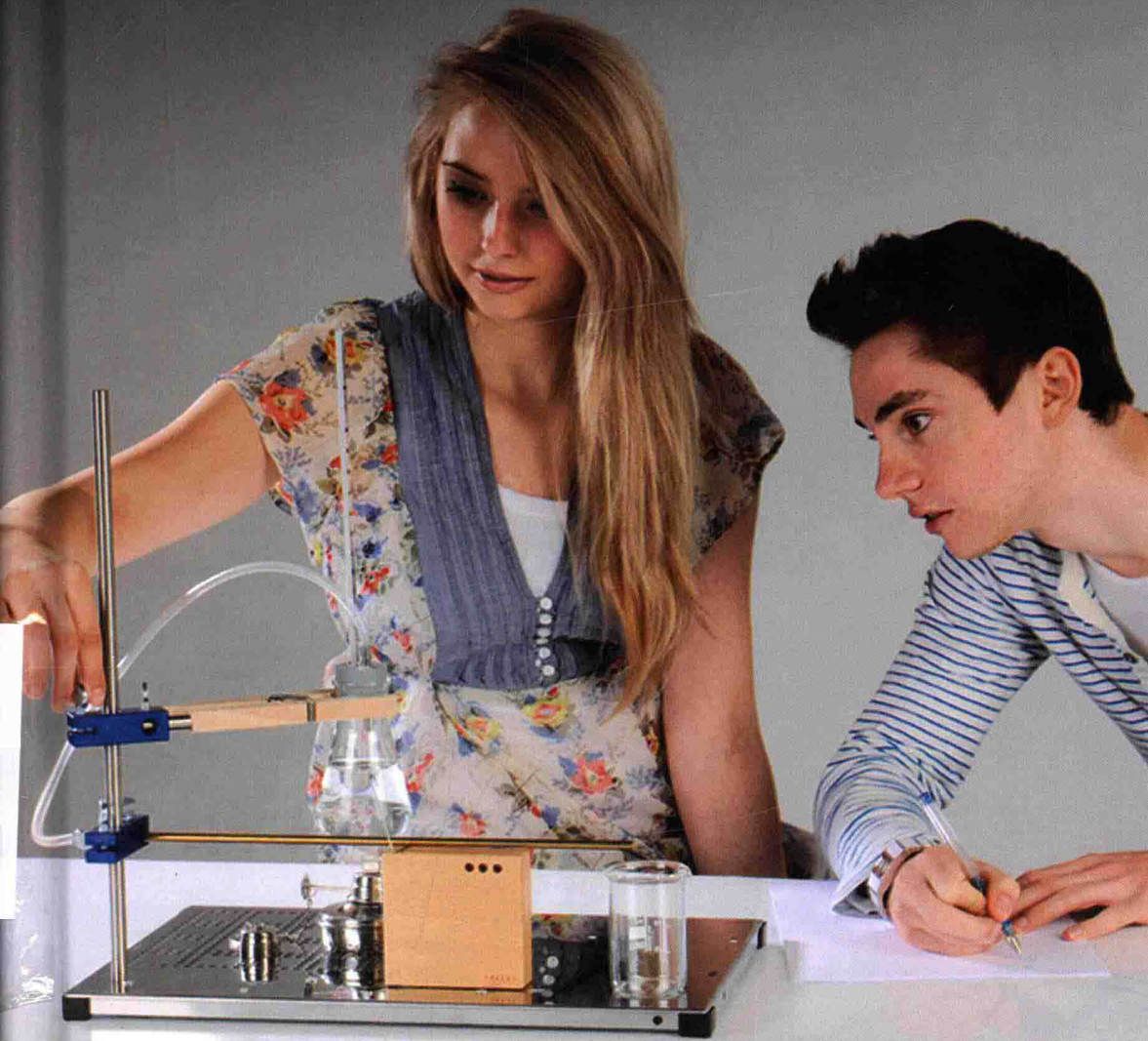


Thermodynamics in Biology

Contributors

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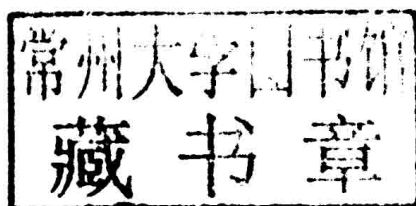
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List of Contributors

Andreas Bremges

Computational Biology and Bioinformatics Group, Fundamental and Computational Sciences Directorate, Pacific Northwest National Laboratory, Richland, Washington, United States of America

Stefanie Schirmer

Computational Biology and Bioinformatics Group, Fundamental and Computational Sciences Directorate, Pacific Northwest National Laboratory, Richland, Washington, United States of America

William R. Cannon

Computational Biology and Bioinformatics Group, Fundamental and Computational Sciences Directorate, Pacific Northwest National Laboratory, Richland, Washington, United States of America

Estefania Azevedo

Instituto de Bioquímica Medica, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Priscila F. Silva

Instituto de Bioquímica Medica, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Fernando Palhano

Instituto de Bioquímica Medica, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

The Scripps Research Institute, La Jolla, California, USA

Carolina A. Braga

Instituto de Bioquímica Médica, Universidade Federal do Rio de Janeiro,
Rio de Janeiro, Brazil

Polo de Xerem, Universidade Federal do Rio de Janeiro, Duque de Caxias,
Brazil

Debora Foguel

Instituto de Bioquímica Médica, Universidade Federal do Rio de Janeiro,
Rio de Janeiro, Brazil

Mizutani Tadashi

Instituto de Bioquímica Médica, Universidade Federal do Rio de Janeiro,
Rio de Janeiro, Brazil

The Scripps Research Institute, La Jolla, California, USA"

Erhan Süleymanoglu

Gazi University; Faculty of Pharmacy; Department Of Pharmaceutical
Chemistry; Hipodrom; 06330-Ankara Turkey

Jun Okada

Department of Material and Life Science, Osaka University, 2-1 Yamada-
oka, Suita, Osaka 565-0871, Japan

Tomohiro Okamoto

Department of Material and Life Science, Osaka University, 2-1 Yamada-
oka, Suita, Osaka 565-0871, Japan

Atsushi Mukaiyama

Department of Material and Life Science, Osaka University, 2-1 Yamada-
oka, Suita, Osaka 565-0871, Japan

Takashi Tadokoro

Department of Material and Life Science, Osaka University, 2-1 Yamada-
oka, Suita, Osaka 565-0871, Japan

Dong-Ju You

Department of Material and Life Science, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

Hyongi Chon

Department of Material and Life Science, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

Yuichi Koga

Department of Material and Life Science, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

Kazufumi Takano

Department of Material and Life Science, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

CREST, JST, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

Shigenori Kanaya¹

Department of Material and Life Science, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

Joshua S Martin

National Evolutionary Synthesis Center, Durham, NC 27705, USA

N Adam Smith

National Evolutionary Synthesis Center, Durham, NC 27705, USA

Clinton D Francis

National Evolutionary Synthesis Center, Durham, NC 27705, USA

Department of Biological Sciences, California Polytechnic State University, San Luis Obispo, CA 93405, USA

Tony B Yates

Oklahoma Baptist University, James E. Hurley College of Science and Mathematics, 500 West University, OBU Box 61772, Shawnee, OK 74804, USA

Edmund A Marek

Department of Instructional Leadership and Academic Curriculum, University of Oklahoma, 114 Ellsworth Collings Hall, Norman, OK 73019-0260, USA

Raphael D Sagarin

Institute of the Environment and School of Natural Resources and the Environment, University of Arizona, Tucson, AZ, 85721, USA

Terence Taylor

International Council for the Life Sciences, 7925 Jones Branch Drive, Suite LL130, McLean, VA, 22102-3365, USA

Daniel L. Cook

Department of Physiology and Biophysics, University of Washington, Seattle, Washington, United States of America

Department of Biological Structure, University of Washington, Seattle, Washington, United States of America

Division of Biomedical and Health Informatics, University of Washington, Seattle, Washington, United States of America

Fred L. Bookstein

Department of Statistics, University of Washington, Seattle, Washington, United States of America

Faculty of Life Sciences, University of Vienna, Vienna, Austria

John H. Gennari

Division of Biomedical and Health Informatics, University of Washington, Seattle, Washington, United States of America

Federica Censi

Department of Technologies and Health, Istituto Superiore Di Sanita`,
Rome, Italy,

Giovanni Calcagnini

Department of Technologies and Health, Istituto Superiore Di Sanita`,
Rome, Italy,

Pietro Bartolini

Department of Technologies and Health, Istituto Superiore Di Sanita`,
Rome, Italy,

Alessandro Giuliani

Department of Environment and Health, Istituto Superiore Di Sanita`,
Rome, Italy

Paul Oldham

ESRC Centre for Economic and Social Aspects of Genomics (Cesagen),
Lancaster University, Lancaster, United Kingdom

Institute of Advanced Studies (UNU-IAS), United Nations University, Yo-
kohama, Japan

Stephen Hall

ESRC Centre for Economic and Social Aspects of Genomics (Cesagen),
Lancaster University, Lancaster, United Kingdom

Geoff Burton

Institute of Advanced Studies (UNU-IAS), United Nations University, Yo-
kohama, Japan

Preface

Biological thermodynamics is the quantitative study of the energy transductions that occur in and between living organisms, structures, and cells and of the nature and function of the chemical processes underlying these transductions. Biological thermodynamics may address the question of whether the benefit associated with any particular phenotypic trait is worth the energy investment it requires. The field of biological thermodynamics is focused on principles of chemical thermodynamics in biology and biochemistry. This book is divided into ten chapters. The first chapter refers to simulating metabolism with statistical thermodynamics. The aim of second chapter is to study thermodynamics of molecular recognitions between antineoplastic drug taxol and phosphatidylcholine. Thermodynamics of the slow unfolding of hyperstable monomeric proteins has been presented in third chapter. Fourth chapter clarifies the relationship between evolution, entropy, and the second law of thermodynamics. The focus of fifth chapter is to identify the types and prevalence of biological evolution misconceptions held by Oklahoma high school introductory biology teachers and to correlate those findings with demographic variables. In sixth chapter, we analyze biological evolutionary systems to develop a framework for applying lessons of natural adaptability to security concerns in society. Seventh chapter refers to simulating metabolism with statistical thermodynamics. Eight chapter deals with physical properties of biological entities. Ninth chapter describes a systems biology strategy on differential gene expression data discloses some biological features of atrial fibrillation. Last chapter emphasizes on synthetic biology.

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Chapter 1

SIMULATING METABOLISM WITH STATISTICAL THERMODYNAMICS

William R. Cannon

Computational Biology and Bioinformatics Group, Fundamental and Computational Sciences Directorate, Pacific Northwest National Laboratory, Richland, Washington, United States of America

ABSTRACT

New methods are needed for large scale modeling of metabolism that predict metabolite levels and characterize the thermodynamics of individual reactions and pathways. Current approaches use either kinetic simulations, which are difficult to extend to large networks of reactions because of the need for rate constants, or flux-based methods, which have a large number of feasible solutions because they are unconstrained by the law of mass action. This report presents an alternative modeling approach based on statistical thermodynamics. The principles of this approach are demonstrated using a simple set of coupled reactions, and then the system is characterized with respect to the changes in energy, entropy, free energy, and entropy production. Finally, the physical and biochemical insights that this approach can provide for metabolism are demonstrated by application to the tricarboxylic acid (TCA) cycle of *Escherichia coli*. The reaction and pathway thermodynamics are evaluated and predictions are made regarding changes in concentration of TCA cycle intermediates due to 10- and 100-fold changes in the ratio of $\text{NAD}^+:\text{NADH}$ concentrations. Finally, the assumptions and caveats

regarding the use of statistical thermodynamics to model non-equilibrium reactions are discussed.

INTRODUCTION

Ideally, models of metabolism should predict metabolite levels, characterize the thermodynamic requirements of pathways and processes, be testable with experimental data, and provide insight into the principles of cellular function and self-organization. Simulations based on the law of mass action, such as kinetic simulations, can in principle meet these requirements. However, these simulations require knowledge of the thousands of rate constants involved in the reactions. The measurement of rate constants is very labor intensive, and hence rate constants for most enzymatic reactions are not available. Moreover, the same *prima facie* enzymes (ortholog) from different species, or even different strains, have differing rate constants. For example, for dihydrofolate reductase, the turnover rates for the substrate 7,8-dihydrofolate measured *in vitro* vary five orders of magnitude across species – from 284 s^{-1} to less than 1 s^{-1} [1]. If one were to model the metabolism of an organism using kinetic simulations, the rate constants for each enzyme would first need to be measured.

Currently, flux-based approaches are the methods of choice for modeling metabolism because they do not require the use of rate constants. Instead, flux-based approaches are based on fitting reaction flux values to an experimentally measured growth rate. However, this computational convenience also limits the predictive power of the methods, in that the prediction of metabolite levels from flux values [2]–[4] relies on the assumption of reversibility for non-equilibrium reactions [5], [6]. Consequently, predicted levels of metabolites may have large uncertainties, especially when the range of calculated fluxes consistent with the steady state assumption can span many orders of magnitude [7]. Moreover, flux-based methods do not provide any information on energy requirements of pathways, sets of pathways, or organisms in a community without likewise making assumptions about the reversibility of non-equilibrium reactions [8], [9].

An alternative to both these approaches is to model metabolism using simulations of states rather than simulations of reactions.

State-based simulations were in fact the first computer simulations ever performed and were reported in the classic Metropolis Monte Carlo paper, Equation of State Calculations by Fast Computing Machines, which came out of the Manhattan project [10]. Similar time-independent, statistical mechanical methods are now widely used in adsorption physics [11], quantum Monte Carlo simulations [12], protein engineering [13], drug design [14] and elsewhere. In the context of metabolic modeling, the state consists of the set of concentrations of all metabolites. A change of state occurs when the concentrations of the metabolites change due to a reaction. The change of state is evaluated using state function such as the Gibbs energy, the isothermal-isobaric free energy, or any other appropriate state function. Therein lies the advantage of simulations that model states rather than time-dependent reactions – the parameters needed to model states (standard free energies of reaction) are much easier to determine than the parameters needed to model reactions (rate constants). An assumption used in this study is that each reaction occurs with a frequency proportional to the thermodynamic driving force on the reaction, although this assumption can be alleviated by including activities in the model. The disadvantage is that the specific time-dependence of each reaction is lost, which has some consequences as discussed below. The simulations can be carried out stochastically or deterministically, and equilibrium as well as nonequilibrium processes can be modeled. The usual caveat for state simulations regarding dynamic bottlenecks in phase space apply [15], and are discussed below.

As biology emerges as a physical science, researchers will likely need different modeling approaches – kinetic, flux-based, or statistical thermodynamic – based on the details of the question being asked. In computational chemistry, for example, many different models are employed depending on the research question, ranging from electronic structure calculations with electron correlation, to hybrid QM/MD, to molecular mechanics models. The approach outlined in the paper can provide a detailed model of metabolism that provides in-depth information, but not all questions may require this level of information.

Here, the basic aspects of the statistical thermodynamics background needed for simulating metabolic systems are presented. The methods section does require some mathematical background

in multinomial statistics, however this background is not necessary to understand the application presented in the results section. The application is that of the tricarboxylic acid cycle from *Escherichia coli*, for which the free energy, energy and entropy profiles are determined as well as predictions of metabolite concentrations. However, the point of this report is not to model a particular process in high fidelity, but rather to demonstrate the principles of applying statistical thermodynamics to metabolic reaction networks. Finally, this report concludes with a discussion of the advantages and limitations of using state-based simulations to model metabolism.

METHODS

Theory - Statistical Thermodynamics of Coupled Reactions

This section provides the basic statistical thermodynamic background that is needed to implement and characterize simulations of coupled reactions based on modeling states. Consider the reaction



This set of reactions is comparable to the conversion of citrate to isocitrate via aconitate in central metabolism in which the waters involved in the reactions are modeled implicitly. The number m of molecular species is three (A, B and C), the number of particles of type j is n_j , and there are $N_{total} = \sum_{species j}^m n_j$ total particles in the system. For classical systems, the distribution of states are rooted in Boltzmann statistics in which the particles are assumed to be distinguishable. The partition function for the system is

$$Q = N_{total}! \prod_{species j}^m \frac{1}{n_j!} q_j^{n_j}.$$

The q_j are the molecular partition functions for species j , and $\sum q_j = q$. Conceptually, q is not only the sum of the molecular partition functions, but it is also the molecular partition function of the hypothetical boltzon particle that can be in one of m states with corresponding energy levels $G_i = -RT \log q_i$, $i = 1 \dots m$. When

corrected for indistinguishability (corrected Boltzmann statistics), the partition function for the system is given by [16], [17],

$$Q = \prod_{\text{species } j}^m \frac{1}{n_j!} q_j^{n_j}.$$

The issue whether to use Boltzmann or corrected Boltzmann statistics depends on whether the particles are distinguishable or not. For example, when considering a high density of particles at low temperature such that the N-body Schrodinger equation can't be separated, corrected Boltzmann statistics are appropriate. However, the interest here is in considering particles that exist as distinguishable chemical species. As a result, in the rest of the discussion and for demonstration purposes Boltzmann statistics will be used.

In statistical thermodynamics the free energy of the system is,

$$-A/k_B T = \log Q$$

$$= \log \left(N_{total}! \prod_j^m \frac{1}{n_j!} q_j^{n_j} \right)$$

In comparison, the multinomial probability mass density for a set of independent and distinguishable objects is,

$$\Pr(n_1, \dots, n_m | N_{total}, \theta_1, \dots, \theta_m) = N_{total}! \prod_{\text{species } j}^m \frac{1}{n_j!} \theta_j^{n_j}, \tag{1}$$

where θ_j is the probability of an object being of type j . Identifying objects with chemical species, and taking the species probability as the Boltzmann probability, $\theta_j = q_j/q$, the free energy can be expressed in terms of the probability mass density [18],

$$-A/k_B T = \log Q = \log \left(N_{total}! \prod_j^m \frac{1}{n_j!} q_j^{n_j} \right) \tag{2}$$

$$= \log \Pr(n_1, \dots, n_m | N_{total}, \theta_1, \dots, \theta_m) + \log q^{N_{total}} \tag{3}$$

The difference between the multinomial probability mass function \Pr and the system partition function Q is $\log q^{N_{total}}$ – the log of a multinomial expansion of q . The multinomial expansion is simply the number of configurations that the system can obtain – the extent of state space,