Preface

The summer of 2013 was very good; we found a series of papers published by Gregory D. Smith and his coauthors. We spent several weeks trying to understand the paper [35], which introduces and carefully studies a stochastic model of calcium release from internal stores in cells. Then we found a whole series of papers [36, 57, 102, 103], and the results more or less kept us busy for months. The beauty of the theory presented in these papers is that they introduce a systematic way of analyzing models that are of great importance for understanding essential physiological processes.

So what is this theory about? It has been fairly well known for a while that stochastic models are useful in studying the release of calcium ions from internal storage in living cells. Some authors even argue that this process *is* stochastic. That is debatable, but it is quite clear that stochastic models are well suited to study such processes. Stochastic models are also very well suited to study the change of the transmembrane potential resulting from the flow of ions through channels in the cell membrane. Both these processes are of fundamental importance in understanding the function of excitable cells. In both applications, ions flow from one domain to another according to electrochemical gradients, depending on whether the channel is in a conducting or nonconducting mode. The state of the channel is described by a Markov model, which is a wonderful tool used to systematically represent how an ion channel or a receptor opens or closes based on the surrounding conditions. In this context, the contribution of the papers listed above is to present a systematic way of analyzing the stochastic models in terms of formulating deterministic differential equations describing the probability density distributions of the states of the Markov models.

As pointed out in the papers by Smith et al., this approach is not really new; the authors cite a number of earlier papers and we have been quite influenced by the paper of Nykamp and Tranchina [63] because of its elegant way of developing the deterministic differential equation describing the probability density functions of the states involved in the stochastic process. The key observation is that we can study stochastic release in two fundamentally different ways: (1) We can run a number of simulations using a stochastic model. Because of the stochastic state

of the channel, the results will differ, but we can gather numerous results and summarize them in terms of histograms describing the probability density functions of being in a given state. (2) We can find a deterministic partial differential equation modeling the probability density functions and obtain the distributions by solving this system numerically. By increasing the number of simulations in (1) and by refining the numerical discretization in (1) and (2), we observe that the results of the two methods converge to the same distributions. Therefore, we have a very powerful tool for analyzing the stochastic models: We can simply solve deterministic partial differential equations to find the probability density functions. In some simple cases, the deterministic partial differential equations can be studied analytically and no numerical solution is needed. The relation between the stochastic simulation and the solution of the deterministic partial differential equations will be studied repeatedly in these notes.

More recently, we found the book by Bressloff [6] to be an astonishing source of material concerning stochastic processes in cells. It will clearly become a standard reference in the field together with its companion volume [7]. The theory of stochastic processes is also introduced in a most readable manner by Jacobs [39], and elements of the theory are covered in the monumental work of Keener and Sneyd [43, 44].

One reason for our enthusiasm in finding the papers listed above is that, for a while, we have been trying to understand how to theoretically devise suitable drugs for mutations affecting both ion channels and receptors. It has been clear for some time that the effect of mutations on ion channels and various receptors can be successfully modeled using Markov models to describe the state of the channel. A comprehensive review is presented by Rudy [74] (see also Rudy and Silva [75]). Clancy and Rudy and their coauthors (e.g., [16]) have also shown how to use Markov models to describe the function of various drugs aimed at repairing the function of mutated channels or receptors. This is very useful, since it allows simulation based on stochastic models and the models can also be interpreted as continuous representations for whole cell simulations. However, analysis of the Markov models is taken to a new level by the introduction of probability density functions defined in terms of deterministic partial differential equations.

Our approach has been as follows: Let the properties of the drug be free parameters and use a setup based on Markov models to find the best possible drugs. This problem is much easier to approach using the results of Smith et al. because it amounts to understanding how the solution of the extended system of partial differential equations (including the effect of the drug) behaves as a function of the parameters characterizing the drug. Typically, we will end up comparing the solutions of three systems of partial differential equations: (1) a system modeling the dynamics of healthy (wild type) cells, (2) a system modeling the dynamics of non-healthy (mutant) cells, and (3) a system modeling the dynamics of non-healthy cells with a drug added to repair the effect of the mutation. *The problem we would like to address is how to adjust the parameters describing the drug such that the solution of (3) is as close to the solution of (1) as possible.* This turns out to be

much easier using a deterministic system of partial differential equations describing the probability density functions than using stochastic simulations.

We have decided to present our results in the form of lecture notes. There are several reasons for this choice. First, we strongly believe that the theory described above is very useful, and we want to help make it as comprehensible as possible. That is more or less impossible to do in scientific papers because their focus must be on new results and not on careful derivations of established insights. A second reason is that the problem of understanding cell physiology and how drugs affect their function is inherently multidisciplinary, and we therefore write these notes in such a way that we hope readers who are not primarily applied mathematicians can understand. We also hope to give applied mathematicians glimpses of interesting problems of great importance.

As mentioned above, these notes aim to explain known theory that we think can be useful to researchers working on a mathematical understanding of living cells. There are also new results. We show in some detail how to derive formulas describing the optimal properties of theoretical drugs. Most of the results are stated for rather simple models, but it is quite clear that the methods can be extended to more intricate cases.

The million dollar question when you read these notes is, of course, can these drugs actually be created? Do they exist? We do not know. We know that Markov models have been used to successfully represent the actions of drugs, but is it possible to go the other way and first compute what properties the drug should have and then create it? We have found no clear answers in the literature or through discussions with colleagues, so we decided to just formulate these ideas as precisely as possible in the hopes that someone will find them useful. We have tried to carefully underline in the notes that we are discussing *theoretical drugs*, and we state in many places that this work is about possible drugs.

Acknowledgments

It is pleasure to thank Dr Martin Peters at Springer for a very fruitful collaboration through many years.

We would also like to thank the six reviewers of these notes. One reviewer wrote an unusually comprehensive and encouraging report counting seven pages; we spent two months working on his or her comments and it was clearly worth the effort. We have never experienced a referee report of equal depth and usefulness and we deeply appreciate the reviewer's labor.

These lecture notes were largely written during visits to the University of California, San Diego, and the authors are grateful for the hospitality of the Department of Bioengineering and the Department of Computer Science and Engineering.

Finally, we would like to thank Karoline Horgmo Jæger, who read the entire document twice and found numerous small (and actually some not so small) errors.

Her efforts are highly appreciated. We would also like to thank Achim Schroll for helpful discussions regarding the hyperbolic problems encountered in this text.

This work was supported by a Centre of Excellence grant from the Norwegian Research Council to the Center for Biomedical Computing at Simula Research Laboratory.

Lysaker, Norway — Aslak Tveito
Lysaker, Norway — Glenn T. Lines
October 2015

http://www.springer.com/978-3-319-30029-0

Computing Characterizations of Drugs for Ion Channels and Receptors Using Markov Models

Tveito, A.; Lines, G.T.

2016, XVI, 261 p. 129 illus., 30 illus. in color., Hardcover
ISBN: 978-3-319-30029-0