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O modelování vzniku samovolného uspořádání

On modelling the emergence of self-organisation

Summary

Nowadays models for self-organisation are being used in systems with a great degree of complexity and across disciplines. We show that the used Turing model is sensitive to parameters, type of domain growth, but also to the precision of model formulation itself. Hence it is necessary to revise Turing's model for self-organisation. For this purpose we consider derivation of evolution equations within non-equilibrium thermodynamic to identify physically relevant formulations. Only then we subject these models to a detailed mathematical analysis. We offer possible extensions of the concept of self-organisation to more general situations and discuss its physical interpretation.

The essence and importance of these ideas is illustrated on the reaction-diffusion-advection system, where we indicate that such a system should be preferred from both physical and mathematical viewpoint. Further we point to the indispensable role of physical viewpoint during relevant model formulations. Using the non-equilibrium thermodynamic framework physically consistent extensions of Turing model are revealed as well as functional constraints for present parameters.

Souhrn

V současné době se modely pro prostorové uspořádání hojně užívají i ve složitých systémech napříč disciplínami. Ukazujeme, že používaný Turingův model je citlivý na parametry, charakter růstu oblasti, ale i na samotnou přesnost formulace modelu. Proto je nutné revidovat Turingův model pro vznik samovolného uspořádání. K tomuto účelu uvažujeme odvození evolučních rovnic v rámci nerovnovážné termodynamiky, abychom identifikovali fyzikálně relevantní formulace. Až poté podrobujeme tyto modely detailní matematické analýze. Nabízíme též možná rozšíření konceptu sebeorganizace do obecnějších situací a diskutujeme jejich fyzikální interpretaci.

Podstatu a důležitost těchto myšlenek ilustrujeme na reakčně-difuzně-advekčním systému, kde naznačujeme, že takovýto systém by měl být preferován jak z fyzikálního tak z matematického pohledu. Dále pak ukazujeme, jakou nezastupitelnou roli sehrává fyzikální pohled při tvorbě relevantních modelů, kdy pomocí konceptu nerovnovážné termodynamiky odhalujeme fyzikálně konzistentí rozšíření Turingova modelu ale i funkční omezení pro vyskytující se parametry modelu.

Klíčová slova: samovolné uspořádání, vznik vzoru, Turingův model, reakčně-difuzní rovnice, matematická biologie, nerovnovážná termodynamika, teorie směsí, termodynamicky konzistentní modely

Keywords: self-organisation, pattern formation, Turing model, reaction-diffusion equations, mathematical biology, non-equilibrium thermodynamics, theory of mixtures, thermodynamically consistent nmodels

Contents

1 Motivation

Self-organisation in nature is widely recognised and is extensively modelled. Particularly, pattern formation due to chemical instability is believed to be of the essential importance in many non-equilibrium systems, ranging from developmental biology [19, 1] (e.g. morphogenesis [21], hair follicles [23] or fish pigmentation [31, 16]) to chemical reactions [3, 14] or in coupling of heat and mass transfer (the so-called Rayleigh-Bénard convection cells) [4]. For a review about reaction-diffusion models and a great variety of spatial patterns that they can exhibit see [5].

Systematic description of self-organisation in nature was initiated by Turing [32] (from mathematical perspective) and also by Prigogine [26] (from non-equilibrium thermodynamics perspective, NET). Turing showed that small local spatial fluctuations in an otherwise well-mixed system of autocatalytic and inhibitory diffusing species (also known as morphogens) could become unstable due to diffusion and that an amplification of these fluctuations could lead to pattern development. Specifically, heterogeneous concentrations of chemicals form a 'pre-pattern'. Subsequent differentiation of tissue/cell type is in response to whether or not concentration of one of these morphogens in the pre-pattern exceeds some threshold locally. Hence Turing realised that this so-called diffusion-driven instability (DDI, or Turing instability, TI) can be considered as a symmetry breaking mechanism. Interestingly, Prigogine defines dissipative structures as a self-organisation that results from a connection between stability and dissipation [26] and where a pattern is driven by the distance from an equilibrium or nonlinearity in the system. Turing instability is, therefore, a special case of dissipation structures where particular choices of dissipation and system complexity are considered.

For completeness we should mention that not all processes leading to pattern formation are of Turing type. To demonstrate this we take a well-studied example from developmental biology, the mechanism of spatial organisation in the Drosophila embryo. In this system a morphogen called bicoid is produced at the future anterior pole of the embryo and diffuses from this source to form a concentration gradient across the embryo. This concentration gradient of bicoid ultimately serves as a positional guide, instructing nuclei of their position relative to the anterior pole. In the Drosophila embryo no true symmetry ever exists to be broken, as bicoid localisation to the future an-

terior pole is achieved during the formation of the egg by maternal inputs [33, 7]. Thus, this morphogen gradient system leads to positional information, but the spatial pattern is not self-orchestrated.

On the other hand, Turing instability represents a fundamentally different mode of pattern formation, and one which is capable of breaking symmetry without pre-existing positional information. This mechanism has driven numerous experimental studies even in the context of developmental systems (e.g [22, 8, 30, 24]) which suggest that Turing-like morphogen interactions and patterns can occur in such scenarios. However, a direct verification of Turing's mechanism in biology at the level of molecular details has remained elusive.

In this talk we shall first recall the classical work of Turing and identify some of its weaknesses. After that we will combine both the mathematical and physical viewpoints, draw ideas about plausibility of the used modelling approaches and also look for extensions there in order to assess a physically sound model for the emergence of self-organisation in nature.

2 Diffusion-driven instability, Turing

With a given model we use analytical tools to reveal when the self-organisation can be expected. This is done via the so-called stability analysis. Its precise meaning is context dependent and reflects what is meant by the self-organisation in a given system. Typically pattern formation is considered to correspond to a disruption of stability of a reference state due to a certain critical phenomenon taking place. Such a situation is also known as a bifurcation and where the corresponding bifurcation parameter has a physical interpretation relevant for the considered context. In the case of standard Turing instability we shall discuss this matter in more detail below.

2.1 Turing instability on static domain

Diffusion-driven or Turing instability is defined for reaction-diffusion (RD) systems

$$\partial_t \mathbf{u} = \mathbf{D}\partial_x^2 \mathbf{u} + \mathbf{f}(\mathbf{u})$$

with diagonal diffusion matrix $\mathbf{D} = \mathrm{diag}(D_1, D_2)$ as a situation where a homogeneous steady state solution (HSS) $\mathbf{u}^*$, $0 = \mathbf{f}(\mathbf{u}^*)$, is stable in the

absence of diffusion and unstable once diffusion is introduced into the system. In this setting it can be equivalently rephrased as a requirement that the HSS is stable with respect to spatially homogeneous perturbations but unstable with respect to heterogeneous perturbations. As soon as we depart from such reaction-diffusion system with constant diffusion coefficients by considering a more complex transport operator, these two concepts may split up and also other admissible definitions of Turing instability may seem plausible. Hence we shall firstly discuss the motivation for the classical definition of Turing instability. For its discussion it is convenient to define a critical length and to relate it to TI.

Let us solve a RD initial-boundary value problem in 1D with domain length L being a bifurcation parameter, i.e. to observe the effect of the (growing) domain size on the stability and solution properties. Particularly, let us consider a one-dimensional RD model for a single species with, for example, Dirichlet boundary conditions

$$\partial_t u = D\partial^2_{xx} u + f(u), \quad u(0,t) = 0 = u(L,t)$$

where $L > 0$ is the size of the domain and with $u^* = 0$ being the HSS, i.e. $f(u^*) = 0$. To explore DDI we would like to solve the above system when accompanied by a small initial perturbation of the HSS

$$0 \leq u(x,0) \ll 1.$$

Using the method of separation of variables and invoking completeness of eigenfunctions of Laplacian on $L^2(0,L)$ we have that the homogeneous solution is of the form

$$u_H(x,t) = \sum_{n=1}^{\infty} A_n(t) \sin\left(\frac{n\pi x}{L}\right).$$

The nonhomogeneous solution is then obtained by expanding $f(u)$ in terms of the orthonormal basis $\left\{\sin\left(\frac{n\pi x}{L}\right)\right\}_{n=1}^{\infty}$. As we are interested in small initial perturbations only (linear stability analysis), the expansion is at hand as $f(u) \approx f'(0)u(x)$. This gives that the time-dependent coefficients satisfy

$$\frac{\mathrm{d}}{\mathrm{d}t} A_n = \frac{Dn^2\pi^2}{L^2} A_n + f'(0) A_n.$$

For (linear) stability we require the solution to decay to the zero HSS or equivalently in this case all amplitudes of eigenfunctions have to vanish as

$t \to \infty$. Thence we require that

$$L < \sqrt{\frac{Dn^2\pi^2}{f'(0)}} \stackrel{def}{=\!=} L_{crit} \quad \forall n.$$

Thence there is a critical lengthscale L_{crit} below which spatial self-organisation cannot occur as no eigenfunction fits in such a domain.

These ideas extend to higher dimensions for Dirichlet boundary conditions as from the spectral properties of minus Laplacian for bounded domains it follows (from the method of Rayleigh quotient and minmax principles) that $\Omega_1 \subseteq \Omega_2 \Rightarrow \lambda_n(\Omega_1) \geq \lambda_n(\Omega_2)\ \forall n$ with λ_n being the countable eigenvalues. The same conclusion does not hold for Neumann boundary conditions in general but holds for scaled domains, i.e. $\Omega_1 \subseteq \Omega_2,\ \Omega_2 = \alpha\Omega_1 \Rightarrow \lambda_n(\Omega_1) \geq \lambda_n(\Omega_2),\ \forall n$.

2.2 Why considered as a model for self-organisation?

As we are about to study the emergence of self-organisation in more general systems, we first need to extend the concept of Turing instability to systems outside of RD. Two immediate possibilities from the above characterisation of TI are:

S-O *the emergence of self-organisation.* We believe/propose that this situation can be characterised by: one, the existence of a critical domain size below which system is stable to small perturbations and above which instability may occur; two, the existence of only a finite number of unstable modes as otherwise continuum description would break down (and no structure in spatial organisation would appear except salt-and-pepper pattern). This S-O instability can be also termed as a domain-size driven in which case the instability induces symmetry breaking (in a system that is continuously subjected to perturbations).

TDI *Transport-driven-instability* requiring stability (of the HSS) without transport and instability once transport is considered. Naturally, the condition on the existence of finite numbers of unstable modes is present as well. Hence this TDI is equivalent to heterogeneity amplifying instability, i.e. the system is stable until a small heterogeneity perturbs it, and thus the instability amplifies symmetry breaking rather than inducing it.

Particularly, if one would like to study the transport-driven instability, one should adopt the above TDI concept of TI extension requiring the stability of the HSS without transport. Finally, if one addresses the spontaneous emergence of the spatial self-organisation in a reaction-diffusion-advection (RDA) system, one could adopt the above S-O extension which induces symmetry breaking (and hence self-organisation) while requiring the stability of the HSS only if zero is an eigenvalue of the transport operator with given BCs.

Is it reasonable to promote diffusion-driven instability over other potential causes of instabilities when analysing the possibility of spatial self-organisation in a system? Why would one enforce the strict condition for stability of the HSS without diffusion in a system when this is not relevant to a real system where diffusion either is or is not present? In the case of RD system, answer to the first question is that the emergence of spatial self-organisation is related exactly to DDI as can be seen from the above S-O characterisation of Turing instability. Particularly, the requirement of the existence of a critical length is related to the requirement of stability of the HSS in the following way. In the case of

Neumann BCs the stability of a homogeneous steady state is required. The reason is that the existence of critical length enforces decay of perturbations for small enough lengths and hence, as orthonormal basis (ONB) contains a constant eigenfunction, stability of the HSS with respect to spatially homogeneous perturbations is required.

Dirichlet BCs the stability of the HSS is not implied from the stability of the system to perturbations as a constant is not part of ONB (nonzero spatially homogeneous perturbation does not satisfy Dirichlet BC). For example consider a 1D domain $\Omega = [0, L]$, then eigenvalues of minus Laplacian are $\frac{n\pi}{L}$ for a natural number n. As zero eigenvalue is not permissible due to the BCs, the zero homogeneous state is automatically stable in a linearised system for small enough L as eigenvalues of the linearised kinetics will be dominated by $-\frac{n\pi}{L}$ [12] and hence without any condition on the stability of the HSS without diffusion.

Therefore the stability of the HSS without diffusion in Turing instability (TI) is an *additional* requirement only for Dirichlet BC.

Note that these considerations refer to a more general question: should Turing instability be a method/concept/model for an emergence of spatial

self-organisation or a particular type of (transport) driven spatial organisation? Also note that the requirement of the existence of a critical length or that there is only a finite number of unstable modes might not be always required although they seem to be reasonable requirements for studying self-organisation in nature, especially in biology. In RD systems, these scenarios coincided as discussed above but in other situations we should choose an appropriate extension following a given aim.

3 Is Turing model a plausible model for self-organisation?

We shall now raise some of the known issues of Turing model and discuss whether it stands as a plausible model for self-organisation.

3.1 $D_1 \neq D_2$ and binding to substrate

One of the well-known problems of Turing's approach is the requirement for unequal diffusion coefficients where for typical parameter values of reaction kinetics the diffusion coefficients of a putative morphogen pair need to differ by an order of magnitude. This condition is, however, in contrast with Einstein-Smoluchovski relation for an estimate of diffusion coefficient as it would require the putative morphogens to significantly differ in size which is not observed.

We recently showed that if at least one of the morphogens interacts with (binds to) underlying substrate (like the extracellular matrix), this issue can be resolved [17]. Consider linearised kinetics of two morphogens where one binds to a substrate

$$\begin{aligned}
\partial_t u &= D_u \Delta u + (f_u - k_+)u + f_v v + k_- w \\
\partial_t v &= D_v \Delta v + g_u u \qquad\quad + g_v v \\
\partial_t w &= \qquad\quad k_+ u \qquad\qquad\quad - k_- w
\end{aligned}$$

and Neumann BC for $u,\ v$. Note that $k_- > 0$ (self-inhibitory) in order to have a chance for DDI [12].

Does fast binding change DDI conditions? Not in the quasi steady state limit as all the binding contributions dissapear. Instead we shall try to identify a higher order approximation of this quasi steady state approximation.

Solving the last equation for bounded morphogen w yields (Laplace method):

$$w(t) = e^{-k_- t}\left[\int_0^t k_+ e^{-k_-\tau} u(\tau)\mathrm{d}\tau\right] = k_+ \int_0^t e^{-k_-(\tau-t)} u(\tau)\mathrm{d}\tau \approx$$
$$\approx k_+ \int_{t-\epsilon}^t e^{-k_-(\tau-t)} u(\tau)\mathrm{d}\tau \approx$$
$$\approx k_+ \left[u(t)\frac{1-e^{-\epsilon k_-}}{k_-} + \partial_t u(t)\frac{e^{-\epsilon k_-}\left(1-e^{-\epsilon k_-}+\epsilon k_-\right)}{k_-^2}\right],$$

where the expansion of the solution $u(\tau) = u(t) + (\tau - t)\partial_t u(t) + \ldots$ was used. Hence ($\epsilon k_- \ll 1$)

$$w(t) \approx \frac{k_+}{k_-}\left[\underbrace{u(t)}_{QSS} - \frac{1}{k_-}\partial_t u(t) + O\left(\frac{1}{k_-^2}\right)\right]$$

Therefore the higher order quasi steady state approximation results in a rescaling of the relation for u

$$\underbrace{\left(1+\frac{k_+}{k_-}\right)}_{>1}\partial_t u = D_u \Delta u + f_u u + f_v v$$
$$\partial_t v = D_v \Delta v + g_u u + g_v v.$$

Consequences on DDI conditions are easily assessed (the rescaling denoted by a prime $()'$ affects D_u and $f_u,\ f_v$):

$$\mathrm{tr}\mathbf{J}' < 0, \det \mathbf{J} > 0, D_u g_v + D_v f_u > 2\sqrt{D_u D_v \det \mathbf{J}} > 0$$

where $D_u > D_v$ is no longer a contradiction.

3.2 Reductionism

As the above note about the prominent effect of considering binding of morphogens to a substrate indicates, the level of detail included in a model for self-organisation may significantly change the prediction of pattern formation.

The problem of reductionism was addressed in [12] pointing to the fact that a complete knowledge of morphogen interaction network is necessary

for plausible predictions of system's behaviour. Particularly we showed that model predictions can be exactly opposite from reality. In one example the full model (say reality) does not yield patter but a reduced model, where one of the interacting morphogens is neglected (is undetected), does. Similarly, another example is provided but where the situation is reversed.

3.3 Growing domain vs L as bifurcation parameter

In DDI mechanism for the emergence of self-organisation the domain size is treated as a bifurcation parameter, i.e. without the explicit time dependence. In 2010 Madzvamuse, Gaffney and Maini showed that tracking the actual slow growth has a qualitative impact on the results of analysis [18], e.g. a new type of reaction kinetics is allowed to give rise to DDI (although the parameter space is somewhat limited), different types of growth yield different Turing spaces (regions in parameter space where the necessary DDI conditions are met). Hence these findings are highlighting a qualitative difference between the two approaches although the actual effect of domain growth on DDI conditions was found to be only via a correction to the classical DDI conditions of a small order.

Based on this study we recently showed [13] that the actual picture of conditions for the emergence of a pattern on growing domains is more complex than previously thought and that the classical approach with domain size being the bifurcation parameter is a plausible approximation only for very slow growth. Additionally, for faster growth we show that prediction becomes even more out of reach. Particularly due to the intrinsic growth, modes can first substantially transiently grow prior to decay, but this behaviour is highly dependent on initial conditions or noise thence making predictions impossible. Further, for some growth rates we observed that all modes with a high enough wavenumber transiently grow yielding a breakdown of the continuum description itself.

For illustration consider a RD system on a growing domain which can be simplified to the following dimensionless formulation

$$\partial_t \mathbf{u} + h(t)\mathbf{u} = \frac{1}{\varphi^2(t)}\mathbf{D}\Delta_\xi \mathbf{u} + \gamma \mathbf{F}(\mathbf{u}) \tag{1}$$

in normalised Lagrange coordinates[1] and with the following definitions of

[1] $x = \chi(\xi, t)$ where $\chi(\xi, 0) = \xi$ and $\xi \in [0, 1]$

parameters: $\mathbf{D} = \text{diag}(1, d)$, $d = D_v/D_u$, $\gamma = L_0^2/D_u$. The advection term, $\nabla.(\mathbf{au})$, representing growth is transformed into an effective time-dependent diffusion coefficient[2], $\frac{1}{\varphi^2(t)}\mathbf{D}$, and an additional linear term $h(t)\mathbf{u}$. This explicit dependence of the RD equation on time as a consequence of intrinsic domain growth is making the stability analysis difficult. However, with the assumption of a slow uniform linear growth one can approximate the qualitative evolution of a perturbation about a reference state $\mathbf{u}_s$ (a spatially homogeneous but time-dependent solution to the RD problem) yielding an analogue to DDI conditions for pattern formation [18].

A point in parametric space is a member of the so-called *Turing space* iff the corresponding reference state is stable without diffusion and unstable once diffusion is present for the reasons discussed above. Hence a point in the parametric space is not in Turing space iff either the reference state itself is unstable or that diffusion failed to destabilise the stable reference state. In the classical treatment one can access this information via evaluation of DDI conditions for such a value of parameters. But when DDI conditions are evolving, as is the case with the intrinsically growing domain, Turing space has to be more carefully assessed. As a result, when time-evolving DDI conditions are plotted (as reported in [18] e.g. for linear growth) one needs to track the reason why a given point changed its property with respect to DDI conditions. In fact, if the plotted DDI region is moving into a region of parameter where the reference state itself was unstable (being the reason why Turing space was not here in preceding times) this region cannot be considered as DDI leading to self-organisation (e.g. due to the lack of existence of critical length) and, as a result, should not be included in the Turing space. Hence, one needs to track the evolution of stability of the reference state in addition to evolution of intersection of DDI conditions in order to correctly capture the parametric space leading to the emergence of spatial self-organisation on growing domains.

Particularly, Madzvamuse et al [18] showed that DDI conditions evolve as

[2] $\chi(\xi, t) = \varphi(t)\xi = \xi \exp(\int_0^t h(\tau)\mathrm{d}\tau)$

follows

$$\left.\begin{aligned} -\gamma \operatorname{tr} \mathbf{J}_{\mathbf{u}_s(t_1)} + 2h(t_1) > 0 \\ -h(t_1)\gamma \operatorname{tr} \mathbf{J}_{\mathbf{u}_s(t_1)} + \gamma^2 \det \mathbf{J}_{\mathbf{u}_s(t_1)} > 0 \end{aligned}\right\} \mathcal{S}(t_1)$$

$$\left.\begin{aligned} -\gamma\left[df_u + g_v\right] + h(t_1)(1+d) < 0 \\ \left[h(t_1)(1+d) - \gamma(df_u + g_v)\right]^2 - 4d[\gamma^2 \det \mathbf{J}_{\mathbf{u}_s(t_1)} - \gamma h(t_1) \operatorname{tr} \mathbf{J}_{\mathbf{u}_s(t_1)}] > 0 \end{aligned}\right\} \mathcal{U}(t_1)$$

where $\mathbf{J}_{\mathbf{u}_s(t_1)}$ denotes the Jacobian of linearised kinetics $\mathbf{F}(\mathbf{u})$ evaluated at $\mathbf{u}_s(t_1)$ and $f_u,\ f_v,\ g_u\ , g_v$ represent its elements. Consider $t \in [0, T]$. A bifurcation due to a DDI occurs, for the first time, at $t = T > 0$ on the set

$$\left\{ \underbrace{\left[\bigcup_{t\in[0,T]} \overline{\mathcal{S}(t)}\right]}_{\substack{\text{stability w.r.t. homogeneous} \\ \text{perturbations always}}} \cap \left[\underbrace{\overline{\mathcal{U}(T)}}_{\substack{\text{instability} \\ \text{at time } T}} \setminus \underbrace{\bigcup_{t\in(0,T)} \mathcal{U}(t)}_{\substack{\text{but not unstable} \\ \text{at any earlier time } t>0}} \right] \right\} \setminus \underbrace{\left[\overline{\mathcal{S}(0)} \cup \overline{\mathcal{U}(0)}\right]}_{\substack{\text{assuming not} \\ \text{destabilised via} \\ \text{DDI at } T=0}}.$$

Turing instability will have occurred in the Turing space below by time T

$$\underbrace{\left[\overline{\mathcal{S}(0)} \cap \overline{\mathcal{U}(0)}\right]}_{\text{DDI occurs at } t=0} \cup \left\{ \bigcup_{s\in(0,T]} \underbrace{\left[\left(\bigcup_{t\in[0,s]} \overline{\mathcal{S}(t)} \right) \cap \left(\overline{\mathcal{U}(s)} - \bigcup_{t\in[0,s]} \overline{\mathcal{U}(t)} \right) \right]}_{\substack{\text{Turing instability for first time at } t=s \\ \text{neglecting subset where in fact DDI occurs at } t=0}} \right\}.$$

Note that these ideas were illustrated for two types of reaction kinetics where the complexity of conditions yielding self-organisation is apparent [13].

3.4 NET - constantness of D?

Physical perspective and insight is a key in mathematical modelling. As we shall illustrate in this and the following subsections, a detailed mathematical analysis of a given problem (in this case the Turing's RD problem with constant diffusion coefficient) may yet provide misleading conclusions due to the

weak correspondence of the model to reality. In all the three above examples point to the sensitivity of the results to the model formulation and hence the formulation of a model for self-organisation should be careful.

We shall show here that the typical assumption of constantness of diffusion coefficient in Fick's law may be in many situations false by yielding a thermodynamically inconsistent model. We use the non-equilibrium thermodynamic framework for formulating physically sound models. A typical and most used example of such framework is the classical irreversible thermodynamics (CIT) which has been shown to be a very powerful tool for modelling transport, reaction kinetics or viscous effects. The theory has been described [20] and thoroughly summarized [6]. It has been applied to engineering problems, including coupled heat and mass transport [10]. A fundamental assumption of the theory are the linear force-flux relations

$$\mathbf{J}_i = \sum_j L_{ij}\mathbf{X}_j, \tag{2}$$

where $\mathbf{J}_i$ and $\mathbf{X}_i$ are the thermodynamic fluxes and forces, respectively. Phenomenological coefficients L_{ij} form a matrix of phenomenological coefficients $\mathbf{L}$ and in general they depend on the local thermodynamic state of the system, expressed in terms of the state variables.

The success of CIT is closely related to the accessibility of experimental assessment of the closure (constitutive) relations. Nevertheless, for n coupled processes n^2 phenomenological parameters need to be identified together with their dependence on state variables (and boundary conditions). Not all are, however, easily accessible and hence any a-priori relations among the coefficients mean a significant reduction of the necessary experimental effort to assess all the model parameters. To this end the second law of thermodynamics, which is expressed as non-negativity of local entropy production $\sigma_s = \sum_i \mathbf{J}_i\mathbf{X}_i \geq 0$, imposes constraints on $\mathbf{L}$, particularly $\mathbf{L}$ being positive semi-definite, and the Onsager reciprocal relations (ORR) [27, 28] reduce the number of unknown parameters to $n^2/2 + n/2$.

Recently we showed [15] that there are further constraints on phenomenological coefficients in addition to ORR within CIT where this claim was motivated by our observation about correlation of transport coefficients in water and proton transport across Nafion membranes at low applied electric potentials [2]. We hypothesised that in addition to Onsager's relations the coefficients have to share the same functional dependence on the local

thermodynamic state of the system and proved this statement for a certain class of nonequilibrium thermodynamic models using the maximum principle. Thence mathematical models and experimental data should be checked for consistency in the above sense and we discussed this issue on some examples. Particularly, we showed that (by studying a thermodiffusion model which in an isothermal case reduces to Fick's diffusion law) that the widely used assumption of constant diffusion coefficient is thermodynamically inconsistent once the considered system would have a nonzero thermodiffusion coupling in the nonisothermal case, i.e. the presence of temperature gradients would cause a diffusion flux to appear as in the classical Rayleigh-Bénard convection. On the other hand, if we let the diffusion coefficient to scale as $D \propto c^{-1}$ with c being the concentration we obtain a thermodynamically consistent model.

3.5 NET (theory of mixtures) - extension of RD to RDA

If we subject the Fick's law of diffusion to scrutiny, particularly if we derive the evolution equations for reacting mixtures from first principles and use the CIT or EIT (extended irreversible thermodynamic [9]) constitutive theory, we observe that advection can appear as a pure consequence of chemical reactions among constituents. Particularly, from a careful formulation of mixture theory of fluids [29] it follows that chemical kinetics is not only driven by chemical affinity $\mathcal{A}_s$ but by diffusion flux $\mathbf{u}_\alpha$ as well. We have shown that the chemical reaction rate $\dot{\xi}_r$ is governed by

$$\dot{\xi}_r = \sum_s L_{rs}^{rr} \frac{1}{T} \left(\mathcal{A}_s + \sum_\alpha -\nu_{s\alpha} M_\alpha \frac{\mathbf{u}_\alpha}{2} \right),$$

where $\nu_{s\alpha}$ denotes stoichiometric coefficient of species α in s-th reaction and M_α stands for molar mass. The effect of affinity on chemical reaction rate is typically modelled by Law of mass action. Crucially, the identified term reveals a new effect: diffusion can drive chemical reactions but also vice-versa, chemical reactions alone can cause diffusion flux.

Substitution of this relation together with Fick's law of diffusion into the

balance of mass yields

$$\partial_t c_\alpha = \nabla(D_\alpha \nabla c_\alpha) + \sum_r \nu_{r\alpha} M_\alpha \dot{\xi}_r = D_\alpha \nabla^2 c_\alpha + \sum_\beta K_\beta (\nabla c_\beta)^2 + R(c_1, \ldots, c_n)$$
$$= D_\beta \nabla^2 c_\alpha + \sum_\beta \underbrace{K_\beta(\nabla c_\beta)}_{\mathbf{v}_\beta} . (\nabla c_\beta) + R(c_1, \ldots, c_n),$$

where the kinetics $R(c_1, \ldots, c_n)$ is determined from law of mass action and interaction network [11]. Note that the new term may be formally regarded as an advection. Moreover, advection with velocity $\mathbf{v}_\alpha$ may be present regardless of the presence of Fickian diffusion and thus should be taken into account. In summary, this suggests that the effect of (small) advection on RD models should be studied.

3.6 Self-organisation in RDA systems

Let us consider a RDA system and for simplicity let us restrict the analysis to a 1D domain $G = [0, L]$. Particularly, we have

$$\partial_t \begin{pmatrix} r(x)\ a \\ r(x)\ b \end{pmatrix} = \begin{pmatrix} D_a\ \mathcal{L}(a) \\ D_b\ \mathcal{L}(b) \end{pmatrix} + r(x) \begin{pmatrix} f(a,b) \\ g(a,b) \end{pmatrix}$$

where $\mathcal{L}a = \partial_x (p(x)\partial_x a) + q(x)a$ is an operator discussed below, $D_a,\ D_b$ are two constants and a, b are concentrations of two morphogens.

First, note that stability analysis of a stationary solution that is spatially dependent is beyond the scope of this work. Hence, we restrict ourself to the standard case when the existence of a homogeneous stationary solution a^*, b^* is required. Thus

$$\mathbf{0} = q(x) \begin{pmatrix} D_a a^* \\ D_b b^* \end{pmatrix} + r(x) \begin{pmatrix} f(a^*, b^*) \\ g(a^*, b^*) \end{pmatrix},$$

the fraction $q(x)/r(x)$ is a constant and hence the $q(x)$ term can be absorbed into the reaction kinetic terms. As a result we can assume WLOG $q(x) = 0$ in the subsequent analysis, although such a shift of linearised kinetics can have a profound yet straightforward effect on the character of stability of the HSS and also on the emergence of self-organisation.

Hence we consider the above equations subjected to non-homogeneous Robin, $\alpha_1 y(0) + \alpha_2 y'(0) = \alpha_1 y^*,\ \beta_1 y(L) + \beta_2 y'(L) = \beta_1 y^*$, or periodic,

$y(0) = y(L),\ y'(0) = y'(L)$, boundary conditions that are compatible with the HSS y^*. The spatial operator $\mathcal{L} = \partial_x\left(p(x)\partial_x\right)$ with these boundary conditions is a Sturm-Liouville operator. It is a self-adjoint operator when defined on $L^2(0, L)$ and the set of its eigenfunctions satisfying the above boundary conditions form a complete basis set of those square-integrable functions which satisfy the given boundary conditions as can be shown with the help of Rayleigh quotient. Note that for the periodic BCs they also form a complete set of eigenfunctions, only in this case there might not be a unique linearly independent eigenfunction corresponding to each eigenvalue and would need to use Gramm-Schmidt process first.

Let $\gamma_n(x)$ solve $\partial_x\left(p(x)\partial_x\gamma_n(x)\right) = -\lambda_n r(x)\gamma_n(x)$ and let

$$\begin{pmatrix} a \\ b \end{pmatrix} = \begin{pmatrix} a^* \\ b^* \end{pmatrix} + \begin{pmatrix} \alpha \\ \beta \end{pmatrix}$$

with $\begin{pmatrix} \alpha \\ \beta \end{pmatrix} = \sum_n \mathbf{A}_n\gamma_n(x)$ where we take advantage of the fact that $\gamma_n(x)$ form an ON basis of $L^2(G)$ and $\mathbf{A}_n = \begin{pmatrix} A_n^1 \\ A_n^2 \end{pmatrix}$.

Linearising about $\begin{pmatrix} a^* \\ b^* \end{pmatrix}$ yields

$$\sum_n r(x)\gamma_n(x)\left(\mathbf{A}_n + \begin{pmatrix} D_a\lambda_n A_n^1 \\ D_b\lambda_n A_n^2 \end{pmatrix} - \mathbf{J}(a^*, b^*)\mathbf{A}_n\right) = \mathbf{0}$$

where $\mathbf{J}(a^*, b^*)$ denotes the jacobian of reaction kinetics evaluated at the HSS (e.g. $J_{12} = \partial_b f|_{a=a^*, b=b^*}$). As γ_n form ON basis we have that

$$\mathbf{A}_n = -\left(\lambda_n \begin{pmatrix} D_a & 0 \\ 0 & D_b \end{pmatrix} - \mathbf{J}\right)\mathbf{A}_n$$

and hence the so-called dispersion relation is obtained

$$\det\left(\sigma_n\mathbf{I} + \lambda_n \begin{pmatrix} D_a & 0 \\ 0 & D_b \end{pmatrix} - \mathbf{J}\right) = 0.$$

Its roots σ_n correspond to eigenvalues of the linearised system governing the linear behaviour and consequently determine the linear stability of the HSS.

The difficulty, of course, lies in the eigenvalue problem of the S-L operator $\mathcal{L}$. To illustrate the above ideas we shall discuss in detail a situation of a RDA

problem and study what implication it has on TDI and S-O in relation to Turing instability. We shall consider both possible concepts and extensions of Turing instability proposed above and study systems with advection. The main aim of this section is to estimate the consequences of negligence of (small) advection in Turing instability studies.

We consider a system of two interacting species a, b without differential transport, i.e. where both species are diffusing and advecting with the same magnitude ($D_a = D_b$ and advection is the same)

$$\partial_t \begin{pmatrix} a \\ b \end{pmatrix} = \begin{pmatrix} D\partial^2_{x^2} a + V\partial_x a \\ D\partial^2_{x^2} b + V\partial_x b \end{pmatrix} + \begin{pmatrix} f(a,b) \\ g(a,b) \end{pmatrix} \tag{3}$$

where functions f, g describe reaction kinetics. The above S-L theory can be applied as the choice $r(x) = p(x) = e^{Vx/D}$ with $D = D_a$ yields a RDA system with a constant advection V.

Three types of boundary conditions are relevant for RDA problems. Particularly with (a^*, b^*) being the HSS about which linear stability is of interest we explore (analogous BCs are required for species b)

Dirichlet BC $a(x) = a^*$ at $x \in \{0, L\}$,

Fixed-flux BC $D_a\partial_x a(x) + Va(x) = Va^*$ at $x \in \{0, L\}$,

Periodic BC $a(0) = a(L)$ and $\partial_x a|_{x=0} = \partial_x a|_{x=L}$,

Danckwerts BC $D_a\partial_x a(x) + Va(x)|_{x=L} = Va^*$ and $\partial_x a(x)|_{x=0} = 0$,

so that the HSS is a plausible solution of the problem at hand. However, for the sake of illustration, we shall consider only the fixed-flux BC for species a, b (other BCs can be analogically analysed), i.e. $\mathcal{L}^{bc}a = Va(x) + D\partial_x a(x) = Va^*$ and $\mathcal{L}^{bc}b = Vb^*$ at $x \in \{0, L\}$, and a small perturbation of the HSS as an initial condition, i.e. $a(t = 0, x) = a^* + a_0(x)$, $b(t = 0, x) = b^* + b_0(x)$, $|a_0| \ll a^*$, $|b_0| \ll b^*$. Compatibility of the boundary and initial conditions requires $Va_0(x) + D\partial_x a_0(x) = 0$ at the boundary and similarly for species b.

Linearisation about the HSS (a^*, b^*) with $(\bar{a}, \bar{b}) = (a, b) - (a^*, b^*)$ yields

$$\partial_t \begin{pmatrix} \bar{a} \\ \bar{b} \end{pmatrix} + \begin{pmatrix} \mathcal{L}\bar{a} \\ \mathcal{L}\bar{b} \end{pmatrix} = \mathbf{J} \begin{pmatrix} \bar{a} \\ \bar{b} \end{pmatrix} \tag{4}$$

under the assumption of small perturbations (aiming at linear stability analysis and hence dropping the higher order terms), $|\bar{a}| \ll a^*, |\bar{b}| \ll b^*$, and

with the matrix of linearised kinetics, $\mathbf{J}$, evaluated at the HSS (a^*, b^*). The nonhomogeneous Robin boundary condition is transformed into a zero-flux boundary condition $(\mathcal{L}^{bc}\bar{a}, \mathcal{L}^{bc}\bar{b}) = \mathbf{0}$ at both boundaries of $[0, L]$. The initial conditions are $\bar{a}(t = 0, x) = a_0(x)$, $\bar{b}(t = 0, x) = b_0(x)$ and are automatically compatible with the zero-flux boundary conditions.

Now we are ready to employ the ONB of $L^2(0, L)$ that consists of eigenfunctions γ_n of $\mathcal{L}$, i.e. $\mathcal{L}\gamma_n = \lambda_n\gamma_n$ subjected to homogeneous BCs $\mathcal{L}^{bc}\gamma_n = 0$, as all the terms appearing in the bulk equation satisfy zero-flux BCs. Hence, stability of the HSS (a^*, b^*) can be assessed from the decays of the amplitudes of the eigenmodes in the problem (4). With $\bar{a} = \sum_n A_n(t)\gamma_n(x)$, $\bar{b} = \sum_n B_n(t)\gamma_n(x)$ we have

$$\sum_n \left[\partial_t \begin{pmatrix} A_n \\ B_n \end{pmatrix} + (\lambda_n \mathbf{I} - \mathbf{J}) \begin{pmatrix} A_n \\ B_n \end{pmatrix}\right] \gamma_n = 0.$$

Thus the HSS is linearly stable if the roots $\sigma_\pm$ of the dispersion relation

$$\det\left(-\sigma_\pm \mathbf{I} - (\lambda_n \mathbf{I} - \mathbf{J})\right) = 0 \tag{5}$$

have negative real parts and is unstable if at least one of the roots has a positive real part.

Except for fine parameter tuning (that would be hard to justify due to the required robustness) we have $\mathbf{J} = \mathbf{U}^T \begin{pmatrix} \mu_+ & 0 \\ 0 & \mu_- \end{pmatrix} \mathbf{U}$ and hence the dispersion relation (5) can be rewritten as

$$\det\left[\mathbf{U}^T \left(-\sigma_\pm \mathbf{I} + \begin{pmatrix} \mu_+ - \lambda_n & 0 \\ 0 & \mu_- - \lambda_n \end{pmatrix}\right) \mathbf{U}\right] = 0$$

with roots $\sigma_\pm = \mu_\pm - \lambda_n$. Thus we may conclude (it can be easily shown that the conclusion does hold even when $\mathbf{J}$ is not diagonalisable via Jordan blocks) that the HSS (a^*, b^*) is linearly stable iff

$$\Re(\lambda_n - \mu_+) > 0 \text{ and } \Re(\lambda_n - \mu_-) > 0, \quad \forall n \in \mathbb{N}_0 \tag{6}$$

where λ_n are eigenvalues of the spatial operator $\mathcal{L}$ subjected to BCs $\mathcal{L}^{bc}u = 0$ at $x \in \{0, L\}$ and $\mu_\pm$ are two eigenvalues of linearised kinetics matrix $\mathbf{J}$.

To conclude the stability analysis it suffices to identify eigenvalues of the spatial operator $\mathcal{L}$. Namely,

$$\mathcal{L}\gamma_n = -(D\partial_{x^2}^2 + V\partial_x)\gamma_n = \lambda_n\gamma_n$$

subjected to zero-flux BCs

$$\mathcal{L}^{bc}\gamma_n = (D\partial_x + V)\gamma_n = 0 \text{ at } x \in \{0, L\}.$$

The spatial operator $\mathcal{L}$ is a non-self-adjoint operator but can be transformed into a self-adjoint operator [25] via transformation $\gamma_n = e^{-\frac{V}{2D}x}\varphi_n$ with appropriately modified BCs (note that the eigenfunctions ξ_n are orthogonal with respect to the weighted inner product $\langle \xi_n, \xi_k \rangle = \int_0^L \xi_n(x)\xi_k(x)e^{\frac{V}{D}x}\mathrm{d}x = 0$ for $n \neq k$). We shall use, however, the above outlined S-L theory to illustrate its generality and applicability. With the choice of $p(x) = r(x) = e^{xV/D}$, finding eigenfunctions requires solving

$$e^{-xV/D}\partial_x(e^{xV/D}\partial_x\gamma_n) = \lambda_n\gamma_n$$

with constraints $V\gamma_n + D\partial_x\gamma_n = 0$ at $x \in \{0, L\}$. One finds that such eigenvalues are

$$\lambda_n = D\left(\frac{n\pi}{L}\right)^2 + \frac{1}{4}\frac{V^2}{D} > 0. \quad n \in \mathbb{N}_0.$$

Hence we may summarise this subsection that in the case of prescribed fixed-flux BCs there is no TDI as it requires stability of the HSS (and hence $\Re\mu_+ < 0$, $\Re\mu_- < 0$) but for (S-O) we may have an emergence of self-organisation for arbitrarily small magnitude of advection V where the fixed-flux BCs approach zero-flux BCs used in RD systems. This is in contrast with classical TI in RD systems but also in the case when we would adopt the definition of (S-O) for TI. The reason is that in the classical problem the stability of the HSS is required as zero-flux BCs allow for a constant (a HSS) solution (zero is an eigenvalue) whereas the fixed-flux BCs in the case of RDA do not permit the HSS to be part of the ONB (zero is not an eigenvalue) and hence stability of the HSS is not required for the emergence of self-organisation. Finally, note that the existence of critical length below which instability cannot occur together with the finite number of unstable modes are satisfied.

4 Conclusion

Let us summarise the main observations from this talk as

1. we do not have a plausible model for self-organisation (for applications in nature)
2. nonequilibrium thermodynamics is a suitable framework to use to identify model formulations
3. only then (after a suitable model is identified) a detailed mathematical analysis is needed and can reveal conditions for the emergence of self-organisation.

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Curriculum Vitae

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Work experience

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Projects

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Stays abroad

July - September 2015: A three-months stay at Newton's Institute, Cambridge University (research programme Coupling Geometric PDEs with Physics for Cell Morphology, Motility and Pattern Formation, 13.7 - 18.12. 2015)

May-July 2014: A two-months stay in Centre of Mathematical Biology, Mathematical Institute, University of Oxford; Platform grant with EA Gaffney

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May 2011: A one-month stay at the OCCAM, Mathematical Institute, University of Oxford; continuation of initiated research; short-term visitor of OCCAM

July - October 2010: A three-months stay at the OCCAM, Mathematical Institute, University of Oxford; Visiting Postdoctoral Research Assistantship award

May - July 2010: A two-months stay in Research Group on Structural Mechanics and Materials Modeling (GEMM), I3A, University of Zaragoza; travel grant from Instituto Aragones de Ciencias de la Salud, research project PIPAMER10/015

October 2005: One month stay in LIAB (prof Yahia) of Ecole Polytechnique, Montreal

Awards

- the second place in Reinhart Heinrich Doctoral Thesis Award 2011 from European Society of Mathematical and Theoretical Biology
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Other

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  - Mathematics of Pattern Formation 2016, Mathematical Research and Conference Center, Bedlewo, Poland, September 12-17 2016
  - Keynote lecture, BIOMATH 2014, V Klika: Emergence of spatial organisation in real systems and its modelling, Sofia, Bulgaria, 22-27 June 2014
  - The European Conference on Mathematical and Theoretical Biology ECMTB 2011, V. Klika, F. MarÅąÃŋk: Tissue adaptation driven by chemo-mechanical coupling with application to bone in mini-symposium on Mathematical modeling of biomechanical regulation in bone tissue, Krakow, Poland, June 28- July 2 2011
  - V. Klika - Biochemical model of bone remodelling including mechano-chemical coupling. Banff International Research Station workshop, topic Mathematical Foundations in Mechanical Biology, September 2010

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