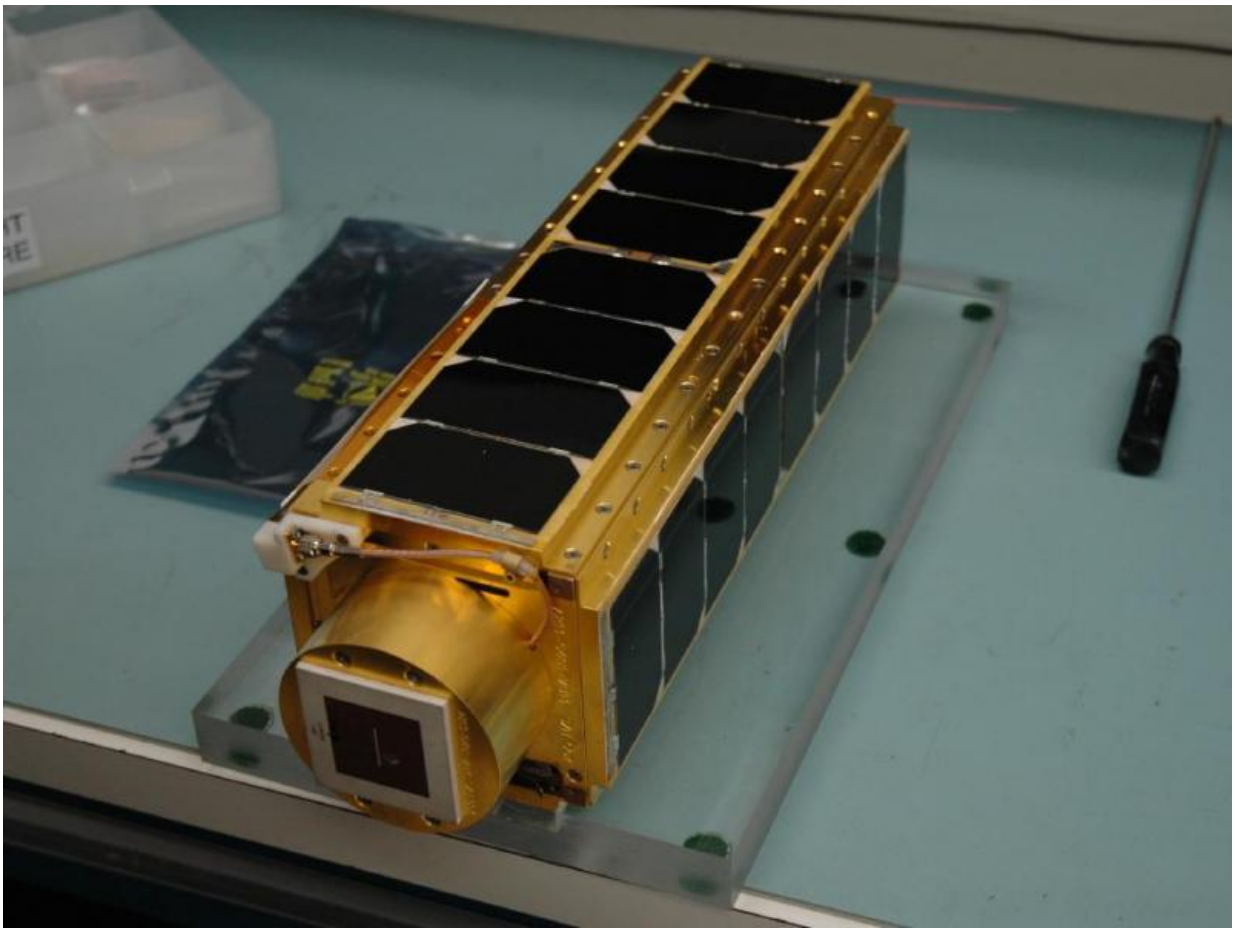
How synthetic biology will solve biological mysteries and make humans safer in space

February 3 2016, by Lucas Hartsough

The release of the hit movie *The Martian* highlighted the diverse engineering challenges in visiting the distant surface of another world. More recently, the historic landing of SpaceX's Falcon first stage gives hope that access to space will only become cheaper in the years to come. Yet, there are biological hurdles to spaceflight that neither of these successes address, and which increase the danger of long sorties into the desolate, hostile waters of interplanetary space.

We have known for some time, based on experiments conducted on the International Space Station and Space Shuttle, that simply sloughing Earth's gravity by going to orbit will have damaging, and in some cases, long-term health effects on astronauts. Relief from the pull of Earth's gravity allows the heart and other muscles to atrophy, the bones to become brittle from disuse, and the spinal fluid that surrounds the brain to accumulate, impairing vision. These effects on human physiology are well-studied, but their solutions are bound to be as complex as every other engineering challenge in space – pressure suits and religious exercise regimens will likely not be sufficient if we want to eventually live and work in space.

More recently, we are discovering that microgravity can have important and mysterious effects on even single-celled microbes. While the mechanism underlying exactly how these tiniest of organisms are affected by microgravity is unclear, what is apparent is that our most rigorous, controlled experiments to date verify that gene expression and cell physiology change in response to spaceflight [Paul 2012, Crabbe 2011, Rosenzweig 2010, Wilson 2007]. The particulars and extent of these intracellular changes seem to vary between organisms, since no known organism has evolved to live in anything other than 1G of gravity. Each organism responds in its own unique way to this evolutionarily unprecedented affront to its environment, likely since each organism's genetic software and protein wiring are perturbed slightly differently.



In response to these microgravity-induced short-circuits, most microorganisms enter damage-control mode and activate stress-response pathways [Crabbe 2011, Wilson 2007], which would normally help them mitigate incoming damage from environmental stressors such as extreme heat, pH, osmolarity, etc. by turning off all non-essential genes and producing repair and chaperone proteins instead. Unfortunately, this very response is to blame for some major threats to astronaut health in space and limits the reliability of engineered probiotic and food-producing organisms we may one day use.

One pressing concern for NASA is the increased virulence and antibiotic resistance of pathogens in space [Wilson 2007, Klaus 2006]. Additionally, spaceflight can cause dysbiosis in the human gut microbiome [Li 2015, Foster 2014], meaning that the healthy balance of commensal bacteria in the gut is disturbed, causing indigestion, intestinal inflammation, and increased susceptibility to pathogenic microbes. Biofilm growth is also encouraged in microgravity [Mauclaire 2010], which may help explain all the above, and which is likely related to the general stress response microbes activate. These dangers are a big deal for NASA since missions to Mars would require months of isolated travel each way, and astronauts may be poorly equipped to deal with a life-threatening antibiotic-resistant outbreak, placing the entire mission at risk. Fighting a resilient pathogen in a closed environment months away from help in the depths of interplanetary space definitely qualifies as a worst-case scenario.

More broadly, the effects of microgravity on microorganisms will confound any efforts to engineer organisms for use in space. As synthetic biologists, we would like to engineer genetically modified organisms that can help produce food & oxygen or serve as probiotics in astronauts' intestines (defending them from antibiotic-resistant pathogens, perhaps). However, the carefully constructed genetic programs we add to these microbes are very likely to be ignored or misinterpreted in microgravity, as a result of the cell's inherent stress response mechanisms. Even worse, it is incredibly expensive and slow to experiment on this phenomenon, meaning efforts to use synthetic biology in space are further fettered by sparse data.

To adapt from *The Martian*'s Mark Watney, we're "going to have to science [and engineer] the shit out of this," to make space exploration easier and safer.

The PharmaSat nanosatellite (above) is a small, 10lb CubeSat launched in 2009 to measure the effects of spaceflight on yeast growth rate and its resistance to antifungal agents. Relatively inexpensive spacecraft like this (or similar versions for use on the International Space Station) are crucial for rapid biological experimentation in space. Source: NASA.gov

The first step is to build on the foundational biological research that has already been conducted . We know that stress response is a major culprit, and a few target pathways have been identified in Salmonella and Pseudomonas [Crabbe 2011, Wilson 2007]. But studying

microbiology in space is still in its infancy – we need basic biological insight, and (more importantly) the ability to do very well controlled experiments. We will have to engineer additional hardware that can support these biological experiments in space, and this hardware must be cost effective enough to be used at scale for results to accrue soon. Toward these goals, NASA Ames Research Center has flown three CubeSat missions to study the effects of spaceflight on gene expression, antimicrobial drug response, and microbe longevity, as well as demonstrate their unique fluidic system for microbial cell culture [Ricco 2007, Ricco 2010, Mattioda 2012]. These missions are the first steps toward high-throughput, automated biological hardware for space, which does not require the valuable time of an astronaut and is relatively inexpensive [Woellert 2011]. Innovations of this nature must continue for the study of biology in space to prosper.

In the next decade, we will augment these new tools by using synthetic biology to build new versions of life in order to understand how it works [Elowitz & Lim 2010], or in this case, how it breaks in microgravity. We will use modern gene editing techniques [Esvelt 2013] to make large numbers of genetic modifications to microbes, and use these to understand exactly how and why their gene regulation is disrupted in space, leveraging all the next-generation tools we can bring to bear in their analysis. For example, we can perform deep sequencing on astronaut microbiomes collected in space to understand how the distribution of organisms changes over time in microgravity and learn about the dynamics of intestinal dysbiosis. We can use light, cheap, optogenetic systems to perturb microbial gene regulation [Olson 2014], to either recreate the effects of microgravity for study on Earth, or mitigating them in space. We can engineer genetic circuits that activate in response to microgravity (or its effects on the host cell) to learn more about how cells respond in this environment. Experiments such as these will lead to drastic advances in our ability to both understand and engineer biology in space.

Probiotic bacteria that help maintain astronaut health and produce mineral & vitamin supplements in space could be added in an inert state to food items (above) before launch and reactivated by water when needed. Source: NASA.gov

The next, longer-term, step is to use this greater understanding to engineer novel bacterial strains that are robust to spaceflight, or that actively counteract the effects of un-engineered, microgravity-sensitive microbes. For example, simple probiotics have already been tested as a treatment for spaceflight-induced intestinal dysbiosis, with some effect [Cervantes 2015]. However, a targeted, engineered, microgravity-insulated probiotic microbe would likely be the best option for treatment, since the human gut ecosystem is highly complex and therapeutics may be most effective when tailored to an individual [Cervantes 2015]. Similarly, NASA is already testing microbes that could be grown as a supplementary food source on long-duration missions. But a microgravity-insulated organism that has been engineered to provide essential dietary supplements, and (more importantly) taste good is the next logical step. Of course, others have proposed further important applications of biology in space, including resource mining, life support, manufacturing, and eventually terraforming [Menezes 2014, Menezes 2015]. Difficult as they will be, fantastic as they may sound, these goals are not nearly as far away as you may think.

As Mark Watney would say: Time to get to work.

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