Searching for new antibiotics using digital images of infected worms

Introduction

This exercise will allow students to learn about how image analysis can be applied to screening chemicals for antibiotic drugs. The data is from a published study in which the nematode *C. elegans* was used as an animal model to find small molecules that cure infection by the *E.faecalis* pathogen. In this exercise, you will have access to the following materials:

- Background information on bacterial resistance, antibiotic discovery and *C. elegans* as a model organism for antibiotic research.
- Open-source, freely available analysis software for use in quantifying biological features in image data.
- Images from an actual screen in which several compounds and extracts were found to rescue the worms from infection but had not previously been reported to have antimicrobial properties.

Goals

The exercise is written to familiarize the student with the following concepts:

- Basic principles behind screening for drug discovery and the use of model organisms
- Application and challenges of using fluorescence markers and additional biological features as a quantitative readout of viability
- Use of software for quantifying biological features and making investigative decisions based on the measurements obtained.

The exercise is written as a set of modules, such that the activities can be done up until any point (e.g., only Activity #1, only Activities #1 & #2, etc). It consists of a wide range of questions, from short and straightforward all the way to long-term open-ended project-based assignments that require students to solve multi-faceted problems, design experiments, and apply the analysis software to other types of studies. Activities #1-4 are of the problem posing and problem solving format, whereas Activities #5 and #6 fall under peer persuasion. We envision this exercise being used at multiple levels:

- Activity #1 only could be used with high school students.
- Activities #1 and #2 could be used with intro bio college students.
- Activities #1 through #4 for college students in a more upper level course over ~2-3 hours of class time depending on the students' level.
- Adding on Activity #5 for upper-level college biology students as a project-based assignment requiring time outside of class.
- Adding on Activity #6 for students in a college class on computational biology students as a project-based assignment requiring time outside of class.

Data

The images used in this exercise are from a compound screen used by Moy et al to identify small molecules that enhance survival of *C. elegans* nematodes. Each image was produced by an automated microscope acquiring pictures from a 384-well microplate containing live, infected worms dispensed by a robot.

Tools

CellProfiler is free open-source software designed to enable biologists without training in computer vision or programming to measure phenotypes from thousands of images automatically. The software is available for download at http://cellprofiler.org for Windows or Mac.

Bibliography

Moy TI, Conery AL, Larkins-Ford J, Wu G, Mazitschek R, Casadei G, Lewis K, Carpenter AE, Ausubel FM. High throughput screen for novel antimicrobials using a whole animal infection model. ACS Chem Biol. 2009 July 17; 4(7): 527–533. (Pub Med ID: 19572548). This is the original paper presenting and analyzing the data on which this exercise is based.

Carpenter AE, Jones TR, Lamprecht MR, Clarke C, Kang IH, Friman O, Guertin DA, Chang JH, Lindquist RA, Moffat J, Golland P, Sabatini DM. CellProfiler: image analysis software for identifying and quantifying cell phenotypes. Genome Biology 2006; 7:R100. (Pub Med ID: 17076895). The original paper describing the use and capabilities of the CellProfiler software.