HoloMoA: Combination of time-lapse quantitative phase imaging with deep learning for rapidly detecting the Mechanism of Action of an antimicrobial and its potential novelty

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Background. The discovery of new antimicrobial agents, natural or synthetic, displaying innovative mechanisms of action (MoA) is urgently needed to tackle the emergence and spreading of antimicrobial resistance. From a regulatory standpoint, determining the precise MoA of novel antimicrobial drug candidates is highly desirable to predict the potential for toxicity, yet it can be a time-consuming and expensive process. Moreover, a rapid, robust, inexpensive, and versatile MoA screening tool able to detect the main inhibition target of a drug candidate or suspect a novel mechanism would be most favourable to help lead candidate selection.

Methods and results. We propose an innovative technology to classify the MoA (i.e. inhibition class) of an antimicrobial and possibly detect its novelty. HoloMoA is based on the combination of time-lapse Digital Inline Holographic Microscopy (DIHM) and Deep Learning (DL). In combination with proper image reconstruction, DIHM enables a label-free, time-resolved screening of bacterial cell morphology and phase map (i.e. refractive index × thickness) to reveal phenotypic responses to antibiotics. DL techniques are powerful tools to extract discriminative features from sequences of images and classify them. DL is here challenged by the high dimensionality (space and time) of the holographic image dataset, a set of molecules belonging to different inhibition classes (sometimes with off-target or multi-target effects), and some biological variability. We assess the performance of the HoloMoA technology for a wild type *E. coli* strain treated with 27 marketed antibiotic molecules representing the 5 main inhibition classes (i.e. Cell Wall synthesis inhibitors, Cell Membrane inhibitors, Proteins synthesis inhibitors, DNA and RNA synthesis inhibitors). First, a 3D Convolutional Neural Network classifier is used to detect the mode of action of known antibiotics with 89% accuracy. Secondly, we show how our models and Siamese neural networks can be used for the novelty assessment of the MoA of a candidate antibiotic.

Conclusion. We successfully demonstrate that combining Digital Inline Holographic Microscopy and Deep Learning is a promising screening tool of new antimicrobial candidates provided that a large and complete database for known antimicrobials is available.

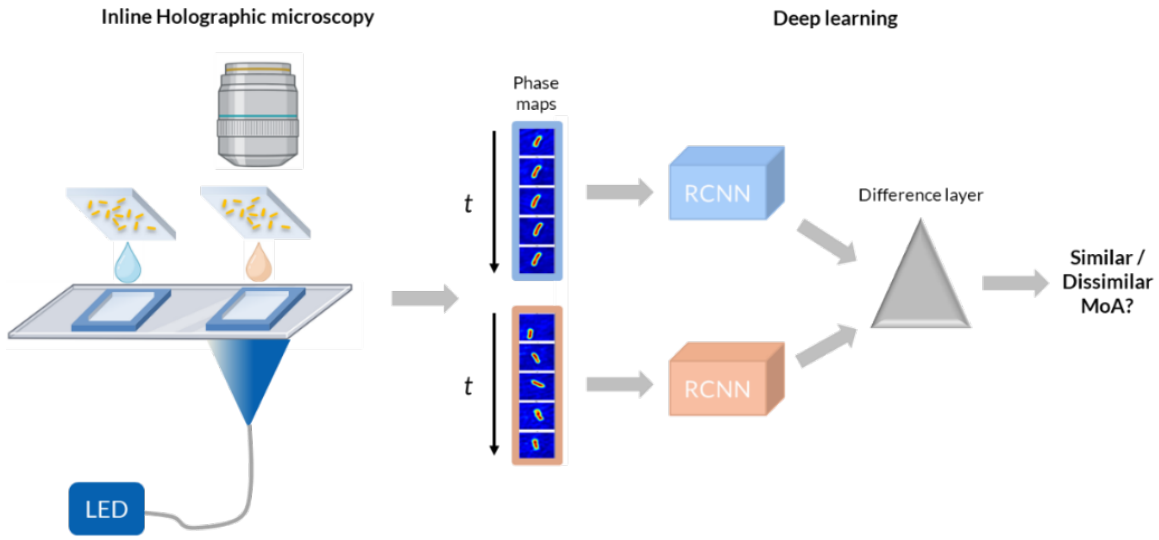

Figure 1. Principle of the HoloMoA screening technology for detecting new mechanisms of action of drug candidates