SUMMARY OF THE 2016 WHOLE-CELL MODELING SUMMER SCHOOL

Jonathan Karr[1], Maria Lluch-Senar[2], Luis Serrano[2] and Javier Carrera[3]
[1]Mount Sinai School of Medicine, USA. [2]Centre for Genomic Regulation, Spain. [3]Stanford University, USA.

Introduction

Background. Despite substantial research, we do not have a complete understanding of biology. Consequently, bioengineers cannot design microorganisms and physicians cannot personalize medicine. Whole-cell (WC) models that represent every gene function and predict the dynamics of every molecule are needed to predict how genotype influences phenotype [1–3]. Such models could transform bioscience, bioengineering, and medicine.

Recently, Karr et al. demonstrated a WC model of *Mycoplasma genitalium* which represents every known gene function [4]. To achieve the model, they combined pathway/genome databases (PGDBs), rule-based modeling, multi-algorithm modeling, model reduction, and unit testing.

To achieve larger and more accurate models, we must assemble a strong interdisciplinary community that can systemize and accelerate every aspect of WC modeling. To achieve this, we must recruit and train WC modelers.

2016 whole-cell modeling summer school. In April 2016, we organized the first WC school to (1) provide the first WC training, (2) recruit interdisciplinary WC researchers, and (3) brainstorm ways to improve WC modeling. Here, we summarize the school and describe our plans to continue to build a WC community.

Summary of the school

Date, location, and venue. The school was held April 3-8 at the CRG in Barcelona, Spain. The CRG was a great venue for the course due to its modern facilities, dedicated conference staff, proximity to a major airport, proximity to inexpensive accommodations and food, and proximity to tourist sites. Future meetings should (1) use larger rooms with more space for interaction among the participants and (2) have more reliable WiFi.

Course staff. The school was organized by Javier Carrera (Stanford), Jonathan Karr (Mount Sinai), Maria Lluch-Senar (CRG), and Luis Serrano (CRG) and managed by Sharon Bel Nieto (CRG). The staff also included 10 lecturers and five tutors. The organizers, lecturers, and tutors were chosen to represent a broad range of researchers (scientific: experimental, computational; geographic: six countries, 37% women).

Advertising. We advertised the course through several online conference calendars, scientific communities, social media websites, and the organizers' personal networks.

Student selection. We selected students via a competitive application process based on the applicants' CVs and descriptions of their background and interest in the course. 80 students, postdoctoral fellows, senior scientists, and faculty members applied to the course. The course organizers chose the students by (1) ranking all of the applicants, (2) giving preference to women and underrepresented minorities, and (3) balancing the scientific and geographic distribution of the students. We sent course invitations three months prior to the course. Future meetings should send invitations earlier to provide students more time to obtain visas.

Students. The course included 21 students. The students had a broad range of backgrounds in biology and computation. The students represented 11 countries; included 18 graduate students, one postdoctoral fellow, and two professors; and included eight women (38%) and 13 men.

Registration fee and travel scholarships. The student registration fee was €400. All of the US students received scholarships for their registration fees supported by NIGMS and NIH. Future meetings should provide more travel scholarships, particularly for students from developing countries.

Lectures and tutorials. The course focused on teaching students the fundamental concepts of WC modeling including genomics, data curation, PGDBs, multi-algorithmic modeling, standards, and several core pathways. The course included lectures which introduced fundamental concepts and tutorials which reinforced those concepts. To involve multiple people in the course, we invited 19 people to give the lectures and tutorials. This exposed students to a wide variety of research, but also decreased the cohesiveness of the lectures and tutorials. In the future, the lectures and tutorials should be more tightly integrated with each other.

Student talks and posters. To provide the students opportunities to share their research, the course included student oral and poster presentations. Future meetings should allocate more time for student talks.

Community discussions. The course also included two discussions on (1) what WC models should represent and (2) what problems WC modeling should be applied to. The participants proposed a variety of WC applications, indicating great interest in WC modeling. To advance WC modeling while enabling researchers to simultaneously pursue multiple WC applications, we plan to unite the WC field around developing a common methodology.

Social activities. We organized several social activities to foster the WC community: (1) we began the first day by introducing all of the participants, (2) we organized a group dinner on the first night, (3) we organized group lunches each day, (4) we organized a poster session or discussion each evening, and (5) we organized a city tour on the final day. This provided several opportunities for interaction among the participants. Future meetings should be held at more all-inclusive venues to provide even more opportunities for interaction.

Accommodations. The participants stayed at several nearby inexpensive hotels. To facilitate more interaction among participants, future meetings should arrange accommodations at a single hotel.

Website. We created a website (see appendix) to distribute all of the course information including the schedule; slides; codes; reading list; participant list; and links to the online forums.

Laptops and virtual machines. To minimize the software installation effort needed for the course, we provided pre-loaded laptops and virtual machines. Almost all of the students used the pre-loaded laptops.

Online discussion forums. We created a LinkedIn group and an email list to facilitate communication among the course participants. Unfortunately, the participants did not use these resources.

Course evaluation. We solicited feedback from the participants in several ways: (1) after the course we asked all of the participants to complete a web-based survey, (2) we organized a 30-minute group feedback discussion at the end of the course, and (3) we informally solicited feedback throughout the course. Below is a summary of the participants' feedback and our recommendations for future WC meetings based on this feedback.

Outcomes of the school

The school produced four major outcomes: (1) the school produced the first WC training materials, (2) the school produced the first toy WC model, and (3) the school expanded the WC community.

WC training materials. To teach the school, we created the first WC curriculum. In particular, we developed the first multi-algorithmic modeling tutorial. All of the course materials are available from the course website [4]. We plan to use this curriculum as the basis for self-service online tutorials.

Toy WC model. To teach multi-algorithmic modeling, we developed the first clearly described toy WC model and an associated toy WC simulator. We also plan to use this model to engage other researchers in collaborations to formalize the description, simulation, fitting, verification, and analysis of WC models.

WC community. The school was the first meeting to gather experts in WC modeling. This led to discussions about how to use PGBDs to build WC models and how to use rule-based modeling to describe WC models. This also led to discussions on the potential bioengineering applications of WC modeling.

Participant feedback

49% of the participants completed the course survey. Here, we summarize the surveys and feedback discussion.

- 89% rated the school "excellent" or "very good". All of the lectures and tutorials were rated highly.
- 89% would "definitely" recommend the school to colleagues.
- 89% would "definitely" or "probably" attend future WC meetings.
- 72% would "very likely" or "likely" engage in WC modeling.
- 72% recommended the creation of a WC community to sustain the development of WC modeling.
- Several participants reported that the best aspects of the course were the tutorials on multi-algorithmic modeling, the exposure to a wide variety of concepts, and the networking opportunities.
- The students had conflicting feedback on the balance of lectures and hands-on exercises. Some students requested more lectures and some students requested more coding and practical skills exercises.

Opportunities for improvement

The 2016 school provided excellent training. Nevertheless, there are several ways to improve future schools.

- Tighter integration among the lectures and tutorials. The lectures and tutorials should be better integrated by orienting them around building a toy model. This would help students integrate all of the concepts.
- Greater faculty and senior scientist participation. The training and conference aspects of the meeting should be separated to enable more senior scientists to participate in the conference portion.
- More discussion time. More discussions are needed to coordinate the field beyond the meeting.
- Longer student presentations. More time should be allocated for student oral presentations.
- All-inclusive venue. The school should be held at an all-inclusive venue to facilitate more interaction.
- Larger room. The school should be held in a larger room to facilitate more interaction.
- Earlier invitations. Students should be selected earlier to provide more time to obtain visas.
- Reliable wireless internet. More reliable wireless internet is needed for participants to research ideas.
- Funding. Additional sponsorship is needed to subsidize participation.

Future steps

Based on the school, we have identified three activities to continue to drive the development of WC modeling: (1) we will organize a WC working group to develop a consensus WC methodology, (2) we plan to refine the tutorials and distribute them as online videos, and (3) we plan to organize a second meeting in two years.

WC working group. To sustain the development of WC modeling, we will organize a monthly virtual WC working group. Initially, the group will focus on formalizing the representation and simulation of WC models. Initially, the group will be composed of a core group of dedicated investigators:

- Peter Barnes (Lawrence Livermore National Laboratory, USA): parallel simulation
- James Faeder (University of Pittsburgh, USA): rule-based modeling
- Jonathan Karr (Mount Sinai, USA): dynamical modeling
- Edda Klipp (Humboldt University of Berlin, Germany): dynamical modeling
- Maria Lluch-Senar (CRG, Spain): genomics
- Chris Myers (University of Utah, USA): standards
- Luis Serrano (CRG, Spain): genomics

Online self-service tutorials. To provide self-service WC training, as well as teaching materials that faculty can use to teach WC courses, we plan to refine all of the lectures and tutorials based on the course feedback, record videos of all of the lectures, and post all of the materials on WholeCell.org. In particular, we plan to reorganize all of the lectures and tutorials around building a toy WC model.

2018 WC meeting. To continue to build the WC community, we plan to organize a second WC meeting in two years. The meeting will include a five-day school followed by a two-day conference. This structure will enable students to learn about the foundation of WC modeling and enable a larger group of researchers to share progress and discuss problems in WC modeling. To provide a more cohesive educational experience, we plan to use a small teaching team and we plan to orient the entire course around building a toy WC model. To facilitate discussion about how to advance WC modeling, the conference portion will feature breakout discussion sessions. To facilitate interaction among the participants, we plan to hold the meeting at an all-inclusive venue. We plan to hold the meeting in the New York region. We plan to seek DoE, NIH, and NSF support for the meeting.

Conclusion

We organized the 2016 school to begin to assemble an interdisciplinary community that can address the challenges to WC modeling. The school made significant progress in building this community including providing the first WC forum, providing the first WC training, and creating the first WC curriculum. To further develop the field, we plan to (1) continue to conduct WC research in our own laboratories, (2) organize a WC methods working group, (3) create online WC tutorials, and (4) organize a second WC meeting in 2018.

Appendix

Course website: http://www.wholecell.org/school-2016/private (user: student, password: barcelona)

References

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4. Karr JR et al. A whole-cell computational model predicts phenotype from genotype. *Cell*. 2012.