ANALOGIES AMONG CURRENT AND FUTURE LIFE DETECTION MISSIONS AND THE PHARMACEUTICAL / BIOMEDICAL INDUSTRIES.

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Introduction

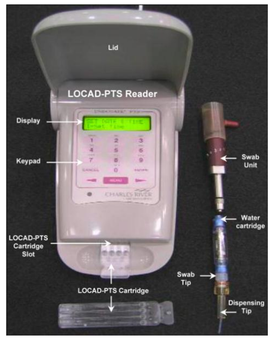
: From the earliest days of modern pharmaceutical manufacturing, the producers have been on a life detection mission. While governmental regulation has been primarily focused on ensuring the safety and efficacy of the products for the public, establishing the Food and Drug Administration in the early twentieth century in the U.S., manufacturers were equally driven by the financial impact of product contaminated by microbes. In 2004, the FDA has pressed for modernization of analytical approaches to quality control in its PAT (Process Analytical Technology) initiative. [1] While simple, traditional culture methods became adopted by the industry to quantify contamination, linking the results to some criterion of safety, the methods were far from perfect. Which species should be grown on defined media, under what conditions? Is it acceptable to hold a product in limbo for several days to achieve release? The food industry similarly focused concern on potential pathogens that spoiled product could transmit to the public. However, the pharmaceutical industry further became responsible for toxicity that could result from fractions of microbial cells that confer toxicity upon injection. As the value of sophisticated new drugs has gone up, more sensitivity and specificity of testing is demanded, like-wise the pressure to get results faster to minimize costs of halting the production lines. Whether the milieu is a highly purified drug, or the barren, surface of an asteroid or planet, the quest for life is on similar paths.

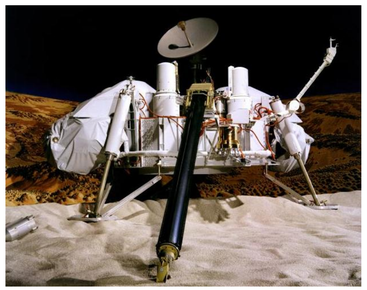
Viking and Planetary Protection

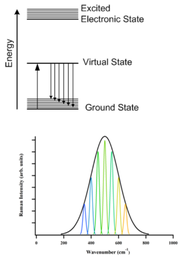
: The seminal life detection mission of the 1970's forced a new approach to life detection. [2] Not only did the technology of onboard experiments become increasingly sophisticated, but issues of potential transfer of Earth life to the surface of Mars become an issue, not only for interference with detection experiments, but for planetary protection as well. Elimination of Earth microbes involved creatively sterilizing the spacecraft after assembly by dry heat in a custom built oven, essentially analogous to "Pasteurizing" the product before use.

Non-Culture Methods:

Limitations. More recently, the realization that microbial species cultivable on defined media are a minority of the biodiversity in the environment causes concern for both Astrobiology and commercial needs. It relinquishes culture results from the definitive to the indicative. It also exposes that there is much more bioburden potentially present than can be accounted for by culture.
Methods such as specific biomarker or ATP detection came into focus. PCR and DNA sequencing became eagerly adapted to the issue. [3] These methods did find very useful application where specific species and DNA sequences were known, but unknown organ-isms, potential false positive and negative results due to sample acquisition and preparation add some un-certainty; further improvements and refinements will certainly follow.
LAL and LOCAD. An example of non-culture de-pendent methods, the Limulus Amebocyte Assay (LAL) test found eager acceptance in the pharmaceutical industry for quantifying bacterial endotoxin, a potent pyrogen when contaminating human injectable drugs. The FDA approved its use in the 1970's and it has become widely accepted in the industry. Its use was adopted for Technology Evaluation flights to ISS Expeditions 14 and 15 as part of NASA's LOCAD (Lab-on-a-Chip Application Development) Mission. Small, portable equipment developed for the Pharmaceutical industry was adapted for spaceflight and the LAL test for endotoxin became a rapid, non-culture assessment of microbial contamination of spacecraft surfaces in flight.





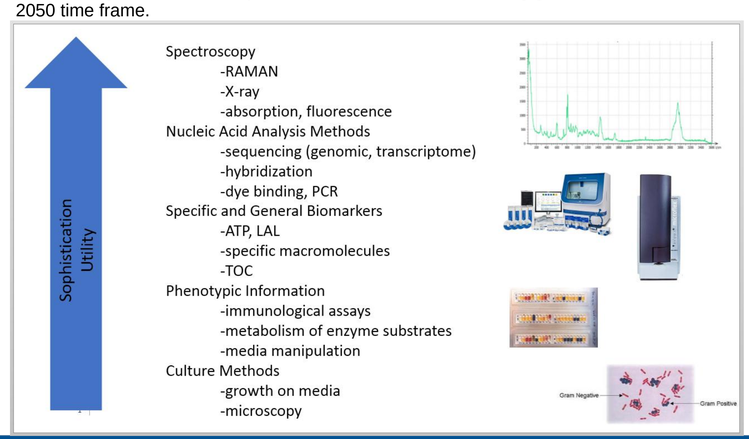


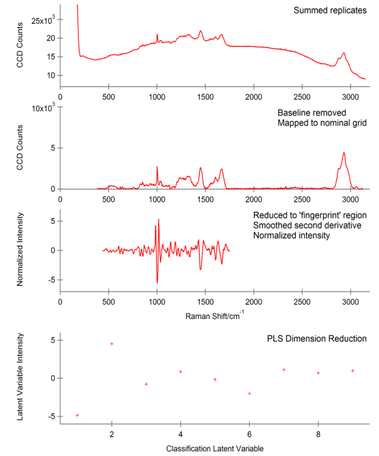
Application of Raman

- DNA/RNA, spore coat, capsule, cell membrane, intracellular contents all contribute to the measured spectra
- Bonds and conformation both contribute to identification
- Spectral measurement does not degrade viability/activity
- Cell viability, in some instances, is discernible in spectra
- Single cell/particle measurements removes interferant confusion
- Capability to identify mixed contaminants
- Factors influencing growth (extrinsic variability) are discarded
- No primers, probes, liquids reagents or substrates needed

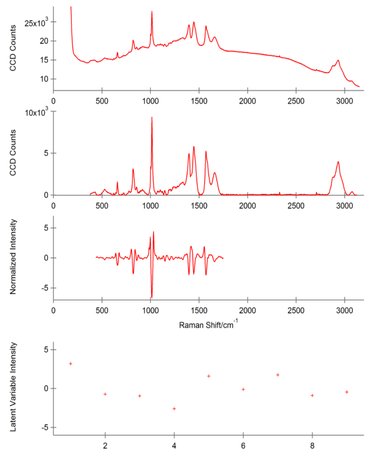
Future Progression:

Increased specificity and sensitivity. For both space-based science missions as well as the biomedical industry, technology must develop further.
Multipurpose development. The need for timely information during a manufacturing process to keep products safe and affordable are employing many of the same tools used to probe for the presence of extra-terrestrial life. Rather than to develop custom tools for each mission or job at hand, a better use of resources would be to develop tools general enough, yet powerful enough to be tailored to specific mission requirements. One way to visualize this concept is to realize that in many cases the hardware for sample preparation, sample inoculation, sample analyses and data read out and interpretation are very similar across the range of applications such as; life detection planetary protection, environment monitoring and astronaut health. That being said it becomes a simple proposal to tailor the assays for each purpose but have the hard-ware be standardized. With every increasing laboratory instrument sensitivities being translated into field or person portable instrumentation and with the realization of micromachining and microfluidic technologies in the medical and environmental monitoring fields it becomes a simple extrapolation to a miniaturized plat-form that could be deployed on human and robotic missions where the assays are tailored to specific life / organic chemistry or health and environmental priori-ties. We advance the proposition that the best place for this platform development is within the commercial sector where issues such as FDA approval, quality control and fabrication are already rigidly controlled and that assay development alone is the bailiwick of space technology development. Just as in the commercial space flight world, there is a move away from government organizations to fulfill space flight goals, there should be an impetus to involve the medical and environmental technology industry in the cost effective controlled production of the next generation techniques to fulfill science and monitoring goals for missions in the 2050 time frame.





Vegetative *Bacillus subtilis* spectra at successive data processing stages. Summed raw spectra (top), baseline removed and placed on a nominal wavenumber grid (middle-top), second derivative and extraction of fingerprint region (middle-bottom) and PLS dimension reduction (bottom).



Spectra of a sporulated *Bacillus subtilis* particle at successive data processing stages. Summed raw spectrum (top), baseline removed and placed on a nominal wavenumber grid (middle-top), second derivative and extraction of fingerprint region (middle-bottom) and PLS dimension reduction (bottom).

Wish list.

Projecting twenty or more years into the future is necessarily uncertain, however the direction that would be worthy of considering should include:

1- Production of small low cost probes to detect life or organics in a drone-like format that can be employed en mass to survey the surface of an icy moon or planet for signs of life, organics, radiation environment etc.
2- Personalized medical diagnosis and treatment of Astronauts based on small analyte, genomic and proteomic monitoring.
3- Air, water and materials quality monitoring on human missions for both organisms and chemometric tests for anion and cation concentrations.
4- Planetary protection monitoring to verify procedures for "breaking the chain" of possible forward and backward contamination during sample return missions from Mars and icy moons.
5- Laboratory based rapid analysis of returned samples for the presence of specific organic species, terrestrial contamination and possible presence of life.
6- Instruments and algorithms capable of assessing complexity, i.e., able to discriminate unknowns of high complexity from uniform or known material background.

References:

[1] Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. http://www.fda.gov/downloads/Drugs/Guidances/ucm070305.pdf.
[2] DeVincenzi, D.L. et al. (1996) Advances in Space Research. 18, 1-2, 311-316.
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[4] Morris, H.C., et al. (2012) Astrobiology, 12(9): 830-840.