

# BOOK REVIEWS

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*Free energy and self-interacting particles*, by Takashi Suzuki, Birkhäuser Boston, Inc., Boston, 2005, xiv+366 pp., US\$129.00, ISBN 0-8176-4302-8

## 1. INTRODUCTION

This book is primarily concerned with systems of partial differential equations of elliptic-parabolic type. Such systems are special cases of systems of partial differential equations that occur naturally in biochemistry, biophysics, molecular biology and in chemical thermodynamics and statistical mechanics—in short wherever chemical kinetics and diffusive processes are present in a system. The particular system in the text has the following form in  $\Omega \times (0, T)$  where  $\Omega$  is a bounded region in two or three dimensions with a smooth boundary,  $\partial\Omega$ :

$$(1.1) \quad \begin{aligned} u_t &= \nabla \cdot (\nabla u - u\nabla v), \\ 0 &= \Delta v - av + u. \end{aligned}$$

Here  $\Delta$  is the usual Laplace operator,  $a \geq 0$  and  $\nabla$  is the spatial gradient. The unknown functions  $u, v$  are nonnegative. The second equation is elliptic in  $v$ , while the first equation is parabolic in  $u$  and hence the nomenclature for such systems. It is assumed that the normal derivatives of both functions vanish on the boundary and that  $u(\mathbf{x}, 0) \equiv u_0(\mathbf{x})$  is prescribed initially.

The system can be formally “solved” by writing  $v = (-\Delta + aI)^{-1}u$  from the second equation, introducing this expression in the first equation and then treating the problem as an initial-boundary value problem for the single function  $u$ . However, the justification—indeed, the determination of conditions under which one can justify this formalism is in part the subject of this book. The primary purpose of the book is to establish the result that if the existence (in time) interval of the solution of the resulting nonlocal parabolic initial boundary value problem is finite, the solution  $u$  converges weakly (in measure) to a sum of delta functions (point masses) supported on a finite set  $S \subset \overline{\Omega}$  plus an  $L^1$  function which is continuous in  $\overline{\Omega} - S$ . There is more to this story, but I am getting ahead of myself.

So who cares about (1.1)? Is it just another mathematical toy problem? Or does it, like much of good mathematics, come from the real world? And while we are at it, what about “free energy”? What is it? The last time I bought gasoline or paid my electric bill, I noted that energy is anything but free!

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Thus my goals in this review are (1) to get at these equations from elementary (i.e. undergraduate) mathematics, (2) to explain the term “free energy” in the context of how it is understood in thermodynamics and (3) to discuss the principal theme of the book, namely the two theorems on singularity formation for such systems due to the author and his colleagues.

To get at the first goal, consider a very large population of particles of type  $\mathcal{N}$  in a region  $\Omega$  say. (These could be cells on the surface of a Petri dish or protozoa in a pond for example.) Suppose that the particle density (in particles or moles per unit volume) is viewed as a smooth function of position and time,  $N(\mathbf{x}, t)$ . Suppose moreover that there is no source or sink of particles in the region. Then Fick’s first law (a consequence of the divergence theorem, but see also [2]) says that the local density is changing with time via

$$(1.2) \quad \frac{\partial N}{\partial t} = -\nabla \cdot \mathcal{J}$$

where  $\mathcal{J}$  is the local flux of the particle density. The flux magnitude has units of particles or moles per unit area per unit time.

The fundamental problem of the theoretical chemist or molecular biologist is to relate the flux of the particles to other properties of their environment. To simplify the discussion a bit, suppose there is no overarching fluid momentum to consider. Here are two possibilities:

- Brownian motion (random diffusion) due to bombardment of the particles by the surrounding fluid. (This assumes that the fluid is “isotropic”, i.e. random diffusion is direction independent.)
- The particles can signal each other by means of one or more chemical signals and move in response to those signals.

As a crude example of this second type, consider a very large number of blindfolded folks in a large ballroom. Suppose someone is cooking food in one corner of the room, some highly perfumed folks are socializing in another corner of the room and a few folks in sweaty gym clothes are chatting in a third corner of the room. That is, other people are secreting chemical signals of their own making. The random motion of the blindfolded individuals will be influenced by these chemical odors (signals), positively in the case of the first two, negatively in case of the third case. “The nose knows!” This attraction or repulsion due to chemical gradients of one sort or another is called chemotaxis. The random walk that the blindfolded folks make under these circumstances is called a biased or reinforced random walk [3]. This is what is meant by self interacting particles.

In mathematical terms, the component of the flux that is due to Brownian motion is of the form  $\mathcal{J}_1 = -D\nabla_{\mathbf{x}}N$  where  $D$  is usually (but not always) a constant. See [1, 2] for example. This says that the particles will move from regions of high density to low density if left to their own devices.

Now suppose we have chemical signals present produced by our particles that induce them to move toward (positive chemotaxis) or away from (negative chemotaxis) each other. Consider first a single such species,  $\mathfrak{W}$ , and let  $W(\mathbf{x}, t)$  denote its local density. Then the component of the flux has an additional term of the form  $\mathcal{J}_2 = N\Psi(W)\nabla W$  (in the simplest case this component is taken to be linear in  $N$ ). In this situation,  $\Psi(W)$  is called the chemotactic sensitivity. We see that  $\mathcal{J}_1 + \mathcal{J}_2 = -D\nabla N + N\Psi(W)\nabla W$ . Thus if  $\Psi$  is positive, we say that the gradient of

$W$  works against the gradient of diffusion of  $N$ , while if  $\Psi$  is negative, the gradient of  $W$  works with the gradient of  $N$ .

If there are several chemical species  $\mathfrak{W}_i, i = 1, \dots, m$  as in the case of the odors in the ballroom, for example, we write  $\mathcal{J}_2 = N \sum_{i=1}^m \Psi_j(\vec{W}) \nabla W_i$ . The densities and the fluxes of the chemical species also satisfy Fick's law in their own right.

Let us assume, which is usually the case when  $\mathfrak{N}$  is a cell type and  $\mathfrak{W}$  is a chemical attractant or repellent, that the cells express  $\mathfrak{W}$  at a rate  $\alpha > 0$  proportional to the cell density and that  $\mathfrak{W}$  has a turnover rate  $\beta > 0$ . (The turnover rate is, up to a factor of  $\ln 2$ , the reciprocal of the half life.) Suppose that  $D$  is constant and that  $\Psi(W) \equiv D\Psi_0$  is a nonzero constant.

Then we can write the following system:

$$(1.3) \quad \begin{aligned} \frac{\partial N}{\partial t} &= D\nabla \cdot (\nabla N - \Psi_0 N \nabla W), \\ \frac{\partial W}{\partial t} &= D_w \Delta W + \alpha N - \beta W. \end{aligned}$$

(Local existence and uniqueness theorems for such systems and their generalizations have been established. See [15] for a history of these issues.) This system admits two special subsystems. In the first subsystem the operating assumption is  $\alpha = D_w \hat{\alpha}, \beta = D_w \hat{\beta}$  where the hatted quantities are order zero in  $D_w$  as it becomes large. (See [6] where the assumption is made that  $\hat{\beta}$  is order zero.) Then one makes the time scale change  $\tau = Dt$ , fixes  $D$  and lets  $D_w \rightarrow +\infty$ . Reverting to  $t$  (in place of  $\tau$ ), one has formally:

$$(1.4) \quad \begin{aligned} \frac{\partial N}{\partial t} &= \nabla \cdot (\nabla N - \Psi_0 N \nabla W), \\ 0 &= \Delta W + \hat{\alpha} N - \hat{\beta} W. \end{aligned}$$

The first equation in (1.3) can be written in the form

$$(1.5) \quad \frac{\partial N}{\partial t} = \nabla \cdot \left[ N \nabla \ln \left( \frac{N}{\exp(\Psi_0 W)} \right) \right].$$

Now the sign of  $\Psi_0$  becomes critical. If this number is positive (attractive chemotaxis), we can find positive constants  $\lambda, \mu$  such that  $u = \lambda N$  and  $v = \mu W$  that will permit the reduction of (1.4) to (1.1). If  $\Psi_0$  is negative, i.e. in the case of repulsive chemotaxis, this reduction can be made only if we allow  $\lambda$  and  $\mu$  to be negative. Because it is attractive chemotaxis that leads to aggregation, we take  $\Psi_0 = 1$ .

For the second subsystem, the operating assumption is that the diffusivity  $D_w$  is very small in comparison with  $\beta/\mu_n$  for the first few nonzero Neumann eigenvalues  $\mu_n$ . This will be true if the half life of the chemical species  $\mathfrak{W}$  is very small, as is the case for various growth factors. Then we can write the following system:

$$(1.6) \quad \begin{aligned} \frac{\partial N}{\partial t} &= D\nabla \cdot (\nabla N - N \nabla W), \\ \frac{\partial W}{\partial t} &= \alpha N - \beta W. \end{aligned}$$

In this case, we drop the boundary conditions on  $W$ . This system is no less intriguing than (1.1). It is possible for this system to exhibit singularity formation in finite time. This possibility was demonstrated numerically in [10]. Singularity formation for (1.6) was analyzed in [8] for  $\beta = 0$  and in [5, 7, 9] when  $\beta > 0$ .

Turning to the second goal, recall from thermodynamics, [13] for example, that the energy,  $E$ , the Kelvin temperature,  $T$ , and the entropy,  $S$ , for a system of particles undergoing reversible processes and  $PV$  work are related by the differential form  $dE = dQ_{rev} - dW = TdS - PdV$ , according to the first and second laws of thermodynamics. The energy and the entropy differentials are exact while the  $PV$  work is path dependent. Chemists have found that the Gibbs free energy, namely,  $G = E + PV - TS$ , is more useful for isothermal processes, as the contribution to the total energy from the entropy is removed. The total differential for the Gibbs free energy is  $dG = -SdT + VdP$ . For example, if we have an isothermal expansion of an ideal gas,  $dT = 0$  and  $PV = nRT$  where  $R$  is the universal gas constant. Then  $dG = nRTdP/P$  so that  $G = nRT \ln(P/P_0) + G_0(T) = nRT \ln(N/N_0) + G_0(T)$  where the subscript denotes some fixed reference state and where  $N = n/V = P/RT$  is the concentration of the gas. Chemists prefer to use something called the chemical potential, i.e., the free energy per mole. Thus we write  $\Gamma = (G - G_0)/n = RT \ln(N/N_0) + \Gamma_0(T)$ .

It is reasonable to assume that the flux is down the free energy gradient and is proportional to the local concentration of the gas. Hence  $\mathcal{J} = -\sigma N \nabla \Gamma = -\sigma RT \nabla N$  where sigma is some proportionality constant. Then  $D = \sigma RT$ . Unfortunately, an ideal gas is just that, ideal. Therefore, [13], chemists have replaced  $N_0 = N_0(T)$  by a factor,  $1/\gamma$ , called the activity coefficient, and the density  $N$  by  $A = N\gamma$ , called the activity as a correction factor, in order to keep the same form of the equation for the chemical potential in the nonideal case. Thus, we define the activity coefficient by  $\Gamma = RT \ln(\gamma N) + \Gamma_0(T)$  and identify  $W = -\ln(\gamma)$ . Then the dynamics for  $W$  is equivalent to dynamics for the activity coefficient. (In gas dynamics, the term “fugacity” is used in lieu of the pressure when the gas is not ideal.) In [8] we followed the dynamics for  $1/\gamma$ , the approach taken in [10] in their modeling of the continuous (pde) version of reinforced random walk of [3].

How does this notion of free energy relate to that described in the book? We return to (1.4). By rescaling  $N$  we can take  $\hat{\alpha} = 1$ . Then we have, after multiplying both sides of the first of (1.5) by  $\Gamma - \Gamma_0 = \ln(Ne^{-W})$ , integrating over the region  $\Omega$  and noting the zero flux boundary conditions on both  $W$  and  $N$ ,

$$\frac{d}{dt} \int_{\Omega} (\Gamma - 1)N \, d\mathbf{x} = -D \int_{\Omega} N |\nabla \Gamma|^2 \, d\mathbf{x}$$

if we take the reference potential,  $\Gamma_0 = 0$ . The author defines

$$\mathcal{W}(N, W) = \int_{\Omega} (\Gamma - 1)N \, d\mathbf{x}$$

as the free energy. More precisely, it is the total free energy of the system, a weighted integral of the local chemical potential or just an integral of the local free energy. More importantly it is decreasing in time, as it should from a thermodynamic point of view. From the dynamical systems point of view, it is an example of a Lyapunov functional.

One can carry this a little further by writing (with  $a = \hat{\beta}$ )  $W = (aI - \Delta)^{-1}N = \int_{\Omega} G_a(\mathbf{x}, \mathbf{x}')N(\mathbf{x}', t) \, d\mathbf{x}'$  where  $G_a$  is the Green's function for  $aI - \Delta$  with no flux boundary conditions. Using this to eliminate  $W$  from  $\mathcal{W}$  leads to a functional in  $N$  that depends only on time. We denote it by  $\mathcal{F}(N)$ .

The content of the book is centered around two very interesting theorems of the author [12] and the author and Senba [11]. To set the stage, we let  $\Omega$  be a bounded

region in the plane with a smooth boundary. Let  $\mathcal{M}(\overline{\Omega})$  denote the set of measures on  $\overline{\Omega}$  and let  $\rightharpoonup$  denote weak-\* convergence. Of special interest is the measure defined by the  $L^\infty$  function

$$m_*(x) = \begin{cases} 8\pi & (x \in \Omega) \\ 4\pi & (x \in \partial\Omega). \end{cases}$$

Suppose the solution  $(u, v)$  of (1.1) exists on  $\overline{\Omega} \times [0, T_{max})$  and that  $T_{max} < \infty$ . Then there is a finite set of points  $\mathcal{S} \subset \overline{\Omega}$ , a nonnegative function  $f \in L^1(\Omega) \cap C(\overline{\Omega} \setminus \mathcal{S})$  and a function  $m \in L^\infty(\Omega)$  such that  $m(\mathbf{x}_0) \geq m_*(\mathbf{x}_0)$  for  $\mathbf{x}_0 \in \mathcal{S}$  and

$$(1.7) \quad u(x, t) dx \rightharpoonup f(x)dx + \sum_{\mathbf{x}_0 \in \mathcal{S}} m(\mathbf{x}_0)\delta(x - \mathbf{x}_0) dx$$

as  $t \uparrow T_{max}$ . Moreover, the set  $\mathcal{S}$  is precisely the set of blow-up points of  $u$  and  $\lim_{t \uparrow T_{max}} \|u(t)\|_{L^\infty} = +\infty$ . Because  $\|u(t)\|_{L^1} = \|u_0\|_{L^1}$ , one sees that

$$2\#\mathcal{S} \cap \Omega + \#\mathcal{S} \cap \partial\Omega \leq \|u_0\|_{L^1} / (4\pi)$$

where  $\#\mathcal{S}$  denotes the finite cardinality of  $\mathcal{S}$ . The meaning of this result is that the chemotaxis has a strong localizing effect on the evolution of the particle density  $u$ , the aggregation of the particles occurring at most at a finite number of points either in the domain or on its boundary. Notice that when  $\|u_0\|_{L^1} < 4\pi$ , aggregation cannot occur.

The author refined this result in [12]. This refinement is concerned with the asymptotic behavior of the solution near each point of  $\mathcal{S}$ . For the growth of the solution at the singularities, there are two possibilities:

1.  $\mathbf{x}_0 \in \mathcal{S}$  is type I if for all  $C > 0$ ,

$$\limsup_{t \uparrow T_{max}} \sup_{|\mathbf{x} - \mathbf{x}_0| \leq C(T_{max} - t)^{1/2}} (T_{max} - t)u(\mathbf{x}, t) < +\infty.$$

2.  $\mathbf{x}_0 \in \mathcal{S}$  is type II if there is  $C > 0$ ,

$$\limsup_{t \uparrow T_{max}} \sup_{|\mathbf{x} - \mathbf{x}_0| \leq C(T_{max} - t)^{1/2}} (T_{max} - t)u(\mathbf{x}, t) = +\infty.$$

Clearly blowup is more rapid at a type II singularity than at a type I singularity. Define the local backward self-similar change of variables  $\mathbf{y} = (\mathbf{x} - \mathbf{x}_0) / (T_{max} - t)^{1/2}$ ,  $s = -\ln((T_{max} - t))$  and  $z(\mathbf{y}, s) = (T_{max} - t)y(\mathbf{x}, t)$ .

Then  $m(\mathbf{x}_0) = m_*(\mathbf{x}_0)$ . (This is called mass quantization.) Moreover

1. If  $\mathbf{x}_0 \in \mathcal{S}$  is type II and  $t_n \uparrow T$  is a sequence along which the superior limit in the definition is infinite, then

$$z(y, s_n + \cdot) dy \rightharpoonup m_*(\mathbf{x}_0)\delta(\mathbf{y}) dy$$

in  $C_*(R^1, \mathcal{M}(R^2))$ . (Here  $z = 0$  outside the region where it is not defined by  $u$ .)

2. If  $\mathbf{x}_0 \in \mathcal{S}$  is type I, then the local free energy blows up. That is,

$$\lim_{t \uparrow T_{max}} \mathcal{F}_{bR}(u(t)) = +\infty$$

for all  $b > 0$  where the local free energy is given by

$$\mathcal{F}_R(u) = \int_{\Omega} \psi_{x_0, R, 2R} u (\ln u - 1) dx - \frac{1}{2} \int_{\Omega} \int_{\Omega} (\mathbf{x}) \psi_{x_0, R, 2R}(\mathbf{x}') G(\mathbf{x}', \mathbf{x}) u(\mathbf{x}') u(\mathbf{x}) dx dx'$$

where  $\psi_{x_0, R, 2R}$  is unity in  $B(\mathbf{x}_0, R)$ ; vanishes outside  $B(\mathbf{x}_0, 2R)$ ; and on  $\Omega \setminus B(\mathbf{x}_0, 2R)$  takes values in  $[0, 1]$ , is smooth, and has zero flux on  $\partial\Omega$ .

The author remarks that the existence of type (I) singularities, i.e. singularities that aggregate to a delta function even in similarity variables, has yet to be demonstrated. He also remarks that it is possible for type II singularities to show the same finite time blowup in the local free energy.

In the context of biological systems, the classic model for (1.1) is that of *Dictyostelium discoideum*, one of a class of cellular slime molds, [4, p. 498ff.]. On these pages one will find a very nice biological discussion of the formation of singularities in the density function for these slime molds. (To paraphrase Kevin Costner in *Field of Dreams*: “If you starve them, they will aggregate!”) Roughly speaking, the amoeba that constitute the slime mold bacteria are commonly found in the soil. As long as there is sufficient food supply they are more or less uniformly spread. As the food supply becomes exhausted, they first aggregate in a pulsating wave like manner. Because a picture is worth a thousand words, I refer the reader to two Web sites for some truly fascinating movies, namely [cosmos.bot.kyoto-u.ac.jp/csm/movies.html](http://cosmos.bot.kyoto-u.ac.jp/csm/movies.html) and [asb.aecom.yu.edu/segall/dicty/dictwel.htm](http://asb.aecom.yu.edu/segall/dicty/dictwel.htm). There one can see the aggregation and the presumptive formation of delta functions in real time.

An interesting question, among many, that remains open for the system (1.1) is the question of blowup in infinite time. In Chapter 12, the author shows that if this does happen, the solution evolves weak-\* to a set of blow-up points (which may be infinite) in the same manner as stated in (1.7) with  $m = m_*$  (mass quantization).

The organization of the book is briefly summarized as follows. Chapters 1 and 2 are concerned with a summary and introduction of the problem as well as with a classification of the problem in the hierarchy of equations of particle dynamics. Chapters 3-5 involve issues arising in the classical theory of differential equations, local existence, uniqueness, blowup, etc. Chapters 6-10 are concerned with the stationary problem for system (1.1), while the last five chapters, 11-15, deal with the results we described above. These last ten chapters are not easy reads by any means. (There are some errors involving the historical development of the subject. For example, the author refers to a paper ([14]) (with an incorrect date of publication) that appeared several years after [8].)

The book itself is well organized and readable although very technical. It is a book about the mathematics of system (1.5) and not biology or thermodynamics. In that sense, I found the title somewhat misleading. In any case, it certainly belongs on the bookshelf of specialists in nonlinear pde/math biology.

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