

Thermodynamics for Systems Biology

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This paper aims to provide a comprehensive introduction to thermodynamics designed specifically for the needs of the systems biologist. It departs from modern treatments in paying attention to the macroscopic aspects of the subjects rather than focusing purely on the statistical character of the facts. It also makes a real effort to communicate certain lesser known aspects of the subject that have to do with modeling, i.e. to communicate thermodynamics as a body of worldviews, methods and interpretations. Here macroscopic thermodynamics is an example of systems thinking, and a body of thought which is methodologically and conceptually different from mechanics. To focus on this aspect of the subject, we follow its historical development.

Most people are aware that there are three laws of thermodynamics. The first law is the conservation of energy and is relatively straightforward. The second law states that energy can only be degraded. It specifies the “arrow of time”. This law is subtler and merits much more discussion. The third law concerns the behavior of thermodynamic systems near the absolute zero of temperature and will not concern us in the present treatment. Less well known is the zeroth law which is part definition part postulate and asserts the well definedness of thermal equilibrium and of the ordinal scale of temperature that determines which of two systems is hotter.

Underlying all of thermodynamics is the definition of the sort of system to which thermodynamic arguments truly apply. Understanding this definition in detail is important for applying the subject to systems biology where the notion of “system” will be stretched to (and sometimes a little beyond) its limits. What can constitute a thermodynamic system has proved to be a remarkably robust notion; it will surely be able to accommodate further generalizations appropriate for systems biology. The key to recognizing what can or cannot constitute a system in the thermodynamic sense revolves around issues of time scales that serve to separate processes into fast and slow. The reason for this is that the “dynamics” in thermodynamics is a misnomer. The theory describes what can happen between *equilibrium* states of thermodynamic systems, i.e. the theory is really comparative statics insofar as it concerns net effects of moving between an initial static situation and a final one. Thermodynamics asserts whether certain net effects are or are not possible.

One consequence of the above is that we need to recognize what *equilibrium* means; this is difficult for at least two reasons:

- (1) Equilibrium is approached asymptotically and thus we never quite reach it.
- (2) Equilibrium means something very different on ordinary versus on astronomical time scales.

The first fact follows from the nature of equilibrium as the state where change-inducing forces are zero. Insofar as such forces get smaller as we approach equilibrium, such approach is asymptotic. The second fact is due to the very large waiting times for relaxation of degrees of freedom corresponding to large activation energies. Examples of

such degrees of freedom include nuclear transitions. In fact, the “true” (infinite time) equilibrium of any chunk of matter would have to be Fe⁵⁶ [ref Tolman].

The point of the preceding paragraph is that equilibrium is a notion that makes sense only once a time scale has been specified¹. We say that a system is in equilibrium once all the degrees of freedom of the system change sufficiently slowly that they can be regarded as constant. In other words, the necessary condition for thermodynamic arguments is what is referred to as the separability of time scales.

Before seeing how to put this subtle concept to work for systems biology, we present the laws of thermodynamics in the context of the simplest thermodynamic systems where the classical ideas apply rigorously. We thus take our system to be homogeneous and occupying a well defined region in space known as the control volume. The paradigm example of such a system is a gas in a container. In fact historically the ideal gas and the ideal gas law have contributed a great deal to thermodynamics – without this example of a simple system whose simple equation of state was known explicitly and allowed everything to be calculated analytically, the subject would have taken much longer to develop.

The Zeroth Law

¹ Connected to such a time scale Δt at any temperature T is a closely associated energy scale ΔE , where $\Delta t \approx \exp(-\Delta E / kT)$ gives the mean first passage time out of a valley with excitation energy ΔE . Thus we could alternatively say that equilibrium is a notion that does not make sense until an energy scale has been specified.

The zeroth law postulates the well definedness of thermal equilibrium and a phenomenological (ordinal) temperature scale. The postulate describes one possible result of establishing “thermal contact” between two systems: when establishing such contact brings no sensible change in either system, we say that the two systems are *at the same temperature*. Furthermore we postulate that if thermodynamic systems A and B have the same temperature and systems A and C have the same temperature then it must be the case that B and C have the same temperature.

The first law

The first law expresses the conservation of energy. The law was constructed from separate older conservation laws for mechanical energy in mechanics and for caloric in the theory of heat. In retrospect, the ability to rub two sticks together to produce heat flagrantly contradicts any conservation of caloric, and it was clear to the scientists even before the first law that their laws had only context limited validity [ref Tisza]. However, the one-way nature of the conversion – mechanical energy to thermal energy – kept things mysterious and no doubt delayed the formulation of the combined version. With the advent of the steam engine (and its immense economic importance) it became possible to investigate the production of work from heat and the first law soon followed.

This conservation of energy was then used to *construct* a function of state known as internal energy, E . This function is defined for one system by how it changes

$$\Delta E = Q - W ,$$

where Q is the heat entering the system and W is work done by the system on the surroundings. This formulation uses the interconvertibility of mechanical energy and caloric to combine the conservation laws in these separate domains into one larger conservation law.

Of more interest to systems biology is the fact that this law can be extended into the chemical domain, i.e. we can include the conversion of chemicals in the phenomena described. Since such conversion can be associated with large heat and work effects we delay the discussion of how this is done until after the second law.

The Second Law

The second law is the only physical law that expresses the unidirectionality of time. All other physical laws allow for each possible process to proceed in either direction, i.e., forwards or backwards. Since the world as we experience it is certainly unidirectional (in fact especially so for living systems) this means that the second law plays a very important role.

There are many equivalent formulations of the second law [Pippard]. Perhaps the most intuitive is in terms of the second possibility concerning what can happen when two thermodynamic systems are brought into thermal contact. The first possibility was contact between two systems at equal temperatures, in which case the zeroth law asserts that nothing happens. The second possibility is thermal contact between two systems at

different temperatures, in which case the second law asserts that heat always flows from the hotter to the colder system, i.e. from higher temperature to lower temperature. In other words, it is impossible to have a process whose only net effect is to transfer heat from a cold reservoir to a hot one. Equivalently, it is impossible to have a heat engine whose only net effect is to take heat from a single reservoir and convert it entirely into work. In fact recent studies have adopted the useful convention of viewing work as heat at infinite temperature, in which case the second formulation becomes a specific instance of the first one.

The second law is often expressed by saying that “energy is always degraded”. What this means is that it spontaneously moves to lower and lower temperatures. Note that this encompasses both friction in which work (infinite temperature heat) is degraded to heat at finite temperature and spontaneous heat flow in which thermal energy at one temperature becomes thermal energy at a lower temperature. In fact it is remarkable that this one statement encompasses all irreversible processes, i.e. provided no heat moves to a lower temperature, the process is reversible! For mechanical processes, reversibility means only that no friction is involved. For thermal processes, reversibility requires that all heat move between systems at equal temperatures. For reversible processes, we can *construct* an additional conservation law as shown below.

Based on the second law, we can construct a second state function similar to internal energy. This state function is *designed* to quantify the unidirectionality of time and is known as entropy. While reversible processes cannot in fact occur, they can be

approached to arbitrary accuracy, at least as gedanken processes. In such processes we define a conserved quantity, the entropy, again by how it changes. For one system, the differential change in its entropy, S , is defined in terms of the differential amount of heat dQ_{rev} entering or leaving the system, where the *rev* subscript reminds us that we can count this way only for reversible processes:

$$dS = \frac{dQ_{rev}}{T}.$$

By the foregoing discussion, a reversible process will always keep the total entropy S (added up over subsystems) constant since heat moves only between systems at the same temperature. Irreversible processes on the other hand increase entropy. Note that for processes with friction, entropy is produced since the appearance of heat corresponds to the appearance of entropy. Similarly, when heat Q moves from a higher temperature T_1 to a lower temperature T_2 , the total amount of entropy increases by $\left(\frac{Q}{T_2} - \frac{Q}{T_1}\right)$.

To calculate how the entropy of a certain subsystem changes, we have to calculate what would happen in a reversible process that goes from the system's initial to its final state. It is a fact that all reversible processes would end up transferring the same amount of entropy to/from our subsystem. We usually state this by saying that entropy is a function of state.

It is worth pausing here to discuss these ideas in light of the more modern statistical theories of thermal physics. From this perspective, we think of heat as energy transfer

that is completely “thermalized”, i.e. as randomized as the temperature allows. Thermal energy at a high temperature is more ordered than thermal energy at a low temperature. In this connection, work can be viewed as heat from an infinite temperature system, i.e. not randomized at all but rather directible entirely into lifting a weight. This randomization is at the heart of the statistical view of thermodynamics. From this perspective, the second law describes how energy gets mixed up as it spreads out to the many molecular degrees of freedom. A quantitative handle on this aspect of the subject comes from the microscopic interpretation of entropy as the logarithm of the number of states consistent with a given macroscopic state. In this context, the increase of entropy corresponds to things getting mixed up and it is *entropy production* that gives us a quantitative measure of irreversibility.

In this regard we mention a cautionary note: heat and work are not state functions but rather transfers of energy. Just as work is energy *flow* that shows up as mechanical energy, heat is energy *flow* that shows up in a purely randomized form. Thus although the environment does work on our system, all or part of this work could enter our system as heat. From a mathematical perspective, heat and work are differential forms that are not exact, i.e., they are not in general the differentials of a function of state. As differential forms, they assign numbers to processes (paths in the set of states) but not to states.

Entropy has another nice property. Recall that if we consider the amount of work extractible from a mechanical process such as a water wheel, one pound of water moving one foot lower can produce at most one foot-pound of work. Our definitions allow an

analogous statement for how much work can be produced by a certain amount of entropy moving (reversibly) from T_1 to T_2 : the maximum work is the product of the entropy that moved and the temperature difference. To see this, consider a heat engine in which a working fluid picks up heat Q_1 from system 1 at temperature T_1 and deposits heat Q_2 in system 2 at temperature T_2 . By the first law, the work produced by the process will be the difference $Q_1 - Q_2$. Since we are interested in the *maximum* work, we want the process to go reversibly which means that $Q_1 = T_1\Delta S_1$ and $Q_2 = T_2\Delta S_2$, with $\Delta S_1 = -\Delta S_2$. The above fact then becomes,

$$\begin{aligned} W_{\max} &= (T_1 - T_2)\Delta S \\ &= (T_1 - T_2)\frac{Q_1}{T_1} \\ &= \left(1 - \frac{T_2}{T_1}\right)Q_1 \end{aligned}$$

i.e. the maximum work is the famous Carnot efficiency $\left(1 - \frac{T_2}{T_1}\right)$ times the heat.

Standard States and Tables

For both the internal energy and the entropy, the foregoing discussion talks only about changes. Thus it follows that each of these functions are defined only up to an additive constant which is usually specified by the selection of a particular state for which the value of the function is to be zero. The choice of such *reference states* with respect to which energies and entropies are calculated is an important freedom that can be used to simplify a particular calculation. The older texts choose standard temperature and pressure to define the standard states for all the elements for which the internal energy and the entropy are chosen to be zero. More modern sources use zero temperature as the

reference state for the zero of entropy, a choice particularly convenient for the third law. Since ultimately our calculations deal with comparative statics, the choice of reference states drops out and as long as we are careful and consistent all choices are equally correct. Nonetheless, switching between references that differ in their choice of standard states can be confusing.

States versus processes

Historically, thermodynamics was born as a theory of heat engines. Its growth was spurred primarily by the success of the steam engine. A full generation later, in the hands of J.W. Gibbs, the subject underwent its most profound transformation – it changed from a theory of processes to a theory of states. Before this it had only dealt with the transfer of heat and work between systems. After the transformation, it became a theory of equilibrium states for one system. The first law became

$$dE = TdS - pdV = dQ - dW ,$$

where E , S , T , p , and V all refer to the properties of a single system. The main impetus for the transformation was the need to include chemical processes in the first and second laws.

Gibbs noted that chemical phenomena were associated with heat and work and thus that their analysis should be combined with the thermodynamic laws. He achieved the required unification by introducing the notion of chemical potential. The chemical potential, μ_i , of the i^{th} molecular species plays the role for molecules of type i that

temperature plays for heat. When two systems are brought into contact of a sort that allows transfer of species i , mass of species i moves from the system with the higher chemical potential to that with the lower one. Furthermore, the maximum work that could be obtained from a spontaneous process of mass flow is the product of the mass dM and the chemical potential difference between the two systems

$$dW_{\max} = (\mu^2 - \mu^1)dM.$$

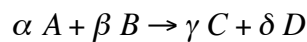
This forces

$$\mu_i = \frac{\partial E}{\partial M_i}$$

and adds new terms to the differential form of the first law

$$dE = TdS - pdV + \sum_{\text{species } i} \mu_i dM_i.$$

The notion of chemical potential extended the definition of a reversible process to mass transfer, with reversibility holding in exactly those processes in which mass is transferred across zero chemical potential differences. More interestingly, it can now be used to define reversible chemical reactions to be those where the stoichiometric combination of the reactants' chemical potentials equals the stoichiometric combination of the products' chemical potential. For example, for the reaction



between reactant species A and B forming product species C and D with stoichiometric coefficients α , β , γ , and δ , the reversibility condition is

$$\alpha \mu_\alpha + \beta \mu_\beta = \gamma \mu_\gamma + \delta \mu_\delta.$$

In fact this is also the equilibrium condition, with the result that a reaction is reversible if and only if it takes place at equilibrium.

Once chemical interconversion is allowed into the set of processes we consider, the reference states with zero energy and entropy are no longer independently selectable.

While such reference states remain arbitrarily selectable for the *elements* in their natural states they imply definite nonzero values for chemical compounds. For example, we can take the energy and the entropy of gaseous hydrogen and gaseous oxygen at STP² to be zero but then are forced to take the energy and entropy for liquid water at STP to be the energy and entropy change associated with the reversible reaction forming water from H₂ and O₂.

Reformulations

Most physical theories admit reformulations and such reformulations are important for making the theory usable in a wide variety of contexts. The thermodynamic theory of states developed above gives a complete characterization of equilibrium states for an isolated system: its total internal energy remains constant and any spontaneous process inside the system, i.e., interaction among its subsystems, will increase the total entropy of the system. It follows that when entropy is as large as it can get, no further spontaneous processes are possible and the system is at equilibrium. Thus the final characterization is that entropy is maximized for a constrained energy.

² Zero degrees Centigrade and one atmosphere.

While energy has become a familiar concept from mechanics, entropy has not fared nearly as well. Gibbs made use of a general duality between objective and constraint functions in an optimization problem to transform the conditions of equilibrium into one that seems more palatable for intuitions steeped in mechanics. Instead of saying that entropy is maximized subject to a fixed energy we can say equivalently that energy is minimized subject to a fixed entropy.

A similar reformulation is possible at the process level: there, the second law's assertion that entropy increases in any spontaneous process changes to an assertion that available work is lost in any spontaneous process. Such available work was introduced by Gibbs and has enjoyed a recent resurgence of popularity among engineering thermodynamicists under the name of *exergy*. The fact that exergy can only be lost is a common way to state the second law.

Closely related to exergy is the notion of free energy, also introduced by Gibbs. In fact given certain constraints on the allowable processes, free energy is just exergy. For example, for processes at constant temperature and pressure, the change in Gibbs free energy ΔG of some subsystem is exactly the change in exergy of the total system.

Free energies are important in another context because isolated systems are not nearly as common as systems that are coupled to their surroundings. If these surroundings maintain the pressure and the temperature of the system at a constant value, then it is possible to

consider a larger system made up of our system and its surroundings. If we can consider this larger system isolated, then the laws of thermodynamics as stated above characterize the equilibrium of the composite system. When the surrounding system is large enough so that its temperature and pressure are effectively unchangeable by interaction with our small system, then it turns out that the equilibrium of the small system can be characterized by minimizing the free energy

$$G = E + pV - TS.$$

Such reformulations of the principles are known as Legendre transforms. They have been generalized beyond the usual free energies [salamon, dissertation] to determine the equilibrium conditions for systems in contact with surroundings that fix any function of state. While to date this has not been the case, it is our belief that such generalizations will prove of interest for systems biology.

Implications for living systems

As noted above, thermodynamics's change from a theory of processes to a theory of states required describing interactions between subsystems, each of which may be viewed as a thermodynamic system in its own right. In the process, our notion of thermodynamic system lost some of its simple character as a homogeneous region in space with well defined boundaries. In fact, for chemical reactions, the systems can consist of one type of molecule with a volume that is completely superimposed on the volume of a second system consisting of different molecules. Recent analyses have gone further and treated only the (say) vibrational degrees of freedom of certain molecules as a thermodynamic

system. These analyses are responsible for our modern notion that what is needed for thermodynamic arguments is a separability of time scales. If equilibration within a certain degree of freedom is sufficiently fast while its interaction with other degrees of freedom is significantly slower, then this interaction can be thought of as taking place between different thermodynamic systems, each with its own temperature. In biological systems the appropriate time scales for many interactions are yet to be measured but analyses of the thermodynamics of cellular processes will surely extend our current notions of thermodynamic system to new and biologically important examples.

The implications of the two laws for biological systems have been masterfully analyzed by Erwin Schrödinger in a classic little book called What is Life? [ref Schrodinger]. He posed and answered the question of how living systems manage to maintain their organization rather than yielding to the inexorable law of increase of entropy and loss of order. Schrödinger makes the point that this is possible only because living system feed on negentropy (or equivalently on exergy) taken in with their foodstuffs or, in the case of photosynthesizers, in the form of organized light. The energy from these exergy sources is excreted in a much degraded form and this keeps the living system organized. The molecular details of this mechanism proceed by the production of molecules such as ATP that are rich in free energy and can therefore be used as an exergy currency for cellular processes. Since spontaneous processes are exactly those which degrade exergy, cells can accomplish any needed cellular processes, including those which require input of exergy, by coupling the processes to ATP degradation in such a way that the coupled processes create a net degradation of exergy in keeping with the second law.

The Information Connection

The above-mentioned connection between entropy and randomness has a flip side – the connection between negentropy and information. In fact, as defined in the classic work by Claude Shannon [Brillouin], negentropy is exactly information, the log of the number of possibilities. This fact has allowed thermodynamic analyses of coding algorithms and has resulted in thermodynamics-like theorems regarding the extent to which noisy communication channels can be made immune to the noise levels. Despite these facts, there is little agreement regarding how exactly to merge the modern theories of information and of thermodynamics. This failure will surely be remedied by systems biology where the chemical degrees of freedom carry large amounts of information that must be transmitted nearly free of error from one generation to the next. Determining the exact details of how this can be done remains an important open problem.

Finite-Time Thermodynamics

In the foregoing discussion we mentioned reversible processes and the possibility of approaching them with real processes. In point of fact, heat transfer can only approach reversibility as we slow the process down. This is also true for chemical reactions and for all transport processes whose rates are proportional to generalized forces (differences in

intensive variables) that must be made to approach zero as we approach reversible operation.

This fact has spurred a body of results known collectively as finite time thermodynamics [ref Energy]. The central organizing fact is that once we require a process to proceed at a certain rate, we are not able to make it go close to reversibly. Bounding its rate away from zero can give positive bounds on minimum entropy production (minimum exergy loss) that must accompany the process. Finite-time thermodynamics has focused on maximizing power and on minimizing the dissipation that must accompany a process taking place at a certain rate. This line of investigation is likely to be useful for systems biology where higher efficiency at the cost of lower power is not usually of interest.

While many of the processes so crucial for the bioenergetics of the cell are well understood as measured in comparison to reversible processes, how they compare to optimal processes subject to the constraint of operating at a given rate is not known. In an attempt to pique the readers interest in more specialized monographs [berry, stan, bjarne, wu], we close our discussion by mentioning a couple of the more intriguing results that have come out of this line of investigation.

In finite time there are essentially two extremes of optimal operation corresponding to maximum power and minimum exergy loss. These extremes can be loosely identified with the points of view of an industrialist who wants as much product as possible and of an environmentalist who wants to minimize the expenditure of resources.

The maximum power operation of a process has no exact analog in traditional thermodynamics although it appears that simple and general principles may surround such operation. For example, the efficiency of a heat engine operating at maximum power between a heat source at temperature T_H and a heat sink at temperature T_C is quite generally given by

$$\eta_{MaxP} = 1 - \sqrt{\frac{T_C}{T_H}},$$

a formula whose similarity to Carnot's efficiency is striking.

Minimum exergy loss operation also points to a general principle. It turns out that there is a distance on the set of states of a physical system and the minimum production of entropy is just the square of this distance divided by twice the number of relaxation times for the process. The distance is defined using the second derivative of the system's entropy as a metric matrix³. The result can be generalized to quantify the losses which are incurred during the coevolution of two systems when there is a cost to adjustment and one of the systems follows some prescribed path. This result, known as the horse-carrot theorem, has been applied in thermodynamics, economics, and coding theory [prl, epl, econ, coding]. Its implications for coevolution in biological systems are likely to be interesting.

³ Interpreted in terms of statistical thermodynamics, this metric is equivalent to Fisher's statistical distance used in quantifying genetic drift.

Our final example is more speculative and concerns the question: Is it possible to construct additional functions of state on a par with energy and entropy? One hope for extending the constructions afforded by classical thermodynamics is to focus on a class of processes satisfying some optimality condition such as minimum entropy production subject to some constraints. In this case the optimality condition represents an additional equation holding, and we should be able to use the additional equation to construct a quantity that will be conserved for optimal processes of this type. There will of course be a corresponding inequality for processes that are not optimal in the sense considered. We believe that this will be successfully carried out for biological systems; the development presented above was intended as the required steppingstone toward achieving this goal.