Non-equilibrium thermodynamical principles for chemical reactions with mass-action kinetics

Alexander Mielke\textsuperscript{1,2}, Robert I. A. Patterson\textsuperscript{1}, Mark A. Peletier\textsuperscript{3,4}, D. R. Michiel Renger\textsuperscript{1}

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\textsuperscript{1} Weierstraß-Institut
Mohrenstraße 39
10117 Berlin
Germany
E-Mail: alexander.mielke@wias-berlin.de
robert.patterson@wias-berlin.de,
d.r.michiel.renger@wias-berlin.de

\textsuperscript{2} Institut für Mathematik
Humboldt-Universität zu Berlin
Rudower Chaussee 25
12489 Berlin-Adlershof
Germany

\textsuperscript{3} Department of Mathematics and Computer Science
Technische Universität Eindhoven
P.O. Box 513, 5600 MB Eindhoven
The Netherlands
E-Mail: m.a.peletier@tue.nl

\textsuperscript{4} Institute for Complex Molecular Systems
Technische Universität Eindhoven
P.O. Box 513, 5600 MB Eindhoven
The Netherlands

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Abstract

We study stochastic interacting particle systems that model chemical reaction networks on the microscopic scale, converging to the macroscopic Reaction Rate Equation. One abstraction level higher, we also study the ensemble of such particle systems, converging to the corresponding Liouville transport equation. For both systems, we calculate the corresponding large deviations and show that under the condition of detailed balance, the large deviations enables us to derive a non-linear relation between thermodynamic fluxes and free energy driving force.

1 Introduction

Large-deviation techniques in statistical mechanics facilitate the derivation of important quantities and relations in equilibrium thermodynamics [Var84, Ell85]. Following the ideas of Onsager, we show how similar techniques can be used to say much more about non-equilibrium thermodynamics. We stress here that we study thermodynamically closed systems, i.e. without in- and outflow of matter, that are not in their equilibrium state, and are thus evolving in time. This is distinct from the study of stationary states and evolutions of non-closed systems, which is a different part of non-equilibrium thermodynamics, see for example [DLE01] and [BDSG+09].

1.1 Gradient structures in thermodynamics

The key to understanding the non-equilibrium setting is the notion of gradient flow, which links thermodynamic driving forces to rates of change in the state variables. The mathematical theory of gradient structures has recently seen a significant development and remains a major research topic today (see [AGS08] for an overview). With the insights from [JKO98, Ott01], it is now clear that Fokker-Planck equations have a gradient structure that is driven by the free energy. In this construction, the amount of dissipated free energy between two states is modelled by the squared Wasserstein distance. Similar results for discrete systems show that (linear) chemical reactions have free-energy-driven gradient structures, with a discrete-space counterpart of the Wasserstein distance as dissipation [CHLZ12, Maa11, Mie13].

1.2 Gradient structures from microscopic fluctuations

It is a priori not so clear why these specific dissipation mechanisms should be the right objects from a physical point of view. With this in mind, we recently showed that a large class of gradient
structures can be related to dynamic large-deviation principles of microscopic particle systems [MPR14]. This mimics the equilibrium setting, where the free energy can be related to large-deviation principles as we explain below in Section 2.3. In the same paper, we discussed two principal side-results. The first is the by now well-understood fact that the Wasserstein gradient structure for the Fokker-Planck equation is indeed related to the large deviations of a microscopic particle system [DG87, Sec. 3], [ADPZ11], [MPR14, Sec. 4.2]. The second side-result shows that, from a large-deviation point of view, the discrete-space Wasserstein distance from [Maa11, CHLZ12, Mie13] is not the right dissipation mechanism to model chemical reactions; instead, a nonlinear relation between thermodynamic driving forces and velocities should be used. Such structures can be seen as generalisations of Onsager’s near-equilibrium relations [Ons31].

The case of a single unimolecular reaction was already included in [MPR14, Sec. 4.1]; in Section 2 we use the unimolecular setting as a guiding example to explain the main ideas and their physical implications before we progress to more general chemical reactions.

1.3 Reacting particle system and reaction rate equation

The novelty of the current paper lies in the application of the techniques in [MPR14, Sec. 2, Subsec. 3.3] to the derivation of a previously unknown, energy-driven gradient structure for a general network of coupled chemical reactions,

$$\sum_{y \in Y} \alpha_y(r) A_y = \sum_{y \in Y} \beta_y(r) A_y, \quad r \in R,$$

where $y \in Y$ denotes the species, $r$ denotes the reaction, and $\alpha_y(r)$, $\beta_y(r)$ are the stoichiometric coefficients. Moreover, we not only derive gradient structures for the reaction rate equation, but also for the related Liouville equation, which describes how a collection of such systems evolves. We study microscopic stochastic fluctuations, the many-particle limit equations and the corresponding large-deviation principles. More specifically, we consider microscopic stochastic models where the propensities $k_{\text{fw}}^{(r,v)}(c)$, $k_{\text{bw}}^{(r,v)}(c)$ with which a forward or backward reaction $r$ takes place may depend on the concentrations $c_y$ and the total volume $V$. We restrict our analysis to the case where the limit propensities per unit volume are of the form

$$V^{-1}k_{\text{fw}}^{(r,v)}(c) \to \bar{k}_{\text{fw}}^{(r)} c^{\alpha(r)} \quad \text{and} \quad V^{-1}k_{\text{bw}}^{(r,v)}(c) \to \bar{k}_{\text{bw}}^{(r)} c^{\beta(r)}, \quad \text{as } V \to \infty,$$

using the notation $c^\alpha := \prod_{y \in Y} c_y^{\alpha_y}$. The specific form of the limits in (2) is known as mass-action kinetics. In 3.5 we consider more general propensities, and give a motivation for the mass-action type propensities. If the limits (2) hold, then as $V \to \infty$ the stochastic concentrations converge to the deterministic solution of the reaction rate equation

$$\dot{c}(t) = \sum_{r \in R} (\bar{k}_{\text{fw}}^{(r)} c^{\alpha(r)} - \bar{k}_{\text{bw}}^{(r)} c^{\beta(r)}) (\beta(r) - \alpha(r)).$$

This equation describes the evolution of a deterministic concentration, whenever the initial concentration has a deterministic limit. For the general mathematical theory of chemical reaction networks and limits of microscopic reacting particle systems, we refer the reader to [AK11].
If initially, the concentration is randomly distributed, then the probability \( \rho_t(c) \) of concentrations is transported according to the Liouville equation,

\[
\dot{\rho}_t(c) = \text{div} \left( \rho_t(c) \sum_{r \in R} (k_{fw}^{(r)} c^{\alpha^{(r)}} - k_{bw}^{(r)} c^{\beta^{(r)}}) (\alpha^{(r)} - \beta^{(r)}) \right). \tag{4}
\]

This equation can be found by studying the distribution \( \rho^{(V,N)}(c) \) of concentrations in an ensemble of \( N \) independent particle systems, and then simultaneously passing to the limit \( V, N \to \infty \).

In Section 3 and 4 we show how the microscopic fluctuations lead to energy-driven gradient structures for (3) and (4).

1.4 Model I: chemical master equation

Our work is mainly motivated by two specific models that fit into this framework. The first model is the chemical master equation, which describes the evolution in time of the probability on the number of molecules of each type \( y \). Since we will be taking a large-volume limit, we scale the numbers of molecules by \( V \) and consider the probability distribution on rescaled numbers \( (c_y)_{y \in \mathcal{Y}} = V^{-1} (n_y)_{y \in \mathcal{Y}} \).

The evolution is determined by the propensities \( k_{fw}^{(r,V)}(c) \) and \( k_{bw}^{(r,V)}(c) \), defined by

\[
k_{fw}^{(r,V)}(c) = \alpha^{(r)}! \bar{k}^{(r)} B^{(r)}_\alpha V^{\alpha(y)}(cV), \quad \text{and} \quad k_{bw}^{(r,V)}(c) = \beta^{(r)}! \bar{k}^{(r)} B^{(r)}_\beta V^{\beta(y)}(cV). \tag{5}
\]

where

\[
B^\alpha_V(n) := \begin{cases} \left( \frac{1}{V}\right)^{\alpha(y)} \frac{n!}{\alpha(y)} \frac{\alpha(y)!}{(n-\alpha)!}, & \forall y \in \mathcal{Y}, \, n_y \geq \alpha_y, \\ 0, & \text{otherwise.} \end{cases}
\]

Here we use the convention \( \alpha! := \prod_y \alpha_y! \).

This expression arises from the following reasoning. For the forward reaction \( r \) to take place, a selection \( \alpha^{(r)} \) of the \( n \) molecules should meet, and this selection can be made in \( B^{(r)}_\alpha V^{\alpha(y)}(n) \) different ways. Given such a selection, then assuming well-mixedness, the fraction of time during which this selection of molecules is in a single volume of size 1 is equal to \( V^{-\alpha(y)+1} \); we assume that the reaction rate is proportional to this fraction of time.

For fixed \( V \), the evolution of the probability is described by the Kolmogorov backward equation, also known as the master equation. With the specific choice (5), it is then called the chemical master equation. We will introduce the more general master equation in Section 3.1.

In the limit \( V \to \infty \), we then find the limit propensities (2), yielding the reaction rate equation (3) and its corresponding Liouville equation (4). For the rigorous convergence of the chemical master equation to the reaction rate equation we refer to [Kur72].
1.5 Model II: Smoluchowski-type equation

The second model that fits into the framework of Section 1.3 models systems with coagulation and fragmentation, where (1) is of the form

\[ A_{y_1} + A_{y_2} \rightleftharpoons A_{y_1+y_2}, \quad y_1, y_2 \in \mathcal{Y}. \]

The set of species \( \mathcal{Y} \) may be countably infinite, and should be equipped with an additive structure \( + \). For example, \( \mathcal{Y} = \mathbb{N} \) can be used to describe the length of a single polymer chain. A forward or backward reaction is now indexed by \( r = (y_1, y_2) \in R = \mathcal{Y} \times \mathcal{Y} \) and the stoichiometric coefficients are \( \alpha^{(y_1, y_2)} = \mathbf{1}_{y_1} + \mathbf{1}_{y_2} \) and \( \beta^{(y_1, y_2)} = \mathbf{1}_{y_1+y_2} \). The microscopic forward and backward reaction rate are assumed to be of the form [Mar68, Jeo98]:

\[
\begin{align*}
k_{\text{fw}}^{(y_1, y_2; V)}(c) &= \begin{cases} V \frac{1}{2} \text{Coag}(y_1, y_2)c_{y_1}c_{y_2}, & y_1 \neq y_2, \\ V \frac{1}{2} \text{Coag}(y_1, y_1)c_{y_1}^2 - \frac{1}{2} \text{Coag}(y_1, y_1)c_{y_1}, & y_1 = y_2,
\end{cases} & (6a) \\
k_{\text{bw}}^{(y_1, y_2; V)}(c) &= V \text{Frag}(y_1, y_2)c_{y_1+y_2} & (6b)
\end{align*}
\]

where \( \text{Coag} \) and \( \text{Frag} \) are the coagulation kernel and fragmentation kernel respectively. The factor \( 1/2 \) compensates for double counting of pairs since the order is not significant, and the negative diagonal term, which vanishes asymptotically, subtracts self-coagulations. Clearly, the limit propensities per unit volume are then

\[
\begin{align*}
\lim_{V \to \infty} \frac{1}{V} k_{\text{fw}}^{(y_1, y_2; V)}(c) &= \frac{1}{2} k(y_1, y_2)c_{y_1}c_{y_2} =: \bar{k}_{\text{fw}}^{(r)} c_{y_1}c_{y_2} , & (6a) \\
\lim_{V \to \infty} \frac{1}{V} k_{\text{bw}}^{(y_1, y_2; V)}(c) &= F(y_1, y_2)c_{y_1+y_2} =: \bar{k}_{\text{bw}}^{(r)} c_{y_1+y_2} , & (6b)
\end{align*}
\]

and we again find the reaction rate equation (3) in the deterministic limit, and its corresponding Liouville equation (4). With this limit propensities, the reaction rate equation is now a countable set of ODEs, very similar to the Smoluchowski equation [Smo16, Bar81].

1.6 Overview

This paper presents the part of a recent programme of research that is focussed on applications. A closely associated article [PPR16] deals with the significant technical issues needed to prove all the results rigorously.

The current paper is built up as follows. In Section 2 we use a simple unimolecular reaction to present the main ideas. In particular, we introduce gradient structures and large deviations, and argue why and how gradient structures can be related to the large deviations. In Section 3 we consider general chemical reactions as the limit of stochastically reacting particle systems. We will formally calculate the large deviations, and derive a natural gradient structure for the reaction rate equation. Similarly, in Section 4 we consider the Liouville equation (4) as the limit of the ensemble process, formally calculate the large deviations, and derive a natural gradient structure for the Liouville equation.
2 A guiding example: unimolecular reactions

In a sense, the most simple reaction is the unimolecular reaction

$$A_1 \xrightarrow{k_{fw}} \xleftarrow{k_{bw}} A_2,$$

in a closed system (i.e. no in- and outflow of mass) under constant temperature $T$. For simplicity, we assume a well-mixed solution, so that we can ignore spatial dependence. Let us say that the corresponding energy landscape is as schematically depicted in Figure 1. By Arrhenius’ Law we can couple the reaction rates to the activation energies $E'_1, E'_2$:

$$\bar{k}_{fw} = \exp\left(-\frac{1}{\kappa_B T}E'_1\right) \quad \text{and} \quad \bar{k}_{bw} = \exp\left(-\frac{1}{\kappa_B T}E'_2\right). \quad (7)$$

![Energy landscape for a unimolecular reaction. Note that the process variable is shown here as continuous, to indicate the form of the energy landscape; in the treatment of Section 2, however, the state space is the discrete two-state space $\{A_1, A_2\}$.](image)

2.1 From microscopic to macroscopic description

On a microscopic level, we label each molecule $n \in \{1, \ldots, N\}$ and denote by $X_n(t) \in \mathcal{Y} = \{1, 2\}$ the type of molecule $n$ at time $t \geq 0$. We assume that all molecules react independently. The probability $p(t) = (p_1(t), p_2(t))$ for one molecule $n$ to be of either one of the two types at time $t$ satisfies the (chemical) master equation,

$$\dot{p}(t) = Q^T p(t), \quad Q = \begin{pmatrix} -\bar{k}_{fw} & \bar{k}_{fw} \\ \bar{k}_{bw} & -\bar{k}_{bw} \end{pmatrix}. \quad (8)$$

To pass to a macroscopic description, we consider a volume $V$ containing $n = Vc_{\text{tot}}$ molecules. Let us denote by

$$C^{(v)}(t) := \frac{1}{V} \sum_{i=1}^{n} \mathbf{1}_{X_i^{(v)}(t)}$$

the empirical measure, i.e. $C^{(v)}_y(t)$ is the number of molecules of type $y$ at time $t$ per volume $V$. The propensities in the total volume are now $\bar{k}_{fw}^{(v)}(c) = c_1 V\bar{k}_{fw}$ and $\bar{k}_{bw}^{(v)}(c) = c_2 V\bar{k}_{bw}$, which
yields in average per unit volume, the propensities \( \bar{k}_{fw} c_1 \) and \( \bar{k}_{bw} c_2 \). Therefore, if the initial concentration \( C^{(V)}(0) \) converges to a deterministic concentration, the limit satisfies the reaction rate equation \( \dot{c}(t) = Q^T c(t) \), which coincides with (3). In this simple case where all reactions are independent, the reaction rate equation also coincides with the master equation (8), where \( c(t) = c_{tot} \).

2.2 Free energy via thermodynamic arguments

In what follows we derive the internal energy, entropy and free energy per unit volume.

Since the energy levels corresponding to types \( A_1 \) and \( A_2 \) are \( E_1 \) and \( E_2 \), the internal energy corresponding to a concentration \( c \) is

\[
U(c) = \sum_{y=1}^{2} c_y E_y.
\]

To calculate the total entropy, observe that for fixed \( V \), the number of microstates \( (X_1, \ldots, X_N) \) corresponding to a macrostate \( c \) is \( \frac{(V c_{tot})!}{(V c_1)!(V c_2)!} \), so that the Boltzmann entropy is

\[
\kappa_B \log \frac{(V c_{tot})!}{(V c_1)!(V c_2)!} + \text{const.} \approx -\kappa_B V \sum_{y=1}^{2} c_y \log c_y + \kappa_B V c_{tot} \log c_{tot} + \text{const.},
\]

using Stirling’s formula whenever \( V \) is large. Hence in the thermodynamic limit \( V \to \infty \), the entropy per unit volume converges to

\[
\text{Ent}(c) = -\kappa_B \sum_{y=1}^{2} c_y \log c_y + \kappa_B c_{tot} \log c_{tot} + \text{const.},
\]

and we find for the Helmholtz free energy per unit volume,

\[
F(c) = U(c) - T \text{Ent}(c) = \kappa_B T \sum_{y=1}^{2} c_y \log c_y - \kappa_B T c_{tot} \log c_{tot} + \sum_{y=1}^{2} c_y E_y + \text{const.} \quad (10)
\]

2.3 Free energy via large deviations

We now explain how the free energy (10) can also be derived via large deviations around the macroscopic equilibrium state. In macroscopic equilibrium, all molecules \( X_1, \ldots, X_N \) are independent and identically distributed according to the stationary measure for (8),

\[
p^* := \frac{1}{k_{fw} + k_{bw}} \left( \frac{k_{bw}}{k_{fw}} \right).
\]

Again, by the Law of Large Numbers, \( C^{(V)} \) converges to a deterministic concentration \( c^* = c_{tot} p^* \) as \( V \to \infty \). Stochastic deviations around \( c^* \) are characterised by Sanov’s Theorem [DZ87,
If we substitute (11) and (7) in (13), and use $E'_y + E_y = E_r$ (see Figure 1) together with $c_1 + c_2 = c_{tot}$, we find:

$$S(c | c^*) = 2 \sum_{y=1}^{2} c_y \log \frac{c_y}{c^*_y} - c_{tot} \log c_{tot} + \frac{1}{\kappa_B T} c_1 E'_1 + \frac{1}{\kappa_B T} c_2 E'_2.$$

Here the last concentration-independent term can be identified with the additive constant in (10), tailored to ensure that the minimum is zero. Hence we see that the large-deviation rate $S$ is indeed the free energy $F$, non-dimensionalised with the constant factor $(\kappa_B T)^{-1}$. Correspondingly, it is not uncommon in the literature to identify the free energy with the large-deviation rate around equilibrium, see for example [OM53, Spo91, DLE01].

In this paper, we show a similar relation between the large deviations around the expected trajectory on one hand, and the free-energy-driven gradient structure on the other. The latter concept is best understood through Onsager’s near-equilibrium thermodynamics.

### 2.4 Near-equilibrium thermodynamics

Let us now discuss Onsager’s famous argument of [Ons31, Sec. 3] to derive a thermodynamic description of the evolution near equilibrium. One of the main ingredients is the vector $\nabla F(c)$, often called the thermodynamic force, affinity, or the thermodynamical conjugate to the displacement. For small displacements $c - c^*$, we have

$$\frac{\partial}{\partial c_y} F(c) = \kappa_B T (\log \frac{c_y}{c^*_y} + 1) \approx \kappa_B T \frac{c_y - c^*_y}{c^*_y}. \quad (14)$$

With this approximation, the evolution of the concentration can be directly related to the thermodynamic force:

$$\dot{c}(t) \overset{8}{=} Q^T c(t) \overset{14}{=} -K \nabla F(c(t)),$$  \quad (15)

if we define the Onsager matrix $K_{y_1 y_2} := - (\kappa_B T)^{-1} c^*_y Q_{y_1 y_2}$. Because of the detailed-balance condition,

$$c^*_1 Q_{12} = \bar{k}_{fw} c^*_1 = \bar{k}_{bw} c^*_2 = c^*_2 Q_{21}, \quad (16)$$
which is always satisfied for two-state irreducible Markov chains (8), it follows that the matrix \( K \) is symmetric. In this context, the symmetry (16) of the matrix \( K \) is known as the **Onsager** reciprocal relations. Moreover, it is easily seen that, if we require that the free energy decreases along solutions, \( K \) must be positive semi-definite, since

\[
0 \geq \frac{d}{dt} F(c(t)) = \nabla F(c(t))^T \dot{c}(t) \overset{(15)}{\approx} - \nabla F(c(t))^T K \nabla F(c(t)).
\]

The equation (15) with a symmetric and positive semi-definite matrix \( K \) is the first instance that we encounter of a gradient structure. This is thermodynamically very important, not only because it implies that the free energy must decrease, but also because it precisely shows how the gradient of the free energy drives the system towards its equilibrium.

One of Onsager’s crucial insights was that the macroscopic gradient structure, i.e. the symmetry and semidefiniteness of \( K \), is related to the microscopic notion of detailed balance. This insight plays an essential role in our paper as well.

### 2.5 Gradient structures

Naturally, the structure (15) is valid only in approximation near equilibrium. Away from equilibrium, as we will see, we must allow for a more general class of gradient structures.

In some cases the matrix or operator \( K \) may depend on the state \( c \). In [Maa11, Mie13, CHLZ12] it was revealed that the full evolution (8), i.e. not only close to equilibrium, can be written as

\[
\dot{c}(t) = -K(c(t)) \nabla F(c(t)),
\]

where \( K(c) \) is the symmetric, positive semi-definite matrix

\[
K(c) := \frac{1}{k_B T} c_1^2 k_{fw} \Lambda \left( \frac{c_1}{c_2}, \frac{c_2}{c_1} \right) \begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix},
\]

with logarithmic mean \( \Lambda(x, y) = (x - y) / (\log x - \log y) \) for \( x \neq y \) and \( \Lambda(x, x) = x \).

This is however not the only possible gradient structure that describes (8). In [MPR14] we discovered that (8) can also be written as a nonlinear relation between forces and velocities:

\[
\dot{c}(t) = \nabla_\xi \Psi^* \left( c(t), -\nabla F(c(t)) \right),
\]

where

\[
\Psi^*(c, \xi) := \sqrt{c_1 c_2 k_{lw} k_{bw}} \left( \cosh(\xi_1 - \xi_2) - 1 \right),
\]

and (throughout this paper),

\[
\tilde{F}(c) := \frac{1}{2k_B T} F(c) = \frac{1}{2} S(c \mid c^*),
\]

and \( S \) is the relative entropy (13). We will comment on the factor \( 1/2 \) in the Discussion in Section 2.9.
Just like the symmetry and positive semi-definiteness of $K(c)$ in (17), the following set of conditions on $\Psi^*$ make (20) into a \textit{generalised gradient system} such that $\tilde{F}(c(t))$ decreases in time (see Section 2.6):

\begin{align*}
\Psi^*(c, \cdot) & \text{ is convex for all } c, \tag{22a} \\
\Psi^* & \text{ is non-negative,} \tag{22b} \\
\Psi^*(c, 0) & \equiv 0. \tag{22c} \\
\Psi^*(c, \xi) = \Psi^*(c, -\xi) & \text{ for all } c, \xi. \tag{22d}
\end{align*}

In the next Section we explain how these conditions can be interpreted physically.

We see that there are at least two gradient structures that describe the same evolution (8). The question is then which is the ‘right’ structure from a physical point of view. In order to answer this question, we first need to introduce a different formulation of (17) and (19).

\subsection*{2.6 Energy-dissipation balance}

Let us first look at the linear structure (17). Observe that the matrix $K(c)$ defines state-dependent norms on thermodynamic forces and on velocities:

\[ \|\xi\|^2_{K(c)} := \xi^T K(c) \xi \quad \text{and} \quad \frac{1}{2} \|v\|^2_{K(c)^{-1}} := \sup_{\xi \in \mathbb{R}^2} \xi \cdot v - \frac{1}{2} \|\xi\|^2_{K(c)^{-1}}. \]

Then (17) can also be formulated as an \textit{energy-dissipation balance}:

\[ \frac{1}{2} \|\dot{c}(t)\|^2_{K(c(t))^{-1}} + \frac{1}{2} \|\nabla F(c(t))\|^2_{K(c(t))} + \frac{d}{dt} F(c(t)) = 0. \tag{23} \]

Indeed, by the definition of $\frac{1}{2} \|\cdot\|^2_{K(c)^{-1}}$ as a Legendre dual and the chain rule $\frac{d}{dt} F(c(t)) = \nabla F(c(t)) \cdot \dot{c}(t)$, the left-hand side in (23) is non-negative for any curve $c(t)$, and zero if and only if the curve satisfies the equation (17). Similarly, for the non-linear structure (19), we define the Legendre dual $\Psi(c, v) := \sup_{\xi \in \mathbb{R}^2} \xi \cdot v - \Psi^*(c, \xi)$, and the corresponding energy-dissipation balance becomes

\[ \Psi(c(t), \dot{c}(t)) + \Psi^*(c(t), -\nabla \tilde{F}(c(t))) + \frac{d}{dt} \tilde{F}(c(t)) = 0. \tag{24} \]

As the name suggests, (24) postulates a balance between the production $-\frac{d}{dt} \tilde{F}$ and the dissipation $\Psi + \Psi^*$ of free energy. With this in mind, we can understand the meaning of the conditions (22). First of all, (22a) implies that an increase in velocity or force results in more dissipation. Secondly, the last two conditions (22b) and (22c) imply that $\Psi(c, 0) + \Psi^*(c, 0) = 0$, so that no energy is dissipated if the system does not evolve. Thirdly, (22b) and (22c) imply that $\Psi + \Psi^* \geq 0$ so that in addition with (24), the free energy must be non-increasing. Finally, the symmetry (22d) means that the dissipation is invariant under time reversal.

Recall that we aim to settle which of the two gradient structures (17), (19) can be physically justified. Instead, we can now look at the balances (23) and (24). However, since both (23) and
(24) are zero for the macroscopic trajectory \( c(t) \) solving (8), we can not distinguish between the two structures by studying this curve only. In order to see the difference, we need to study microscopic deviations around this curve; such deviations should be related to a positive energy discrepancy in the balances (23), (24).

2.7 Dynamic large deviations

To study microscopic fluctuations, let us go back to the concentration \( C(V(t)) \) defined by (9).

The probability that this stochastic process deviates from the expected solution between \( t = 0 \) and \( t = T \) satisfies a large-deviation principle [Fen94, MPR14]

\[
\text{Prob} \left( C(V) \approx c \right) \sim e^{-VI_0(c(0)) - \int_0^T L(c(t),\dot{c}(t)) \, dt} \quad \text{as } V \to \infty,
\]

where \( L \) is defined through the Legendre transform \( L(c,v) = \sup_{\xi \in \mathbb{R}^2} \xi \cdot v - H(c,\xi) \), and

\[
H(c,\xi) = \bar{k}_{fw} c_1(e^{\xi_2 - \xi_1} - 1) + \bar{k}_{bw} c_2(e^{\xi_1 - \xi_2} - 1).
\]

Large-deviation results of the type (25) are generally hard to prove. We therefore dedicate a separate paper on the rigorous proof, see [PPR16]. Nevertheless, at least formally, they can be calculated in a direct way by the Feng & Kurtz method [FK06]. We will carry out these formal calculations for the more general chemical reactions in Section 3.3.

2.8 Gradient structure induced by large deviations

The cost function \( L \) can be immediately connected to the free-energy discrepancy in formulation (24). Let us assume that there are dual potentials \( \Psi, \Psi^* \) and a functional \( \tilde{F} \) such that

\[
L(c,s) = \Psi(c,s) + \Psi^*(c,-\nabla \tilde{F}(c)) + \nabla \tilde{F}(c) \cdot s,
\]

where we continue to use \( s \) as a placeholder for \( \dot{c} \). Indeed, this would show that (i) the optimal curve for which \( L(c(t),\dot{c}(t)) = 0 \) is the solution of the Reaction Rate Equation (3), and (ii) the stochastic cost to deviate from this curve is exactly the discrepancy in the energy-dissipation balance. In this sense, the gradient structure would be in accordance with the large deviations.

From (27) it immediately follows that, given \( L \) and its Legendre transform \( H \), the \( \tilde{F} \) and \( \Psi, \Psi^* \) can be found through (see [MPR14, Th. 2.3]):

\[
\nabla \tilde{F}(c) = \nabla_s L(c,0) \quad \text{and} \quad \Psi^*(z,\xi) = H(c,\nabla \tilde{F}(c) + \xi) - H(c,\nabla \tilde{F}(c)),
\]
and $\Psi$ is the Legendre transform of $\Psi^*$. For the unimolecular reaction, we have (26), and thus

$$\tilde{F}(c) = \frac{1}{2\kappa_B T} F(c),$$

$$\Psi^*(c, \xi) = \sqrt{c_1 c_2 k_w \bar{k}_{bw}} \left( \cosh(\xi_1 - \xi_2) - 1 \right),$$

$$\Psi(c, s) = \sqrt{c_1 c_2 k_w \bar{k}_{bw}} \left( \cosh^* \left( \frac{s_1 - s_2}{4 \sqrt{c_1 c_2 Q_{12} Q_{21}}} \right) + 1 \right),$$

where $\cosh^*(z) = \sup_{x \in \mathbb{R}} x z - \cosh(x) = s \arcsin(s) - \sqrt{1 + s^2}$ is the Legendre transform of the hyperbolic cosine.

### 2.9 Discussion

We see that there is one unique generalised gradient structure for which (27) holds. This gradient structure is indeed, apart from the constant factor $(2\kappa_B T)^{-1}$ driven by the free energy $F$. Naturally, the factor $\kappa_B T$ is needed to nondimensionalise the free energy; after all, the energy discrepancy (24) is measured in units of entropy (per unit time). The required factor $1/2$ in (29) is more subtle. Without going too deep into the reasons, let us mention briefly that in Gallavotti-Cohen-type relations, the free energy is measured as the difference in logarithmic probability between evolving forward in time and backward in time. Therefore, characterising systems that evolve forward in time rather than not evolve at all requires the factor $1/2$ in front of the free energy. See [MPR14, Subsec. 1.6] and [MRV00] for more details. We will see that in the more complex settings of this paper, we will always need to work with the scaled free energy $\tilde{F}(c)/2$.

Furthermore, observe that the first relation in (28) really encodes a condition, since in general $\nabla_s L(c, 0)$ may not be the gradient of some function with respect to $c$. In [MPR14, Th. 3.3 & Th. 3.7] we proved that this condition is always satisfied if the microscopic detailed balance condition is satisfied (in fact, detailed balance is a necessary condition if one requires in addition that the dissipation potential must be symmetric: $\Psi(c, s) = \Psi(c, -s)$). This can be seen as the equivalent of Onsager's famous relation between microscopic detailed balance and the macroscopic reciprocal relation for near-equilibrium thermodynamics, as we discussed above in Section 2.4. Again, for Markov chains on a two-state space, detailed balance always holds, but this is no longer true for more complicated situations. Besides, for non-linear evolutions, a generalisation of detailed balance (16) is needed. In the context of this paper, we can always use (28) to derive the appropriate form of that generalised detailed balance condition.

Moreover, $\Psi^*$ has a simple expression (28), but $\Psi$ is defined through a Legendre transform, which may not always yield a convenient explicit expression. For more complicated systems, we will simply focus on $\Psi^*$ and define $\Psi$ implicitly. The same can be said about large-deviation cost functions $L$, which are often derived as the Legendre transform of some explicitly given function $H$.

To conclude, we see that, if we require (27), the physically correct gradient structure is the $\cosh$-structure (19) rather than the linear structure (17).
3 Gradient structure for the reaction rate equation

We now place ourselves in the setting of a general network of chemical reactions

\[\sum_{y \in \mathcal{Y}} \alpha^{(r)}_y A_y \equiv \sum_{y \in \mathcal{Y}} \beta^{(r)}_y A_y, \quad r \in R,\]

on an arbitrary finite or countable state space \(\mathcal{Y}\).

It was shown in [Yon08, Mie11] that under the condition of detailed balance for an equilibrium state \(c^*\) with \(c^*_y > 0\) (see Section 3.2 below), the reaction rate equation (3) can be written as a linear gradient flow

\[\dot{c}(t) = -K(c(t)) \nabla F(c(t)),\]

where \(F\) is the free energy and \(K(c)\) is a generalisation of (18) for non-linear reactions.

Similarly to what we concluded for the unimolecular setting, we will argue that this linear gradient structure is not consistent with the large deviations of the ‘natural’ reacting particle system. We first explain the particle system in more detail. After this we introduce flow-invariant subsets of the state spaces that we will need. Then we derive the large deviations in a formal manner, and apply the theory of [MPR14] to find a corresponding notion of detailed balance and the corresponding non-linear gradient structure.

3.1 Reacting particle system

We first describe the stochastically reacting particle system from Section 1.3 in more detail. Contrary to the unimolecular setting of Section 2, we now have interaction between particles. To avoid the explicit labeling of particles, which would require relabeling at each reaction, we again describe the state of the system by the empirical measure \(C^{(V)}(t) := V^{-1} \sum_{i=1}^{N(t)} 1_{X_i(t)}\), where the number of particles \(N(t)\) may now vary over time, cf. (9). With propensities \(k_{fw}^{(r,v)}(C^{(V)})\), a reaction \(r\) takes place, which amounts to updating \(C^{(V)} \to C^{(V)} - \frac{1}{V} \alpha^{(r)} + \frac{1}{V} \beta^{(r)}\), and analogously for the backward reactions. The random concentration \(C^{(V)}(t)\) is then a Markov process in \(V^{-1} \mathbb{N}_0^{\mathcal{Y}}\) with generator

\[(Q^{(V)}\Phi)(c) = \sum_{r \in R} \left[ k_{fw}^{(r,v)}(c) \left( \Phi(c - \frac{1}{V} \alpha^{(r)} + \frac{1}{V} \beta^{(r)}) - \Phi(c) \right) \right.\]

\[\left. + k_{bw}^{(r,v)}(c) \left( \Phi(c - \frac{1}{V} \beta^{(r)} + \frac{1}{V} \alpha^{(r)}) - \Phi(c) \right) \right], \quad (31)\]

or equivalently, the probability \(P_t^{(V)}(c) = \text{Prob} \left( C^{(V)}(t) = c \right)\) satisfies the master equation

\[\dot{P}_t^{(V)}(c) = (Q^{(V)}T P^{(V)})(c)\]

\[= \sum_{r \in R} \left[ k_{fw}^{(r,v)}(c + \frac{1}{V} \alpha - \frac{1}{V} \beta) P_t^{(V)}(c + \frac{1}{V} \alpha - \frac{1}{V} \beta) - k_{fw}^{(r,v)}(c) P_t^{(V)}(c) \right.\]

\[+ k_{bw}^{(r,v)}(c + \frac{1}{V} \beta - \frac{1}{V} \alpha) P_t^{(V)}(c + \frac{1}{V} \beta - \frac{1}{V} \alpha) - k_{bw}^{(r,v)}(c) P_t^{(V)}(c) \right]. \quad (32)\]
Using (2), the generator $Q^{(V)}$ converges as $V \to \infty$ to
\[
(Q^{(\infty)}\Phi)(c) = \sum_{r \in R} \left[ \tilde{k}_{fw}^{(r)} c^{(r)} (\beta^{(r)} - \alpha^{(r)}) \cdot \nabla \Phi(c) + \tilde{k}_{bw}^{(r)} c^{(r)} (\alpha^{(r)} - \beta^{(r)}) \cdot \nabla \Phi(c) \right].
\]
Since this generator depends on the test function $\Phi$ through $\nabla \Phi$ only, it describes the deterministic process satisfying the reaction rate equation (3) whenever the initial value $C^{(\infty)} = c(0)$ is deterministic. This can be seen by making the ansatz $P_t = 1_{c(t)}$ for some curve $c(t)$, and then writing
\[
\dot{c}(t) \cdot \nabla \Phi(t) = \frac{d}{dt} \Phi(c(t)) = \frac{d}{dt} \int_{\mathbb{R}^Y} \Phi(\dot{c}) P_t(\dot{c}) d\dot{c}
\]
\[
= \int_{\mathbb{R}^Y} (Q^{(\infty)}\Phi)(\dot{c}) P_t(\dot{c}) d\dot{c} = (Q^{(\infty)}\Phi)(c(t)),
\]
which is indeed true if $c(t)$ satisfies the reaction rate equation (3). Naturally, if the initial condition is not deterministic, we can always approximate $P_0(\dot{c})$ by a sum of deterministic initial conditions $\frac{1}{N} \sum_{I=1}^{N} 1_{c(t)(0)}(\dot{c})$ to get that the probability $P_t$ satisfies the Liouville equation (4).

**Remark 3.1.** It was shown in [MM15a, MM15b] that the chemical master equation (i.e. (32) with propensities (5)) automatically satisfies the detailed balance condition for the steady state

\[
P^{(V)*}(c) = \prod_{y \in \mathcal{Y}} e^{-c_y V} \frac{(c_y V_c^y)^{c_y}}{(V_c^y)!}, \quad c \in \frac{1}{V} \mathbb{N}_0^\mathcal{Y},
\]

and that hence, the chemical master equation also has a linear gradient structure. \hfill \Box

### 3.2 Stoichiometric simplices and mass conservation

In most cases the reaction directions $\alpha^{(r)} - \beta^{(r)}, r \in R$, do not span the full space $\mathbb{R}^\mathcal{Y}$, which in chemistry is often attributed to atomic mass conservation, as we will now explain. First observe that if the initial condition is deterministic $C^{(V)}(0) = c(0)$, then the process will almost surely lie in the space $c(0) + \text{Ran } B$, where $B$ is the matrix

\[
B := [\beta^{(1)} - \alpha^{(1)} \quad \beta^{(2)} - \alpha^{(2)} \quad \ldots ].
\]

Similarly, solutions of the reaction rate equation (3) lie in $c(0) + \text{Ran } B$. These subspaces, fixed by $c(0)$, encode conserved quantities, which are related to the matrix $B$. More specifically, there are $\omega := \dim \text{Ker}(B^T)$ conserved quantities, and we collect all of them in a matrix $M \in \mathbb{R}^{\omega \times \mathcal{Y}}$, in the sense that $MB = 0$, and the rows of $M$ are linearly independent. Indeed, this implies that $MC^{(V)}(t) = MC(0)$ for the reacting particle process and $MC(t) = MC(0)$ for the reaction rate equation.

Under reasonable conditions on $\alpha^{(r)}, \beta^{(r)}$ and $\tilde{k}_{bw}^{(r,\mathcal{Y})}$ (a sufficient set of technical assumptions is given in [PPR16]), the random concentrations $C^{(V)}(t)$ as well as the limit concentrations $c(t)$ remain non-negative and summable, i.e. they lie in

\[
I_+(\mathcal{Y}) := \{ c \in \mathbb{R}^\mathcal{Y} : c \geq 0 \text{ and } \sum_{y \in \mathcal{Y}} c_y < \infty \}. 
\]
For any \( q \in \mathbb{R}^\omega \) we define the stoichiometric simplex (sometimes called the positive stoichiometric compatibility class, see [AK11, Sec. 3.5]):

\[
l^1_q(\mathcal{Y}) := \{ c \in l^1_+(\mathcal{Y}) : Mc = q \}.
\]

If the initial concentration is deterministic, \( C(V)(0) = c(0) \), then by the structure of the process (31), the concentration \( C(V)(t) \) will remain in the set \( l^1_{Mc(0)}(\mathcal{Y}) \cap \frac{1}{V} \mathbb{N}^m_0 \). Similarly, the simplex \( l^1_{Mc(0)}(\mathcal{Y}) \) is flow-invariant for the reaction rate equation (3). The whole state space \( l^1_+(\mathcal{Y}) \) decomposes into a countable number of sets of this form, thus producing a decomposition into irreducible components, cf. [AK11, MM15b].

For simplicity, we only allow for mass-conserving reactions, i.e. there exists a vector \( m \in \mathbb{R}^\mathcal{Y} \) with \( \inf_{y \in \mathcal{Y}} m_y > 0 \) such that \( m = M^T w \) for some weight vector \( w \in \mathbb{R}^m \). With this assumption, the stoichiometric simplices \( l^1_q(\mathcal{Y}) \) are automatically compact, see [PPR16, Sec. 2.1].

The matrix \( M \) has a natural interpretation in terms of atomic mass conservation. For example, for the reaction \( 2 \text{H}_2 + \text{O}_2 \gtrless 2\text{H}_2\text{O} \) we have three species \( \mathcal{Y} = (\text{H}_2, \text{O}_2, \text{H}_2\text{O}) \) and we find two conserved quantities:

\[
M c(t) = \begin{pmatrix} 2 & 0 & 2 \\ 0 & 2 & 1 \end{pmatrix} \begin{pmatrix} c_{\text{H}_2}(t) \\ c_{\text{O}_2}(t) \\ c_{\text{H}_2\text{O}}(t) \end{pmatrix} = \left( \frac{\# \text{H-atoms}}{V}, \frac{\# \text{O-atoms}}{V} \right) = q
\]

along solutions of the corresponding reaction rate equation for this single reaction. Another example is the semiconductor reaction \( \emptyset \gtrless N + P \), where pairs of electrons and holes are generated or annihilated. Indeed, \( M = \begin{bmatrix} 1 & -1 \end{bmatrix} \) corresponds to the electric charge conservation, but the sets \( l^1_q(\mathcal{Y}) \) are unbounded intervals and hence no longer compact. Note that there does not exist a strictly positive conserved quantity, so that this case is ruled out by our mass conservation assumption.

The stoichiometric simplices also play an important role in determining the free energy functional. Indeed, the expression (21) for the (scaled) free energy includes a steady state \( c^* \), but we can not expect a globally unique steady state as the stoichiometric simplices are flow-invariant. Even within each stoichiometric simplex there can be more than one steady state, which typically occurs for autocatalytic reactions. However, one can often assume that there exists a strictly positive \( c^{\bowtie} \in \mathbb{R}^\mathcal{Y}_+ \) for which detailed balance holds:

\[
\tilde{k}_{\text{fw}}^{(r)} c^{\bowtie \alpha(r)} = \tilde{k}_{\text{bw}}^{(r)} c^{\bowtie \beta(r)} \quad \text{for all } r \in \mathcal{R}.
\]

Under this condition, each stoichiometric simplex \( l^1_q(\mathcal{Y}) \) has a unique strictly positive steady state \( c^{*(q)} \), and each of these states are in detailed balance themselves [GH97, MHM14]. Therefore, the initial condition \( c(0) \) with \( Mc(0) = q \) fixes a unique reversible steady state \( c^{*(q)} \) within the same stoichiometric simplex \( l^1_q(\mathcal{Y}) \), which we will use to define the free energy \( \tilde{F} \).

**Remark 3.2.** Since the probability of jumping outside \( l^1_{Mc(0)}(\mathcal{Y}) \) is zero, the large deviations satisfy

\[
L(c, s) = \infty \quad \text{for all } s \notin \text{Ran } B \quad \text{and} \quad H(c, M^T q) = 0 \quad \text{for all } q \in \mathbb{R}^\omega.
\]
For the corresponding gradient structure this will imply that $\Psi, \Psi^*$ are degenerate in the sense that

$$\Psi(c, s) = \infty \quad \text{for all } s \notin \text{Ran } B \quad \text{and} \quad \Psi^*(c, M^Tq) = 0 \quad \text{for all } q \in \mathbb{R}^w.$$  

In fact, the same will be true for the linear gradient structure (30).

**Remark 3.3.** We stress that the detailed-balance condition (33) is on invariant concentrations, and not on invariant probabilities as common in the probabilistic literature. Nevertheless, detailed balance is closely connected to probabilistic detailed balance of the microscopic system. This notion is well-known in the literature, see for example [dGM84, ÉT89, Jos14, MM15a], and is related to the large deviations as we will see below. Observe that we require a condition on the limit rates $\tilde{k}_{iw, bw}^{(r)}$ only, so that it suffices that the microscopic system is approximately in probabilistic detailed balance.

### 3.3 Dynamic large deviations

As mentioned in Section 2.7, we are only interested in fluctuations due to the stochastic dynamics, and will therefore assume that

**The initial concentrations** $C^{(V)}(0) = c^{(V)}(0)$ are deterministic and converge to some $c(0)$ within the stoichiometric simplex $I_{Mc(0)}^1$.

(3.35)

This condition kills initial fluctuations, so that $I_0$ in (25) equals $+\infty$ when the initial concentration deviates from $c(0)$. Therefore we can always assume that the fixed initial condition holds, and we henceforth omit $I_0$.

We provide the rigorous mathematical proof of the large-deviation principle in the companion paper [PPR16, Sec. 3]. We now use the method of Feng & Kurtz [FK06, Par. 8.6.1.2] to formally calculate the large-deviation rate. We divide the procedure into four steps.

1. For fixed $V$, recall the generator (31) and define the non-linear generator, acting on test functions $\Phi$,

   $$(H^{(V)})\Phi(c) := \frac{1}{V}e^{-V\Phi(c)}(Q^{(V)}e^{V\Phi})(c)$$

   $$= \sum_{r \in R} \left[ \frac{k_{iw}^{(r,V)}}{V} \left( e^{V\Phi(c) - \frac{1}{V}\alpha^{(r)}} + \frac{1}{V}\beta^{(r)} - V\Phi(c) - 1 \right) \right]$$

   $$+ \frac{k_{bw}^{(r,V)}}{V} \left( e^{V\Phi(c) - \frac{1}{V}\beta^{(r)}} + \frac{1}{V}\alpha^{(r)} - V\Phi(c) - 1 \right).$$

2. Using the mass-action assumption (2), we find $H^{(V)} \to H$ as $V \to \infty$, where

   $$\left( H\Phi \right)(c) = \sum_{r \in R} \left[ \tilde{k}_{iw}^{(r)} e^{\alpha^{(r)} \cdot \nabla\Phi(c) - 1} + \tilde{k}_{bw}^{(r)} e^{\beta^{(r)} \cdot \nabla\Phi(c) - 1} \right].$$
3 We verify that the limit non-linear generator above indeed depends on \( \Phi \) through \( \xi := \nabla \Phi(c) \) only; this condition is consistent with the fact that the limit process satisfies a Liouville transport equation, and is hence deterministic. We then define, with a slight abuse of notation,

\[
H(c, \xi) = \sum_{r \in R} \left[ \frac{\xi}{k_{\text{fw}}(r)} e^{(\beta(r) - \alpha(r)) \cdot \xi} + \frac{\xi}{k_{\text{bw}}(r)} e^{(\alpha(r) - \beta(r)) \cdot \xi} \right].
\]  

(36)

4 Finally, we define the Legendre transform of this function:

\[
L(c, s) = \sup_{\xi \in \mathbb{R}^y} \xi \cdot s - H(c, \xi).
\]

(37)

The function \( L \) then defines the large-deviation rate that we are after, see below. We stress this function generally does not have an explicit formulation. Nevertheless, many of its properties can be studied through the explicitly known Legendre dual \( H(x, \xi) \).

We now reiterate the rigorous result from our associated mathematical paper:

**Theorem 3.4 ([PPR16]).** Let Assumption (35) and [PPR16, Assumptions 3.1] be satisfied. Then the sequence \( (C^{(V)}(t))_{t=0}^T \) satisfies a large-deviation principle of the form

\[
\text{Prob} \left( C^{(V)}(\cdot) \approx c(\cdot) \right) \sim e^{-V \int_0^T L(c(t), \dot{c}(t)) \, dt} \quad \text{as } V \to \infty,
\]

(38)

where \( L \) is given by (36) and (37).

For the details of the technical assumptions, the spaces and topologies, we refer the interested reader to the referenced paper.

### 3.4 Gradient structure from large deviations

We will now construct a gradient structure for the reaction rate equation (3) from the large-deviation cost function \( L \). More specifically, as we explained in Section 2.8, we aim to find a dissipation potential pair \( \Psi, \Psi^* \) that satisfy (22a–d) and (27), i.e.

\[
L(c, s) = \Psi(c, s) + \Psi^*\left(c, -\nabla \tilde{F}(c)\right) + \nabla \tilde{F}(c) \cdot s.
\]

In [MPR14, Sect. 2] it was discovered that the existence of such potentials is equivalent to the time-reversibility of \( L \) or \( H \), i.e.

\[
L(c, s) - L(c, -s) = 2 \nabla \tilde{F}(c) \cdot s, \quad \text{or equivalently,}
\]

\[
H(c, \nabla \tilde{F}(c) + \xi) = H(c, \nabla \tilde{F}(c) - \xi)
\]

(39)

for all \( c, s \) or for all \( c, \xi \) respectively. Observe that this condition fixes the driving force \( \nabla \tilde{F} \) uniquely.
For completeness, let us briefly recall from [MPR14] how the dissipation potentials $\Psi, \Psi^*$ can be found once the time-reversibility condition (39) holds. Assume that (27) holds, and calculate the Legendre transform of this expression at $\nabla \tilde{F}(c) + \xi$, yielding

$$H(c, \nabla \tilde{F}(c) + \xi) = \sup_v \xi \cdot v - \Psi(c, v) - \Psi^*(c, -\nabla \tilde{F}(c)) = \Psi^*(c, \xi) - \Psi^*(c, \nabla \tilde{F}(c)).$$

Since we require (22c), we must have $H(c, \nabla \tilde{F}(c)) = -\Psi^*(c, \nabla \tilde{F}(c))$, so that the line above can be written as

$$\Psi^*(c, \xi) = H(c, \nabla \tilde{F}(c) + \xi) - H(c, \nabla \tilde{F}(c)). \quad (40)$$

It is easily checked that this $\Psi^*$ indeed satisfies all conditions (22a–d). For the ‘and only then’-part, condition (22d) together with (40) immediately implies that $H$ is time-reversible. Finally, from the dual potential $\Psi^*$ we find the primal potential $\Psi$ through a Legendre transformation.

Let us now apply these arguments to the case where $L$ and $H$ are associated to the large deviations of the reacting particle system, as derived in (37) and (36). Fix an initial condition $c(0)$ and assume from now on that the detailed balance condition (33) holds for some $c^\circ$. As explained in Section 3.2, we then have a unique steady state $c^*$ in the stoichiometric simplex $\mathcal{V}_{\text{Mec}}(\mathcal{Y})$ satisfying detailed balance $\tilde{k}^{(r)}_{\text{fw}} c^{(r)} = \tilde{k}^{(r)}_{\text{bw}} c^{(r)}$. We devise the calculation into three steps:

1. We first check that the free energy indeed makes $L$ and $H$ time-reversible. Observe that it is sufficient for (39) to require that:

$$\tilde{k}^{(r)}_{\text{fw}} c^{(r)} e^{(\beta^{(r)} - \alpha^{(r)}) \cdot (\nabla \tilde{F}(c) + \xi)} = \tilde{k}^{(r)}_{\text{bw}} c^{(r)} e^{(\beta^{(r)} - \alpha^{(r)}) \cdot (\nabla \tilde{F}(c) - \xi)}$$

which is equivalent to

$$(\beta^{(r)} - \alpha^{(r)}) \cdot (2 \nabla \tilde{F}(c) - \log c) = \log \frac{\tilde{k}^{(r)}_{\text{fw}}}{\tilde{k}^{(r)}_{\text{bw}}} = (\beta^{(r)} - \alpha^{(r)}) \cdot (- \log c^*) \quad \text{for all } r, c.$$

But then, up to vectors in $\text{Ker}(B^T)$, i.e. perpendicular to all $\beta^{(r)} - \alpha^{(r)}$, and up to an integration constant, this is implied by

$$\tilde{F}(c) = \frac{1}{2} \sum_{y \in \mathcal{Y}} (c_y \log \frac{c_y}{c^*_y} - c_y + c^*_y). \quad (41)$$

Therefore, we see that time-reversibility (39) holds with the choice (41).

2. By [MPR14, Th. 2.1], the time-reversibility implies that there exist dual dissipation potentials $\Psi, \Psi^*$ satisfying (22) and (27). We now calculate the dual dissipation potential $\Psi^*$ explicitly. Since $H$ is a sum over all forward and backward reactions, we can also write

$$\Psi^*(c, \xi) = \tilde{k}^{(r)}_{\text{fw}} e^{(\beta^{(r)} - \alpha^{(r)}) \cdot (\nabla \tilde{F}(c) + \xi)} - e^{(\beta^{(r)} - \alpha^{(r)}) \cdot \nabla \tilde{F}(c)}$$

which is given by

$$\Psi^*(c, \xi) = A^{(r)}(c) (e^{(\beta^{(r)} - \alpha^{(r)}) \xi} - 1),$$

$$\Psi^*(c, \xi) = A^{(r)}(c) (e^{(\alpha^{(r)} - \beta^{(r)}) \xi} - 1),$$
where because of detailed balance, the factor \( A^{(r)}(c) := \sqrt{\bar{E}^{(r)}_w \bar{E}^{(r)}_b} e^{\alpha^{(r)} + \beta^{(r)}} \) is the same for the forward and the backward reaction. Combining all terms yields the symmetric potential

\[
\Psi^*(c, \xi) = \sum_{r \in \mathcal{R}} \Psi^{(r)*}_w(c, \xi) + \Psi^{(r)*}_b(c, \xi) = \sum_{r \in \mathcal{R}} 2A^{(r)}(c) \left( \cosh \left( (\beta^{(r)} - \alpha^{(r)}) \cdot \xi \right) - 1 \right).
\]  

Finally, we find the expressions of the primal dissipations \( \Psi(c, s) \) by taking the Legendre transforms of \( \Psi^*(c, s) \). Transforming each reaction term separately

\[
\Psi^{(r)}_w(c, s) = \sup_{\xi} \xi \cdot s - \Psi^{(r)*}_w(c, \xi) = \begin{cases} 
\gamma \log \frac{s}{A^{(r)}(c)} - \gamma + A^{(r)}(c), & \text{if } s = \gamma (\beta^{(r)} - \alpha^{(r)}), \gamma > 0, \\
0, & \text{if } s = 0, \\
\infty, & \text{otherwise},
\end{cases}
\]

\[
\Psi^{(r)}_b(c, s) = \Psi^{(r)}_w(c, -s).
\]

By standard convex analysis, the Legendre transform of a sum is the infimal convolution over the Legendre transform of all terms, i.e.

\[
\Psi(c, s) = \left( \sum_{r \in \mathcal{R}} \Psi^{(r)*}_w(c, \cdot) + \Psi^{(r)*}_b(c, \cdot) \right)^*(s) = \bigwedge_{r=1}^R \left( \Psi^{(r)}_w \circ \Psi^{(r)}_b \right)(c, s) \equiv \inf_{(s_w^{(r)}, s_b^{(r)}) \in \mathcal{R}} \Psi^{(r)}_w(c, s_w^{(r)}) + \Psi^{(r)}_b(c, s_b^{(r)}).
\]  

We collect this result in the following Theorem:

**Theorem 3.5.** Fix an initial condition \( c(0) \), assume that the detailed balance condition (33) holds. Let \( \bar{F} \) be given by (41), where \( c^* \) is the unique steady state in \( l_{\text{w}}^1(\mathcal{Y}) \) satisfying detailed balance, and let \( \bar{L} \) be given by (36) and (37). Then there exists a unique convex dual pair \( \bar{\Psi}, \bar{\Psi}^* \) such that (27) and (22a–d) holds, and this pair is explicitly given by (42),(43) and (44).

**Remark 3.6.** Observe for each reaction, the terms \( \Psi^{(r)}_w(c, s) \) in (43) only allow for velocities \( s \) in the (non-negative) direction of the reaction \( \beta^{(r)} - \alpha^{(r)} \), which is to be expected. The infimal convolution in (44) automatically selects a combination of reactions for which the total cost is minimal. Indeed, for directions \( s \) that can not be written as such combination, the system would exit the stoichiometric simplex, and the potential will blow up.

**Remark 3.7.** The reacting particle system that we study is basically a jump process driven by Poisson noise. It is well-known that the large deviations of pure vanishing Poisson noise have the form \( \phi \mapsto \int_0^T \left( \dot{\phi}(t) \log \dot{\phi}(t) - \dot{\phi}(t) + 1 \right) dt, \) see for example [DZ87, pp. 187–188]. The
paper [AK11] discusses a Langevin approximation of the reacting particle system, meaning that the Poisson noise is replaced by Brownian motion. Schilder’s Theorem [DZ87, Th. 5.2.3] shows that the large deviations of vanishing Brownian motion is \( \phi \to \int_0^T |\phi(t)|^2 \, dt \). Therefore, the large deviations of the Langevin approximation are also quadratic. In a similar fashion as above, we can then deduce a different gradient structure, which is exactly the linear structure (30). In a parallel fashion, this same linear structure can be obtained from the nonlinear structure (43) by linearisation; see e.g. [BP14].

\[ \square \]

### 3.5 More general propensities

In this section we study the case where the limits (2) are replaced by

\[
V^{-1}k_{\text{fw}}^{(r,v)}(c) \to \tilde{k}_{\text{fw}}^{(r)}(c) \quad \text{and} \quad V^{-1}k_{\text{bw}}^{(r,v)}(c) \to \tilde{k}_{\text{bw}}^{(r)}(c), \quad \text{as} \quad V \to \infty \tag{45}
\]

for limit propensities \( \tilde{k}_{\text{fw,bw}}^{(r)}(c) \) that are not necessarily of mass-action type. In that case the large-deviation principle (38) still holds (see the twin paper [PPR16]) if we replace (36) by

\[
H(c, \xi) = \sum_{r \in R} \tilde{k}_{\text{fw}}^{(r)}(c) \left( e^{(\beta^{(r)} - \alpha^{(r)}) \xi} - 1 \right) + \tilde{k}_{\text{bw}}^{(r)}(c) \left( e^{(\alpha^{(r)} - \beta^{(r)}) \xi} - 1 \right).
\]

Clearly the limiting reaction rate equation \( \dot{c}(t) = \sum_{r \in R} (\tilde{k}_{\text{fw}}^{(r)}(c) - \tilde{k}_{\text{bw}}^{(r)}(c)) (\beta^{(r)} - \alpha^{(r)}) \) is now in equilibrium \( c = c^* \) whenever \( \sum_{r \in R} \tilde{k}_{\text{fw}}^{(r)}(c^*) = \sum_{r \in R} \tilde{k}_{\text{bw}}^{(r)}(c^*) \). From this we deduce the following generalised notion of detailed balance for some equilibrium state \( c^* \):

\[
\tilde{k}_{\text{fw}}^{(r)}(c^*) = \tilde{k}_{\text{bw}}^{(r)}(c^*) \quad \text{for all} \quad r \in R. \tag{46}
\]

Let us assume that under this condition, the reaction rate equation still has a gradient structure, and that it is driven by the scaled free energy (41). This is equivalent to the time-reversibility conditions (39). Moreover, let us assume that this reversibility holds in fact for each reaction \( r \in R \) separately; we then find from (39) that

\[
\tilde{k}_{\text{fw}}^{(r)}(c)e^{(\beta^{(r)} - \alpha^{(r)}) \cdot \nabla F(c)} = \tilde{k}_{\text{bw}}^{(r)}(c)e^{(\alpha^{(r)} - \beta^{(r)}) \cdot \nabla F(c)},
\]

and hence, using (41)

\[
\frac{\tilde{k}_{\text{fw}}^{(r)}(c)}{\tilde{k}_{\text{bw}}^{(r)}(c)} = \left( \frac{c}{c^*} \right)^{\beta^{(r)} - \alpha^{(r)}}. \tag{47}
\]

From this we deduce that

\[
\tilde{k}_{\text{fw}}^{(r)}(c) = \frac{\phi^{(r)}(c)}{c^{\alpha^{(r)}}} c^{\alpha^{(r)}} \quad \text{and} \quad \tilde{k}_{\text{bw}}^{(r)}(c) = \frac{\phi^{(r)}(c)}{c^{\beta^{(r)}}} c^{\beta^{(r)}},
\]

for some \( \phi^{(r)}(c) \) that is the same for the forward and backward reactions. Moreover, it follows that \( \tilde{k}_{\text{bw}}(c^*) = \tilde{k}_{\text{bw}}(c^*) \), which can be seen as a generalisation of the detailed balance condition (33).

To summarise, we see that if the reaction rate equation has a gradient structure that is driven by the free energy (41), then the ratio between \( \tilde{k}_{\text{fw}}^{(r)} \) and \( \tilde{k}_{\text{bw}}^{(r)} \) must be consistent with mass-action kinetics (2).
4 Gradient structure for the Liouville equation

In this section we move one level higher by considering the ensemble of independent copies \( C^{(V,I)}(t), I = 1, \ldots, N \) of the random concentration discussed in the previous section. We first introduce the process, and then calculate the corresponding large deviations. Next, we discuss the role of the stoichiometric simplices, and finally deduce a gradient structure from the large deviations.

We will use very similar concepts as in Section 3; to distinguish these concepts from the ones used in the previous section we will use blackboard bold letters, e.g. \( \mathbb{L} \), and \( \mathbb{H} \) instead of \( L \), and \( H \).

4.1 The ensemble process

We now study the ensemble of \( N \) independent reacting particle systems, where each particle system \( I = 1, \ldots, N \) is described by the process \( C^{(V,I)}(t) \) from Section 3.1. For fixed \( V, N \), we define the ensemble process

\[
\rho^{(V,N)}(t) := \frac{1}{N} \sum_{I=1}^{N} \delta_{C^{(V,I)}(t)}.
\]

Observe that for each \( t \geq 0 \), the measure \( \rho^{(V,N)}(t) \) is in fact an empirical measure of empirical measures. It takes values in the set \( \{ \frac{1}{N} \sum_{I=1}^{N} \delta_{c(I)} : c(I) \in l^1(Y), I = 1, \ldots, N \} \subset P(l^1_+(Y)) \). Therefore it suffices to specify its generator on these values only. For any \( \rho^{(N)} = N^{-1} \sum_{I=1}^{N} \delta_{c(I)} \), it is not difficult to show that the corresponding generator has the expression (see for example [Ren13, Th. 2.2.2] or [Daw93, Prop. 2.2.1]):

\[
(Q^{(V)}(\Phi))(\rho^{(N)}) = \sum_{I=1}^{N} Q^{(V)} \left[ c(I) \mapsto \Phi \left( \frac{1}{N} \sum_{J=1}^{N} \delta_{c(J)} \right) \right],
\]

where \( Q^{(V)} \) is the generator (31) of one individual concentration, and \( \Phi \) is an arbitrary test functional on probability measures \( P(l^1_+(Y)) \). We note that this expression is well-defined since the right-hand side does not depend on the exact ordering of \( C^{(V,I)}, \ldots, C^{(V,N)} \).

Following [Daw93], we denote the derivative of test functionals \( \Phi \) as above, if it exists, by

\[
D\Phi(\rho^{(N)})(c) := \lim_{\epsilon \to 0} \frac{\Phi(\rho^{(N)} + \epsilon c) - \Phi(\rho^{(N)})}{\epsilon}, \quad c \in l^1_+(Y).
\]

If \( \rho^{(N)} \) converges to some limit measure \( \rho \), then in the limit \( N, V \to \infty \) the generator converges...
(formally) to

\[
\left( Q(V, N) \Phi \right) \left( \frac{1}{N} \sum_{I=1}^{N} \delta_{(I)} \right) = \sum_{I=1}^{N} \sum_{r \in \mathcal{R}} k_{\text{fw}}^{(r,V)}(c^{(I)}) \left[ \Phi \left( \rho^{(N)} - \frac{1}{N} \delta_{c^{(I)}} + \frac{1}{N} \delta_{c^{(I)}-V^{-1} \alpha^{(r)} + V^{-1} \beta^{(r)}} \right) - \Phi \left( \rho^{(N)} \right) \right]
\]

\[
+ \sum_{I=1}^{N} \sum_{r \in \mathcal{R}} k_{\text{fw}}^{(r,V)}(c^{(I)}) \left[ \Phi \left( \rho^{(N)} - \frac{1}{N} \delta_{c^{(I)}} + \frac{1}{N} \delta_{c^{(I)}-V^{-1} \beta^{(r)} + V^{-1} \alpha^{(r)}} \right) - \Phi \left( \rho^{(N)} \right) \right]
\]

\[
\sum_{r \in \mathcal{R}} k_{\text{bw}}^{(r,V)}(c) \left[ D\Phi(\rho)(c - V^{-1} \alpha^{(r)} + V^{-1} \beta^{(r)}) - D\Phi(\rho)(c) \right] \rho(dc)
\]

\[
\sum_{r \in \mathcal{R}} k_{\text{bw}}^{(r,V)}(c) \left[ D\Phi(\rho)(c - V^{-1} \beta^{(r)} + V^{-1} \alpha^{(r)}) - D\Phi(\rho)(c) \right] \rho(dc).
\]

By a similar argument as in Section 3.1 we see that if the initial condition \( \rho^{(N,V)}(0) \) is deterministic, then the limit process is deterministic, and it solves the Liouville equation (4).

### 4.2 Dynamic large deviations

We will now calculate the large deviations of the process \( \rho^{(V,N)}(t) \) as \( V, N \to \infty \). As before, we rule out initial fluctuations by assumption:

The initial measures \( \rho^{(V,N)}(0) = \frac{1}{N} \sum_{I=1}^{N} \delta_{c^{(I)}}(0) \) are deterministic, and they converge to some limit measure \( \rho \) as \( V, N \to \infty \).

(4.48) Similarly to Section 3.3 we formally use the method of Feng & Kurtz [Fen94]; we prove the large deviations principle rigorously in the twin paper [PPR16, Sec. 4]. Again, we divide the calculation in four steps:

1. For any \( \rho^{(N)} = N^{-1} \sum_{I=1}^{N} \delta_{c^{(I)}} \), the non-linear generator associated to \( Q^{(V,N)} \) is:

\[
\left( \mathbb{H}^{(V,N)} \Phi \right) \left( \rho^{(N)} \right) := \frac{1}{V N} e^{-V N \Phi(\rho^{(N)})} \left( Q(V,N) e^{V N \Phi} \right) \left( \rho^{(N)} \right)
\]

\[
= \sum_{r \in \mathcal{R}} \int_{I'_1(Y)} \left[ \frac{1}{V N} k_{\text{fw}}^{(r,V)}(c) \left( e^{V N \Phi \left( \rho - \frac{1}{N} \delta_{c^{(I)}} + \frac{1}{N} \delta_{c^{(I)}-V^{-1} \alpha^{(r)} + V^{-1} \beta^{(r)}} \right) - V N \Phi(\rho) - 1 \right) \right]
\]

\[
+ \frac{1}{V N} k_{\text{bw}}^{(r,V)}(c) \left( e^{V N \Phi \left( \rho - \frac{1}{N} \delta_{c^{(I)}} + \frac{1}{N} \delta_{c^{(I)}-V^{-1} \beta^{(r)} + V^{-1} \alpha^{(r)}} \right) - V N \Phi(\rho) - 1 \right) \right) \rho^{(N)}(dc).
\]

2. Using the mass-action assumption (2), we find in the limit as \( V, N \to \infty \), assuming \( \rho^{(N)} \)
We point out that the second term in (50) depends on \(L\) sets. From this we conclude that for some vector field \(\tilde{\Theta}\) to the same \(S\), the sequence \((\ref{PPR16})\) satisfies the continuity equation as \(V\to\infty\).

3 Indeed, the limit non-linear generator depends on the test functional \(\Phi\) only through its derivative \(\Xi(c) := D\Phi(\rho(c))\). We can thus define, by a slight abuse of notation,

\[
\mathbb{H}(\rho, \Xi) = \int_{\mathcal{L}(\mathcal{Y})} H(\rho, \nabla \Xi(c)) \rho(dc).
\]

4 Finally, we define the Legendre dual, for signed measures \(S(dc)\),

\[
\mathbb{L}(\rho, S) = \sup_{\Xi \in \mathcal{C}_b^1(1^\infty(\mathcal{Y}))} \int \Xi(c)S(dc) - \mathbb{H}(\rho, \Xi),
\]

where we continue to use \(S\) as a placeholder for the variable \(\rho_t\).

We thus get the following result (again, for the details, spaces and topologies, see the twin paper):

**Theorem 4.1** ([PPR16]). Let Assumption (48) and [PPR16, Assumptions 3.1] be satisfied. Then the sequence \((\rho^{(V,N)}(t))_{t=0}^T\) satisfies a large-deviation principle of the form

\[
\text{Prob} \left( \rho^{(V,N)}(\cdot) \approx \rho(\cdot) \right) \sim e^{-VN \int_0^T \mathbb{L}(\rho(t), \rho(t)) dt} \quad \text{as } V, N \to \infty.
\]

We point out that the second term in (50) depends on \(\Xi\) through the derivative \(\nabla \Xi\) only. Therefore, \(\mathbb{L}(\rho, S)\) can only be finite if the first term is a linear functional on \(\nabla \Xi\) as well, up to \(\rho\)-null sets. From this we conclude that \(\mathbb{L}(\rho, S)\) can only be finite if \(S\) satisfies the **continuity equation**

\[
S + \text{div}(\rho \Theta) = 0 \quad \text{in distributional sense},
\]

for some vector field \(\Theta\). Note that any vector field \(\tilde{\Theta}\) such that \(\text{div}(\rho \tilde{\Theta}) = \text{div}(\rho \Theta)\) gives rise to the same \(S\), and therefore there is some indeterminacy. We may then write:

\[
\mathbb{L}(\rho, -\text{div}(\rho \Theta)) = \sup_{\Xi} \int_{\mathcal{L}(\mathcal{Y})} \left[ \nabla \Xi(c) \cdot \Theta(c) - H(c, \nabla \Xi(c)) \right] \rho(dc)
\]

\[
= \inf_{\tilde{\Theta}} \left\{ \sup_{\Xi} \int_{\mathcal{L}(\mathcal{Y})} \left[ \nabla \Xi(c) \cdot \tilde{\Theta}(c) - H(c, \nabla \Xi(c)) \right] \rho(dc) : \text{div } \rho(\Theta - \tilde{\Theta}) = 0 \right\}.
\]

\[
\overset{(37)}{=} \inf_{\tilde{\Theta}} \left\{ \int_{\mathcal{L}(\mathcal{Y})} L(c, \tilde{\Theta}(c)) \rho(dc) : \text{div } \rho(\Theta - \tilde{\Theta}) = 0 \right\}.
\]

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4.3 Splitting into stoichiometric simplices

The stoichiometric simplices induce additional structure, that we will need in the derivation of the gradient structure from the large deviations. To this aim we introduce, for any \( \rho_t \), the push-forward measure \( \nu_t(dq) := (M \# \rho_t)(dq) = \rho_t(\{ c : Mc \in dq \}) \), giving the distribution of mass over the stoichiometric simplices. Consider a curve \( \rho_t, t \in [0, T] \) with \( \dot{\nu}_t(dq) \neq 0 \). Then because of (34),

\[
\mathbb{L}(\rho_t, \dot{\rho}_t) \geq \sup_{\Xi = \phi c, \phi \in C^1_b(R^\omega)} \int_{l_1^+(\gamma)} \Xi(c) \dot{\rho}_t(dc) - \mathbb{H}(\rho_t, \Xi(c))
\]

\[
= \sup_{\phi \in C^1_b(R^\omega)} \int_{R^\omega} \phi(q) \dot{\nu}_t(dq) - \int_{l_1^+(\gamma)} H(c, M^T \nabla \phi(Mc)) \rho_t(dc) = \infty.
\]

From this we see that if \( \mathbb{L}(\rho_t, \dot{\rho}_t) < \infty \) for \( t \in [0, T] \), then \( \nu_t \) must be constant on that interval, which is to be expected.

If for a general \( \rho \) we set \( \nu := M \# \rho \), by the Disintegration Theorem [AGS08, Th. 5.3.1] there is a family of mass-one measures \( (\rho^{(q)})_{q \in R^\omega} = \rho(\{ dc \}) = \int_{R^\omega} \rho^{(q)}(dc) \nu(dq) \). In fact, it is easily verified that \( \rho^{(q)}(dc) = \rho(\{ dc \cap l_1^+(\gamma) \}) / \rho(l_1^+(\gamma)) \). With this disintegration, the expression (49) can be rewritten as

\[
\mathbb{H}(\rho, \Xi) = \int_{q \in R^\omega} \int_{l_1^+(\gamma)} H(c, \nabla \Xi(c)) \rho^{(q)}(dc) \nu(dq).
\]

We will see that this expression is very useful to determine the free energy, as each stoichiometric simplex, parametrised by \( q \), has its own unique strictly positive steady state \( c^{(q)} \), as we explained in Section 3.2.

4.4 Gradient structure from large deviations

Analogously to Section 3.4, we derive a driving force \( \tilde{D} \tilde{F} \) and dual dissipation potentials \( \Psi, \Psi^* \) satisfying conditions (22) such that

\[
\mathbb{L}(\rho, S) = \Psi(\rho, S) + \Psi^*(\rho, -\tilde{D} \tilde{F}(\rho)) + \int_{l_1^+(\gamma)} D \tilde{F}(\rho)(c) S(dc),
\]

where we continue to write a tilda above \( \tilde{F} \) to stress that it should be non-dimensionalised since \( \Psi, \Psi^* \) could be non-polynomial. To this aim, fix an initial measure \( \rho(0) \), and assume that detailed balance (33). Because \( \mathbb{H} \) is related to \( H \) by (49), the concepts that we are after can be directly related to the ‘lower-level’ concepts from the previous section. We again divide the derivation into three steps.

1. In this setting, the existence of such gradient structure is equivalent to the time-reversibility of \( \mathbb{L} \) or of \( \mathbb{H} \), cf. (39),

\[
\mathbb{H}(\rho, \tilde{D} \tilde{F}(\rho) + \Xi) = \mathbb{H}(\rho, \tilde{D} \tilde{F}(\rho) - \Xi) \quad \text{for all } \rho, \Xi.
\]
Using the disintegrated form (54), we see that it suffices to require that within each stoichiometric simplex $l_i^j(Y)$,

$$
H(c, \nabla D\tilde{F}(\rho^{(o)})(c) + \nabla \Xi(c)) = H(c, \nabla D\tilde{F}(\rho^{(o)})(c) - \nabla \Xi(c)) \quad \text{for all } c, \Xi.
$$

From the theory of Section 3, we know that this is true because of detailed balance (33), and moreover, $D\tilde{F}(\rho^{(o)})(c) = \tilde{F}_{c^{\star}((o)}(c)$, where $\tilde{F}_{c^{\star}((o)}$ is the (scaled) free energy (41) relative to the steady state $c^{\star}((o)$. It follows that the right expression for the free energy driving the ensemble Liouville equation is:

$$
\tilde{F}(\rho) := \begin{cases} 
\int_{\mathbb{R}^+} \int_{l_i^j(Y)} \tilde{F}_{c^{\star}((o)}(c) \rho^{(o)}(dc) \nu(dq), & \text{if } \rho(c) = \int_{\mathbb{R}^+} \rho^{(o)}(dc) \nu(dq), \\
\infty, & \text{otherwise}
\end{cases}
= \int_{l_i^j(Y)} \tilde{F}_{c^{\star}((o)}(c) \rho(dc).
$$

(57)

We see that for the free energy of the whole ensemble, we need to calculate, for each concentration $c$, the free energy with respect to the unique reversible steady state that lies in the same stoichiometric simplex as $c$, and then sum over all the concentrations in the ensemble. This expression is consistent with the physical principle that the free energy is an extensive variable.

2 Since $H$ is time-reversible, there is a unique dissipation potential pair $\Psi, \Psi^*$ satisfying (22) and (55) [MPR14, Sec. 2]. To calculate $\Psi^*$ we use the analogue of formula (40):

$$
\Psi^*(\rho, \Xi) = \mathbb{H}(\rho, D\tilde{F}(\rho) + \Xi) - \mathbb{H}(\rho, D\tilde{F}(\rho))
= \int_{l_i^j(Y)} \left[ H\left(c, \nabla \tilde{F}_{c^{\star}((o)}(c) + \nabla \Xi(c)\right) - H\left(c, \nabla \tilde{F}_{c^{\star}((o)}(c)\right) \right] \rho(dc)
= \int_{l_i^j(Y)} \Psi_{c^{\star}((o)}}^*(c, \nabla \Xi(c)) \rho(dc).
$$

(58)

Here, $\Psi_{c^{\star}((o)}}^*$ is defined by (44) where $c^*$ is replaced by $c^{\star}((o)$.

3 The primal dissipation potential is found through a Legendre transform. We find that $\Psi(\rho, S) = \infty$ unless $S + \text{div } \rho \Theta = 0$ for some vector field $\Theta(c)$. In that case, if we handle the indeterminacy in a similar fashion as in (53):

$$
\Psi(\rho, -\text{div}(\rho \Theta)) = \sup_{\Xi} \int_{l_i^j(Y)} \left[ \nabla \Xi(c) \cdot \Theta(c) - \Psi_{c^{\star}((o)}}^*(c, \nabla \Xi(c)) \right] \rho(dc)
= \inf_{\Theta} \left\{ \int_{l_i^j(Y)} \sup_{\xi \in l_i^j(Y)} \xi \cdot \Theta(c) - \Psi_{c^{\star}((o)}}^*(c, \xi) \right\} \rho(dc) : \text{div } \rho(\Theta - \tilde{\Theta}) = 0
= \inf_{\Theta} \left\{ \int_{l_i^j(Y)} \Psi_{c^{\star}((o)}}(c, \Theta(c)) \rho(dc) : \text{div } \rho(\Theta - \tilde{\Theta}) = 0 \right\},
$$

(59)

where $\Psi_{c^{\star}((o)}}$ is the Legendre transform of $\Psi_{c^{\star}((o)}}^*$ defined by (44) where $c^*$ is replaced by $c^{\star}((o)$.

We summarise the results in the following theorem:
Theorem 4.2. Assume the detailed balance condition (33) holds, i.e. for some steady state $c^\circ$, and let $F$ be given by (57). Then there exists a unique dual pair $\Psi, \Psi^*$ for which (22) and (55) hold. This pair is explicitly given by (58) and (59).

5 Discussion

We have seen that for systems in detailed balance, we can derive free energy-driven gradient flow structures for the Reaction Rate and the Liouville equations. Let us make a few comments about the philosophical ideas behind this.

First of all, we stress that the gradient structure is not just an abstract mathematical construct, but it has physical meaning. For instance, the structure can be exploited to calculate the dissipation in case of an additional external driving force. This relates to an important principle in thermodynamics: the mechanism that drives the system towards equilibrium is the same as the mechanism that drives it out of equilibrium if one temporarily imposes an external force. This mechanism is the gradient structure.

Based on an argument that goes back to Onsager, we derived gradient structures from the large deviations of an underlying microscopic particle system. Because of this, the choice of the microscopic model influences the corresponding gradient structure. In particular, if one would model microscopic reactions by white noise fluctuations that vanish proportional to the number of particles, one would find quadratic large deviations, quadratic dissipation potentials, and hence a linear gradient structure [MM13]. Since we modelled the microscopic reactions through jump processes, the large deviations are non-quadratic, resulting in a generalised structure, i.e. a non-linear relation between thermodynamic fluxes and thermodynamic driving forces, see (19).

For linear relations, one can always multiply the free energy with a physical constant, thereby changing the dimension, as long as one changes the Onsager matrix or operator accordingly. For non-linear relations this is no longer the case; therefore, we needed to work with a non-dimensionalised free energy.

Apart from the non-dimensionalisation, we observed that we should use a factor $1/2$ in front of the free energy. This comes from the principle that free energy differences come from a time-reversal principle, or more particularly: from the cost of moving forward minus the cost of moving backward in time, see (39) and (56). Only moving forward in time would then yield $1/2 \times$ the free energy difference plus dissipation terms, and the dissipation terms drop from the reversal relations since we assumed that the dissipation is invariant under time-reversal. The time-reversal relations themselves are naturally related to the Galavotti-Cohen symmetry, see [MPR14, Sec. 1.6].

At first sight, the scaling factor $1/2$ (or any arbitrary factor) does not change the gradient structure if one changes the dissipations as well. However, the scaling will be visible in the energy-dissipation balance. Because it is this energy-dissipation balance that we matched to the dynamic large deviations, the large deviations uniquely determine the ‘proper’ scaling.

This principle holds in fact in much more generality. Indeed, a macroscopic evolution equation
like the Reaction Rate or Liouville equation can be described by a multitude of gradient structures. However, our aim was not only to derive any gradient structure, but to find a structure that is consistent with the large deviations of the microscopic particle system. We argued that for systems in equilibrium, there is a similar relation between large deviations and the free energy. Therefore, a similar relation between the dynamic large deviations and the gradient structure can be seen as an argument that the gradient structure is in some sense the ‘correct’ one.

References


