Aggregation of chemotactic organisms in an advected environment

Javier Muñoz García

http://gisc.uc3m.es/~javier

E-mail: javiermunozgarcia@gmail.com

GISC & School of Mathematical Sciences,

University College Dublin,

Complex and Adaptive Systems Laboratory, Belfield, Dublin 4,

Ireland

Introduction

- **The survival of many organisms depends on their ability to navigate within a complex environment through the detection and processing of a variety of internal and external signals**

- **Chemotaxis: "the movement of biological cells or organisms in response to chemical gradients "**

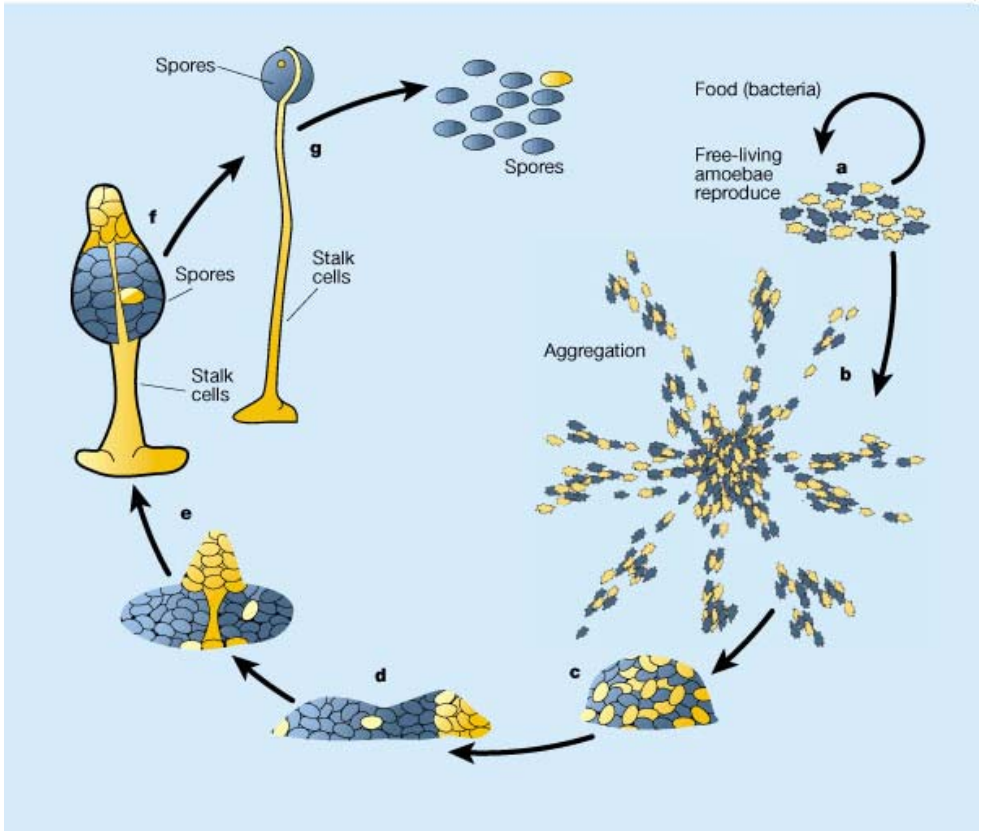
- **A lot of work has been done in order to understand and model this ability for a variety of organisms**

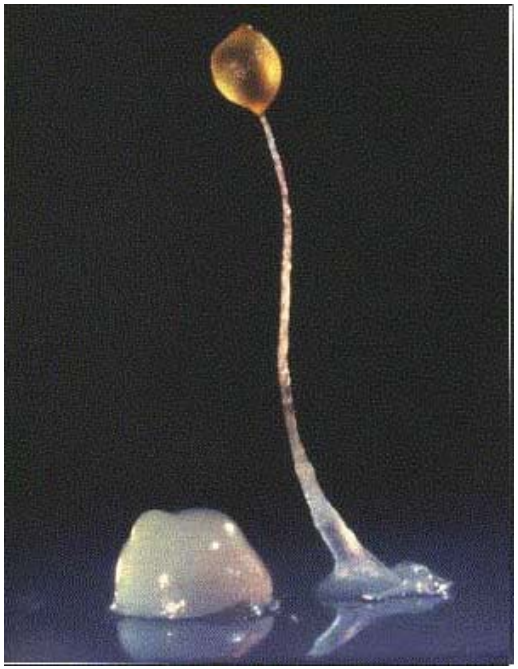
- **Examples:**
  - **Multicellular organims: Drosophila melanogaster (fruit fly), male moths, algae …**
  - **Cell populations: sperm cells, immune cell migration, fibrobalsts, …**
  - **Bacteria: E. coli, salmonella typhimurium,…**
  - **Slime molds: *Dictyostelium discoideum***

Dictyostelium discoideum

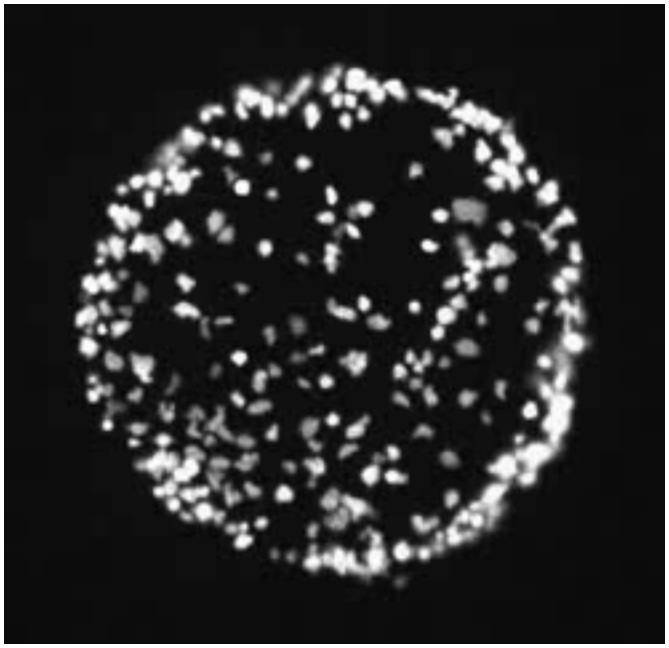
- **When the bacteria are consumed and starvation is imminent, the amoebae stop dividing and aggregate by chemotaxis towards cyclic AMP diffusing from centrally located cells (a-b).**

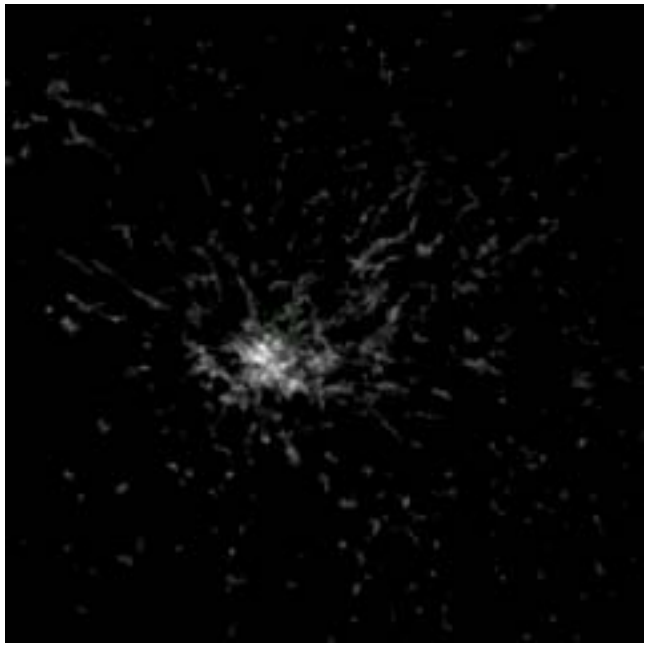
- **These aggregates, wich can contain up to 100,000 cells, transform into motile slugs (c, d) and finally into fruiting bodies (e–g). The fruiting bodies contain 80,000 viable spores supported by 20,000 dead stalk cells.**





Dictyostelium discoideum





Starved cell populations of Dictyostelium cells develop on agar to form slime molds and eventually fruiting bodies (latter not shown). The movies show how the cells aggregate via chemotaxis.

Keller Segel type Models

- **Theoretical and mathematical modelling of chemotaxis dates to the seminal work of Keller and Segel (KS)**

  [E.. F. Keller and L. A. Segel. Initiation of slime mold aggregation viewed as an instability. J.Theor. Biol. 26:399 (1970)]

- **A number of stochastic and discrete approches have arisen but the continuum KS description has become prevailing for its intuitive nature and relative tractability (analytically and numerically) and has been later derived from mechanistic/microscopic descriptions**

- **Describes at the population level the evolution of the density of chemotactic cells, *u*, and the chemoattractant concentration, *v***

$$\frac{\partial u}{\partial t} = \nabla \cdot (k_1(u,v)\nabla u - k_2(u,v)u\nabla v)$$

$$\frac{\partial v}{\partial t} = D_v \nabla^2 v + k_4(u,v) - k_5(u,v)v$$

- **Captures key phenomena such necessary conditions for pattern formation (critical mass, species diffusivity values)**

- **Gives rise to a variety of observed spatial patterns** [Tyson et al. J. Math. Biol. 38:359 (1999)]

- **Similar models have been developed to understand the aggregation process in a variety of organisms and the pigmentation patterning in snakes and fishes, neural crest migration, inflammatory response, tumor growth**

- **In addition to its application to biological systems, a lot work has emerged on its mathematical properties**

Standard (classic) Model

Keller and Segel, J.Theor. Biol. 26:399 (1970)

$$\frac{\partial u}{\partial t} = \nabla \cdot (D_u \nabla u - \chi_0 u \nabla v)$$

$$\frac{\partial v}{\partial t} = D_v \nabla^2 v + fu - sv$$

- **It has rich and and interesting mathematical properties including globally existing of solutions, finite time blow-up and spatial pattern formation**

- **1D solution exists globally** [Osaki y Yagi, Funkcial. Ekvac. 44:441 (2001)]

- **2D solution depends on a critical mass** [Perthame: Transport Equations in Biology. Birkhäuser, Basel (2007)]

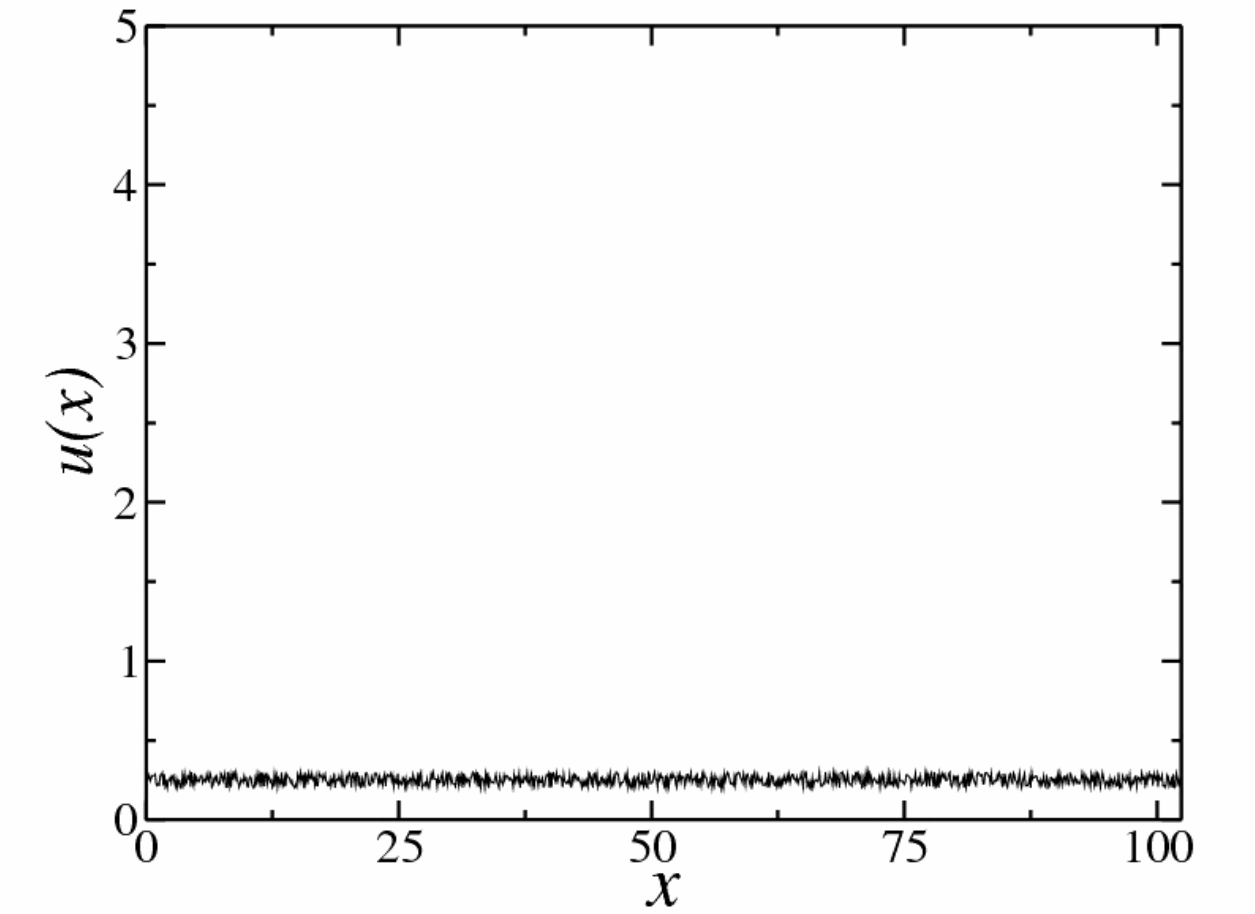
- **While the model predicts the conditions for the existence of aggregation, this takes the form of a finite blow-up in a finite time**

- **Therefore, the model is only valid in the initial stages of aggregation**

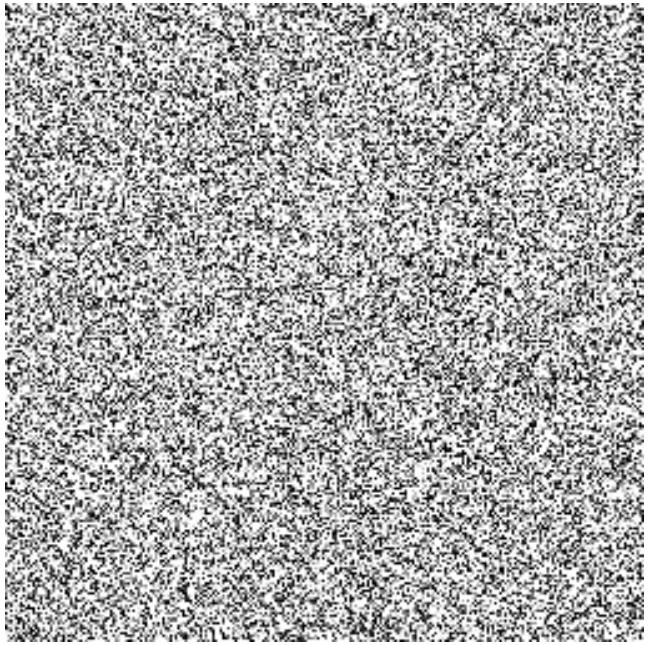
- **A number of modifications has been made to allow global existence of solutions and understand later stages**

Standard (classic) Model

1D



2D



$\chi=\chi_0 u$, $D=1$, $\chi_0=10$, $u_0=0.25$

Volume filling model

Hillen y Painter, Adv. Appl. Math. 26:280 (2001)

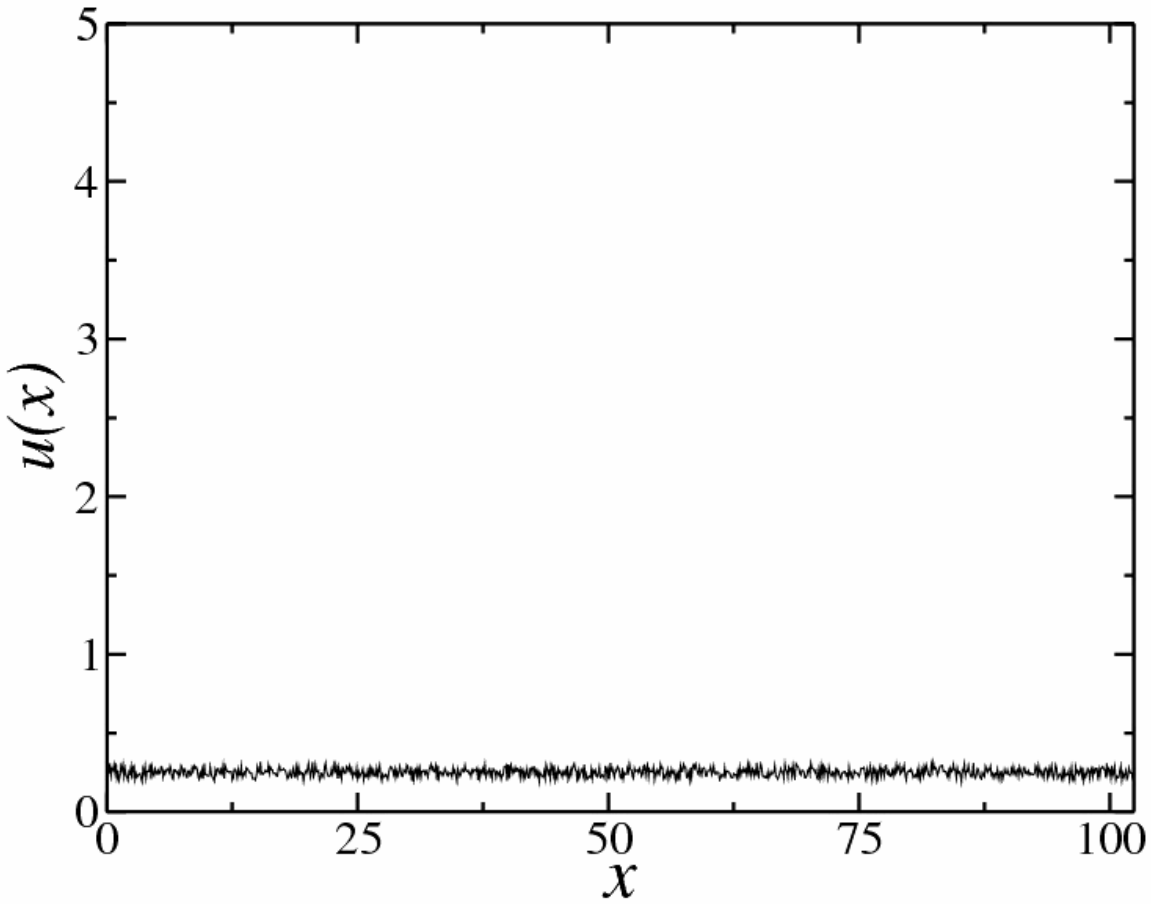
$$\frac{\partial u}{\partial t} = \nabla \cdot (D_u \nabla u - \chi_0 u(1-u/\gamma)\nabla v)$$

$$\frac{\partial v}{\partial t} = D_v \nabla^2 v + fu - sv$$

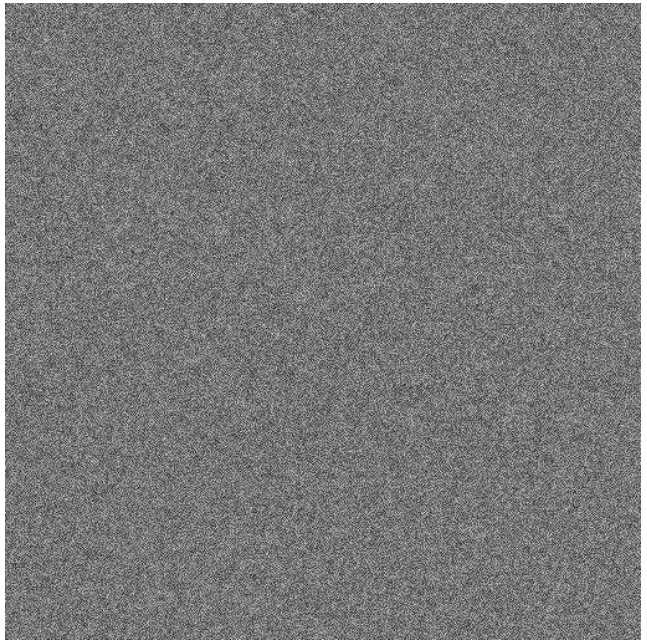
- **Derived assuming that cells has a certain finite size and the number of cells in a certain area is limited**
- **γ denotes the maximum cell density (for $\gamma \to \infty$ the classic model is recovered)**
- **Global existence of solutions has been shown in any D**
- **The volume filling idea was used to model pattern formation of D. discoideum and S. typhimurium in Ref.** [Dolak y Hillen, J. Math. Biol. 46:153 (2003)]
- **Gives rise to uninterrupted coarsening, in contrast with experimental observations**

Volume filling model

1D



2D



$\chi=\chi_0\, u\,(1-u/\gamma)$, $D=1, \chi_0=10$, $u_0=0.25$, $\gamma=1$

Advected environment

- **Often the medium into which the chemical signal is released is not stationary but is a moving fluid (e.g. air or water) while the chemotactic cells or organisms may or not be transported by the flow as they are bound to a solid surface (eg. algae or microbial biofilm communities in natural environments or bioreactors) or may navigate by themselves.**
- **What happen to this biological chemotactic populations in an advected environment?**

$$\frac{\partial u}{\partial t} + \mathbf{V_u} \cdot \nabla u = \nabla \cdot (D_u \nabla u - \chi(u) \nabla v)$$

$$\frac{\partial v}{\partial t} + \mathbf{V_v} \cdot \nabla v = D_v \nabla^2 v + fu - sv$$

- **We consider incompressible flows and we start with the simpliest case of constant flow.**
- **Choosing an appropriate reference system for differential advection $\mathbf{V=V_v-V_u}$ we have**

$$\frac{\partial u}{\partial t} = \nabla \cdot (D_u \nabla u - \chi(u) \nabla v)$$

$$\frac{\partial v}{\partial t} = D_v \nabla^2 v + fu - sv - \mathbf{V} \cdot \nabla v$$

- **To simplify the analysis we can rescale** $x' \to \sqrt{s/D_v}, t' \to st, u' \to u/u_0, v' \to s/(fu_0)v,$

with u_0 the initial total cell density, to obtain

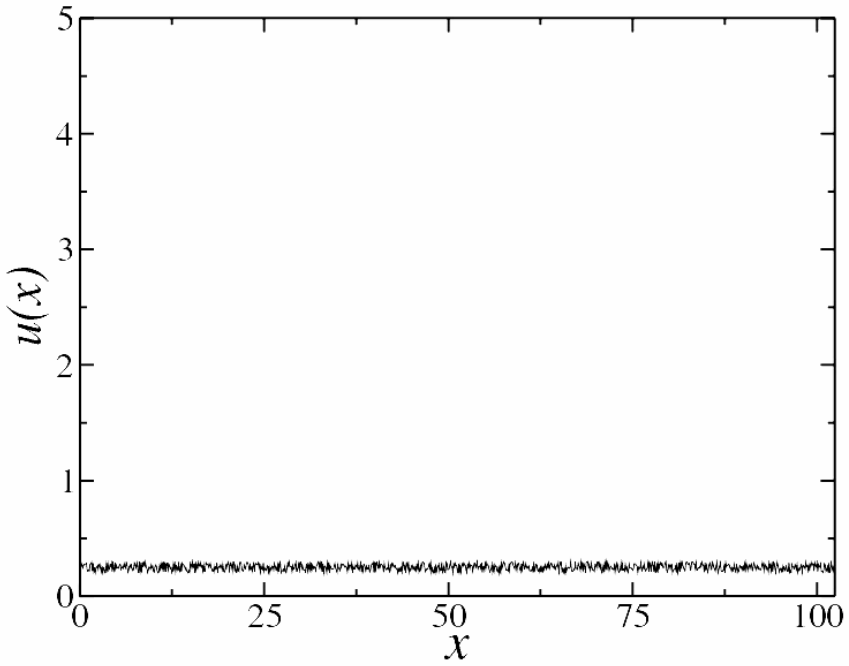
$$\frac{\partial u}{\partial t} = \nabla \cdot (D \nabla u - \chi(u) \nabla v)$$

$$\frac{\partial v}{\partial t} = \nabla^2 v + u - v - \mathbf{V} \cdot \nabla v$$

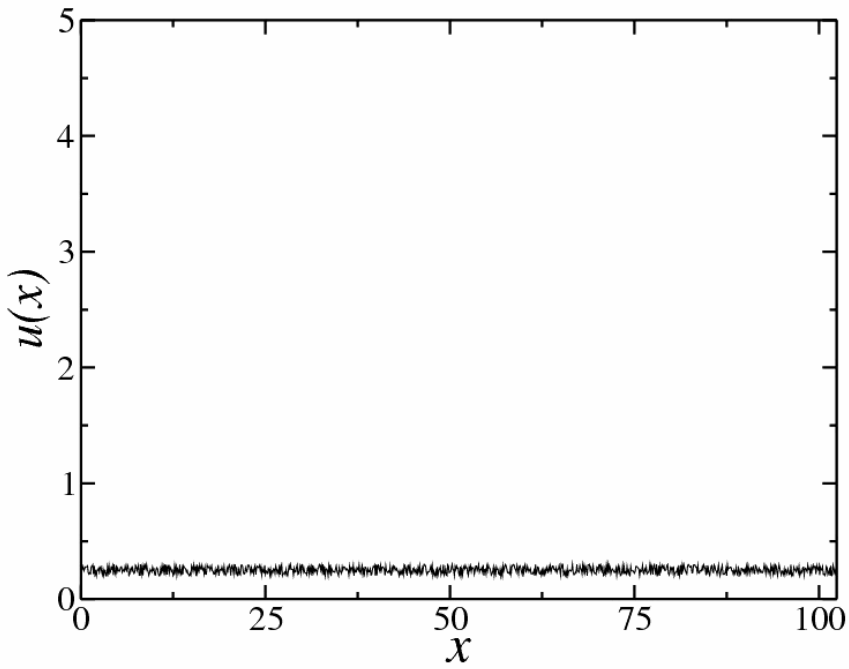
- **Where we have omitted primes and defined** $D' = D_u/D_v, \chi'(u) = f/(sD_v)\chi(u), \mathbf{V}' = (sD_v)^{-1/2}\mathbf{V}'$

Pattern formation in 1D

V=2



V=5

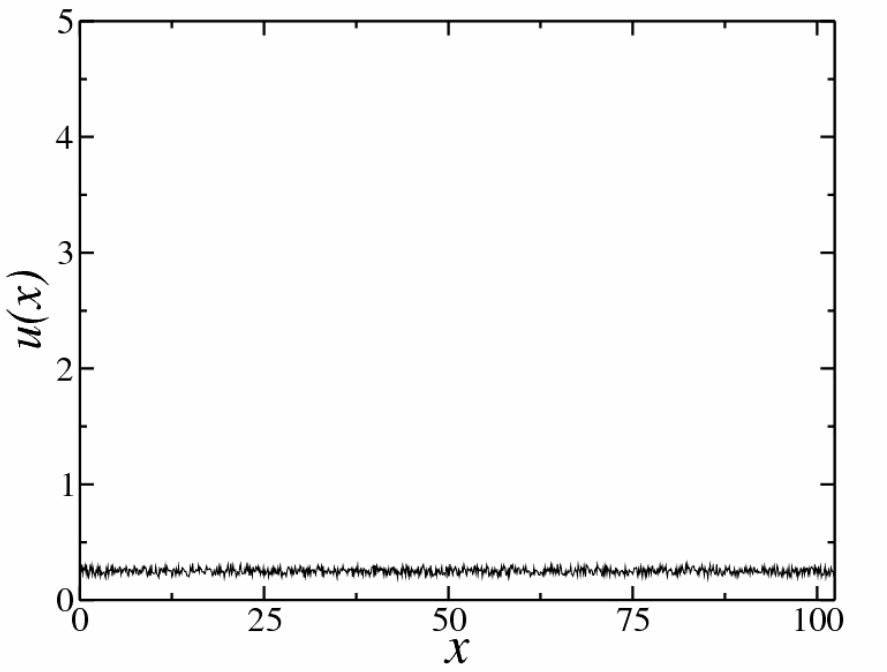


Standard (classic) model: $\chi=\chi_0 u$, $D=1, \chi_0=10$, $u_0=0.25$

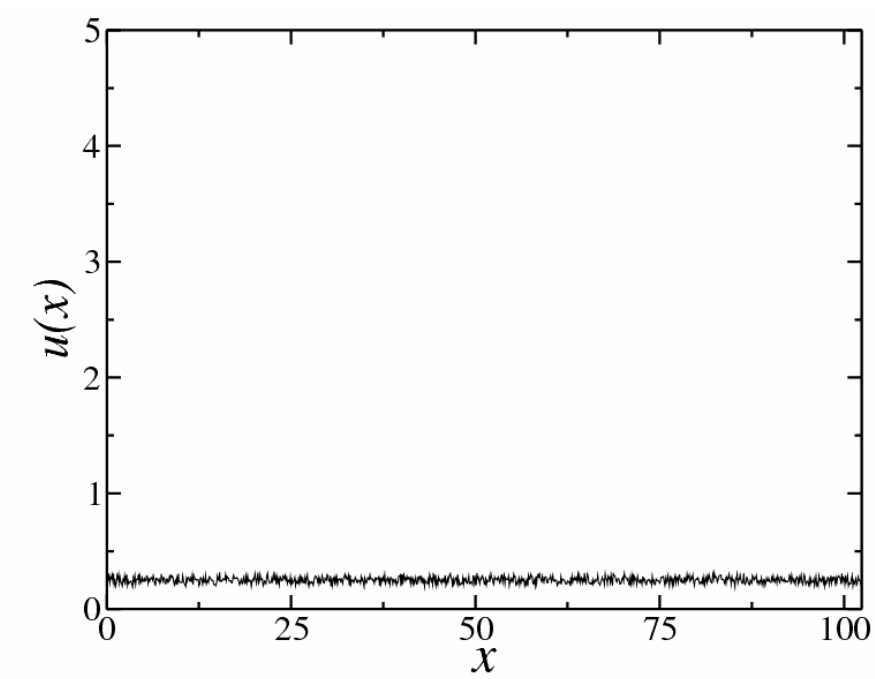
- **For large V the singularity in the classis KS model is suppressed**

Pattern formation in 1D

V=1



V=5



Volume filling model, $\chi=\chi_0\, u\,(1-u/\gamma)$, $D=1$, $\chi_0=10$, $u_0=0.25$, $\gamma=1$

- **In the volumen filling model the advection suppress the coarsening process**

Linear analysis

• **Assuming initial planar condition u_0 and v_0 we obtain the solutions:** $u(t) = u_0, v(t) = u_0 + (v_0 - u_0)e^{-st}$

• **Perturbing this solution with** $u(\mathbf{x},t) = u_0 + \hat{u}\exp\left[i\mathbf{q}\cdot\mathbf{x} + \omega(\mathbf{q})t\right], v(\mathbf{x},t) = u_0 + \hat{v}\exp\left[i\mathbf{q}\cdot\mathbf{x} + \omega(\mathbf{q})t\right]$

$$\omega^2 + \omega(a+ib) + (c+id) = 0$$

$$\begin{aligned} a &= (1+D)q^2 + 1 \\ b &= \mathbf{V}\cdot\mathbf{q} \\ c &= Dq^4 + \left[D - \chi(u_0)\right]q^2 \\ d &= Dq^2\mathbf{V}\cdot\mathbf{q}. \end{aligned}$$

• **For large wavelengths (small wave vectors) we can expand the dispersion relation to obtain**

$$\mathrm{Re}(\omega^+) = \left[\chi(u_0) - D\right]q^2 - \chi(u_0)q^2\{[(1-D) + \chi(u_0)]q^2 + (\mathbf{V}\cdot\mathbf{q})^2\} + \mathcal{O}\left(q^6\right)$$

$$\mathrm{Im}(\omega^+) = -\chi(u_0)q^2\left(\mathbf{V}\cdot\mathbf{q}\right) + \mathcal{O}\left(q^5\right)$$

• **The real part gives the growth or decay rate of the perturbation amplitude and the imaginary part is related with the velocity at which the instability travels across the substrate, $\mathbf{V}^l$, and verifies:** $\mathbf{V}^l\cdot\mathbf{q}^l = -\mathrm{Im}\left[\omega(\mathbf{q}^l)\right]$

• **When** $\chi(u_0) - D > 0$ **there is a band of unstable wave vectors**

• **The stabilizing effect of the flow contrasts with the results by Rovinsky and Mezinger in chemical reactio-difussion equations** [Rovinsky y Menzinger Phys. Rev. Lett. 69:1193 (1992), Phys. Rev. Lett. 72:2017 (1994)]

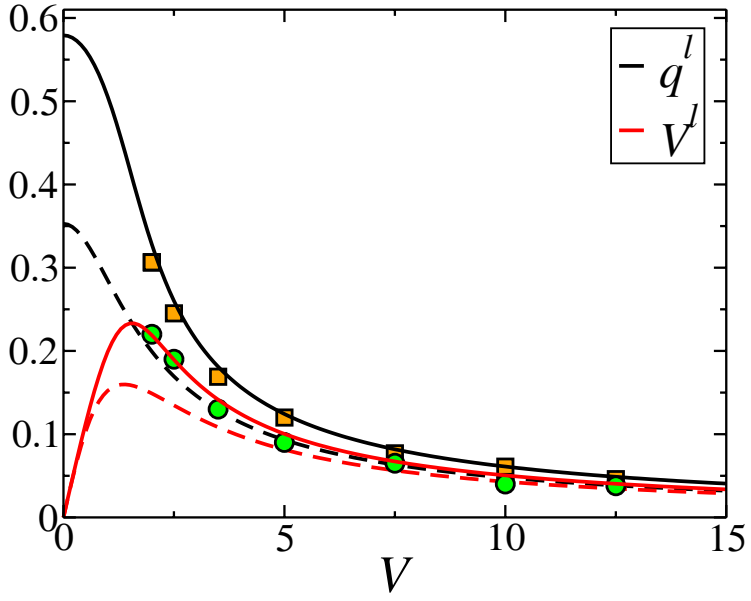
• **Although the particles are not directly advected by the flow, we see that chemotaxis induces a phase velocity inversely proportional to square of the wavelength**

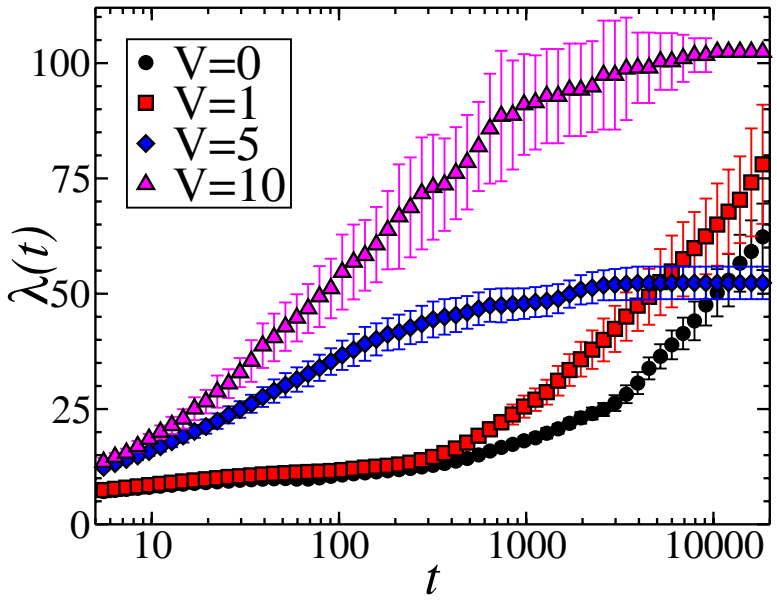
Pattern formation in 1D

•**From the previous results we can estimate the wavelength and pattern velocity for large V and compare with the simulations**

$$q^l \approx \sqrt{\frac{\chi(u_0)-D}{2\chi(u_0)[(1-D)+\chi(u_0)+V^2]}} \qquad V^l \approx \frac{[\chi(u_0)-D]V}{2[(1-D)+\chi(u_0)+V^2]}$$

• **When V exceeds an certain threshold,** $(V_t \approx \sqrt{(1-D)+\chi(u_0)})$ **, stronger advection induces slower pattern movement**

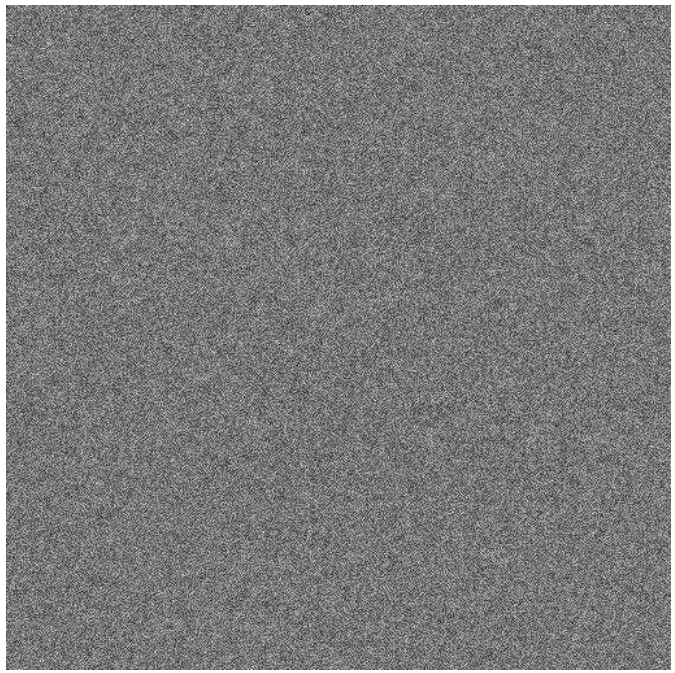




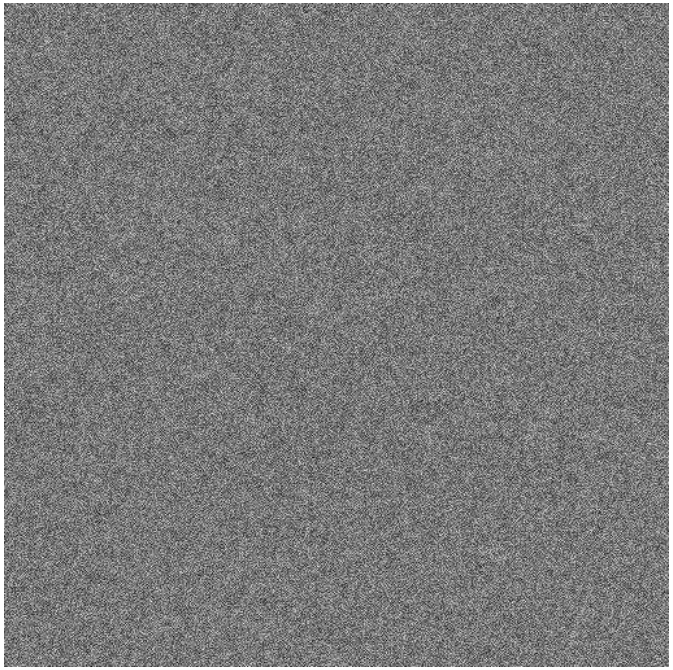
Pattern formation in 2D

Volume filling model, $\chi=\chi_0\, u\,(1-u/\gamma)$, $D=1$, $\chi_0=10$, $u_0=0.25$, $\gamma=1$

V=1



V=2



- **When the advection takes place the resulting pattern is not isotropic**
- **From the linear analysis is concluded that the dominant pattern is oriented perpendicular to the advection and the linear wavelength and coarsening process are not affected by V (in this direction)**
- **In the parallel direction to the advection, the aggregates velocity is proportional to V and decreases with the pattern wavelength following**

$$V_x^l = \frac{4\pi^2 \chi(u_0)}{\lambda_x^2} V$$

Conclusions

- **We have shown how a differential uniform flow affects the aggregation dynamics in KS type models**
- **Even if the cells are not directly advected by the flow, the chemotactic signal induces a movement as the organisms try to follow region of high chemical concentrations**
- **We have studied numerically and analytically the aggregation features and find out that for large enough advection the system remains in the linear regime (obtaining an analytical estimation for that value)**
- **The inclusion of an advected term may limit the aggregation process and the singularities in the KS model**

This work: J. Muñoz-García and Z. Neufeld, *Aggregation of chemosensitive particles in an advected environment* (2009).

arXiv:0901.1831

Future work

- **Test these predictions experimentally**
- **Study the effect of more complex advection such as turbulent flows**
- **Expand this work to other biological system such as phototactic swimming microorganisms** [Colin and Neufeld, Phys. Rev. Lett. 101:078105 (2008)] **using a phototactic source instead cell segregation following**

$$\frac{\partial u}{\partial t} + \mathbf{V_u} \cdot \nabla u = \nabla \cdot (D_u \nabla u - \chi(u) \nabla v)$$

$$\frac{\partial v}{\partial t} + \mathbf{V_v} \cdot \nabla v = D_v \nabla^2 v + f(\mathbf{x}) - sv$$

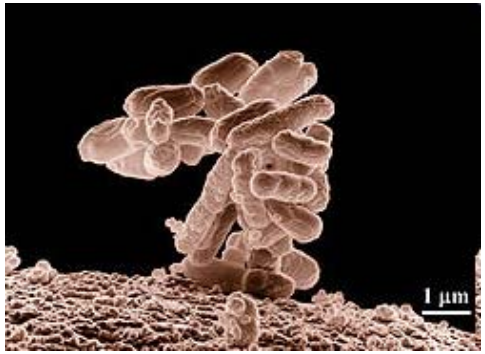
Other work

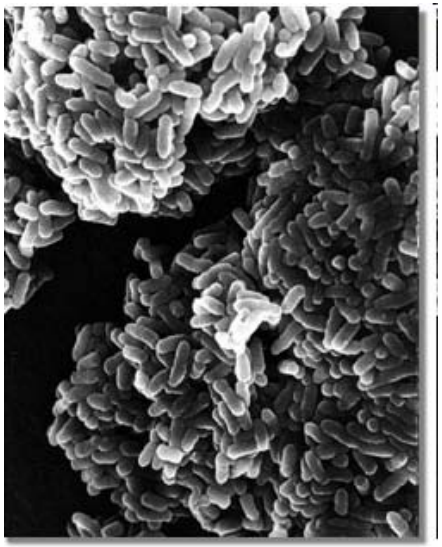
- **Cell signalling transduction**

J. Muñoz-García, Z. Neufeld y B. Kholodenko, *Positional Information Generated by Spatially Distributed Signaling Cascades*, (in press) PLoS Comp. Biol. (2009)

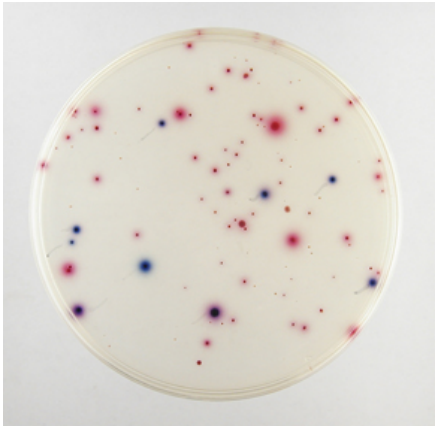
Bacteria:

Escherichia coli (E. coli)



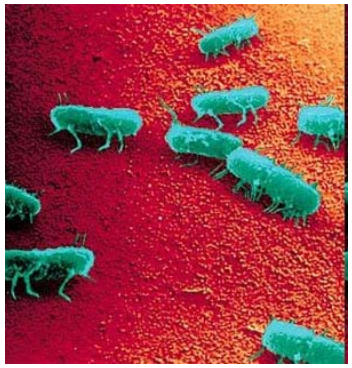


Low-temperature electron micrographs of clusters of *E. coli* bacteria. Each individual bacterium is oblong shaped.`



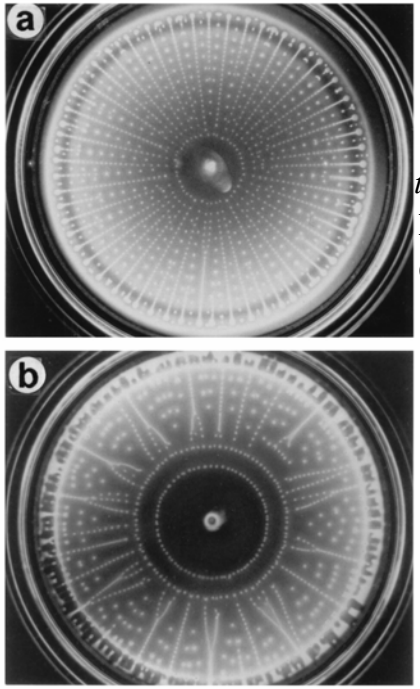
E. Coli bacteria colonies cultured in a Petri dish.

Salmonella typhimurium



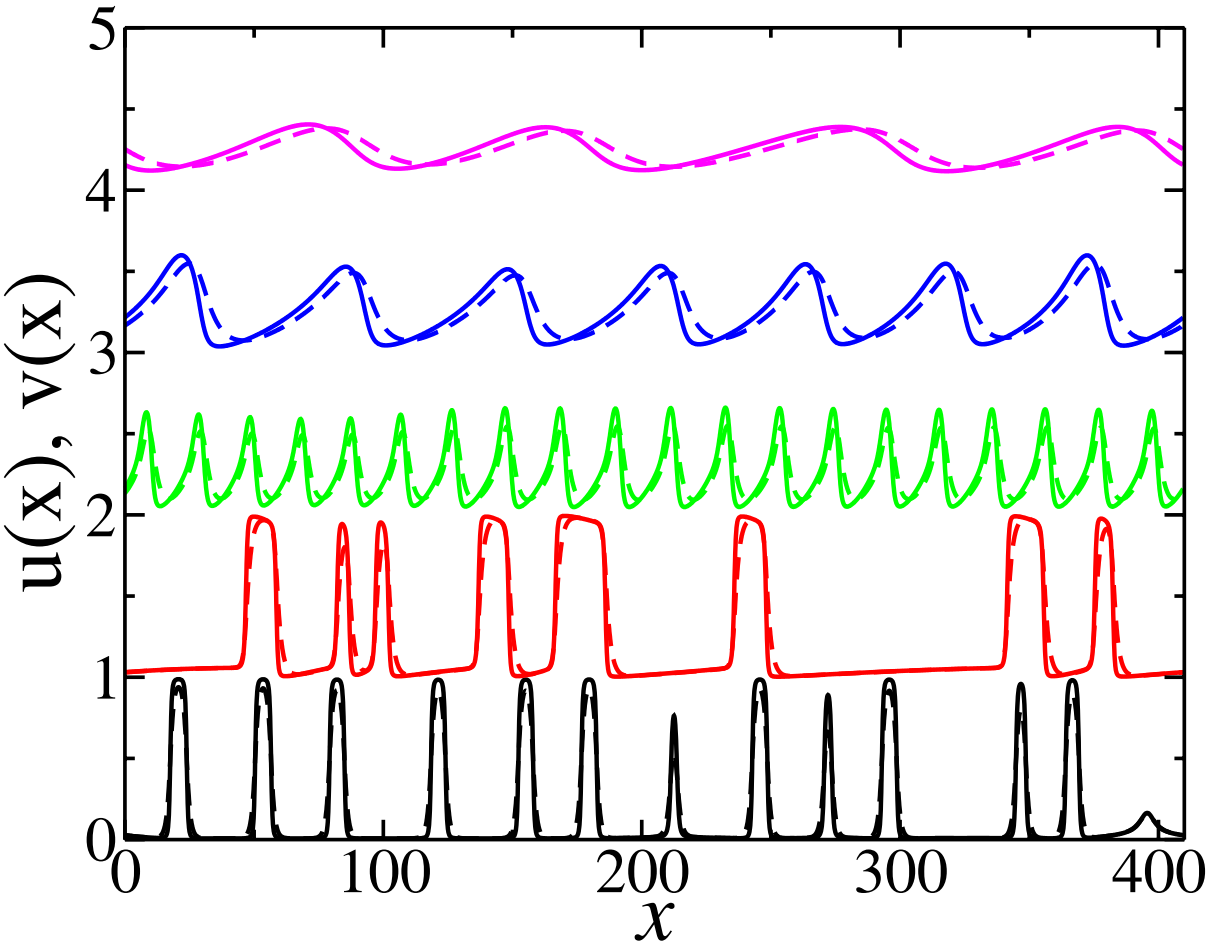
S. enterica Typhimurium. Multiple flagella are shown on the cell surface

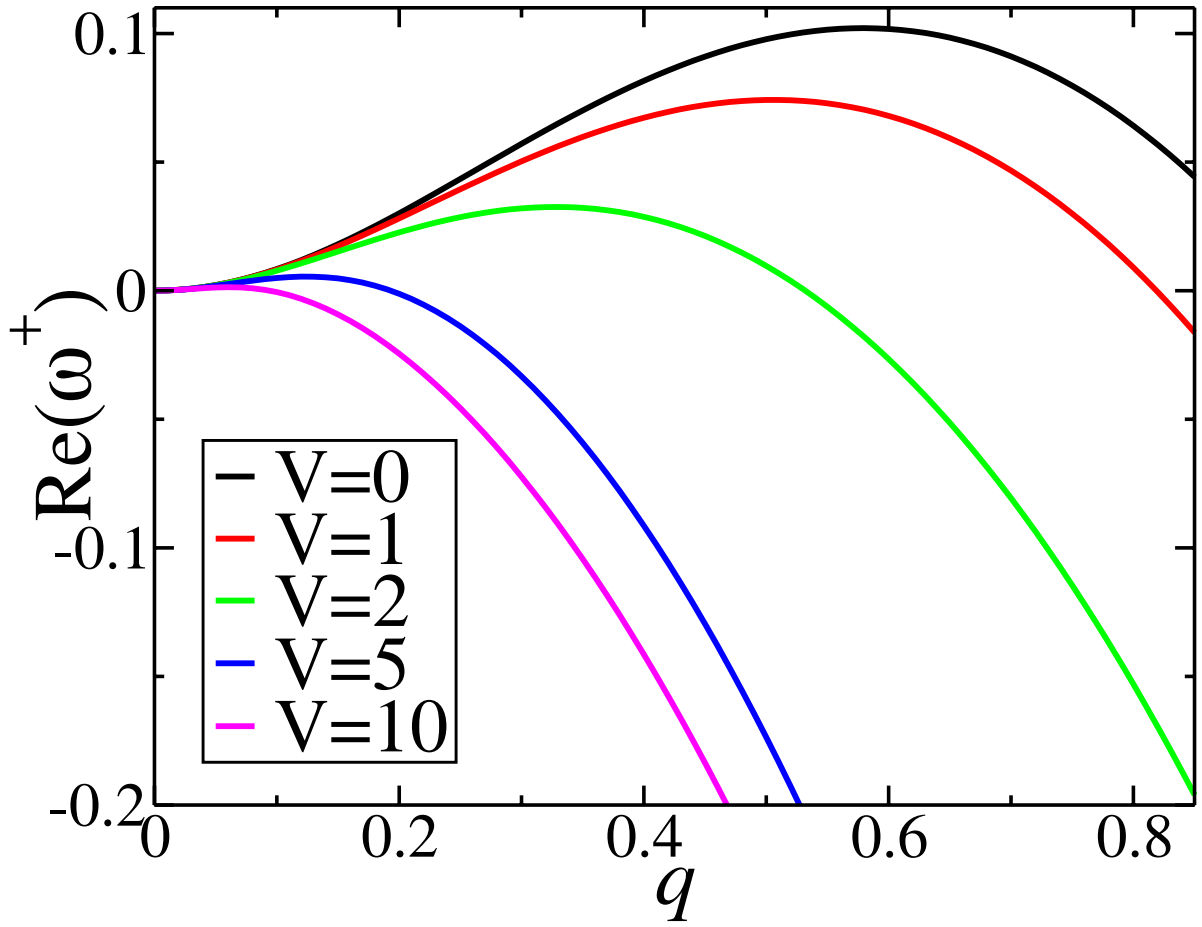
LA plate streaked with *Salmonella* Typhimurium and incubated at 37ºC for 24 hours

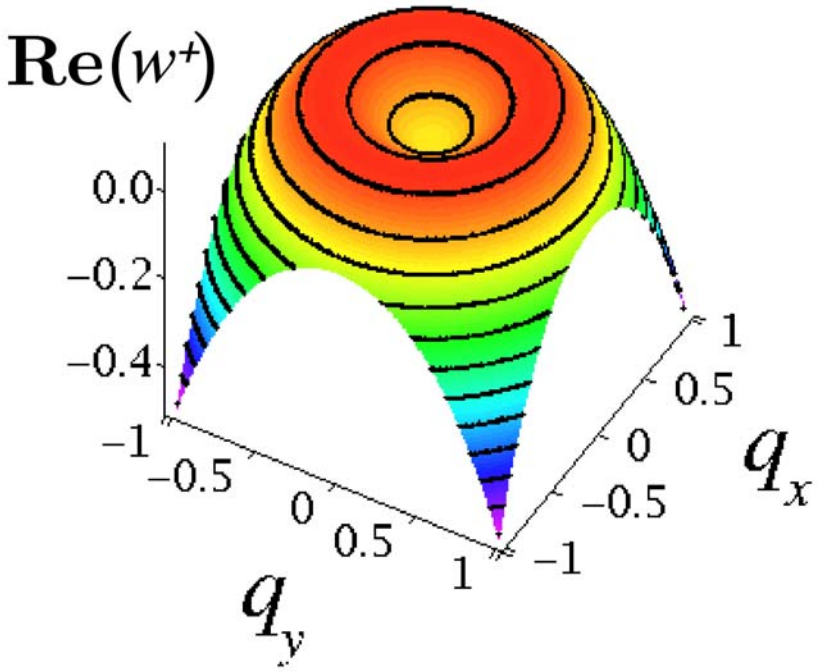


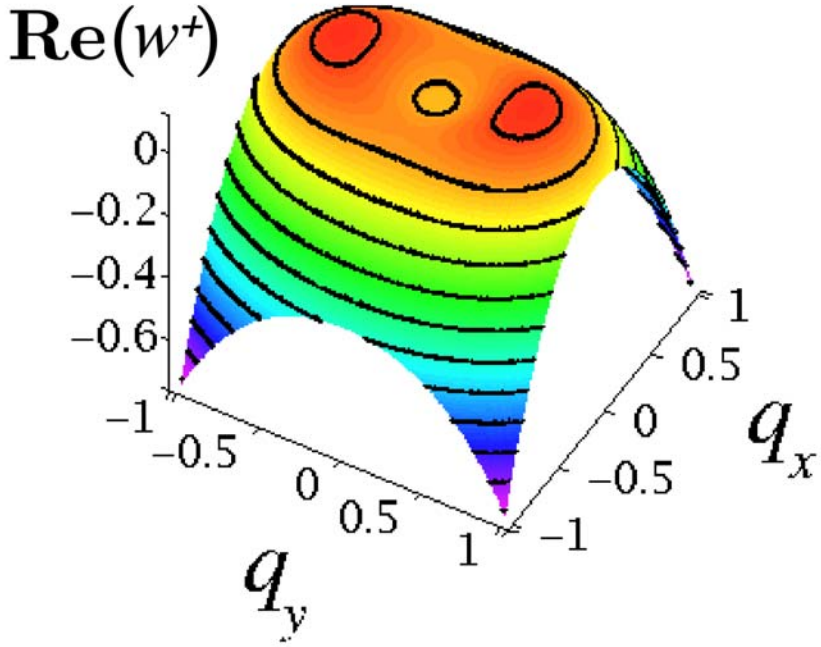
Petri plates (8.5 cm) containing aggregates of *S. typhimurium* wild-type strain LT2 grown in M9 succinate, citrate for72 h at 25°C: (*a*) 5 mM succinate and 1.5 mM citrate. (*b*) 5 mM succinate and 1.7 mM citrate. The inoculum, a remnant of which can be seen at the center of each plate, was 5 µl of a stationary-phase culture grown on M9 glycerol.

H. Berg PNAS 1996


u(x), v(x)
x
0
1
2
3
4
5
0
100
200
300
400


0.1
0
-0.1
-0.2
0
0.2
0.4
0.6
0.8
q
Re(ω+)
V=0
V=1
V=2
V=5
V=10


Re(w+)
0.0
−0.2
−0.4
−1
−0.5
0
0.5
1
qy
1
0.5
0
−0.5
−1
qx


Re(w+)
0
−0.2
−0.4
−0.6
−1
−0.5
0
0.5
1
qy
1
0.5
0
−0.5
−1
qx