Fast and accurate solutions to the chemical master equation for multimeric systems

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Gene regulatory networks (GRNs) operate in the background of a sea of fluctuating molecules constantly synthesized and degraded or transported across the cell membrane. The fluctuations, referred to as noise, are inherent in all biological systems, which means they cannot be eliminated by any known biochemical process. In order to unravel, reverse-engineer, or synthesize a GRN, it is often necessary to know what are the effects of noise on that network. One way in which nature controls noise is through protein-protein binding, i. e. multimer formation. Research exists in support of this hypothesis; however, computational methods for calculating noise in the presence of multimers are limited to stochastic algorithms [1], which do guarantee an answer but often at the expense of impractical running times. Various approximation methods of solving the master equation have been developed [2], as well as moment-closure approximations [3]. Given the complexity of chemically interacting systems, naturally, all these methods have their limitations. For a multimeric system we demonstrate a quick and accurate way to calculate the noise at equilibrium for all, monomers and multimers, based on the assumption that the probability function is a multivariate skewed normal distribution.

Instead of working directly with the master equation, we obtain from it a set of moment equations, containing higher moments for all species as well as correlations between them. For non-linear systems, these equations are not closed: the nth equation contains (n+1)st moment. However, having assumed a skewed normal distribution, all moments and correlations can be expressed in terms of a finite number of parameters dictated only by the

number of species. In order to infer these parameters, we square each moment equation, sum them up, and optimize the sum with respect to the parameters using a standard global minimization algorithm on Mathematica. Constraints are placed on the sign and magnitude of some of the parameters so as to obtain physically relevant quantities. The minimization procedure takes only up to a few seconds. We compared our results for the average and the variance of each species with those obtained by running 500 realizations using the Gillespie algorithm and found agreement to within one percent. The accuracy of this method suggests it may be applicable to other systems.

1. Gillespie, Daniel T (1977) Exact Stochastic Simulation of Coupled Chemical Reactions, *J. Phys. Chem.,* **81:**2340–2361.

2. Verena Wolf et al. (2010) Solving the chemical master equation using sliding windows, *BMC Systems Biology,* **4:**42.

3. Ramon Grima (2012) A study of the accuracy of moment-closure approximation for stochastic chemical kinetics, *J. Chem. Phys.,* **136:** 154105