Aspects of Excitable Media, Oscillations

No study of chemical dynamics would be complete without a discussion of biological oscillators. We start with one of the simplest examples, the *Lotka-Volterra* predator-prey model. Let $N(t)$ by the prey population and $P(t)$ be the predator population. The model is

$$\boxed{\begin{aligned} \frac{dN}{dt} &= N\left(a - bP\right) \\ \frac{dP}{dt} &= P\left(cN - d\right) \ . \end{aligned}}$$

This model embodies four assumptions:

1. Prey, in absence of predation, has constant growth rate. The Malthusian law $dN/dt = aN$.
2. Predation reduces prey's per capita growth rate: $-bP$
3. without prey, predator death is exponential: $-dP$
4. Prey contribute to predator growth rate

Lotka-Volterra Model

As usual, we adopt a set of rescalings:

$$u(\tau) = cN/d \; . \qquad v(\tau) = bP/a \; , \qquad \tau = at \; , \qquad \alpha = d/a \; .$$

Then

$$\boxed{\begin{aligned} \frac{du}{d\tau} &= u(1-v) \\ \frac{dv}{d\tau} &= -\, \alpha v(1-u) \; . \end{aligned}}$$

The nullclines, where $u_\tau = v_\tau = 0$ satisfy

$$\begin{aligned} 0 &= u(1-v) \\ 0 &= v(u-1) \end{aligned}$$

Sketch out the phase portrait...

Lotka-Volterra, continued

There are two fixed points, or equilibria: $u = 0, v = 0$ and $u = 1, v = 1$. Call them (u_0, v_0). As usual, we linearize the governing ODEs in the form $\dot{u} = f(u,v), \dot{v} = g(u,v)$ as $u = u_0 + \xi$ and $v = v_0 + \eta$, finding solutions that grow as $\xi = Ae^{\lambda t}$ and $\eta = e^{\lambda t}$, where λ is obtained from the 2×2 system

$$\boxed{J = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix},}$$

evaluated at (u_0, v_0). The determinental equation is $\lambda^2 - T\lambda + D = 0$, where T is the trace of J and D is its determinant.

- Stability means $Re(\lambda_1, \lambda_2) < 0$ and requires $T < 0$ and $D > 0$
- Instability requires either $D < 0$ or $T > 0$, $D > 0$

where $\lambda_{1,2} = \frac{1}{2}\left(T \pm \sqrt{T^2 - 4D}\right)$.
Let's consider first the fixed point $(0,0)$, where

$$\boxed{J = \begin{pmatrix} 1 & 0 \\ 0 & -\alpha \end{pmatrix},}$$

where clearly $\lambda = 1, -\alpha$. One eigenvalue is positive, and one is negative.

Lotka-Volterra, continued

Let's next consider first the fixed point $(1, 1)$, where

$$J = \begin{pmatrix} 0 & -1 \\ \alpha & 0 \end{pmatrix}.$$

Now, $D = \alpha > 0$ and $T = 0$ so $\lambda = \pm i\alpha$. Both eigenvalues are imaginary, so the solution oscillates and the fixed point is a **centre**.

The trajectory is in fact given by

$$\boxed{\frac{du}{dv} = \frac{u(1-v)}{\alpha v(u-1)}\ ,}$$

which can be integrated to yield $\alpha u + v - \log(vu^{\alpha}) = C$.

See Matlab file Lotka_Volterra.m

However, systems giving rise to centres in this way are not very robust or therefore useful. A small change can give completely different behaviour. For example, let's add some logistic effects:

Lotka-Volterra, continued

Now the dynamics takes the form

$$\boxed{\begin{aligned}\dot{u} =& u(1-v) - \epsilon_1 u^2 \\ \dot{v} =& -\alpha v(1-u) - \epsilon_2 \alpha v^2\end{aligned}}\,.$$

Now the fixed points are $(0,0)$ and $1 - v_0 = \epsilon_1 u_0$ and $1 - u_0 = -\epsilon_2 v_0$. A little calculation shows that now

$$D = \alpha u_0 v_0 (1 + \epsilon_1 \epsilon_2) > 0 \quad \text{and} \quad T = -\epsilon_1 u_0 - \alpha \epsilon_2 v_0 < 0\ .$$

Interestingly, this implies two complex conjugate roote with *negative* real parts. This means the fixed point is a **stable focus**.
Just for fun, what happen if we add harvesting (fishing) to u dynamics, but not v. That is, fish for prey, not predators. Then

$$\begin{aligned}\dot{u} =& u(1-v) - \epsilon u^2 - f \\ \dot{v} =& -\alpha v(1-u)\ .\end{aligned}$$

Fixed points are now at $u - \epsilon u^2 - f = 0$ and $v = 0$ or $u_0 = 1, v_0 = 1 - \epsilon - f$. The latter is interesting: fishing reduces the predator population, not the prey you are fished for. A short calculation shows that $T = f - \epsilon$ and $D = \alpha v_0$. The f.p. is stable if $f < 0$ but unstable if $f > 0$.

Lotka-Volterra, continued

Finally, what happens if we change the dynamics to introduce *competition*?

$$\boxed{\begin{aligned}\dot{N} &= aN - bNP \\ \dot{P} &= -cNP + dP\ .\end{aligned}}$$

Rescaling as before,

$$\begin{aligned}\dot{u} =& u(1-v) \\ \dot{v} =& +\alpha v(1-u)\ .\end{aligned}$$

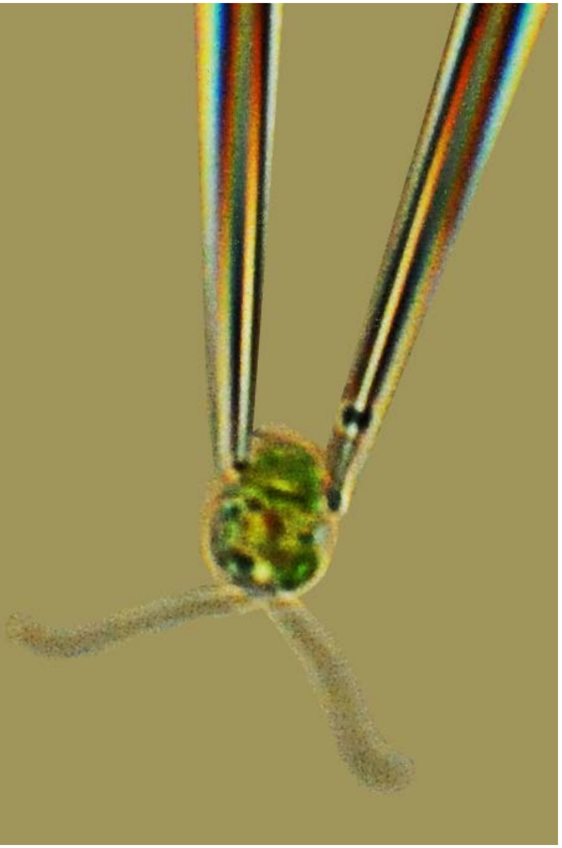
For the fixed point $(1,1)$ now we have $D = -\alpha < 0$ and $T = 0$, so the eigenvalues are real, $\pm\sqrt{\alpha}$. This is an unstable *saddle point*.

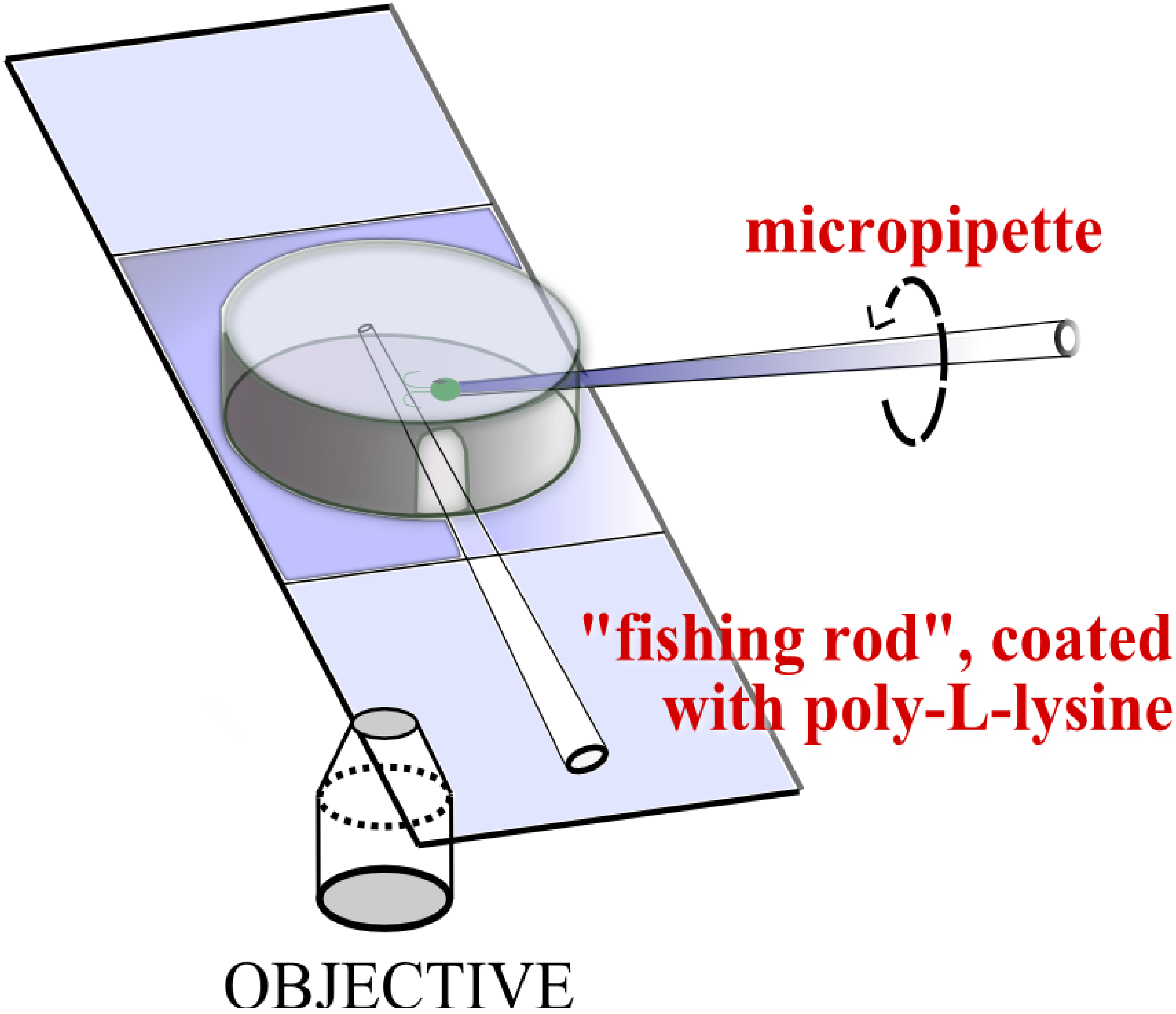
But for $(u_0, v_0) = (0,0)$,

$$J = \begin{pmatrix} 1 & 0 \\ 0 & \alpha \end{pmatrix},$$

for which $D > 0$, $T > 0$ and $\lambda = 1, \alpha$. *Unstable focus*. One species always wins out over the other.

Nonlinear Oscillations. The Example of Flagella



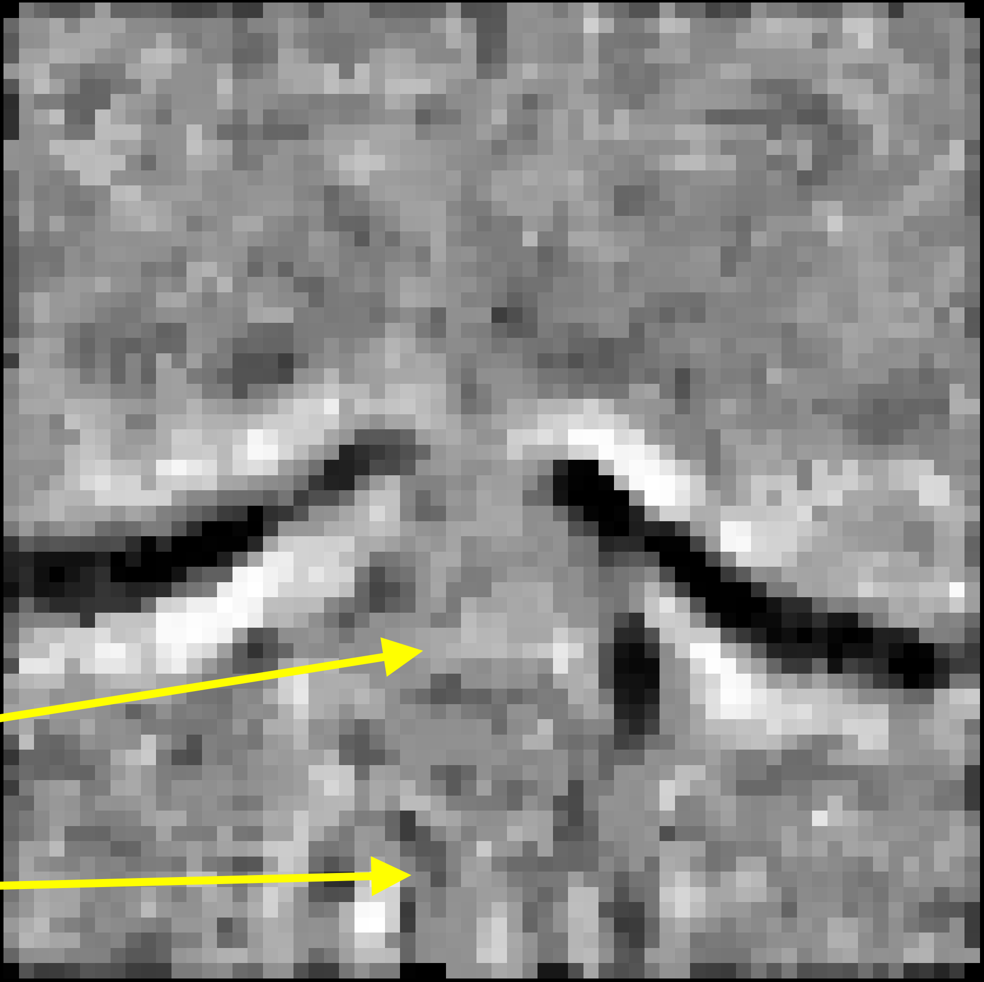


Noisy Synchronization

Experimental methods:

- Micropipette manipulation with a rotating stage for precise alignment
- Up to 2000 frames/sec
- Long time series (50,000 beats or more)
- Can impose external fluid flow

Frame-subtraction

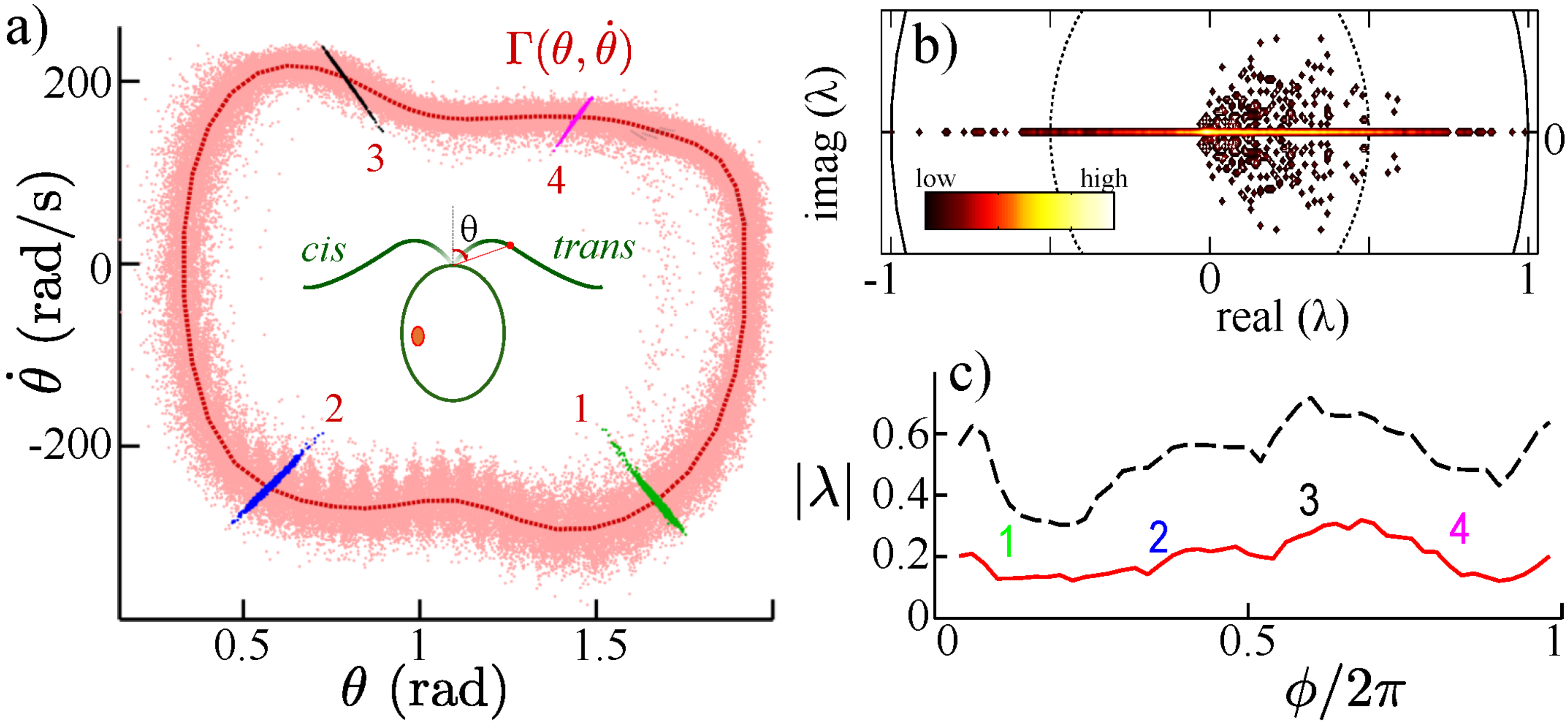


Cell body

Micropipette

Polin, Tuval, Drescher, Gollub, Goldstein, *Science* **325**, *487* (2009)

Phase Portrait – Noisy (Stable) Limit Cycle



Kirsty Wan and REG (2014)

Limit Cycles

Let's consider a more complex predator-prey system (Murray)

$$\boxed{\begin{aligned}\dot{N} &= N\left[r\left(1-\frac{N}{K}\right)-\frac{kP}{N+D}\right]\\ \dot{P} &= P\left[s\left(1-\frac{hP}{N}\right)\right]\ .\end{aligned}}$$

More generally, we might have $\dot{N} = NF(N,P)$, where $F(N,P) = r(1-N/K) - PR(N)$, where the second term represents predation. The functions $NR(N)$ can take on various forms (see blackboard sketches...), represented by $R = A/(N+B)$ or $AN/(N^2+B^2)$, or $A(1-\mathrm{e}^{-aN})/N$. Generally, these embody some form of *saturation*, as in limited predator capability or perseverance, when prey is abundant.

Let's non-dimensionalise: $u(\tau) = N(t)/K$, $v(\tau) = kP(t)/K$, $\tau = rt$, $\alpha = k/hr$, $\beta = s/r$, and $\delta = D/K$. Then

Rescaling as before,

$$\begin{aligned}\dot{u} =& u(1-u) - \frac{\alpha uv}{u+\delta} = f(u,v)\\ \dot{v} =& +\beta v\left(1-\frac{v}{u}\right) = g(u,v)\ .\end{aligned}$$

Limit Cycles

Nullclines at $v = u$ and $1 - u - \alpha v/(u+\delta) = 0$. It is easy to show that the fixed point $(0,0)$ is unstable. The fixed point (u_0, v_0) has

$$J = \begin{pmatrix} 1 - 2u_0 - \alpha u_0 \delta/(u_0+\delta)^2 & -\alpha u_0/(u_0+\delta) \\ \beta & -\beta \end{pmatrix},$$

for which

$$T = \frac{\alpha u_0^2}{(u_0+\delta)^2} - u_0 - \beta \ ,$$

which can be of either sign, and

$$D = \beta u_0 \left[1 + \frac{\alpha\delta}{(u_0+\delta)^2} \right] > 0 \ .$$

Thus, the f.p. is stable iff

$$\boxed{\beta > \frac{\alpha u_0^2}{(u_0+\delta)^2} - u_0 \ .}$$

Now let's think about the possibility of a limit cycle...

Poincaré-Bendixson Theorem

Theorem: If there exists a domain D such that D contains no fixed points and all trajectories sufficiently close to the boundary of D enter D, the D contains at least one stable limit cycle.

This is pretty obvious, really: Suppose there exists one unstable fixed point (focus, not saddle). Then let D be the annulus between a small neighborhood of this point and an outer boundary. In our case, take D as shown.

Thus, given D suitably chosen, a stable limit cycle will exist if

$$\boxed{\beta < \frac{\alpha u_0^2}{(u_0+\delta)^2} - u_0 \; .}$$

Can show that if $\alpha < 1/2$, RHS of above is < 0, but $\beta > 0$, hence stable. If $\alpha > 1/2$, there is a range of values for instability, but no instability for any β if $\delta > \sqrt{\alpha^2 + 4\alpha} - (1+\alpha)$.

See Matlab file Lotka_Volterra2.m

Diffusion and the Stokes-Einstein Relation

If molecules have a diffusion constant D, concentration c, and are advected with speed u, then the flux is:

$$\boxed{J = -D\frac{dc}{dx} + uc}$$

In the low-Re regime we expect a force balance of the form $\zeta u = \text{force} = -d\phi/dx$, where ϕ is a suitable potential energy.

At equilibrium, we must have $J = 0$, so $0 = -D\frac{dc}{dx} - \frac{1}{\zeta}c\frac{d\phi}{dx}$, or

$$\boxed{c \sim \exp(-\phi/D\zeta)}$$

If equilibrium statistical mechanics holds then we must conclude that

$$\boxed{D\zeta = k_B T \quad \text{or} \quad D = \frac{k_B T}{\zeta}}$$

If we is the Stokes drag coefficient for a molecule of radius 2 Å we obtain

$$D \sim \frac{4 \times 10^{-14}}{20 \cdot 0.01 \cdot 2 \times 10^{-8}} \sim 10^{-5}\text{cm}^2/s$$

Excitable Media/Electrophysiology

Now we wish to apply a similar line of reasoning to a neuron, which we start by modelling as a cylinder with a membrane boundary and different concentrations of ions inside/out. For example, $[K^+]_{\rm in} \simeq 130$ mM, $[K^+]_{\rm out} \simeq 4$ mM. We now write a concentration flux in terms of the electrical potential ϕ as

$$J = -D\frac{dC}{dx} + C\frac{-q d\phi/dx}{\zeta} \ ,$$

where q is the molecular charge and ζ is the drag coefficient. At equilibrium, $J = 0$. Integrating this relation, and using the Stokes-Einstein relation we obtain

$$\boxed{\phi_{\rm out} - \phi_{\rm in} = -\frac{k_B T}{q}\ln\left(\frac{C_{\rm out}}{C_{\rm in}}\right) \ .}$$

This is a voltage difference purely because of a concentration difference. Putting in numbers one finds $k_B T/q \simeq 25$ mV. Given the typical concentration ratios, one finds voltage differences around 50 mV.

Excitable Media/Electrophysiology

What is the typical scale of the electric field across the membrane? Given the size of lipid molecules (a few nm), $|\mathbf{E}| \simeq \Delta\phi/\Delta x \simeq 60\times10^{-3}V/6\times10^{-9}m \simeq 10^7$ V/m. A huge field!

Facilitated transport. First, we establish that a simple lipid bilayer is impermeable to ions. Look at the energetics of an ion in the two environments (water, membrane). Model the ion as a conducting sphere of radius a to which infinitesimal bits of charge are added until a final value is reached:

$$dW = -q\,dq\int_{\infty}^{a}\frac{dr}{\epsilon r^2} = \frac{q\,dq}{\epsilon a} \quad \text{hence} \quad W = \int_0^Q dW = \frac{Q^2}{2\epsilon a}\,.$$

Now we compare this *self-energy* in oil and water:

$$\boxed{\Delta W \equiv W_{\mathrm{oil}} - W_{\mathrm{water}} = \frac{Q^2}{2a}\left(\frac{1}{\epsilon_{\mathrm{oil}}} - \frac{1}{\epsilon_{\mathrm{water}}}\right)\,.}$$

Using $a \simeq 1.33$ Åfor a K^+ ion, we obtain $\Delta W \sim 70\ \mathrm{k}_B\mathrm{T}$, so the relative probability of finding a K^+ ion in the membrane versus in water is $\sim \exp(-70)$, which is very small! Need high-dielectric pathways (ion channels) to facilitate transport across the membrane.