Mitochondrial optimization using thermodynamic geometry

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Abstract. The thermodynamic metric for an N-component ideal gas is derived and applied to the cytochrome chain in mitochondria. The resulting thermodynamic length is then used to bound the entropy production in the process and to calculate the optimal concentrations (electrochemical potentials) of all the reactants. Sensitivity to changing the environment is shown. Possible implications for the construction of technical fuel cells are discussed.

1. Introduction

Thermodynamic geometry as part of Finite Time Thermodynamics has been used to analyze and optimize a range of different systems from heat engines to distillation columns as well as systems from economics and computer science [1–4]. However, up to now all of these thermodynamic applications have only dealt with thermal, not chemical systems.

We have developed a thermodynamic metric for an arbitrary N-component ideal gas system, taking into account the added complexity of the chemical potentials of the components. Applied to the specific example of the cytochrome chain in mitochondria (Figure 1), we have calculated the optimal distribution of electrochemical potentials in that reaction sequence. These values are in good agreement with values previously found in experiments [7, 8] (Figure 2).

If the number of steps in the chain is increased, the length of the thermodynamic process decreases, and thus the entropy production may decrease to zero. Using the calculated optimal states, we have analyzed the behavior of the cytochrome chain under changing external conditions like oxygen pressure and pH.

2. Thermodynamic geometry

Thermodynamic geometry was developed primarily by F. Weinhold [5] and further expanded in the context of Finite Time Thermodynamics by a number of authors [1–4]. The metric matrix **M** is defined as the Hessian D^2U of the internal energy U of the system (matrix of second derivatives with respect to all other extensive thermodynamic quantities of the system). This may also be linked to the Hessian D^2S of the entropy S of the system through the environment temperature T:

$$\mathbf{M} = D^2U = \left\{ \frac{\partial^2 U}{\partial X_i \partial X_j} \right\} = -T\, D^2 S. \tag{1}$$

The main result of thermodynamic geometry bounds the entropy production ΔS^u of a thermodynamic process proceeding in N steps by its geometric length L calculated with this metric **M** [5]:

$$\Delta S^{u} \geq \frac{L^2}{2N}. \tag{2}$$

The *Horse-Carrot theorem*, as this relation is called, also relates the optimal length of each individual step D_n of a thermodynamic step process to the total entropy production. Through the Cauchy-Schwarz inequality it is found that minimum entropy production is achieved (equality in eq. (2) above) when the distances of each step are of equal thermodynamic length.

3. The cytochrome chain

The cytochrome chain is responsible for the bulk of ATP production in the mitochondria of our cells under aerobic conditions. It is a three step process where electrons are passed from the donor NADH to the acceptor O_2. This electron transfer is mediated by two free mobile carriers: ubiquinone (UQ), also known as coenzyme Q (CoQ), and cytochrome-c (cyto-c). See Figure 1.

The entire process may be described in terms of the ratio between the concentrations of oxidized and reduced forms of each mediator. This is equivalent to the electrochemical potential which may be measured directly in order to observe the redox state of each mediator.

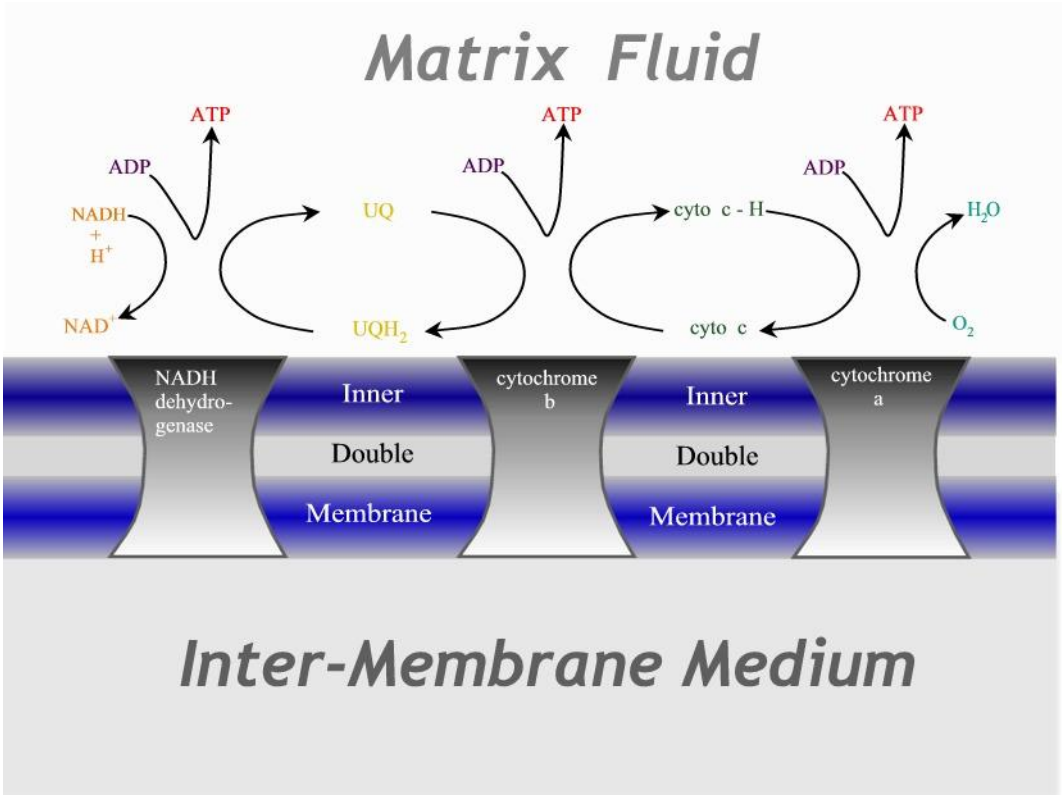

Figure 1. Illustration of the cytochrome chain. Three protein complexes imbedded in the inner mitochondrial double membrane act as catalysts for the redox reactions, transferring electrons in successive steps through ubiquinone and cytochrome-c before terminating as water.

4. Construction of the metric and optimization

Prior analyses have included only a single chemical component. In the calculations for an N-component ideal gas additional terms involving cross derivatives of the energy with respect to each chemical species must be included. This effectively adds an additional N dimensions to the traditional ideal gas matrix on the Legendre submanifold previously studied.

$$\mathbf{M}_U = \begin{pmatrix} \frac{\partial^2 U}{\partial S^2} & \frac{\partial^2 U}{\partial S \partial V} & \frac{\partial^2 U}{\partial S \partial n_i} \\ \frac{\partial^2 U}{\partial V \partial S} & \frac{\partial^2 U}{\partial V^2} & \frac{\partial^2 U}{\partial V \partial n_i} \\ \frac{\partial^2 U}{\partial n_i \partial S} & \frac{\partial^2 U}{\partial n_i \partial V} & \frac{\partial^2 U}{\partial n_i \partial n_j} \end{pmatrix} \tag{3}$$

$$= \begin{pmatrix} \frac{T}{NC_v} & \frac{-p}{NC_v} & \frac{\mu_i}{NC_v} - \frac{T}{N} \\ \frac{-p}{NC_v} & \left(1 + \frac{k}{C_v}\right)\frac{p}{V} & -\frac{k}{C_v}\frac{\mu_i}{V} \\ \frac{\mu_i}{NC_v} - \frac{T}{N} & -\frac{k}{C_v}\frac{\mu_i}{V} & \mu_i\left(\frac{\mu_j}{U} - \frac{1}{N}\right) - \frac{1}{N}\mu_j + \frac{1}{N^2}U + \frac{RT}{N_j}\delta_{ij} \end{pmatrix}$$

For the cytochrome chain, although reasonably simple, the dimensionality of the metric matrix is 14×14. To reduce the number of variables, we may apply standard Legendre transformations to transform an intensive variable to a constant extensive variable (e.g. S to T and V to P) and apply any conservation restriction, e.g. of mass. This reduces the cytochrome chain metric to a 2×2 matrix, only dependent on the redox quotient of each mobile carrier.

The redox quotient may be expressed in terms of the electrochemical potential E given by Nernst's equation,

$$E = E^{\theta'} - \frac{RT}{nF}\ln\left(\frac{[\mathrm{Red}]}{[\mathrm{Ox}]}\right) \tag{4}$$

where $E^{\theta'}$ is the standard electrochemical potential at pH 7 for the reaction in question, R is the gas constant, n is the number of electrons transferred, F is Faraday's constant, and [Red] and [Ox] are the concentrations of the reduced and oxidized forms of the reactant, respectively. Each of the two remaining variables in the metric may then be parameterized through this common, directly measurable, system variable.

Calculating individual step-lengths

In order to calculate the optimal electrochemical configuration, the total length and the length of each individual step is needed:

$$L = \int_{E_{NADH}}^{E_{O_2}} \sqrt{dE\,\mathbf{M}\,dE} \quad \text{and} \quad D_i = \int_{E_{i-1}}^{E_i} \sqrt{dE\,\mathbf{M}\,dE} \tag{5}$$

where the endpoints of the integration are the electrochemical potentials for each substance. Fixing the supply of NADH (and thus the NADH electrochemical potential) and oxygen pressure, the total thermodynamic length of the system is constant. The electrochemical potentials for UQ and cyto-c may then be found by solving the Horse-Carrot equation, finding E_{UQ} and $E_{cyto\text{-}c}$ such that each step is equidistant.

The reaction length element is only explicitly dependent on the concentrations of UQ and cyto-c. The environment does however impact the solution. A change in pH will change the electrochemical potentials of all substances, and a change in either oxygen pressure or NADH supply will change the bounds of the integral used to calculate the total thermodynamic length. By nature of the performed Legendre transformations, the dependence on each removed variable is implicit.

5. Results

Optimal electrochemical configurations were found for a series of varying external operating conditions. The standard conditions are a 1:10 ratio of NAD:NADH and an oxygen pressure of 0.2 atm. Under these conditions the optimal electrochemical potential for ubiquinone was found to be 0.074 V and for cytochrome-c 0.415 V. The cytochrome-c redox potential is significantly higher than its standard reduction potential of 0.215 V due to the fact that it is seven times less concentrated in mitochondria than ubiquinone. As can be seen from figure 2, the optimal electrochemical potential varies almost linearly through the steps of the cytochrome chain. The optimal values correspond well to the values found experimentally under similar conditions [7, 8].

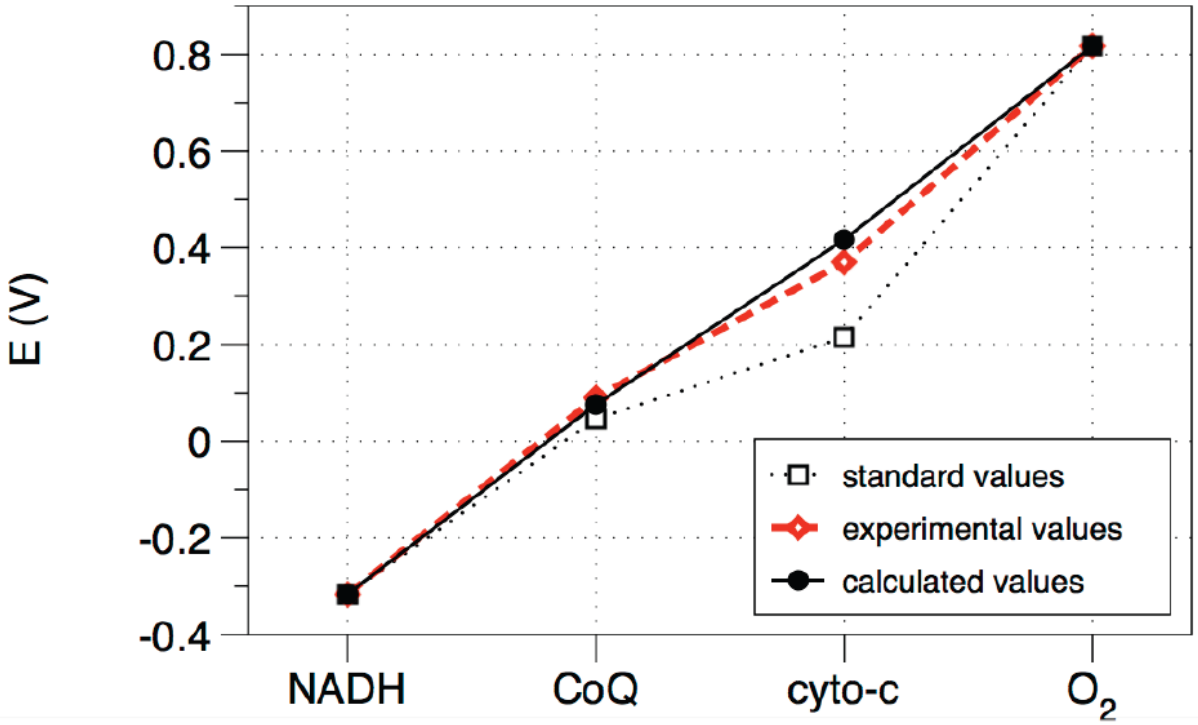

Figure 2. The standard, calculated, and observed [7, 8] values of the electrochemical potential of each electron transfer unit.

The Horse-Carrot theorem provides a specific positive bound for the entropy production, inversely proportional to the number of steps in the process. We found that the optimal total entropy production

decreases if we increase the number of intermediate carriers. We found that the total length of such a process also decreases (Figure 3). This indicates that the process may become reversible in the limit of infinitely many intermediate steps, as is also the case for the distillation column previously analyzed [2].

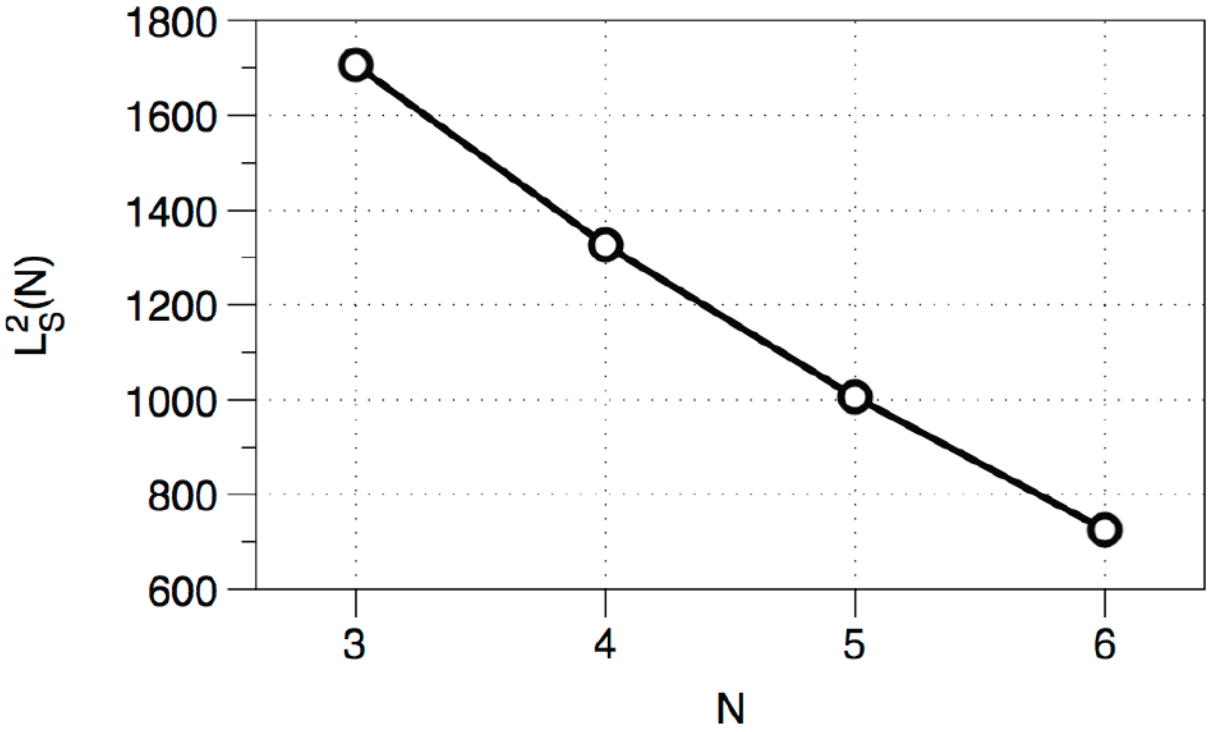

Figure 3. Squared thermodynamic length of the reaction path (arbitrary units) as a function of the number of steps N.

Assuming the mitochondrion is in the calculated optimal state, the influence of external changes was investigated. We found that the middle complex is most susceptible to changes in oxygen pressure and is likely the first complex to halt under oxygen deprivation. The potential ATP production depends on the specific ATP/ADP ratio, and changing this value also effects which oxygen pressure is required for the middle complex to operate. We found that even in extreme cases, the oxygen pressure could still be reduced substantially before the middle complex ceases to operate. Figure 4 shows the possible number of ATPs produced on cytochromes b and a (last two steps) as a function of oxygen pressure for three different concentrations of total ATP; 5 mM total ATP (the middle curve) corresponds to normal operation. This curve drops below a value of 2, and thus stops the reaction chain, at an oxygen pressure in the mitochondrion of 2×10^{-4} atm, corresponding to about 2×10^{-2} atm in the air. This low oxygen pressure is found at an altitude of 12 km.

6. Outlook

Mitochondria are the fuel cells of living cells. By comparison traditional alkaline fuelcells generate electricity by transporting hydroxyl ions across a semi-permeable membrane. This is not an optimal solution since it restricts the reaction kinetics. Mitochondria do not require a membrane to function, relying instead on the specificity of each of the mobile electron carriers.

Two major design points may be extracted from the cytochrome chain, namely the benefit of increasing the number of intermediate steps, and removing the semipermeable membrane in favor of

chemical specificity since this allows the electrochemical reactions to take place in the entire volume. Applying thermodynamic geometry lets us find the specific configuration with minimal entropy production and thus maximum efficiency.

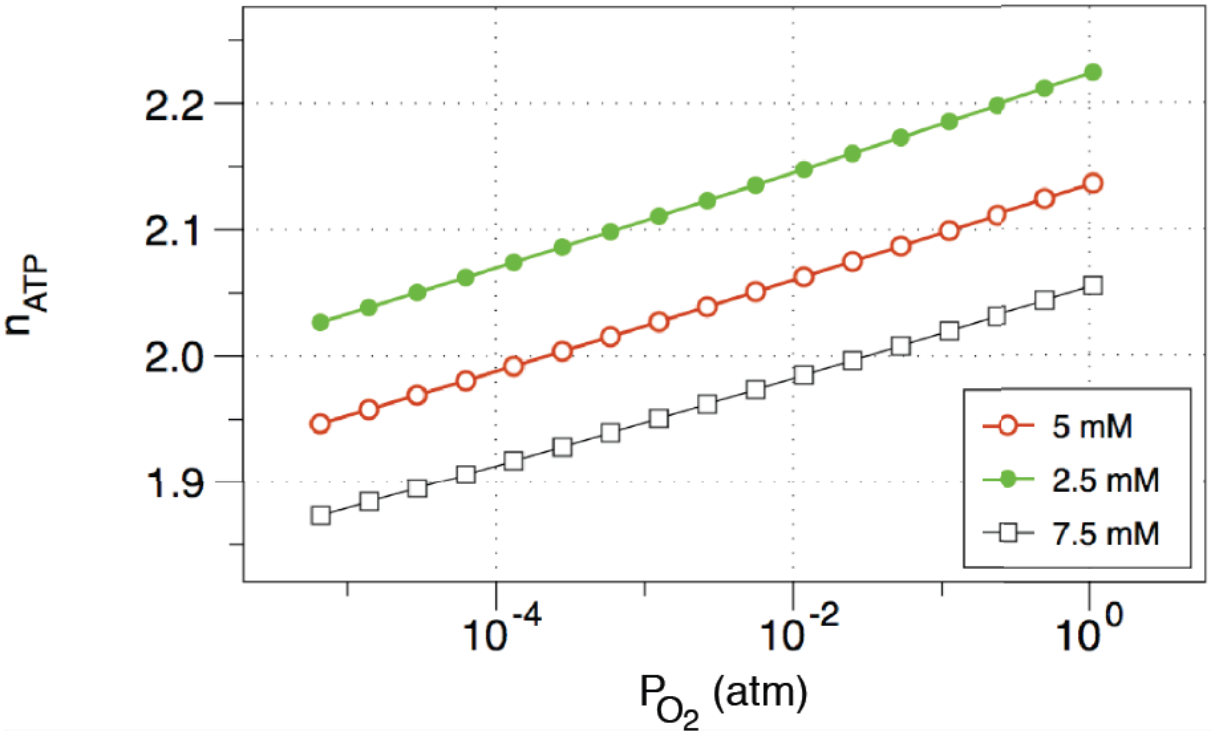

Figure 4. Maximum ATP production on cytochromes b and a (last two steps) as a function of oxygen pressure for three different concentrations of total ATP.

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