Fiona Macfarlane talks with Michael Savageau, Distinguished Professor in the Departments of Microbiology & Molecular Genetics and Biomedical Engineering at The University of California Davis. Professor Savageau is the 2021 recipient of the Akira Okubo Prize which honors outstanding and innovative theoretical work, for establishing superb conceptual ideas, for solving tough theoretical problems, and/or for uniting theory and data to advance a biological subject.

1. What areas of research are you working on?

   The advantages of mechanistic models are seldom realized for complex systems because of the numerous molecular parameters of unknown value. This is a severe bottleneck in the conventional simulation-centric modelling strategies. My recent work on a novel 'phenotype-centric' modelling strategy is an attempt to circumvent this bottleneck; my colleagues and I have shown that behaviour and design at the system level can be predicted from fundamental kinetic parameters at the component level without knowledge of their values. I am currently trying to extend this phenotype-centric approach to predict mutation rates between specific phenotypes at the system level from mutation rates in parameter values at the molecular level, again without knowledge of the underlying parameter values.

2. Who or what inspired you to pursue a career in research?

   This is a difficult question because for me it was a gradual realization involving several nudges along the way, with three that stand out. The first was from my high-school hockey coach, who also was my math teacher. He told me on one of our hockey trips that he thought I would be a good engineer because of my math ability. The second came from an upper-class friend at university who suggested that I switch from civil to electrical engineering because he thought the math would be more interesting and challenging for me. By the time I graduated from university, I learned that most jobs open to me were in aerospace, which did not interest me, that I was becoming more interested in biology, that I was good at taking courses, and that I wanted to teach at the university level. For that I would need to earn a Ph.D., but I was very unsure of my ability to do original research. The third came from my Ph.D. mentor, an immunologist, who not only tolerated but encouraged my unconventional interests combining systems engineering and cell physiology. It was during my Ph.D. training when I discovered that I could do the research, that I found it terribly exciting, and that I became truly committed.

3. Do you have a favourite research paper that you have been involved in?

   This is a bit like asking, "who is your favourite child". But if I had to choose, I guess it would be one for the application or one for the methodology:

Fasani, R.A., and Savageau, M.A. Evolution of a genome encoded bias in amino acid biosynthetic pathways is a potential indicator of amino acid dynamics in the environment. Molecular Biology and Evolution. 31, 2865-2878 (2014) (doi:10.1093/molbev/msu225).

Valderrama Gómez, M.A, Lomnitz, J.G., Fasani, R.A. and Savageau, M.A. Mechanistic Modeling of Biochemical Systems without A Priori Parameter Values Using the Design Space Toolbox v.3.0, *iScience* 23, 1-19 (2020) (doi:10.1016/j.isci.2020.101200).

4. What advice would you give to a junior researcher in the field?

   Find out what you are good at, what you are passionate about, and be persistent in their pursuit. Success typically requires all three.

   Know your community's priorities and learn how to say 'no' the right way. You will be asked to do many things that are necessary but in conflict with these priorities. Do not simply say NO, or you will be considered uncooperative or a poor colleague. Instead, say I would love to, but I cannot do it right now so please give me a 'rain check'. You may be able to do it later, or in many cases the issue will have been resolved and you will not be needed.

5. What do you see as the biggest challenges in your field?

   Causal predictive models of complex systems are the biggest challenge in my view. There are statistical approaches that yield important correlations, but these are neither predictions nor valid in other contexts. On the other hand, mechanistic models, which are the gold standard for prediction, are seldom realized because they involve numerous molecular parameters that must be measured, estimated, or sampled in order to use conventional simulation-centric modelling strategies. This is why my colleagues and I are focused on alternative approaches, such as the phenotype-centric modelling strategy, in an attempt to circumvent this parameter-value bottleneck.

6. What is the best part of your job?

   Being engaged in research with a small number of students and colleagues, and teaching about the subjects I love.

7. What do you do in your spare time?

   I enjoy regular dinners with family and friends, nightly reading, weekly movies and, at least once a month, long week-ends at our vacation home on the Northern California Coast hiking along the bluff trails overlooking the Pacific and in the Redwood forests.