1.3 Multi-scale Chemical Reaction Systems

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The mathematical description of complex processes in nature involves many challenging difficulties. These result from the fact that mathematical models are governed by the trade-off between accuracy and simplicity. A more accurate description, e.g., involving more physical states, provides richer information about the physical problem, which is desirable for a detailed understanding of the physical process. In contrast, a precise description involves many challenges affecting all branches of applied mathematics, namely modeling, analysis, and simulation: First, the validation of an applicable model requires precise measurements that become practically impossible if the state space is too large. Second, the analytic difficulties grow when increasing the complexity of the problem. Thirdly, good numerical algorithms may become too costly if the number of parameters and dimensions increases.

A procedure that reduces the complexity of a system is often called *coarse-graining*. It is a prominent research topic in all areas of natural sciences. These reductions or approximations are often physically motivated by scale separations of the problem and have the aim to derive an effective model that respects and reflects the most prominent features of the system. On different temporal or spatial scales, different processes may govern the physical system, resulting in different levels of description. The derivation of effective systems by reducing a system involving multiple scales to a smaller system with fewer scales, for example, only one distinguished scale, is an important task in applied mathematics and a prominent research area at WIAS. Usually, reductions are made on the level of the physical states. However, in recent years, it became more and more apparent that the intrinsic physical nature cannot be described by the physical states only. Desirably and as explained in the Annual Research Report of WIAS of 2014, a complete coarse-graining procedure should also take the global physical principles into account. Such a structural reduction procedure has many different advantages. First, the derived effective model automatically satisfies the desired physical principles, such as energy conservation and monotonicity of entropy production. Often, the additional information helps in the mathematical analysis of the equations. Moreover, errors in computer-based simulations may be reduced by preserving the physical structure.

Recently, theoretical progress was made for coarse-graining of multi-scale chemical reaction systems. Chemical reactions describe the transformation of species, molecules, or substances. Reaction systems are inevitable in modeling processes in biology, chemistry, physics, as well as social sciences, and economics. In many applications, the number of chemical species can be huge, and the reaction coefficients for the chemical reactions may vary in a large range. In such cases, not only the measurement of all necessary physical quantities, but also analytical or numerical treatment is out of reach. A natural simplification is made by the assumption that reactions can happen with different and distinguished magnitudes of speed. We will consider the case that slow and fast reactions are distinguished, namely the slow ones of order 1 and the fast ones of order $1/\varepsilon$ for a small parameter $\varepsilon > 0$. There are many instances for this kind of assumption in literature. As a biochemical example, we mention an mRNA-DNA system that can be modeled by a slow-fast reaction system (see Figure 1). There, proteins (monomers), synthesized by transcription of a gene, dimerize. Afterwards, they may bind to the gene. Dimerization is a fast reaction, as compared to

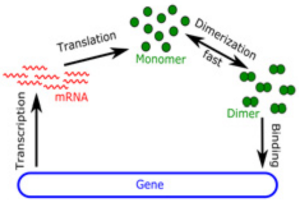

Fig. 1: *A simple model that describes the transcriptional regulatory system in gene production*

transcription, translation, mRNA and protein degradation, and protein binding.

Gradient structures and EDP-convergence

To include the physical structure, we focus on variational structures that define a gradient flow. Physically, they describe a closed physical system that is close to thermodynamic equilibrium. They provide an important modeling framework enjoying many applications in continuum mechanics, semiconductor physics, and also chemical processes. Gradient flows describe an evolution in the direction of the steepest descent of a driving functional, which is often given by the energy or entropy. Mathematically, gradient flow equations are evolution equations that are induced by a so-called *gradient system* $(Q, \mathcal{E}, \mathcal{R}^*)$, consisting of a state space Q (a subspace of a Banach space X), a driving (or energy) functional $\mathcal{E}$, and a geometric or dissipative structure in the form of a dissipation potential $\mathcal{R}$ that describes the geometry of the underlying state space Q (see [2]). Here, $\mathcal{R}$ is called a *dissipation potential* if $\mathcal{R}(q,\cdot) : X \to [0,\infty]$ is lower semicontinuous, convex, and satisfies $\mathcal{R}(q,0) = 0$. Then, $\mathcal{R}^*$ is the (partial) Legendre–Fenchel transform given by $\mathcal{R}^*(q,\xi) := \sup_{v\in X}\{\langle\xi, v\rangle - \mathcal{R}(q,v)\}$. The induced gradient flow equation is then defined by

$$\dot{q} = \mathrm{D}_\xi\mathcal{R}^*(q, -\mathrm{D}\mathcal{E}(q)) \quad \text{or equivalently} \quad 0 = \mathrm{D}_{\dot{q}}\mathcal{R}(q,\dot{q}) + \mathrm{D}\mathcal{E}(q). \tag{GFE}$$

The first equation is a rate equation in the state space $Q \subset X$. The second equation is a force balance, where the viscous force $\mathrm{D}_{\dot{q}}\mathcal{R}(q,\dot{q})$ is balanced by the potential restoring force $-\mathrm{D}\mathcal{E}(q)$. Another equivalent formulation of the gradient flow equation (GFE) plays an important role. Introducing the total dissipation functional (also called the *De Giorgi functional*)

$$\mathfrak{D}(q) = \int_0^T \mathcal{R}(q,\dot{q}) + \mathcal{R}^*(q, -\mathrm{D}\mathcal{E}(q))\,\mathrm{d}t,$$

the gradient flow evolution can equivalently be described by the so-called *energy-dissipation balance*

$$\mathcal{E}(q(T)) + \mathfrak{D}(q) = \mathcal{E}(q(0)).$$

This energy-dissipation balance compares the energy at initial time $t = 0$ with the energy at final time $t = T$. The difference is given by the total dissipation functional $\mathfrak{D}(q)$, which has a particular form, consisting of the two terms $\mathcal{R}$ and $\mathcal{R}^*$. The energy-dissipation balance is a suitable starting point for multi-scale problems using Γ-convergence methods.

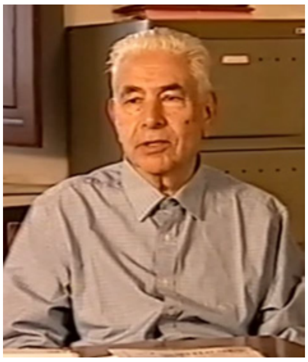
Fig. 2: *Italian mathematician Ennio De Giorgi during an interview in 1996, SNS Channel Mathematical and Natural Sciences, CC BY 3.0*

For families of gradient systems $(Q, \mathcal{E}_\varepsilon, \mathcal{R}_\varepsilon^*)$, where $\varepsilon > 0$ is a small parameter featuring the multi-scale nature, a structural convergence, the so-called *EDP-convergence*, has been established in recent years [3]. Roughly speaking, EDP-convergence is defined by two Γ-convergences: for the energy functionals $\mathcal{E}_\varepsilon$, defined on the state space Q, and the dissipation functionals $\mathfrak{D}_\varepsilon$ given by

$$\mathfrak{D}_\varepsilon(q) = \int_0^T \mathcal{R}_\varepsilon(q,\dot{q}) + \mathcal{R}_\varepsilon^*(q, -\mathrm{D}\mathcal{E}_\varepsilon(q))\,\mathrm{d}t,$$

defined on the dynamic space of trajectories (in a suitable topology). The limit is again given by

$$\mathfrak{D}_0(q) = \int_0^T \mathcal{R}_{\mathrm{eff}}(q,\dot{q}) + \mathcal{R}_{\mathrm{eff}}^*(q, -\mathrm{D}\mathcal{E}_{\mathrm{eff}}(q))\,\mathrm{d}t.$$

The effective gradient system is, then, given by $(Q,\mathcal{E}_{\text{eff}},\mathcal{R}^*_{\text{eff}})$. Physically, the convergence can be motivated from thermodynamics because it takes also fluctuations of solutions of the gradient flow equation (GFE) into account that have finite energy and dissipation.

An almost trivial consequence of EDP-convergence is that (under suitable technical assumptions) solutions with respect to the gradient system $(Q,\mathcal{E}_\varepsilon,\mathcal{R}^*_\varepsilon)$ converge to the solution of the effective gradient system $(Q,\mathcal{E}_{\text{eff}},\mathcal{R}^*_{\text{eff}})$. The great advantage of EDP-convergence is that the limit gradient system is uniquely determined, and hence, the previously hidden physical principles of the effective evolution equation become evident; see Figure 3.

$$\begin{tikzcd}
 & \text{gradient systems} & \text{gradient-flow eqn.} & \text{solutions} \\
 {} \arrow[d, phantom, "\varepsilon \to 0"] & (Q,\mathcal{E}_\varepsilon,\mathcal{R}_\varepsilon) \arrow[r, rightsquigarrow] \arrow[d, "\text{EDP}"] & \dot q = \mathrm{D}_\xi\mathcal{R}^*_\varepsilon(q,-\mathrm{D}\mathcal{E}_\varepsilon(q)) \arrow[r, rightsquigarrow] \arrow[d, rightsquigarrow] & q^\varepsilon\colon[0,T]\to Q \arrow[d] \\
 {} & (Q,\mathcal{E}_0,\mathcal{R}_{\text{eff}}) \arrow[r, rightsquigarrow] & \dot q = \mathrm{D}_\xi\mathcal{R}^*_{\text{eff}}(q,-\mathrm{D}\mathcal{E}_0(q)) \arrow[r, rightsquigarrow] & q^0\colon[0,T]\to Q
\end{tikzcd}$$

Fig. 3: *EDP-convergence leads to a commuting diagram. In particular, EDP-convergence generates the correct limit equation* $\dot q = \mathrm{D}_\xi\mathcal{R}^*_{\text{eff}}(q,-\mathrm{D}\mathcal{E}_0(q))$, *and the solutions* q^ε *converge to solutions* q^0 *of the limit equation. However,* $\mathcal{R}_{\text{eff}}$, *which is uniquely determined by EDP-convergence, provides information not contained in the limit equation.*

In this sense, EDP-convergence can be understood as a structural coarse-graining procedure that derives an effective system from a multi-scale system.

Fast-slow nonlinear reaction systems

In [4, 5, 6], the coarse-graining procedure was applied and extended to different fast-slow reaction and reaction-diffusion systems. We consider species X_i, $i \in I := \{1,\dots,i_*\}$, that undergo r_* forward-backward chemical reactions of mass-action type

$$\alpha^r_1 X_1 + \cdots + \alpha^r_{i_*} X_{i_*} \quad \rightleftharpoons \quad \beta^r_1 X_1 + \cdots + \beta^r_{i_*} X_{i_*}, \qquad r = 1,\dots,r_*,$$

where $\alpha^r = (\alpha^r_i)_{i\in I}$ and $\beta^r = (\beta^r_i)_{i\in I}$ are the stoichiometric vectors in $\mathbb{N}_0^{i_*}$. The fast-slow reaction-rate equation describing the evolution of densities $c \in \mathbf{C} = [0,\infty[^{i_*}$ of the species has the form

$$\dot c = \mathbf{R}_{\text{slow}}(c) + \frac{1}{\varepsilon}\mathbf{R}_{\text{fast}}(c) \ \text{ with } \ \mathbf{R}_{\text{xy}}(c) := -\sum_{r\in R_{\text{xy}}} \kappa_r \left(c_*^{\alpha^r} c_*^{\beta^r}\right)^{1/2} \left(\frac{c^{\alpha^r}}{c_*^{\alpha_r}} - \frac{c^{\beta^r}}{c_*^{\beta_r}}\right)(\alpha^r - \beta^r), \qquad \text{(RRE)}$$

for $\text{xy} \in \{\text{slow},\text{fast}\}$, where $\kappa_r > 0$ are reaction rates, and $c_* = (c^*_i)_{i\in I} \in\,]0,\infty[^{i_*}$ is a positive concentration vector providing the detailed-balance equilibrium.

The fast-slow reaction-rate equation can be understood as a gradient flow equation of the cosh-type gradient structure $(\mathbf{C},\mathcal{E},\mathcal{R}^*_\varepsilon)$, where the ($\varepsilon$-independent) energy functional is the free energy of Boltzmann type

$$\mathcal{E}(c)=\sum_{i=1}^{i_*} c_i^* E_{\mathrm{Bz}}(c_i/c_i^*), \quad E_{\mathrm{Bz}}(r)=r\log r-r+1\,.$$

The dual dissipation potential $\mathcal{R}^*_\varepsilon$ consists of a slow part and a fast part and is given by

$$\mathcal{R}^*_\varepsilon(c,\xi)=\mathcal{R}^*_{\mathrm{slow}}(c,\xi)+\frac{1}{\varepsilon}\mathcal{R}^*_{\mathrm{fast}}(c,\xi), \quad \mathcal{R}^*_{\mathrm{xy}}(c,\xi)=\sum_{r\in R_{\mathrm{xy}}}\kappa_r\big(c^{\alpha^r}c^{\beta^r}\big)^{1/2}\,\mathsf{C}^*\big((\alpha^r-\beta^r)\cdot\xi\big), \tag{dDP}$$

where the cosh function is given by $\mathsf{C}^*(r) = 4\cosh(r/2)-4$. It follows that the reaction-rate equation (RRE) is indeed given by the gradient flow equation $\dot{c}=\mathrm{D}_\xi\mathcal{R}^*(c,-\mathrm{D}\mathcal{E}(c))$.

Heuristically, one expects that in the limit $\varepsilon\to 0$, an equilibration of the fast reactions occurs such that $\mathbf{R}_{\mathrm{fast}}(c(t))\equiv 0$, which defines the slow manifold where the slow evolution takes place. This result can also be shown on the level of the gradient structure by proving EDP-convergence [4]. As it turns out, the gradient system $(\mathbf{C},\mathcal{E},\mathcal{R}^*_\varepsilon)$ converges to $(\mathbf{C},\mathcal{E}_{\mathrm{eff}},\mathcal{R}^*_{\mathrm{eff}})$, where the effective gradient system is given by

$$\mathcal{E}_{\mathrm{eff}}=\mathcal{E}, \quad \mathcal{R}^*_{\mathrm{eff}}=\mathcal{R}^*_{\mathrm{slow}}+\chi_{\Gamma^\perp_{\mathrm{fast}}},$$

where $\chi_K(\xi)=0$ for $\xi\in K$ and infinity, otherwise. The dissipation potential again consists of two parts: one part that captures the slow reactions and one part that restricts the evolution to the set of fast equilibria

$$\mathfrak{E}_{\mathrm{fast}}=\{c\in\mathbf{C}:\mathbf{R}_{\mathrm{fast}}(c)=0\}\,,$$

by forcing the chemical potentials to be transversal to the subspace of fast stoichiometric vectors $\Gamma_{\mathrm{fast}}=\mathrm{span}\left\{\alpha^r-\beta^r : r \text{ is fast}\right\}$. The important assumption is that the manifold of fast equilibria $\mathfrak{E}_{\mathrm{fast}}$ can be parametrized (by a function Ψ) in terms of adiabatic variables or, in other words, the conserved quantities of the fast reactions. These slow adiabatic variables are the natural variables of the coarse-grained systems and are given by $q\in\hat{\mathbf{C}}=Q_{\mathrm{fast}}\mathbf{C}$, where the matrix Q_{fast} satisfies $Q_{\mathrm{fast}}\Gamma_{\mathrm{fast}}=0$. The effective system in its gradient structure can be equivalently expressed in these coarse-grained slow variables, where the state space is $\hat{\mathbf{C}}=Q_{\mathrm{fast}}\mathbf{C}$, and the energy functional and dissipation potential are given by

$$\hat{\mathcal{E}}(q)=\mathcal{E}(\Psi(q)), \quad \hat{\mathcal{R}}^*(q,\hat{\xi})=\mathcal{R}^*_{\mathrm{slow}}(\Psi(q),Q^{\mathrm{T}}_{\mathrm{fast}}\hat{\xi}).$$

In particular, a new physical principle in terms of a yet undiscovered gradient structure is obtained because the coarse-grained driving functional is no longer of Boltzmann type. As an application, a structural reduction from two bimolecular chemical reactions to one trimolecular reaction can be performed; see Figure 4.

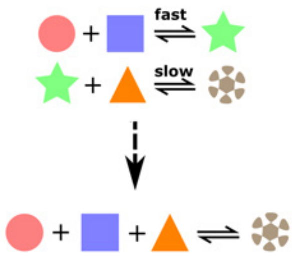

Fig. 4: *One fast and one slow bimolecular reaction coarse-grained to one trimolecular reaction*

Fast-slow linear reaction-diffusion system

Considering two species that, in addition to a fast linear reaction, also diffuse in a medium $\Omega\subset\mathbb{R}^d$, the evolution of their concentrations $c=(c_1,c_2)$ can be described by a linear reaction-diffusion system (complemented by no-flux boundary conditions and initial conditions)

$$\dot{c_1} = \delta_1 \Delta c_1 - \frac{1}{\varepsilon}\left(\frac{c_1}{c_1^*} - \frac{c_2}{c_2^*}\right), \quad \dot{c_2} = \delta_2 \Delta c_2 + \frac{1}{\varepsilon}\left(\frac{c_1}{c_1^*} - \frac{c_2}{c_2^*}\right), \tag{RDS}$$

where $\delta_1, \delta_2 > 0$ are diffusion coefficients and $(c_1^*, c_2^*) > 0$ are the equilibrium concentrations, which define the reaction rates. These reaction-diffusion systems can again be written as a gradient-flow equation induced by a gradient system $(Q, \mathcal{E}, \mathcal{R}_\varepsilon^*)$, where the state space Q is now the infinite-dimensional manifold of probability measures $Q = \mathrm{Prob}(\Omega \times \{1,2\})$, and the driving functional is the free energy $\mathcal{E}(\mu) = \int_\Omega \sum_{j=1}^2 E_{\mathrm{Bz}}\left(\frac{c_j}{c_j^*}\right) c_j^* \,\mathrm{d}x$ for measures $\mu = c\,\mathrm{d}x$ and the stationary measure $c^* = (c_1^*, c_2^*)^{\mathrm{T}} \in Q$. Here, the dissipation potential $\mathcal{R}_\varepsilon^*$ is given by two parts $\mathcal{R}_\varepsilon^* = \mathcal{R}_{\mathrm{diff}}^* + \mathcal{R}_{\mathrm{react},\varepsilon}^*$, describing diffusion and reaction separately. The diffusion part $\mathcal{R}_{\mathrm{diff}}^*$ corresponds to the Wasserstein metric showing the connection to the theory of optimal transport. The reaction part $\mathcal{R}_{\mathrm{react},\varepsilon}^*$ is ε-dependent and defined by a straightforward generalization as in the space-independent situation (dDP). Together, they define a geometry on the space of probability measures that take transport and transformation into account. The reaction-diffusion system (RDS) can now formally be written as a gradient flow equation $\dot{\mu} = \mathrm{D}_\xi \mathcal{R}_\varepsilon^*(\mu, -\mathrm{D}\mathcal{E}(\mu))$.

In [5], EDP-convergence for the gradient systems was shown. In particular, the approach is robust to take also shifts (the so-called *tilts*) by a linear potential $V = (V_1, V_2)$ into account. On the level of the evolution equation, these additional energy shifts give rise to a linear reaction-drift diffusion system with space-dependent reaction coefficients

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} c_1 \\ c_2 \end{pmatrix} = \mathrm{div}\left(\begin{pmatrix} \delta_1 \nabla c_1 \\ \delta_2 \nabla c_2 \end{pmatrix} + \begin{pmatrix} \delta_1 c_1 \nabla V_1 \\ \delta_2 c_2 \nabla V_2 \end{pmatrix}\right) + \frac{1}{\varepsilon}\begin{pmatrix} -\frac{1}{c_1^*}\mathrm{e}^{\frac{V_1 - V_2}{2}} & \frac{1}{c_2^*}\mathrm{e}^{\frac{V_2 - V_1}{2}} \\ \frac{1}{c_1^*}\mathrm{e}^{\frac{V_1 - V_2}{2}} & -\frac{1}{c_2^*}\mathrm{e}^{\frac{V_2 - V_1}{2}} \end{pmatrix}\begin{pmatrix} c_1 \\ c_2 \end{pmatrix},$$

where the new stationary solution is $c^{*,V} = (c_1^{*,V}, c_2^{*,V})$. In the potential-free situation (i.e. $V = \mathrm{const}$), we recover the reaction-diffusion system (RDS).

EDP-convergence provides an effective gradient system, where the effective dissipation potential consists again of two terms $\mathcal{R}_{\mathrm{eff}}^* = \mathcal{R}_{\mathrm{diff}}^* + \chi_{\{\xi_1 = \xi_2\}}$, where the first term describes the diffusion of the species, and the second term provides a coupling of the forces (or chemical potentials), which defines the linear slow manifold. Similar to the space-independent situation, the effective gradient system can also be equivalently described using coarse-grained slow variables $\hat{c} = c_1 + c_2$ such that $\Psi(\hat{c}) = (c_1, c_2)$, and the coarse-grained state space is given by $\hat{Q} = \mathrm{Prob}(\Omega)$. The coarse-grained energy functional and dissipation potential are defined by

$$\hat{\mathcal{R}}^*(\hat{\mu}, \hat{\xi}) = \frac{1}{2}\int_\Omega \hat{\delta}^V |\nabla \hat{\xi}|^2 \,\mathrm{d}\hat{\mu}, \qquad \hat{\mathcal{E}}(\hat{\mu}) = \int_\Omega \left(\log \hat{\mu} + \hat{V}\right) \mathrm{d}\hat{\mu},$$

where the mixed space-dependent diffusion coefficient and the mixed potential are given by

$$\hat{\delta}^V = \frac{\delta_1 c_1^{*,V} + \delta_2 c_2^{*,V}}{c_1^{*,V} + c_2^{*,V}}, \quad \hat{V} = -\log\left(c_1^* \mathrm{e}^{-V_1} + c_2^* \mathrm{e}^{-V_2}\right),$$

respectively. The coarse-grained evolution equation is a scalar drift-diffusion equation of the form

$$\dot{\hat{c}} = -\mathrm{div}\left(\hat{\delta}^V \hat{c}\, \nabla\left(-\frac{\delta\hat{\mathcal{E}}}{\delta\hat{\mu}}\right)\right) = \mathrm{div}\left(\hat{\delta}^V \nabla\hat{c} + \hat{\delta}^V \hat{c}\nabla\hat{V}\right).$$

In the potential-free case $V = \mathrm{const}$, we derive classical results for the PDE (partial differential equation) system [1]. In addition, EDP-convergence shows that the effective model can be derived in a consistent structural manner.

Conclusions and outlook

EDP-convergence provides a thermodynamical consistent way to derive effective gradient systems for multi-scale problems. Advantageously, the derived evolutionary systems satisfy the desired physical principles. Moreover, we have seen that previously unknown physical structures are uncovered. They provide theoretical insights in chemical reaction systems and, in this way, a better understanding of everyday chemical and biochemical processes. Mathematically, there are several interesting research directions. The geometry on the space of probability measures that is induced by a linear reaction diffusion system has to be explored. Moreover, the coupling to mechanical systems including explicit temperature dependence is interesting from the application point of view. Naturally, coarse-graining is connected to numerical simulations where continuous problems are approximated by discrete systems. Connection to discrete models will be further investigated in collaboration with the Collaborative Research Centre 1114 *Scaling Cascades in Complex Systems*, which also funded this research.

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