight. When his bone density was recorded back on earth,

> *"his bone loss had been very low, only around 7 percent in some of his weight-bearing bones, a rate of 0.5 percent per month, confirming once again his belief, shared by other Russian doctors, that the exercise program had kept that loss low-low enough for him to survive a two-year trip to and from Mars*.[5]"

This exercise bike can also be used to generate electricity through kinetic energy. Since this is a system that is already necessary, why not maximize its use?

Radiation is another hazard that is abundant in space. The Earth's atmosphere normally protects us from a large percentage of the incoming radiation. Since shuttles exist without the atmosphere's protection, the crew normally gets exposed the background radiation. Currently

nothing is done to prevent it apart from monitoring levels of radiation. There are methods that the crew can use to protect themselves from that hazard. The two methods that are easiest to use and cheapest are using water and radiotropic fungi.

Water is becoming more and more vital for the crew. Water has the capability of shielding alpha and beta particles, two out of the three particles commonly present in radiation. There is significant documented evidence of water's shielding capabilities. Reed College has a nuclear reactor that uses water to shield both operators and visitors from the radiation. It even allows operators to submerge into the shield so they can maintain the reactor. However, water does not have the ability to stop gamma rays, which is the most dangerous and difficult to shield.

So far, the only documented methods of shielding against gamma rays are lead and gold. Lead is not an option because it needs several meters of thickness to work. Gold can be used in the bare minimum but it is extremely prohibitive in cost. With these methods unavailable, many believe gamma rays to be unstoppable. However, there is a unique method that could protect us given enough research. There is a radiotophic fungi that is found in highly radioactive areas such as Chernobyl. This fungi actually has the capability of eating gamma rays for nutrition, which is documented by Ekaterina Dadachova and Arturo Casadevall.

> *"Fungi in general, and especially melanized ones, are highly radioresistant when subjected to high doses of ionizing radiation under experimental conditions. Understandably, such unusual abilities of eukaryotes to survive or maybe even benefit from exposure to ionizing radiation are in contrast to the general view that radiation is uniformly harmful to life*.[15]"

Since gamma rays can penetrate nearly every surface, the crew can have a layer of this fungis grow within the ship. If this method works, the only radiation that will still be concern is cosmic rays.

Complications and Solutions

There are a number of complications that must be anticipated to deal with a system reliant on regenerative technologies. Disease, negligence, and unforeseen circumstances can cause the system to fail. For this reason, someone who is trained in botany must be added to the crew's roster. If they can anticipate these problems by recognizing the signs of disease and follow a strict schedule of maintaining the life support system, many of these problems can be avoided or dealt with. However, there are still unknown factors that can cause system crashes. We must prepare to anticipate, prevent, and solve such problems.

To deal with a system crash, seeds must be continuously harvested and stored for later use. Food must be likewise stored as a buffer against potential crop failure Current storage techniques used by space programs includes dehydration. Since the regenerative technology system has extensive water requirements for operation, it would be good if we can find ways to reduce that water need. One method that already exists is vacuum packing. Food can be put into a container and the crew can suction out all the air from it, which will not allow any microbe to spoil the food. This air that has been removed can be put back into the system for breathing.

Another method of creating emergency food rations is to put small growing mediums in the crew's quarters. Each crew member can have their own medium for cultivation. This would allow the crew to generate their own rations in case of emergencies. These personal growing mediums can also provide psychological support to the crew members, a phenomena has been documented in various cosmonaut space missions. Should these emergency rations come close to their expiration date, they can be eaten by the crew.

Pollination is another essential factor that plants need for growth. Since this is a closed system, any pollen generated by the plants can be spread by the shuttle's ventilation system.

However, careful selection of plant species must be considered. Any plants using bees a medium for pollination cannot be used. Without gravity, any animal species cannot reproduce without creating mutations. However, there are a lot of plants that can self-pollinate or use male and female versions of the plant for pollination. Regardless of the method, effective ventilation is required.

Since water is a large requirement for the regenerative technology system to work, it is essential for reclamation. However, this is not an infinite system and will eventually need to be replenished with more water. This will make Mars an essential stopping point for increasing the duration of interstellar flight. Mars as extensive polar icecaps, which can be melted and transported to these ships. Currently, humanity's current milestone goal is the colonization of Mars. Regenerative technologies will make this journey more viable and it will generate a new economy for the planet itself.

Conclusion

Though some of this technology is from proven research, a lot of it is also theoretical. It will require extensive research and testing to apply these technologies. This is how I hope to fulfill my dream of becoming a space settler and furthering future endeavors into the interstellar void. However, there is still a lot of unanswered needs such as artificial gravity generation that must be answered for permanent space migration. I remain optimistic that one day someone will come up with an answer. We have accomplished similar impossible milestones before, we just need a fresh perspective to succeed in this one.

Works Cited

1. Merriam-webster. Retrieved from http://www.merriam-webster.com/

2. The Black Plague. (n.d.). *Cultural and Economic Effects of The Black Plague.* Retrieved from ulf.edu
http://plaza.ufl.edu/wlclapp/Cultural%20Effects%20of%20The%20Black%20Plague.htm

3. History.com. (2010). *Cuban Missile Crisis*. Retrieved from history.com
http://www.history.com/topics/cold-war/cuban-missile-crisis

4. Klappenbach, L. (n.d.). Communities and Ecosystems. *About.com,*
Retrieved from http://animals.about.com/od/zoologybasics/a/communitiesecosystems.htm

5. Zimmerman, R. (2003). *Leaving Earth: Space Stations, Rival Superpowers, and the Quest for Interplanetary Travel*. Washington, D.C; Joseph Henry Press.
Retrieved from https://mail.google.com/mail/u/0/?tab=wm&pli=1#inbox/14568914621ad8bf

6. Washington State University. (2014, April). *Postharvest Information Network*. Retrieved from wsu.edu
http://postharvest.tfrec.wsu.edu/pages/PC2000F

7. NASA (2007, April). Progressive Plant Growing is a Blooming Business. *Nasa.gov*,
Retrieved from
http://www.nasa.gov/vision/earth/technologies/aeroponic_plants.html

8. Fulcher, J. (2013, April). Water-Recycling Technology in Space Evolves. *WEF Highlights,*
Retrieved from http://news.wef.org/water-recycling-technology-in-space-evolves/

9. Gosline, A. (2008, February). Survival in Space Unprotected Is Possible—Briefly. Scientific American.
Retrieved from
http://www.scientificamerican.com/article/survival-in-space-unprotected-possible/

10. Matty, C. (2010, January). Overview of Carbon Dioxide Control Issues During International Space Station/Space Shuttle Joint Docked Operations. *Aerospace Research Central,*
Retrieved from
http://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20100021976.pdf

11. Layton, J. (2009, July). How LED Light Bulbs Work. *HowStuffWorks.com,*
Retrieved from http://science.howstuffworks.com/environmental/green-tech/sustainable/led-light-bulb.htm

12. Whiting, D., Roll, M., Vickerman, L. (2011, December). CMG GardenNotes #142: Plant Growth Factors: Light. *Colostate.edu*
Retrieved From
http://www.ext.colostate.edu/mg/gardennotes/142.pdf

13. Kelly-Detwiler, P. (2013, July). As Solar Panels Efficiencies Keep Improving, It's Time To Adopt Some New Metrics. *Forbes.com,*
Retrieved from
http://www.forbes.com/sites/peterdetwiler/2013/07/16/as-solar-panel-efficiencies-keep-improving-its-time-to-adopt-some-new-metrics/

14. Practical Action: Technology Challenging Poverty. (n.d.) Micro-Hydro Power. *Practicalaction.org*
Retrieved from
http://practicalaction.org/docs/technical_information_service/micro_hydro_power.pdf

15. Dadachova, E., Casadevall, A. (2009. December). Ionization Radiation: how fungi cope, adapt, and exploit with the help of melanin. *http://www.ncbi.nlm.nih.gov*
Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2677413/