F7

• Diffusion
  – some examples
  – role in biology
  – calcium diffusion
    • general
    • compartmentalized
    • stochastic
    • interaction with buffers

• Simplified neuron models
Spatial diffusion

• Inhomogeneous concentration
  – 1D propagation in axons, growth of nails
  – 2D diffusion in membranes
  – 3D diffusion between cells or within cells

• Communication, e.g. Ca-signaling
• Macroscopic organization
**Calcium Signalling**

A: Hepatocytes (liver)
B: Rat parotid gland (gland)
C: Gonadotropes (gonad)
D: Hamster eggs (post-fertilization)
E, F: Insulinoma cells (pancreas)
Macroscopic organization

Drosophila (fruit fly) egg
red=ftz gene
blue=eve gene
How can neurons find their place during development?

• Chemoattractant towards target cells. Cone growth towards chemical gradient.
• Chemoattractant from growth cones causes bundling
• Chemorepellant from growth cones, dependent on target cell chemoattractant, causes dispersion near target
Diffusion speed

- glucose (192 u) 660 [D/10^7 cm^2/s]
- hemoglobin (64500 u) 6.9 [D/10^7 cm^2/s]
- tobacco mosaic virus (40590000 u) 0.46 [D/10^7 cm^2/s]
Diffusion time

- 10nm (cell membrane) 0.1µs
- 10µm (small cell) 100ms
- 1mm ???
- 1m (length of longest axon)
Diffusion time

- 10nm (cell membrane) 0.1µs
- 10µm (small cell) 100ms
- 1mm 16.7 min
- 1m (length of longest axon) ???
Diffusion time

- 10nm (cell membrane) 0.1μs
- 10μm (small cell) 100ms
- 1mm 16.7 min
- 1m (length of longest axon) 32 years

- Need for active transport!
Calcium diffusion

• $\text{Ca}^{2+}$ plays an important role in practically every cell type.

• $\text{Ca}^{2+}$ controls secretion, cell movement, muscular contraction, cell differentiation, ciliary beating, and so on.

• Important in both excitable and non-excitale cells.

• Well regulated in cells. Toxic at high concentrations.

• Can activate Ca-sensitive ion channels
Ca diffusion

\[ \frac{\partial C}{\partial t} = D \nabla^2 C + (J_{in} - J_{out}) - k_1 C(b_t - b) + k_2 b \]

- This reaction-diffusion equation is coupled to a system of ODEs (or PDEs), describing the various sources and sinks of a species.
- The specifics of the coupled ODEs depend on which particular model is being used.
- Sometimes the PM fluxes appear only as boundary conditions, sometimes not, depending on the exact assumptions made about the spatial properties of the cell.
- In general the buffering flux is a sum of terms, describing buffering by multiple diffusing buffers.
Calcium diffusion: spatial discretization

- Spatial discretisation depending on structure of compartment and location of calcium influx. Divide cylindrical compartments into shells, spines into stacked cylinders.

Limitations:
- Localised calcium fluxes $\rightarrow$ local calcium domains.
- Calcium induced calcium release $\rightarrow$ calcium waves, calcium sparks. $\rightarrow$ Model 3D diffusion (computationally expensive).
Calcium compartments

- Assume uniform calcium flux across compartment membrane → only need to consider radial (1D) diffusion.
- **Fick’s first law**: flux $J_{Ca}$ (in mol/s) through area $a$ is proportional to negative concentration gradient:

$$J_{Ca} = -aD_{Ca} \frac{\partial [Ca^{2+}]}{\partial x}$$

- Discretised concentration change in volume $v_i$:

$$\frac{[Ca^{2+}]_{i,t+1} - [Ca^{2+}]_{i,t}}{\Delta t} = D_{Ca} \frac{a_{i,i+1}}{v_i} \frac{[Ca^{2+}]_{i+1,t} - [Ca^{2+}]_{i,t}}{\Delta x}$$

- Only parameter: diffusion constant $D_{Ca}$. Depends on ion size and medium, e.g. $D_{Ca}$ (water) ~ 600 μm$^2$/s, $D_{Ca}$ (cytoplasm) ~ 200 μm$^2$/s.
Stochasticity in intracellular Ca dynamics

• Intracellular pathways can involve very small numbers of ions or molecules.
• 100 nM [Ca$^{2+}$] = 5 calcium ions in a spine head with 0.5 µm diameter.
• Use stochastic simulation methods instead of mass action kinetics.

\[ A + B \xrightarrow{k_1} AB \xleftarrow{k_2} \]

• Probability that one molecule of A changes to AB during the time $\Delta t$:

\[ p(A \rightarrow AB) = 1 - e^{-k_1 \Delta t} \]

• Stochastic methods are computationally expensive
  → Use adaptive stochastic methods that switch to deterministic calculations for large numbers of molecules (Vasudeva & Bhalla, 2003).

• Representation of spatial microstructure: use Monte-Carlo simulation where all molecules are represented individually and perform random walks. Simulation software: MCell
Computationally Efficient Stochastic Diffusion Algorithm

- Subdivide dendrites and spines into sub-volumes
- Pre-calculate the probability that one molecule leaves the compartment
- Look-up tables store the probability that \( k \) out of \( N \) molecules leave a compartment
- The number, \( k \), molecules leaving out of \( N \) is determined with single random number
Example: Diffusion of Calcium or Second Messengers in Dendrite with Spines

- Spines Concentrate Molecules
- Large fluctuations in small compartments
Reaction-Diffusion Systems

• An important class of pattern forming systems consists of chemicals diffusing and reacting with each other.
• If the interactions are nonlinear and the diffusion coefficients different, interesting instabilities result.
• Can be modelled with partial differential equations or cellular automata.

\[
\frac{dx_i}{dt} = f(x_1, x_2, \ldots, x_n) + D_i \nabla^2 x_i
\]
Two interacting species

- A basic example with two morphogens A and B (lab 3a). Let $a$ and $b$ be their deviations from equilibrium in each cell:

\[
\frac{da}{dt} = c_1 a + c_2 b + r_a a^3 + D_a \nabla^2 a
\]

\[
\frac{db}{dt} = c_3 a + c_4 b + r_b b^3 + D_b \nabla^2 b
\]
Self Organisation

• Complex patterns can be produced by application of simple rules to simple initial states.
• In biological systems chemical signals combined with non-linear local interaction are able to produce very complex patterns.
• Symmetry breaking: the initial undifferentiated state is unstable. Feedback amplifies deviations, turning noise into pattern.
Belousov Zhabotinsky reaction

0.2 M Malonic Acid
0.3 M Sodium Bromate
0.3 M Sulfuric Acid
.005M Ferroin

Combine to form a solution. Add approximately 5 mL of the solution to a Petri dish, 6 cm in diameter, so that the thickness of the layer is 0.5 -1 mm. Watch until colorful spatio-temporal patterns emerge. In thicker layers there is an interference of hydrodynamic flows with the reaction.
Fish Patterns

*Pomacanthus maculatus*

*Coris formosa*

*Hypostomus plecostomus*
Generic Ca-modeling

- ER
- Mitochondria
- Ca$^{2+}$
- Serca
- RyR
- IPR
- PM pumps
- Ca$^{2+}$-B (buffering)
- $I_{Ca}$
- Leak
Generic Ca-modeling

Set up a typical reaction diffusion equation for calcium:

\[ \frac{\partial C}{\partial t} = D \nabla^2 C + (J_{\text{IPR}} + J_{\text{RyR}} - J_{\text{Serca}}) + (J_{\text{leak}} + J_{\text{PM}} - J_{\text{I}}) + J_{\text{m,out}} - J_{\text{m,in}} - k_1 C(b_t - b) + k_2 b \]

- ER fluxes
- PM fluxes
- Mitochondrial fluxes
- Buffering

- This reaction-diffusion equation is coupled to a system of ODEs (or PDEs), describing the various sources and sinks of a species.
- The specifics of the coupled ODEs depend on which particular model is being used.
- Sometimes the PM fluxes appear only as boundary conditions, sometimes not, depending on the exact assumptions made about the spatial properties of the cell.
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Calcium influx and efflux

Plasma membrane
- \( \text{Ca}^{2+} \text{ ATPase} \)
- \( \text{Na}^+ / \text{Ca}^{2+} \text{ exchanger} \)

Intracellular calcium stores
- Endoplasmic reticulum ER
  - Serca
  - IP3
  - Ryanodine
- Mitocondria

\( \text{Ca}^{2+} \text{ ATPase model} \)

\[
\begin{align*}
J_\infty &= V_{\text{max}} \frac{[\text{Ca}^{2+}]^n}{K^n + [\text{Ca}^{2+}]^n} \\
\frac{dj}{dt} &= \frac{J_\infty - J}{\tau_j}
\end{align*}
\]
Calcium buffers

For each diffusion shell and each buffer:

\[ \rightarrow J \text{Ca}^{2+} + B \rightarrow^{k_1} \text{CaB} \]
\[ \leftarrow^{k_2} \]

\[ \frac{d[\text{Ca}^{2+}]}{dt} = -k_1[\text{Ca}^{2+}][B] + k_2[\text{CaB}] + J \]

Four parameters for each buffer:
- Forward and backward rate constants \( k_1 \) and \( k_2 \).
- Total concentration \([B]_T = [B] + [CaB]\).
- Diffusion constant \( D_B \).

Derived parameters (assume rapid buffer approximation, i.e. steady-state):
- Dissociation constant
- Buffer capacity
  (between 50 and 4000 in neurons)
- Buffering factor

\[ K_D = \frac{[\text{Ca}^{2+}][B]}{[\text{CaB}]} = \frac{k_2}{k_1} \]

\[ K = \frac{d[\text{CaB}]}{d[\text{Ca}^{2+}]} = \frac{K_D[B]_T}{\left(K_D + [\text{Ca}^{2+}]\right)^2} \approx \frac{[B]_T}{K_D} \]

\[ \beta = \frac{d[\text{Ca}^{2+}]}{d[\text{Ca}^{2+}]}_T = \frac{1}{1 + \kappa} \]
Excess buffer approximation

Rapid buffer approximation

- EBA appropriate when the saturability of mobile buffer is negligible. For example, this is the case for millimolar concentrations of Calbindin-D$_{28K}$ in the saccular hair cell.

- RBA appropriate when there is significant saturability of mobile buffer and when buffer kinetics are fast relative to Ca$^{2+}$ diffusion. This is often the case near Ca$^{2+}$ channels in synapses, and near IP$_3$ or ryanodine receptors in the ER/SR.

- Smith et al. (2001) did an asymptotic analysis of buffered Ca$^{2+}$ diffusion near a point source, and determined mathematical conditions for when RBA or EBA are appropriate.

$$\lim_{r \to 0} B \approx B_{bk} \quad \text{(EBA)} \quad \lim_{r \to 0} B \approx 0 \quad \text{(RBA)}$$

buffer unperturbed

buffer saturates
Simplified neuron models

- Each compartment gives one ODE
- Each ion channel gives one (e.g. K) or two (e.g. Na) ODEs.
- Simple Ca-diffusion gives one ODE

- Expensive to simulate
- Needs many parameters
HH dimension reduction

- very fast variable (Na act) at s-s
- fast variable u (membrane potential)
- slow variable w (Na inact + K act)

\[
\frac{du}{dt} = u - \frac{1}{3}u^3 - w + I
\]
\[
\frac{dw}{dt} = e(b_0 + b_1 u - w)
\]

time in units of \(\tau\), ratio of time scales \(e = \tau/\tau_w\)
Integrate and fire IF

- Focuses on the capacitive property of the membrane
- Assumes the action potential acts like a “reset”

\[ \tau \frac{dV}{dt} = -V(t) + RI(t) \]
\[ \tau = RC \]
if \( V \geq V_T \) set \( V = V_{\text{reset}} \)
Calcium dynamics: exponentially decaying pool

\[
\frac{d[Ca^{2+}]}{dt} = - \frac{I_{Ca}}{2Fv} - \beta \left( [Ca^{2+}] - [Ca^{2+}]_{min} \right)
\]

Advantage: only three parameters

- \([Ca^{2+}]_{min}\) baseline calcium concentration ~50nM.
- \(\beta\) decay rate constant, summarises diffusion, buffering, pumps and exchangers.
- \(v\) volume of calcium pool, usually submembrane shell (relevant for activation of KCa channels).

Limitations:

- Not possible to study calcium dependent processes in the cytoplasm (e.g. calcium induced calcium release CICR).
- Different KCa channels sense different \([Ca^{2+}]\)?

Possible extension:

- Use several calcium pools with different \(\beta_i\).