Whole-cell computational models can predict how genes influence behavior

Since the early 1900's, scientists have known that cells are composed of multiple components, including small molecules, DNA, RNA, and protein. Over the past fifty years, scientists have systematically measured these individual components and their interactions. Despite this progress, scientists still do not understand how complex biological behaviors, such as growth and motility, arise from the molecular level.

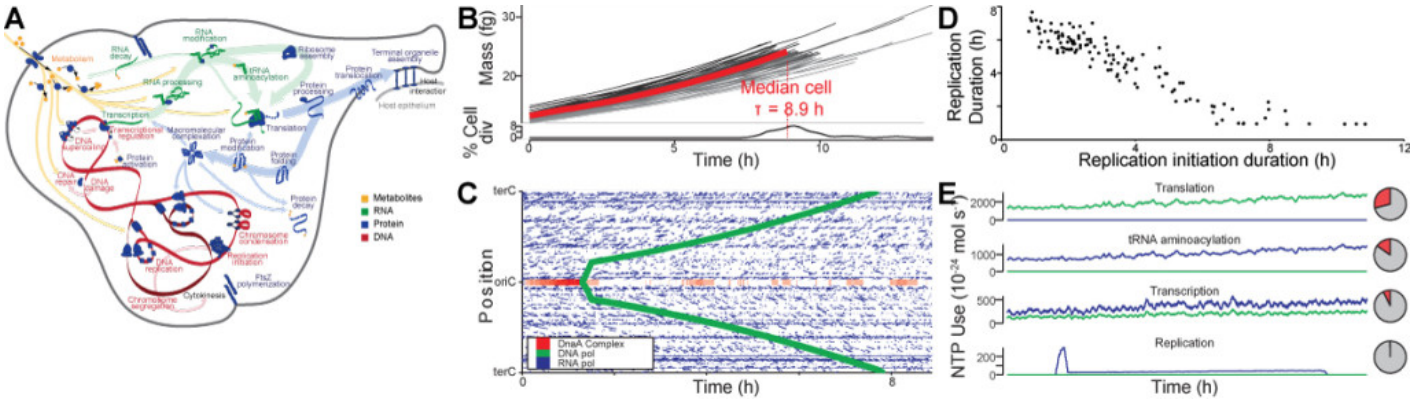

Fig. 1. Whole-cell models predict high-level cellular behaviors from the molecular level. (A) The M. genitalium whole-cell model combines multiple submodels of individual cellular subsystems. We validated the model by comparing its outputs to experimental data which describes its rate of growth (B) and RNA polymerase occupancy (C). We have used the model to understand how cells regulate their cell cycle (D) and allocate energy (E).

Recently, we and others have begun to integrate this knowledge of the individual cellular components into comprehensive "whole-cell" computational models. To date, we have developed one whole-cell model of the small bacterium Mycoplasma genitalium (Fig. 1A). The model represents all of its key functions and predicts how they combine to determine its behavior. The model is composed of multiple submodels of individual cellular pathways. We validated the model by comparison to independent experimental data (Fig. 1B,C). We have used the model to understand how cells regulate their cell cycle (Fig. 1D), to understand how cells use and allocate energy among pathways (Fig. 1E), to estimate the metabolic burden of adding new genes, and to identify new uses for existing antibiotics.

Our recent review, "The principles of whole-cell modeling", details the core principals of whole-cell modeling. The review also outlines how to construct whole-cell models, including the available software tools. In addition, the review outlines the open challenges to achieving complete whole-cell models.

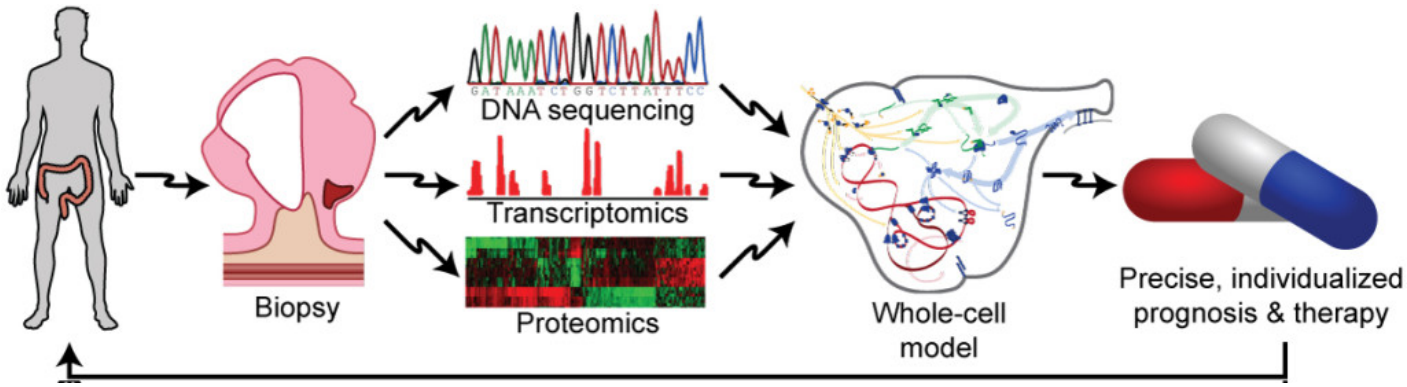

Fig. 2. Whole-cell models have the potential to enable precision medicine. In the future, clinicians could use patient-specific models informed by genomic data to design personalized prognoses and therapies.

We believe that more comprehensive whole-cell models of bacterial and human cells have the potential to transform bioengineering and medicine. In the near-term, bacterial whole-cell models, combined with genome synthesis, editing, and transplantation, could help engineers construct industrially useful bacteria which can synthesize drugs and decontaminate waste. Looking forward, human whole-cell models could also help physicians tailor medicine to individual patients based on their unique clinical symptoms and laboratory results. For example, whole-cell models could help physicians select the best drug combination for each patient (Fig. 2). Achieving complete whole-cell models will require collaboration among computational and experimental biologists, biophysicists, computer scientists, and mathematicians.

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