

Challenging problems for the YISB workshop

On a conference in 1900 the mathematician David Hilbert presented 23 unsolved problems in mathematics. Some of these problems touched the very fundamentals of mathematics, whereas others were difficult but seemed more down to earth; to a mathematician at least. Hilbert challenged mathematicians to solve these problems before the year 2000, and this challenge has kept generations of mathematicians busy and motivated. For example, Gödel solved the problems related to the fundamentals. Today, only four of the Hilbert problems are still open of which the Riemann hypothesis is still considered as one of the most important problems in mathematics.

We do not suggest to propose the equivalent of the Hilbert problems in systems biology, but the example does show that it can be very inspiring to define a set of worthwhile problems, and to keep them on your mind for a good deal of time.

Therefore, each of you is asked to contribute a research question that we can brainstorm about during the YISB workshop. If you are in a creative mood, please write down more ideas. We will select a number of research questions that will be discussed in the *Got a question?* session. The problem description should contain the following elements:

- The problem should be very closely related to your work. In principle, it should be a problem that you would like to solve to get your work a step further
- You should describe the problem very precisely:
 - Title
 - What is the field (background of the problem)
 - What is the question (in one or two sentences)
 - Why is it worth to be solved, what will be the expected effect of solving it
 - If applicable, which -related- work has already been performed by you or by others, or what are the directions in which you have looked.
- The description should be approximately $\frac{1}{2}$ A4, to maximally one A4 page

On the next page you can find an example of a problem description.:

What are the costs and benefits of cellular components?

The field. We (Molenaar *et al.*, 2009) have proposed a model of cellular growth that tries to explain behavior of microorganisms from the perspective of optimization. The nonlinear model contains the growth rate as a variable, and a number of parameters determining the distribution of resources over the different proteins. We adjust these parameters to obtain the maximal growth rate. Depending on environmental factors, in this case substrate concentrations, the resources are allocated to different parts of the cell, or even to different metabolic pathways, i.e. leading to metabolic shifts.

Question. Is it possible to define mathematically a “currency” for the cost and benefits, in terms of the optimality criterion, of individual cellular components?

Why we need this. The models that we use consist of sets of nonlinear equations that are solved numerically in one go. This procedure does not show us why a cell decides at some point to make a little more of one component and a little less of another, let alone that it shows why it shifts (abruptly) between complete pathways. The concept of costs and benefits that I’m looking for should give us handles to reason more intuitively about the decisions made by a cell.

Related ideas and my thoughts. Costs/benefits are used daily in reasoning about the optimization of economical processes: decision making based on the maximization of profits, for example. Also, in linear optimization something called “shadow price” exists, which to my opinion is not really what I’m looking for, because as far as I understand it just shows the dependence of the optimum value of the objective function on the boundary conditions. Similarly, just calculating the dependence (first order derivative) of the maximal growth rate on certain model parameters doesn’t yield something like costs (investments, in terms of the “growth rate currency”) and benefits (similar currency), it just yields a net result. So, I’m stuck in this problem for a while already, but I do use some sort of intuitive reasoning when thinking about the decisions that a cell makes. I’m afraid that this intuition may be incorrect, so I need a more solid basis.