Chapter 8

Dreaming up the future

In this chapter we let our imagination run free. While in the previous chapters, we have relied on what is known and we have carefully added step-by-step building blocks on top of that to show how to build computational models, here we allow leaps, gaps, optimistic speculations and even a pinch of fiction here and there. This chapter is meant as an inspiration about where the cell modeling could lead and what it could be a part of in the future.

More than a hundred years ago, David Hilbert had presented 23 then-open problems that significantly shaped 20th century mathematics. Many of them have been resolved, but a few stubbornly continue to resist to this day.

In a similar fashion, at the beginning of this millennium, Joseph Hoffman summarised eight open areas for blood cell discoveries [94]. These pertained to both human and non-human red blood cells, considered questions both at molecular and cell scales and asked mostly about various mechanisms causing processes and properties of red cells. Some of these questions have partially been answered in the last few years, but overall, they still remain a challenge. Unlike Hilbert's problems, we would argue that with the increasing rate of progress in biosciences, none of these questions will remain without a satisfying answer for a century.

Hoffman's open areas for blood cell discoveries

1. What are the determinants of red cell shape? What is the precise structural/mechanical basis for the biconcave shape of the normal human red cell?

2. What is the high resolution structure of the red cell plasma membrane and how do the membrane properties depend on this structure?

3. What molecular mechanisms underlie the plasma membrane events associated with hemolysis of human red blood cells?

4. What are the genetic mechanisms responsible for the determination of red cell characteristics?

5. What are the regulatory mechanisms that determine a single red cell's volume?

6. What are the events responsible for removal of nuclei during the maturation process of human RBCs?

7. What determines the metabolic structure and function of red cells?

8. What are the genetic mechanisms involved in differentiation of stem cells into erythrocytes?

Sequencing complete genomes was a major step in bringing computational and algorithmic approaches to biological problems. With the computational power increasing, public databases of data made available and improvement of machine learning algorithms that can uncover relationships and build predictive models from observations, we already see further steps towards genetic fortune telling. Even in situations when we do not have sufficient explanation of the mechanisms that drive the outcome, by connecting enough dots among the observations, bioinformatics can undeniably improve the lives of many people. We have seen this, for example, in screening for *BRCA* gene mutations and subsequent preventative steps against breast cancer.

In the future, patient-specific treatment will also be available due to the computational power and models, as well. A patient-specific blood sample could be simulated and its response to various stimuli analysed, such as response to various versions of treatment for blood diseases before they are prescribed and subsequent selection of the best treatment options. Models could factor in an individual's age, diet, family history, environmental factors that influence the body's functions, possible side effects of drugs, etc.

Similar to Silicon Valley as a cradle of technological innovation, very likely there will be another cradle related to bio start-ups. As bluntly pointed out in the science fiction book [181], it is very unlikely that this bio-valley would be in California. While the technological and computational power is available there, the general US climate is not very welcoming to radical biological breakthroughs. On the one hand, this is good. Tinkering with the human genome, producing new organisms and playing with life matter in general should be approached with extreme caution because there could be unexpected irreversible consequences. Yet the realities in America make it more likely that the cutting-edge synthetic biological research will be done elsewhere. China has already started human CRISPR (gene editing) clinical trials and south-east Asia in general seems much more favorable.

What would be useful? Synthetic cells would be extremely useful. If we could produce good enough blueprints, e.g. high-fidelity models, cells could be printed by molecular nano-printers. Print enough blood cells, combine them with an artificial blood plasma and the increasing need for blood transfusion, as our population ages and demand is predicted to outpace supply, could be met. Synthesising other cells with their ability to grow and reproduce could be a clue to the throughput issues.

3D tissue bioprinting is almost available nowadays. The technologies that are needed for printing small pieces of tissue are already available. In these synthetic tissues, the cells can be organized in a fashion very similar to natural tissue. Simulations of cell behavior in the process of printing and cell interactions as they are assembled can aid in the development of these techniques and prototyping of various printers. The continuation of this trend could lead to growing new organic limbs or organs for people who miss or have lost their own. Models could certainly help with personalizing transplants and improving outcomes.

For example to enable the electronic-skin-based vision, the adaptation of soft biological tissue to external stimuli must be perfectly understood. Several models of soft biological tissue adaptation have been presented in [72]. The engineering of such devices leads to the prototypes of e-skins able to *see* things and to replace the potentially damaged retina [39]. But why stop here? Once a bridge between retina and the brain is understood, the e-skin may be placed anywhere on the body and thus people could *see* with their skin.

From here, the natural (and dangerous) next step is biofacturing. What if we do not want to limit ourselves to cells and parts of known organisms? Entirely newly designed bioproducts could be created: manufactured food or drugs tailored specifically to meet an individual's needs, cells that could battle specific diseases, bacteria that could help us decrease environmental pollution... the possibilities are endless, but all of them would heavily rely on biophysically realistic models enabled by future simulation tools and high-performance computing capabilities.

Ethical issues
While in a brainstorming session, such as this one, we can just let our ideas fly in any direction; in practice, these are certainly topics that need to be thought through extremely carefully. Ethical issues need to be considered. One thing is to change somatic cells and treat an individual organism. Quite another is to change germ cells and create and release a change that can propagate to new generations. These are issues already being discussed among the geneticists and others and will become more and more relevant with the increasing capabilities of biosciences.

On the one hand, we have the creation of new things, on the other is removal of those things that kill us. The 2016 Nobel Prize in chemistry was awarded to three scientists who discovered how to build nanomachines out of a chain of atoms. These light powered nanomachines - few specific molecules

bound together - are engineered to be sensitive to specific proteins located on specific types of cells. They target these cells and kill them.

The damage done to cells was observed indirectly. Since there is a three-orders-of-magnitude length scale difference between the cell and the nanomachine, (today) it is not possible to observe both at the same time. The observation of cells showed membranes behaving as if they had so many hydrophilic pores - essentially holes - that they were irreversibly too damaged for the cells to live. Obviously, we would not want to do this to healthy cells, but the same thing happened when the nanomachines were unleashed on cancerous prostate cells.

Now imagine that their cell selection was reliable and could be trusted. It would open a field of nano-surgery, where we would not have to go after tumors and their metastases, but we could evict cancer from the body cell-by-cell. Taken one step further, consider an *inoculation-like* dose given preventively that patrols our bodies and kills the cells that turn cancerous before they can cause any damage. This way the nano-machines act as sensors and surgeons, but other logical steps would be to go into targeted drug delivery [1].

The big *if* here is the reliability and we are back to modeling. While an enormous amount of testing would have to be done with live cells and then tissues, it would be very helpful to accurately model the nanomachine-cell interaction in the design process.

And again, why stop here? What if these small surgeons were *intelligent*? Maybe not the nanomachines themselves since they are too small to contain enough information, but some cell-like vessels carrying these nanomachines that would contain genetic-like programs. Based on what the cell-vessels and their sensors encounter, they produce and release suitable nanomachines, observe the outcome and learn - an artificial immune system. This would need to be very carefully designed and computationally and biologically tested.

Even if these wild ideas do not become reality, similar to the report [145], we predict that computing will assume an increasing role in the working lives of nearly all biologists. Already today we see that a lot of discovery and advancement in biosciences is either directly done with or supported with computing and computational information processing. We expect this trend to continue and even grow further. It is very likely that various hybrid systems will emerge, where the (blood) cell modeling as we have introduced it in this book and its future generations will be one part of a larger model. For such synthesis of models, possibly across scales and approaches, it is likely that a common input/output biological data format or standard will crystallise, similar to json and xml available today.

To conclude, we return to the beginning and close the circle. Models are ultimately judged by their ability to make predictions - about future outcomes and about variables inaccessible to measurements. Simulations take over where analysis ends. But despite their power, models are not the goal. They capture only the essence of reality, not the full details and are tools to increase understanding and gain insight. Any answers they give need to be treated as

hypotheses, tested and validated. Nevertheless, this does not diminish them. Models are tools that give us unprecedented possibilities to look and discover. Use them wisely.