

Lecture Notes

I. Continuum models of Branching Growth in Bacteria

assume : - growth is nutrient limited
 - bacteria move by diffusion (possible nonlinear diffusion due to cooperative effects)

ρ = bacterial density
 n = nutrient density

$$\frac{\partial \rho}{\partial t} = \vec{\nabla} \cdot (D_\rho \vec{\nabla} \rho) + \text{growth (nutrient)}$$

$$\frac{\partial n}{\partial t} = D_n \nabla^2 n - \alpha \cdot \text{growth}$$

by normalization, α can be set to **1**

Start with simplest assumptions

- linear diffusion $\Rightarrow D_\rho$ is constant
- growth is just ρn
- equal diffusivity $D_\rho = D_n$

$$\frac{\partial \rho}{\partial t} = D \nabla^2 \rho + n \rho$$

$$\frac{\partial n}{\partial t} = D \nabla^2 n - n \rho$$

$$\Rightarrow n + \rho \text{ is fixed} \equiv n_0$$

$$\Rightarrow \frac{\partial \rho}{\partial t} = D \nabla^2 \rho + \rho (n_0 - \rho)$$

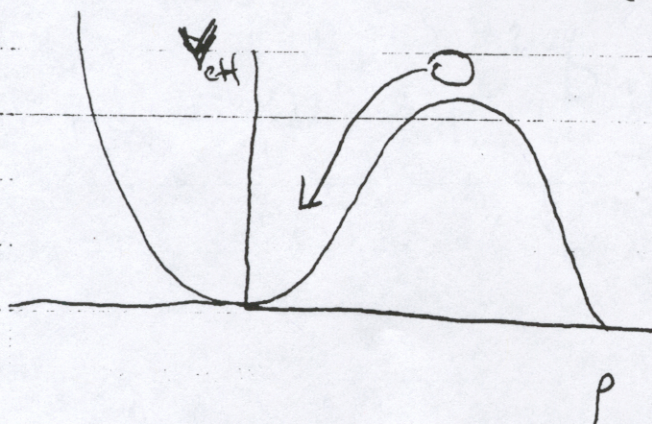
This is called the Fisher equation and is the source of a great deal of work on the issue of velocity selection.

- front solutions ($\rho \rightarrow 0$ as $x \rightarrow +\infty$
 $\rho \rightarrow \rho_0 \equiv n_0$ as $x \rightarrow -\infty$
 ρ as a function of $x - vt$)

1d moving frame equation

$$D \rho'' + v \rho' = - \rho (n_0 - \rho)$$

$$\equiv -V_{\text{eff}}'(\rho) : V_{\text{eff}} = \frac{n_0 \rho^2}{2} - \frac{\rho^3}{3}$$



any v will cause "particle" to come to rest at $\rho = 0$.

So, what selects the velocity?

$$k \neq$$

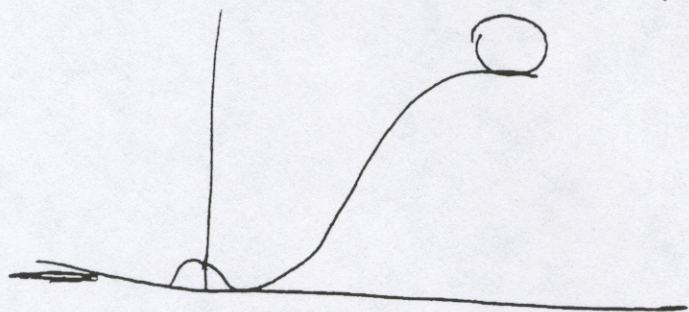
as $x \rightarrow \infty$, $\rho \sim e$

$$z \equiv x - vt$$

$$k = \frac{-v}{2D} \pm \sqrt{\left(\frac{v}{2D}\right)^2 - \frac{n_0}{D}}$$

"marginal" at $v = v_{ms} = 2\sqrt{n_0 D}$
(note: Most localized non oscillatory solution)

$\Rightarrow$ This is the selected velocity. One argument is that of structural stability



add a tiny bump
 $v \rightarrow v_{ms}$ (from below)
as the bump goes away

other argument — solution is marginally stable
 $\Rightarrow$ this argument generalizes to velocity selection
in many different cases of propagating into
a linearly unstable state

Does this pair of RD equations explain branching?

We need to study the stability of the front $\rightarrow$

$$\rho = \rho_0(x-vt) + \delta\rho(x-vt) e^{iqy + \omega t}$$

$$\frac{\omega}{D} \delta\rho = -q^2 \delta\rho + \delta\rho'' + \frac{v}{D} \delta\rho' + (\eta_0 - a\rho_0(z)) \delta\rho$$

$\Rightarrow$ q enters only via the combination $\omega + Dq^2$
 if 1D front is (marginally stable), deforming into 2D
 just makes it more stable $\rightarrow$ don't work

perhaps the problem is the assumption of equal diffusivities
 (in practice $D_n \sim 10^{-5} \text{ cm}^2/\text{sec}$, $D_p \approx 10^{-8}$ or so)

$\Rightarrow$ unavoidably 2 field

$$\frac{\partial \rho}{\partial t} = D_p \nabla^2 \rho + \eta \rho$$

$$\frac{\partial n}{\partial t} = D_n \nabla^2 n - \eta \rho$$

How many front solutions are there?

Moving frame:

$$D_p \rho'' + v \rho' + \eta \rho = 0$$

$$D_n n'' + v n - \eta \rho = 0$$

use counting argument:

near ∞

$$n = n_0 + \delta n, \quad \delta n \text{ small}$$

ρ small

linearize

$$D_p p'' + v p' + n_0 p = 0$$
$$D_n \delta n'' + v \delta n' = 0$$

4 possible modes

δp modes as before, $+2$
 δn $+1$
3 dimensional space

near $-\infty$

$$D_p p'' + v p' = 0$$
$$D_n n'' + v n' - n_0 n = 0$$

δp constant OK $+1$
 n $+1$
2

$3 + 2 = 5$; subtract 1 for translation invariance
 $= 4 \Rightarrow$ matches number of matching conditions: $(n, n'; p, p')$

$\Rightarrow$ solutions can be constructed for continuous range of velocities

(compare to case with small metastability which requires v to be fixed)

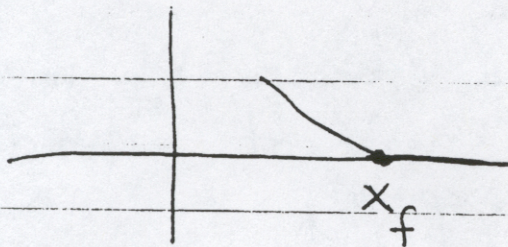
can work out stability $\Rightarrow$ front is stable. Seems to be a general feature of all "pulled" fronts $\rightarrow$ front velocity controlled by n at ∞ , which does not care about gradients in n caused by structure of the interface

How can we get a branching instability?

- $\rightarrow$ real metastability $\Rightarrow$ ruled out experimentally
- $\rightarrow$ effective metastability due to discrete particle effects ($Dn/Dp \geq \ln N$)
(at small p , no particles are present)
possibly true; won't discuss further

* Cooperative motion (due to wetting effects)

assume $D_p \sim p$
one solution for the front equation has compact support. Can see this in the 1 variable model



$$(D_0 p p')' + v p' + (n_0 - p) p = 0$$

$$p \sim (x_f - x) \frac{v}{D_0}$$

solution is unique. Matching to $x \rightarrow \infty$ with one bed mode requires adjusting v (to avoid blow-up)

turns out $v^* = \frac{1}{2}$ for this case

all other solutions decay as power-law

⇒ fastest decaying solution is selected!

adding back in the nutrient field → finite interface whose velocity depends on n at the front position (not ∞)

⇒ Mullins-Sekerka instability

Can construct branching models and begin the task of comparing to the experiments!

II Excitable waves during Dictyostelium aggregation

How can we understand the dynamics of an excitable system? Simplest generic model is due to Fitzhugh-Nagumo

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + \frac{1}{\epsilon} f(u, r)$$

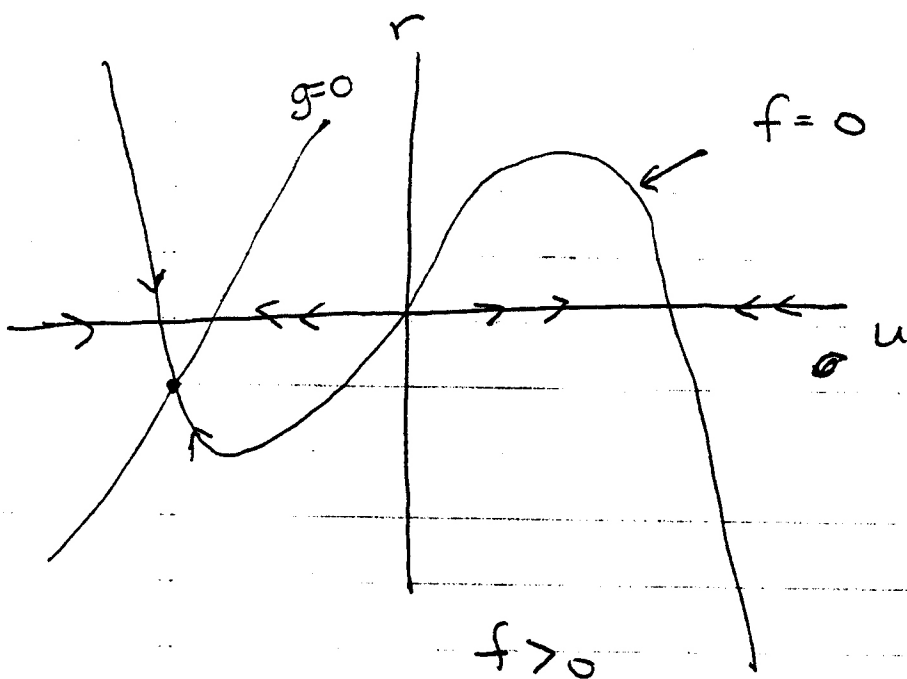
activation variable

$$\frac{\partial r}{\partial t} = D_r \nabla^2 r + g(u, r)$$

recovery variable

$$f = u - u^3 - r$$

$$g = u - \beta r - \Delta$$

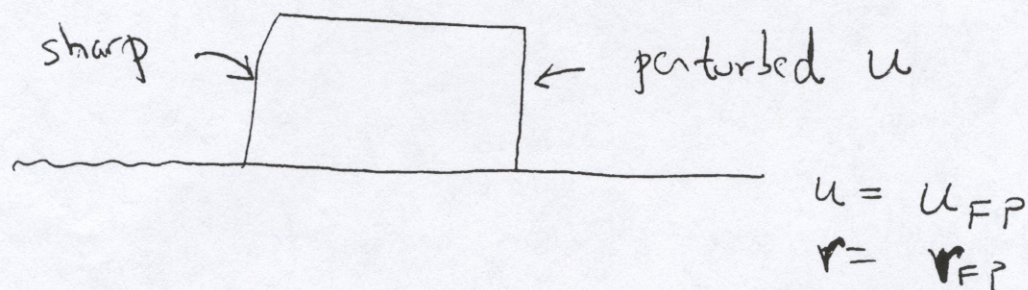


stable fixed point at the intersection of f and g nullclines

But, large u perturbation will cause large response if $\epsilon \ll 1$

For fast time stability $f_u < 0$. Excitable in terms of nonlinear dynamics implies a threshold response and a refractory period for any future excitation

Here, a spatial definition of excitability



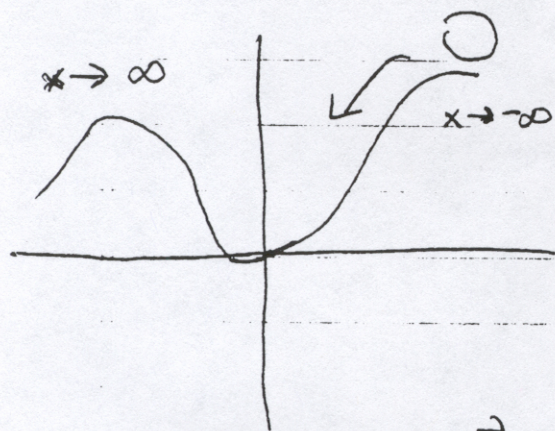
what will happen?

Each edge will go to a moving front (note: length $\sim \sqrt{\epsilon}$, velocity $\sim \frac{1}{\sqrt{\epsilon}}$)

(reduced equation)

$$D_u u'' + v u' = -f(u, v_{FP}) = -F_u(u, v_{FP})$$

$$F = \frac{u^2}{2} - \frac{u^4}{4} - v u$$

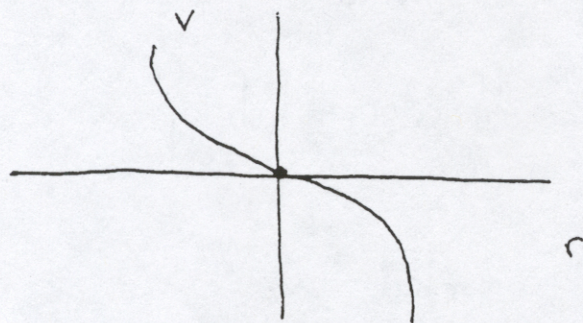


finding a solution with positive velocity (for the front; negative velocity for the "anti-front")

$$\Rightarrow \text{requires } F(u_{excited}) > F(u_{quiescent})$$

$$\Rightarrow v_{FP} < 0$$

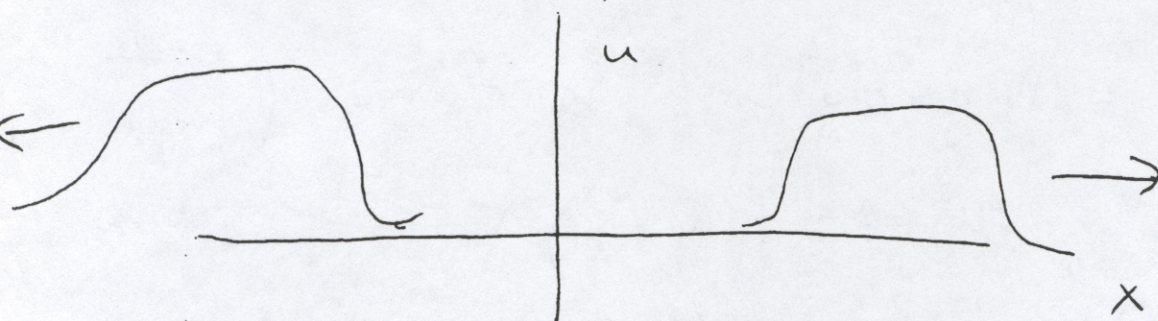
So, pulse will spread at velocity which depends on r_{FP}



$$r_{FP} = 0 \Rightarrow \text{stall}$$

$$\text{"excitability"} \sim r_{\text{stall}} - r_{FP}$$

center part will recover, leading to two oppositely propagating pulses



What determines the width of the pulse. For simplicity, let $D_r = 0$. Then

$$-vr' = g(u_+(r), r)$$

↑
excited branch

$$\frac{\text{width}}{v} =$$

$$\int_{r_{FP}}^{r^*} \frac{dr}{g(u_+(r), r)}$$

r^* fixed by the requirement that the back moves at the same speed as the front

$$V(r^*) = -V(r_{FP})$$

extensions: $D_r \neq 0$ can be done
pulse trains instead of single pulses



- approaches V_{pulse} as $T \rightarrow \infty$

- minimum time to re-excite the system (refractory period)

$\Rightarrow$ dispersion relationship for nonlinear waves in excitable system

$\Rightarrow$ Refractory period leads to crucial phenomenon of wavefront annihilation

$\Rightarrow$ This is how one can use waves to demarcate aggregation territories in the Dicty system

also, this leads to the idea that the fastest source wins $\rightarrow$ motion of annihilation zone

.)) + ((((.

$\uparrow$
place where annihilation takes place

$\Rightarrow$ in Dicty: targets for small density, for overexpression of decay-inducing enzyme -- spirals for wild-type strain, for typical density used in lab expts.

Note: great deal of work done on finding shape and rotation frequency of a spiral. One result follows from a simple scaling argument

$$\frac{1}{2d} \Rightarrow v = v(r) / \sqrt{E} \approx \frac{1}{\sqrt{E}} (r - r_{\text{still}})$$

$$v_n + D_n \kappa = \frac{1}{\sqrt{E}} (r - r_{\text{still}})$$

$\uparrow$
curvature reduces normal velocity, as expected from simple physical argument

(arises from $\vec{v}^2 \sim \vec{v}_n^2 + \kappa \hat{n} \cdot \vec{v}$)

and

$\dot{r} \sim g_{\pm} \sim \text{constant}$ if r is near r_{stall}

consistent scaling :

$$\begin{aligned} r - r_{\text{stall}} &\sim \epsilon^{1/3} \\ \text{length} &\sim \epsilon^{-1/6} \\ \text{time} &\sim \epsilon^{1/3} \quad (\text{fast rotation}) \end{aligned}$$

$\Rightarrow$ spirals are typically faster than typical oscillator (with $\omega \sim O(1)$) and hence will dominate the pattern if they form.

III Discrete vs Continuous $\rightarrow$ when do fluctuations matter

In equilibrium systems, we are used to the idea that thermal fluctuations can be important. In this lecture, we will consider the possible effects that shot noise due to discrete particle number effects (or, in the calcium case, discrete channel number effects) can have.

One effect is the killing of waves — after some amount of propagation, a front will spontaneously abort. Why

Noisy Fisher equation:

$$\frac{\partial u}{\partial t} = D \nabla^2 u + K u (1-u) + \gamma \sqrt{uK}$$

shot noise fluctuations

γ is white-noise
but amplitude of noise depends on the field

This type of stochastic p.d.E can be "derived" from Markov processes which have Fisher as their mean field limit

example : infection model

$A =$ infected person, $B =$ healthy person
 $A + B \rightarrow 2A$ + diffusive ("random-walk") motion
 $\downarrow$

$$\frac{\partial C_A}{\partial t} = D_A \nabla^2 C_A + C_A C_B$$

$$\frac{\partial C_B}{\partial t} = D_B \nabla^2 C_B - C_A C_B$$

But reaction diffusion is only true for infinite number of particles in a typical reaction volume. There is noise proportional to the rate $\sqrt{C_A C_B} \approx K \sqrt{C_A}$ near the front of the spreading epidemic.

$\Rightarrow$ noisy Fisher equation

Why does the noise term stop the motion $\rightarrow$
answer is because the effective growth rate K is renormalized downward via the process of absorption into the state $u=0$

We can see this by looking just at the local equation near the front $\hookrightarrow$

$$\frac{\partial u}{\partial t} = Ku + \sqrt{Ku}$$

$\Rightarrow$ Fokker-Planck equation $\frac{\partial P}{\partial t} = -\frac{\partial}{\partial u} (KuP) + \frac{1}{2} \frac{\partial^2}{\partial u^2} (KuP)$

good exercise in mathematics to solve this equation.

$$P(y, t) = \text{regular piece} + \frac{-\alpha u_0 e^{\alpha t}}{e^{\alpha t} - 1} \frac{1}{g(u)}$$

$(\alpha \sim k)$

irreversible loss into the absorbing state
 $\Rightarrow$ abortive wave front

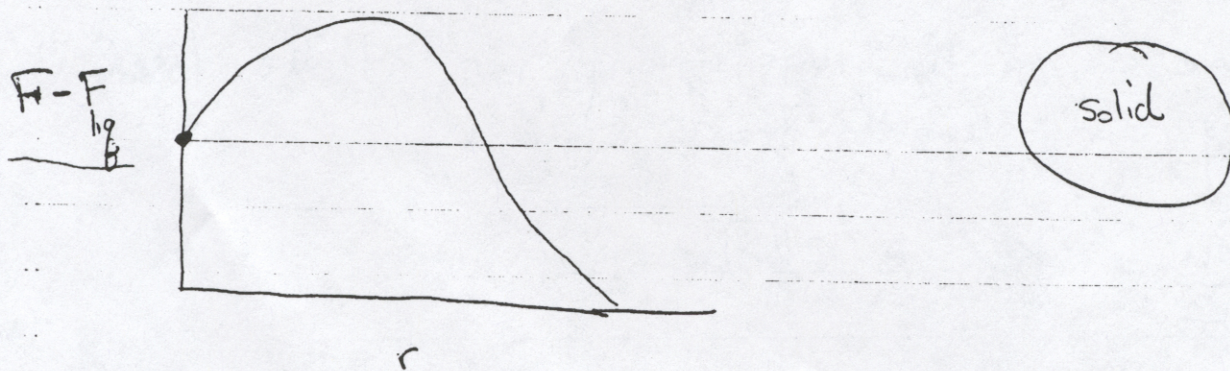
Note: there is a critical value of $k > 0$. The fluctuations also give non-trivial scaling exponents at the phase-transition point

< direction of wave > $\propto t^{-\theta}$

(directed percolation class)

$\Rightarrow$ in all cases except IP_3 is controlling element

Another effect of fluctuations might be the nucleation of nontrivial patterns. Let us first recall standard nucleation ideas for equilibrium first-order phase transition



$$\Delta F = \frac{4\pi}{3} R^3 (F_{\text{solid}} - F_{\text{liquid}}) + 4\pi R^2 \gamma$$

Maximum at $R^* = \frac{28}{F_{lig} - F_{sol}}$

rate $\sim \exp - \Delta F(R^*) / kT$

requirements for this analysis:

- existence of a free energy function
- identification of reaction coordinate
- thermal noise

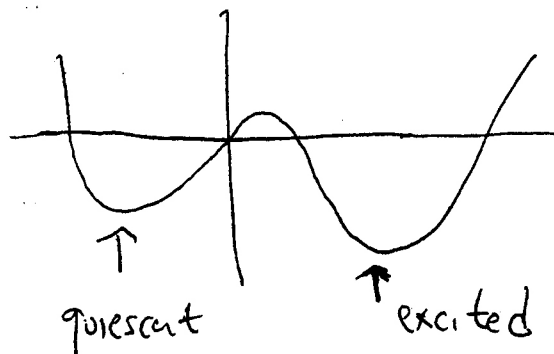
note: finding a reaction coordinate (or even the existence of a reaction coordinate) may be difficult in a system with no symmetry, even if it is in equilibrium (ex. protein folding)

what about for excitable media?

In general, no free energy. One possibly useful approximation is to forget about the recovery field and just compute probability of forming a large enough ring of locally excited case. So, we would use

$-F(u, r_{fp})$ as a free energy

$$= -\frac{u^2}{2} + \frac{u^4}{4} + r_{fp}u$$



or, more generally as the system is recovering from a previous excitation, $-F(u, r(t))$

effective γ can be found by identifying the critical radius

$$V_n + DK = V(r)$$

$$V_n = 0 \text{ at}$$

$$K = \frac{V(r)}{D} = \frac{1}{R^*}$$

$\Rightarrow$ as r relaxes back to r_{FP}

- no possibility of nucleation until r passes r_{stall}
- probability increases as $r \rightarrow r_{FP}$

$\Rightarrow$ almost periodic re-excitation can be seen

Still need $\rightarrow$ a full theory
 $\rightarrow$ detailed comparison to simulation + expt.

Finally, noise seems to be able to induce
spatio-temporal chaos in otherwise stable systems
→ no theory yet

Overall, as we look at intracellular and genetic regulatory
processes, the possible stochasticity of the dynamics must
be considered; the biological function, however, should be
robust in the presence of these inevitable fluctuations.