Systems Biology: Theoretical Biology

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Chapter 9
Hodgkin-Huxley model

Introduction

Hodgkin-Huxley model :
- detailed model for nerve action potential

Perfect illustration of Systems Biology approach:
- carefully observe and think about the system
- perform detailed measurements on the system
- construct models for the system components
- integrate these models into a larger level model

$\rightarrow$ model that generates action potentials
$\rightarrow$ explains different phases action potential
$\rightarrow$ predicts existence of voltage gated channels

Furthermore:
- famous example of Theoretical biology approach
- shows Theoretical biology has a long tradition
- demonstrates importance: Nobel prize 1963!

Background: Neurons

Where:

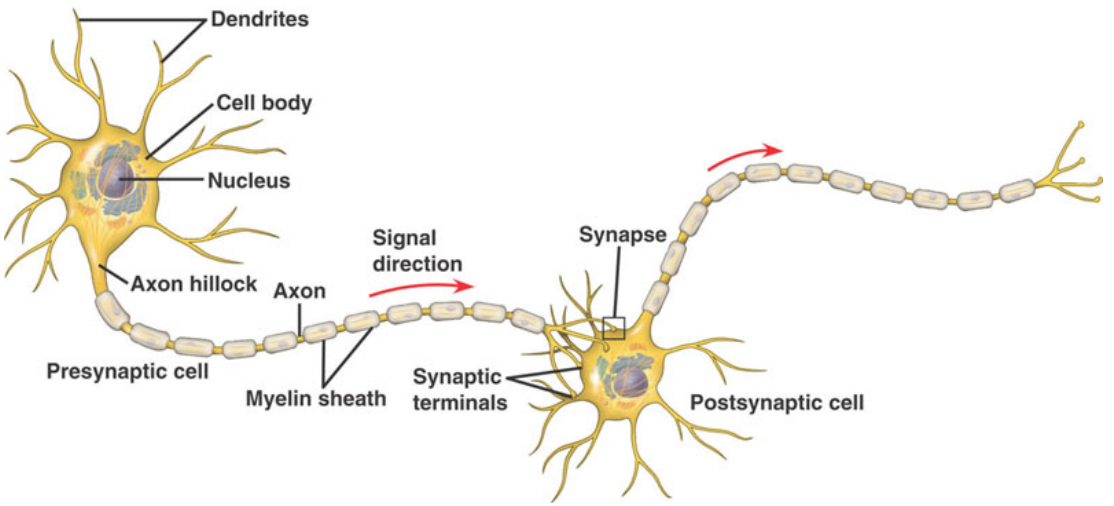
Incoming signals: dendrites and cell body

Outgoing signals: axon

What:

Intracellular signal: electrical

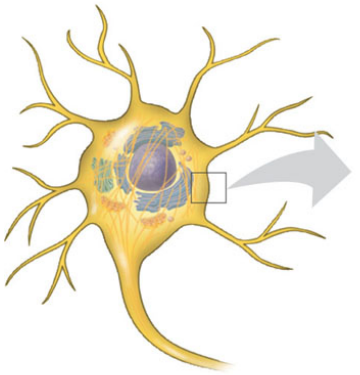
Intercellular signal: chemical

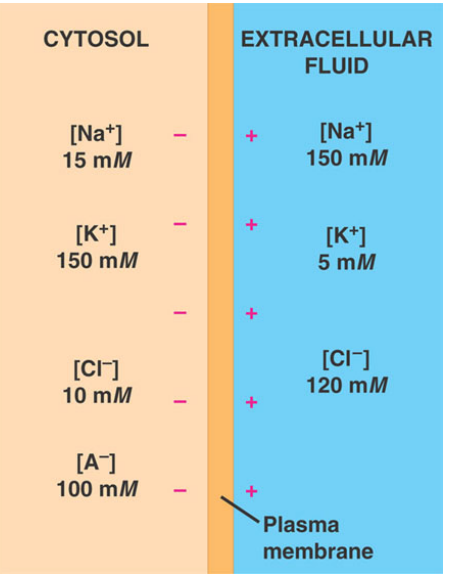


From: Campbell & Reece

Background: Concentration and Charge Differences

Resting conditions:





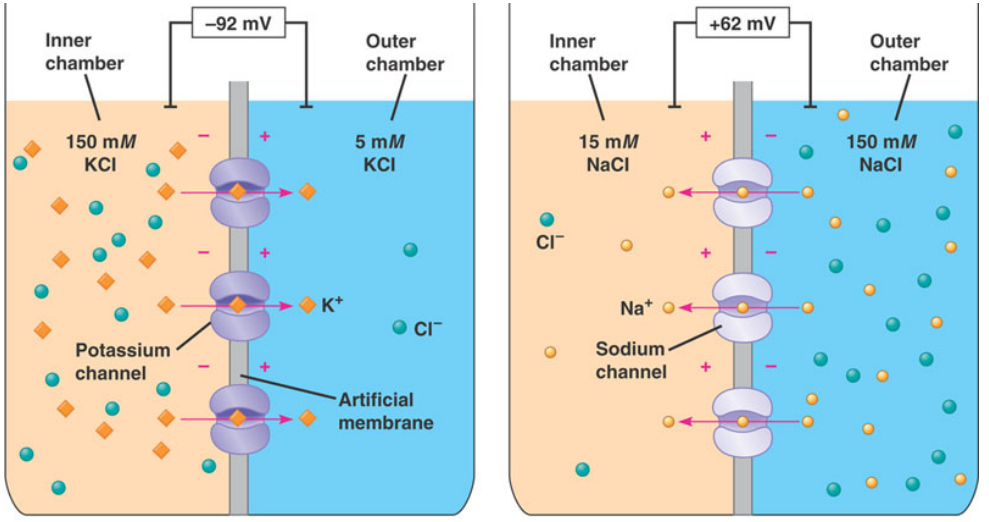
From: Campbell & Reece

Inside: more K+, more A-
Outside: more Na+, more Cl-

So both **concentration differences** and **charge differences**
Charge difference produces **transmembrane potential** of -70mV
So cell acts as a battery!

Background: Ionic Currents

Channels in membrane allow for **ionic currents**.



(a) Membrane selectively permeable to K^+ (b) Membrane selectively permeable to Na^+

From: Campbell & Reece

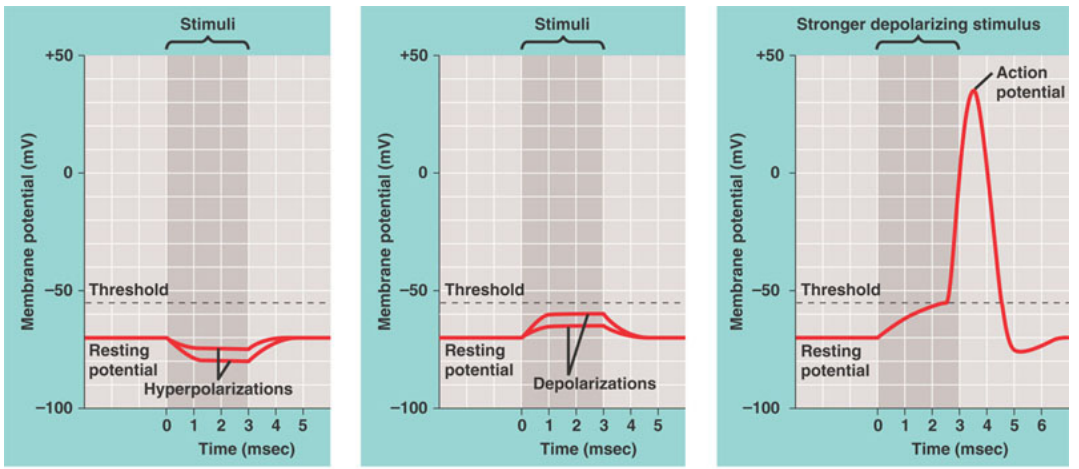
Ionic currents transport ions across membrane through channels

This changes the charge difference / transmembrane potential

Background: Action potentials

Action potential:

change in transmembrane potential due to ionic currents



From: Campbell & Reece

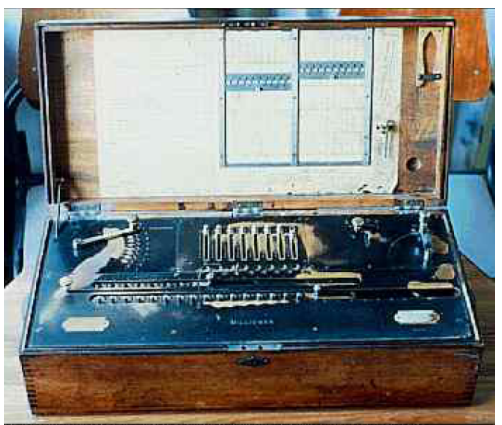
Apparently some opening and closing of channels going on.

Back in time

To appreciate how major Hodgkin and Huxleys accomplishment was:

In those days:
- whole membrane assumed to get permeable to all ions
- specific ion protein channels not yet discovered
- no fine-scale voltage clamp technique
- computers were not yet invented

Their solution:
- be really smart
- use very large axon of the squid
- use mechanical calculating device and compute for weeks



Millionaire Calculator, Dept. of Computer Science, Monash University
Photo L. Allison (c) 1995

Being smart: Nernst potentials

Current only occurs if membrane (channel) is open

If occuring, what is driving force behind current:
- concentration differences (down gradient)
- charge differences (to opposite charge)

$\rightarrow$ **electrochemical gradient**

Current is zero if voltage equals **Nernst potential**:

$$\overline{V_K} = \frac{1}{z} \ln \frac{K_o}{K_i}$$

K^+ is then in equilibrium

So approximation of current size is:

$$I_K = g_K(\overline{V_K} - V)$$

with $g_K = 1/R$ $(I = V/R)$

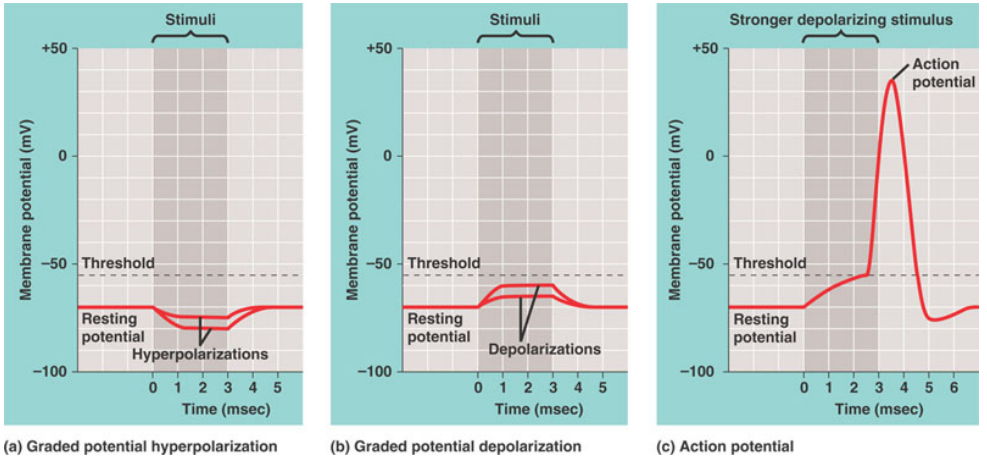
Being smart: What really happens?

We can compute that:

$\overline{V_{Na}} = \pm 50mV$

$\overline{V_K} = \pm -80mV$

Now look again at what happens during action potential:



From: Campbell & Reece

Apparently, first Na^+ current, then K^+ current!

Being smart: Separate I_{Na} and I_K

Complete membrane was thought to change in permeability:

$$C_m \frac{dV}{dt} = I = \Delta V / R_m = g_m \Delta V$$

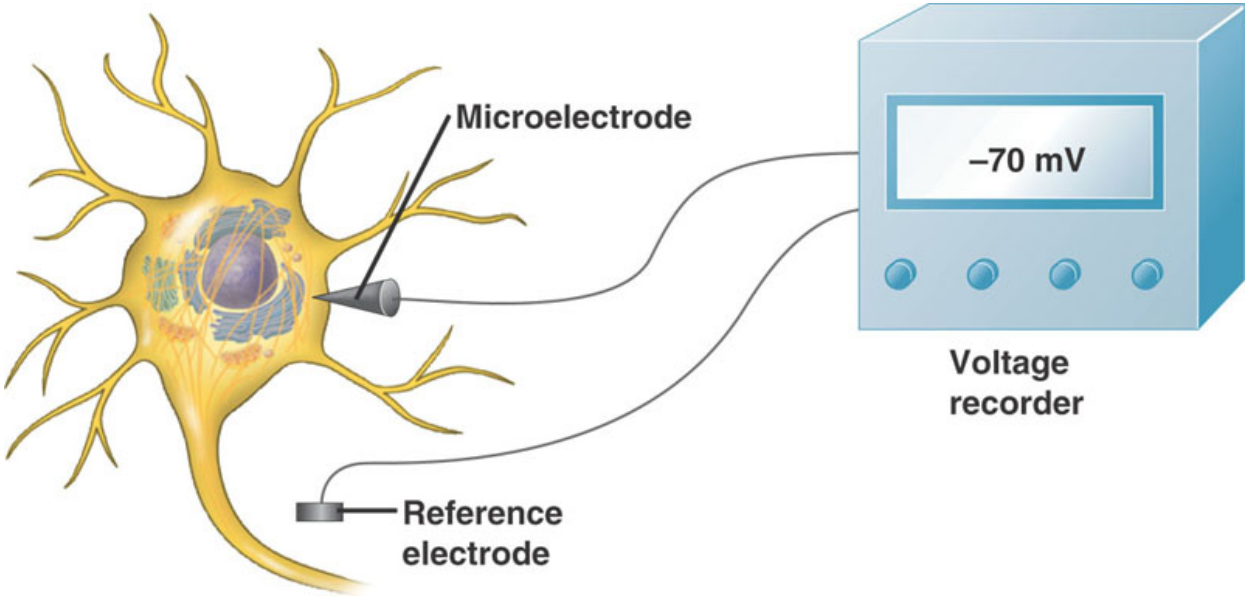
Key insight: V_m first approaches $\bar{V_{Na}}$ (depol.) then $\bar{V_K}$ (repol.)
Implication: Na^+ and K^+ current flows are independent
Prediction: presence of separate membrane channels for different ions

$$C_m \frac{dV}{dt} = I_{Na} + I_K + I_{rest} = g_{Na}(\bar{V_{Na}} - V) + g_K(\bar{V_K} - V) + g_{rest}(\bar{V_{rest}} - V)$$

Approach: measure and model different currents **separately** (to avoid interference) and **put them back together later** for complete model

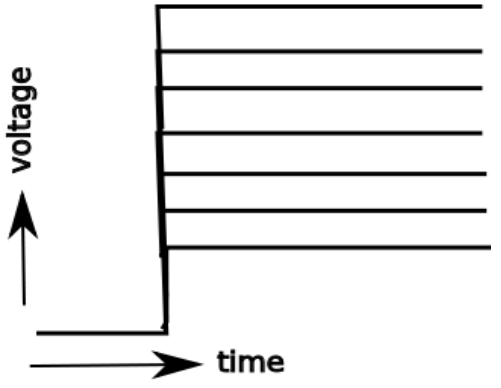
Measuring separate currents

- Suppress other currents, avoiding interference.
- Clamp membrane voltage to a constant value.
- Measure current size and time dynamics.
- Do this for different voltage values.



From: Campbell & Reece

Measuring the I_K current



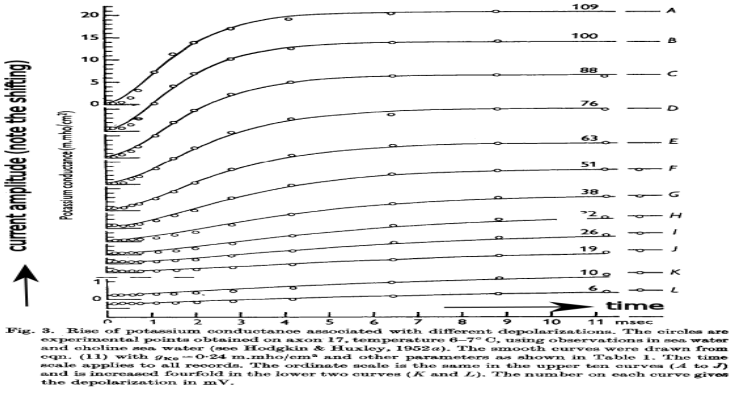


Fig. 3. Rise of potassium conductance associated with different depolarizations. The circles are experimental points obtained on axon 17, temperature 8–7° C, using observations in sea water and choline sea water (see Hodgkin & Huxley, 1952*a*). The smooth curves were drawn from eqn. (11) with $g_{K4} = 0{\cdot}24$ m.mho/cm² and other parameters as shown in Table 1. The time scale applies to all records. The ordinate scale is the same in the upper ten curves (*A* to *J*) and is increased fourfold in the lower two curves (*K* and *L*). The number on each curve gives the depolarization in mV.

Observations:

- voltage increase produces I_K current
- plateau level of current depends on voltage
- time dynamics of current depends on voltage
- current increases in sigmoid fashion

Prediction:

I_K channel has multiple gates that open in response to voltage

Modeling the I_K current

Modeling a gated current:

$$\begin{aligned} I_K &= g_K(E_K - V) \\ g_K &= G_K \times O \\ O &= n^4 \\ dn/dt &= \frac{n_\infty - n}{\tau_n} = \alpha_n(1-n) - \beta_n n \end{aligned}$$

G_K max. cond. if all channels are open

O the fraction of open I_K channels

n the fraction of open channel gates

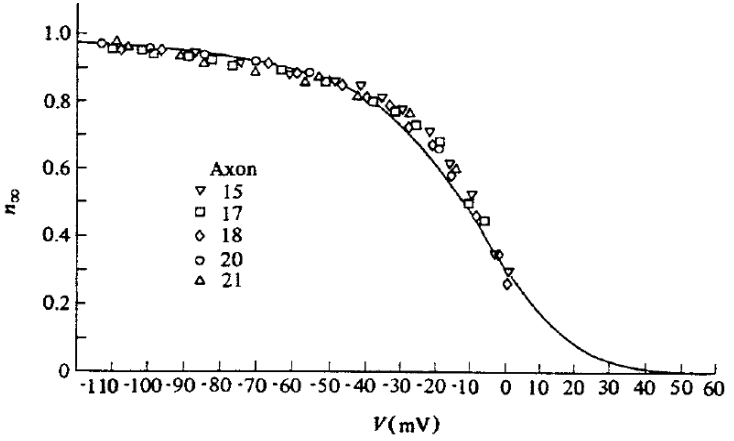
$n_\infty(V)$ steady state value of gate

$\tau_n(V)$ time constant of gate

$\alpha_n(V)$ opening rate of gate

$\beta_n(V)$ closing rate of gate

Fitting the I_K model to the data



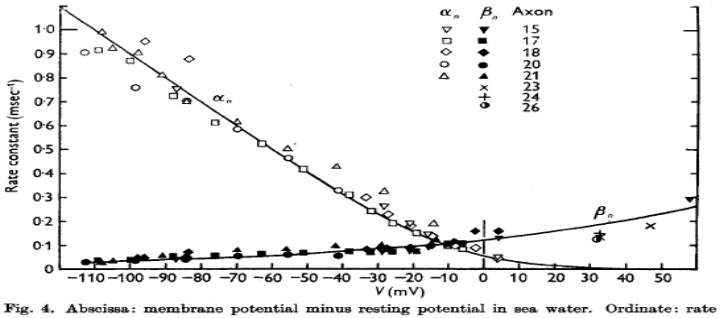


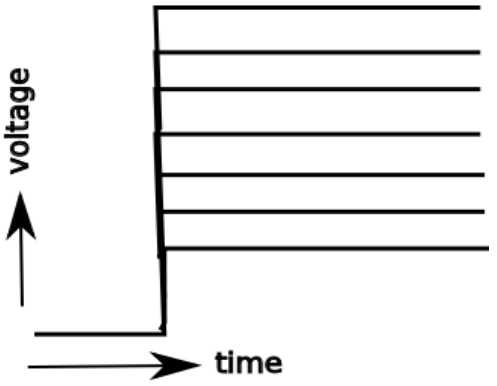
Fig. 4. Abscissa: membrane potential minus resting potential in sea water. Ordinate: rate constants determining rise (α_n) or fall (β_n) of potassium conductance at 6° C. The resting potential was assumed to be 4 mV higher in choline sea water than in ordinary sea water. Temperature differences were allowed for by assuming a Q_{10} of 3. All values for $V < 0$ were obtained by the method illustrated by Fig. 3 and Table 1; those for $V > 0$ were obtained from the decline of potassium conductance associated with an increase of membrane potential or from repolarization to the resting potential in choline sea water (e.g. Fig. 2). Axons 17–21 at 6–11° C, the remainder at about 20° C. The smooth curves were drawn from eqns. (12) and (13).

Fit needed for G_K and $\alpha_n(V)$ and $\beta_n(V)$:

$G_K = 36$
$\alpha_n(V) = 0.01\frac{V+10}{e^{(V+10)/10}-1}$
$\beta_n(V) = 0.125e^{V/80}$

Looks horrible, but just increasing and decreasing functions

Measuring the I_{Na} current



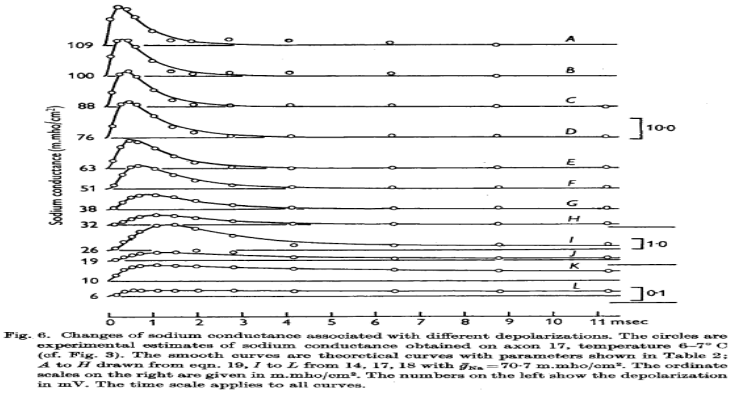


Fig. 6. Changes of sodium conductance associated with different depolarizations. The circles are experimental estimates of sodium conductance obtained on axon 17, temperature 6–7° C (cf. Fig. 3). The smooth curves are theoretical curves with parameters shown in Table 2; *A* to *H* drawn from eqn. 19, *I* to *L* from 14, 17, 18 with $\bar{g}_{Na} = 70{\cdot}7$ m.mho/cm². The ordinate scales on the right are given in m.mho/cm². The numbers on the left show the depolarization in mV. The time scale applies to all curves.

Observations:

- voltage increase produces I_{Na} current
- peak current depends on voltage
- time dynamics depends on voltage
- current increases in sigmoid fashion
- currents shuts itself down again

Prediction:

I_{Na} channel has both multiple activation gates and an inactivation gate

Modeling the I_{Na} current

Modeling a double gated current:

$$
\begin{aligned}
I_N &= g_N(E_N - V) \\
g_N &= G_N O \\
O &= m^3 h \\
dm/dt &= \alpha_m(1-m) - \beta_m m \\
dh/dt &= \alpha_h(1-h) - \beta_h h
\end{aligned}
$$

G_{Na} max. cond if all channels are open

O fraction of open channels

m fraction of opened activation gates

h fraction of still open inactivation gates

Fitting the I_{Na} model to the data

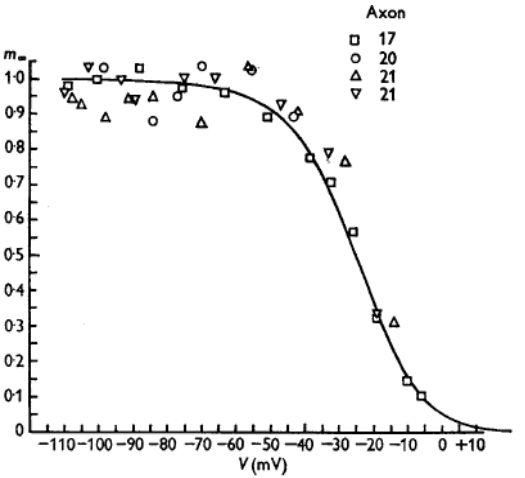


Fig. 8. Abscissa: membrane potential minus resting potential in sea water. Ordinate: m_∞ obtained by fitting curves to observed changes in sodium conductance at different depolarizations (e.g. Fig. 6 and Table 2). The smooth curve is drawn according to eqn. (22). The experimental points are proportional to the cube root of the sodium conductance which would have been obtained if there were no inactivation.

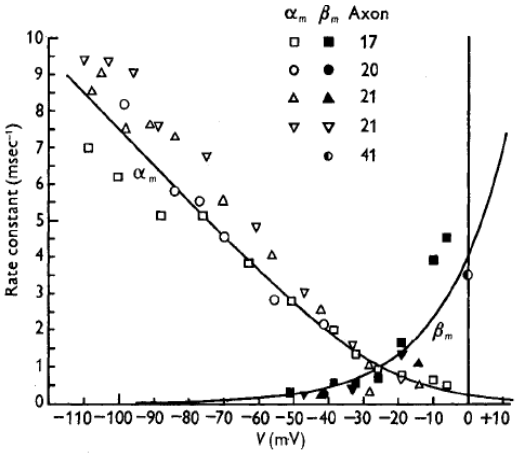


Fig. 7. Abscissa: membrane potential minus resting potential in sea water. Ordinate: rate constants (α_m and β_m) determining initial changes in sodium conductance at 6° C. All values for $V<0$ were obtained by the method illustrated by Fig. 6 and Table 2; the value at $V=0$ was obtained from the decline in sodium conductance associated with repolarization to the resting potential. The temperature varied between 3 and 11° C and was allowed for by assuming a Q_{10} of 3. The smooth curves were drawn from eqns. (20) and (21).

Fit needed for G_N, $\alpha_m(V)$, $\beta_m(V)$

$G_N = 120$

$\alpha_m = 0.1\frac{V+25}{e^{(V+25)/10}-1}$

$\beta_m = 4e^{V/18}$

Just increasing and decreasing graphs

Fitting the I_{Na} model to the data (2)

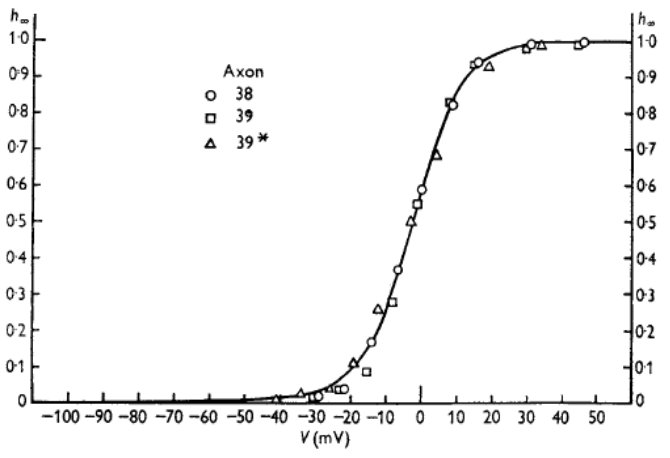


Fig. 10. Steady state relation between h and V. The smooth curve is drawn according to eqn. (25). The experimental points are those given in Table 1 of Hodgkin & Huxley (1952*c*). Axon 38 (5° C) as measured. Axon 39 (19° C) displaced −1·5 mV. Axon 39* (3° C, fibre in dereliet state) displaced −12 mV. The curve gives the fraction of the sodium-carrying system which is readily available, as a function of membrane potential, in the steady state.

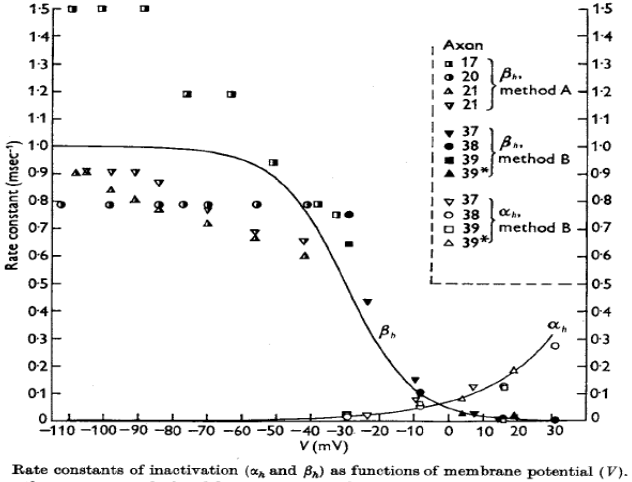


Fig. 9. Rate constants of inactivation (α_h and β_h) as functions of membrane potential (V). The smooth curves were calculated from eqns. (23) and (24). The experimental values of α_h and β_h were obtained from data such as those in Table 2 of this paper (method A) or from the values of τ_h and h_∞ given in Table 1 of Hodgkin & Huxley (1952*c*) (method B). Temperature differences were allowed for by scaling with a Q_{10} of 3. Axon 39 was at 19° C; all others at 3–9° C. The values for axons 37 and 39* were displaced by −1·5 and −12 mV in order to give $h_\infty = 0{\cdot}6$ at $V = 0$.

Fit needed for $\alpha_h(V)$, $\beta_h(V)$

$$\alpha_h = 0.07e^(V/20)$$
$$\beta_h = \frac{1}{e^((V+30)/10)+1}$$

Just increasing and decreasing graphs

Hodgkin-Huxley model

To model the action potential we need to bring the currents together:

$$\mathrm{d}V/\mathrm{d}t = \tfrac{1}{C_m}\left[120m^3h(\overline{V_N}-V) + 36n^4(\overline{V_K}-V) + 0.3(\overline{V_R}-V)\right]$$
$$\mathrm{d}m/\mathrm{d}t = \alpha_m(V)(1-m) - \beta_m(V)m$$
$$\mathrm{d}h/\mathrm{d}t = \alpha_h(V)(1-h) - \beta_h(V)h$$
$$\mathrm{d}n/\mathrm{d}t = \alpha_n(V)(1-n) - \beta_n(V)n$$

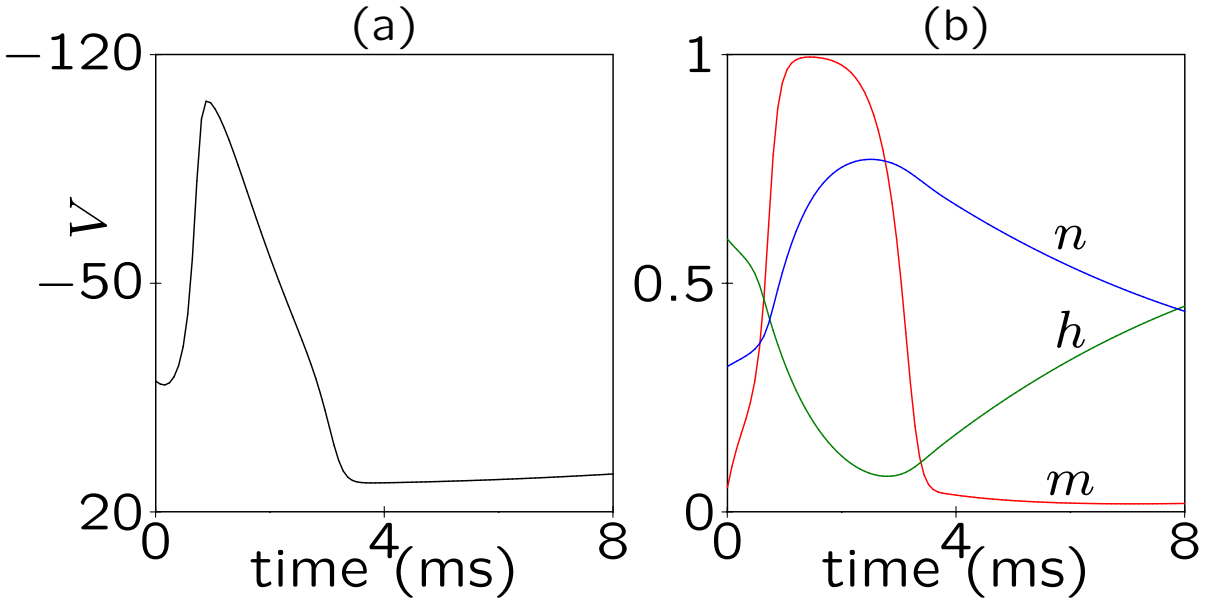
with $\overline{V_N} = -115$, $\overline{V_K} = 12$, and $\overline{V_R} = -10.5989$.

So we obtained a system of 4 ODE's

Stable equilibrium ($V \simeq 0, m \simeq 0.05, h \simeq 0.6, n \simeq 0.3$): **rest potential**.

Using the model: simulate an AP

Note that in HH-model rest potential is $0mV$ and AP is $-90mV$!



a Action potential: voltage dynamics

b Gate dynamics

Using the model: obtaining insights

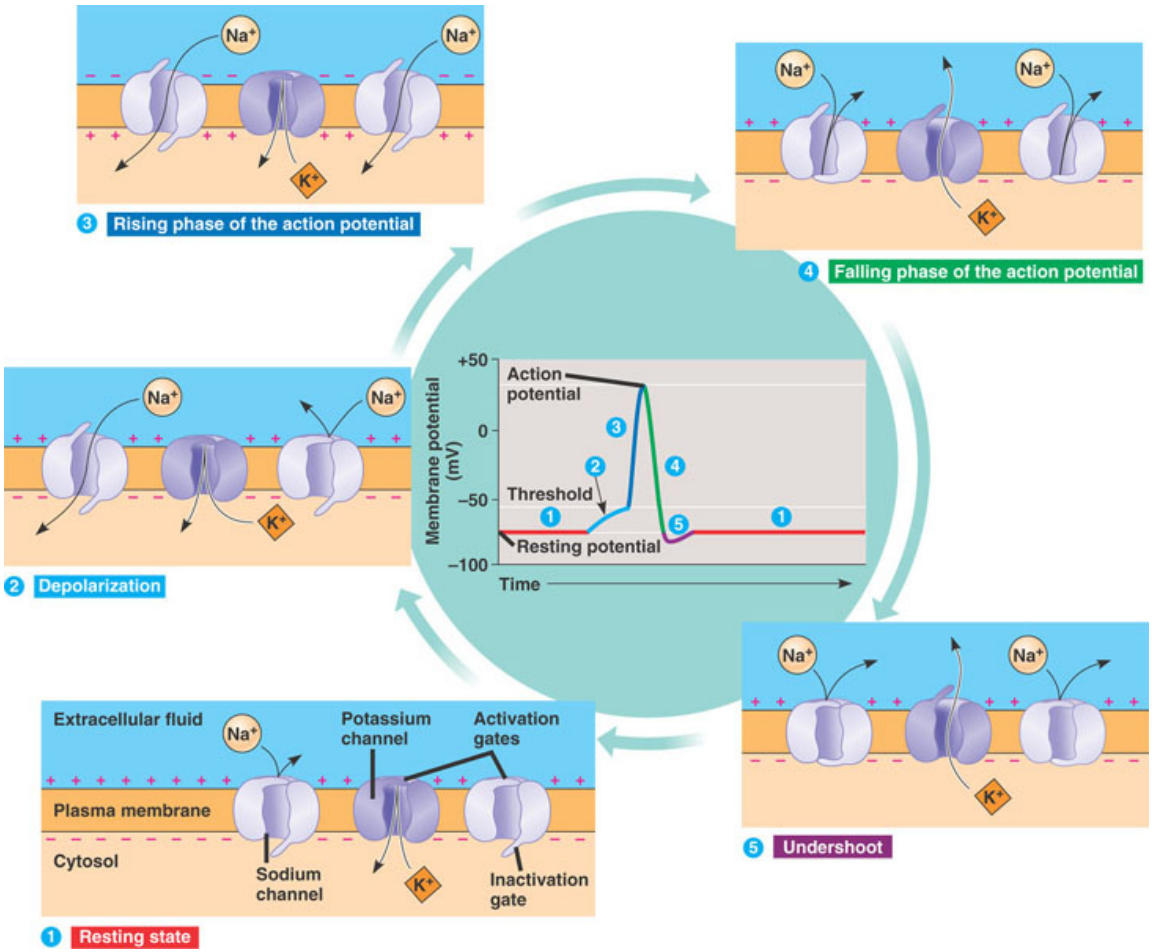
Observations (biological):

- I_{Na} activates first, causes depolarization, determines threshold
- repolarization caused by decrease of I_{Na} and increase of I_K
- refractoriness caused by slow recovery of n and h gates

Observations (technical):

- m gate is much faster than the other gates
- h and n gate are almost exactly complementary

Neuron Action Potential Generation



Simplifying the model

Quasi steady state assumption: m gate is much faster

Taking:

$\mathrm{d}m/\mathrm{d}t = \alpha_m(1-m) - \beta_m m = 0$

Gives:

$m = \frac{\alpha_m}{\alpha_m + \beta_m}$

Conservation assumption: n and h are $\sim$ complementary

Taking:

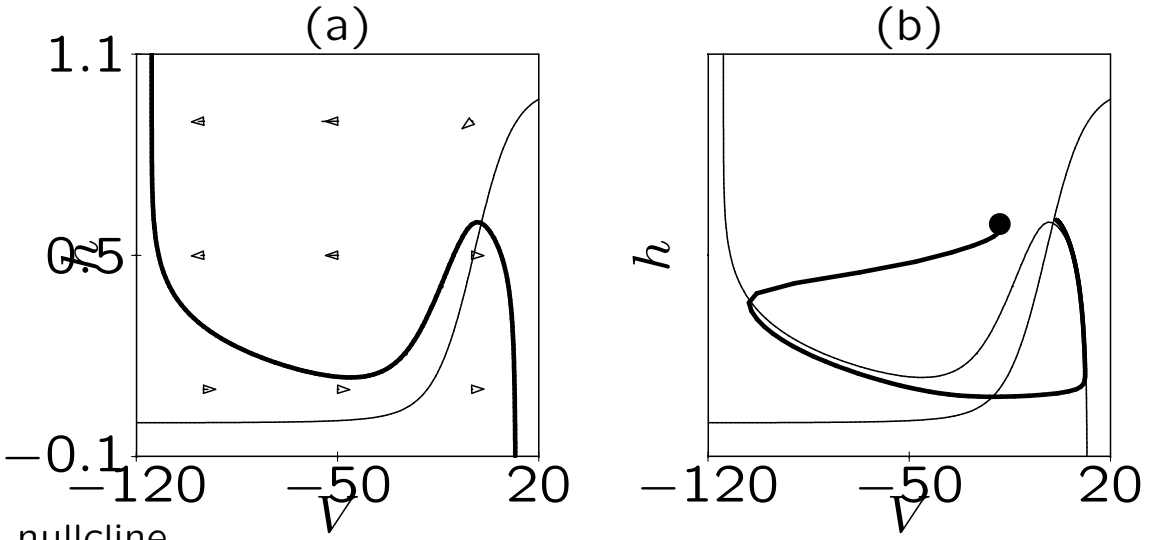
$n + h \simeq 0.91$

Gives:

$n = 0.91 - h$

This leaves us with a 2-variable (V and h) model.

Nullclines and Phase space



thin line: h nullcline

fat line: V nullcline

- Stable equilibrium
- V nullcline determines activation threshold
- AP is excursion through phase space
- Inactivation h gate occurs after while
- Refractoriness caused by recovery h gate

$\rightarrow$ h much slower than V

FitzHugh-Nagumo model

A phenomenological model is

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -V(V-a)(V-1) - W \quad \text{and} \quad \frac{\mathrm{d}W}{\mathrm{d}t} = \epsilon(V - bW) \ ,$$

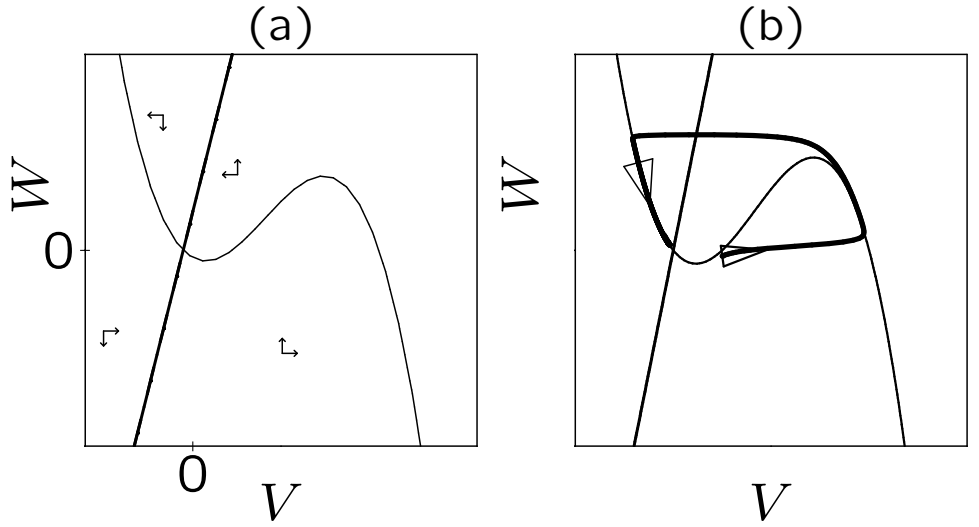
V represents voltage
W follows V, causes inactivation, refractoriness

As ϵ is small, W is a slow variable.

The $\mathrm{d}W/\mathrm{d}t = 0$ nullcline is $W = V/b$.

The $\mathrm{d}V/\mathrm{d}t = 0$ nullcline is $W = -V(V-a)(V-1)$.
It intersects the x-axis at $V = 0$, $V = a$ and $V = 1$.

Nullclines

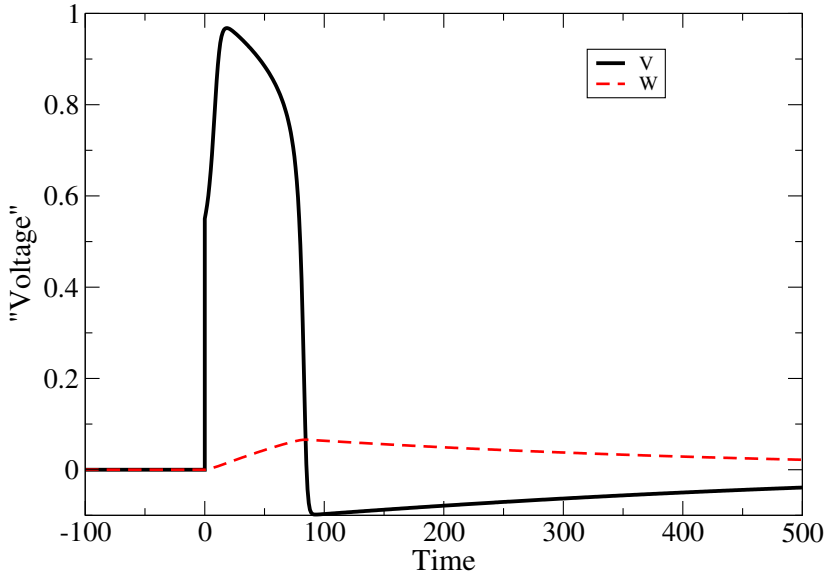


Similar to simplified HH model (V and W axis mirrored)

- Stable equilibrium
- V=a activation threshold
- AP is excursion through phase space
- Inactivation W on right branch $\mathrm{d}V/\mathrm{d}t = 0$
- Refractoriness W on left branch $\mathrm{d}V/\mathrm{d}t = 0$

$\rightarrow$ W much slower than V

Behavior in time



Behavior resembles action potential.

W gate is opposite to h gate, in rest/closed 0 open > 0.

V maximum is scaled at 1, W maximum thus is scaled at 1/b.

http://www.scholarpedia.org/article/FitzHugh-Nagumo_model

Summary

Hodgkin-Huxley model
Key insight: different currents through separate channels
Approach: measure and model them separately, then combine them

Ugly equations are just to fit data precisely. Key is opening and closing of gates that control open state of channels.

Different currents and gates control different phases of the action potential: depolarization, repolarization, refractoriness

Model can be simplified from 4 to 2 equations

The model *predicted* voltage sensitive, time dependent transmembrane protein channels.

Summary

Fitzhugh-Nagumo model:
reaching a similar 2 variable model by considering necessary ingredients:
- below a threshold no real excitation occurs
- beyond a threshold excitation must occur
- after excitation refractoriness must occur

$\rightarrow$ **excitable medium**

$(V - a)$ term ensures threshold at a
slow W repressing V ensures refractoriness

Note how voltage axis runs in opposite direction!

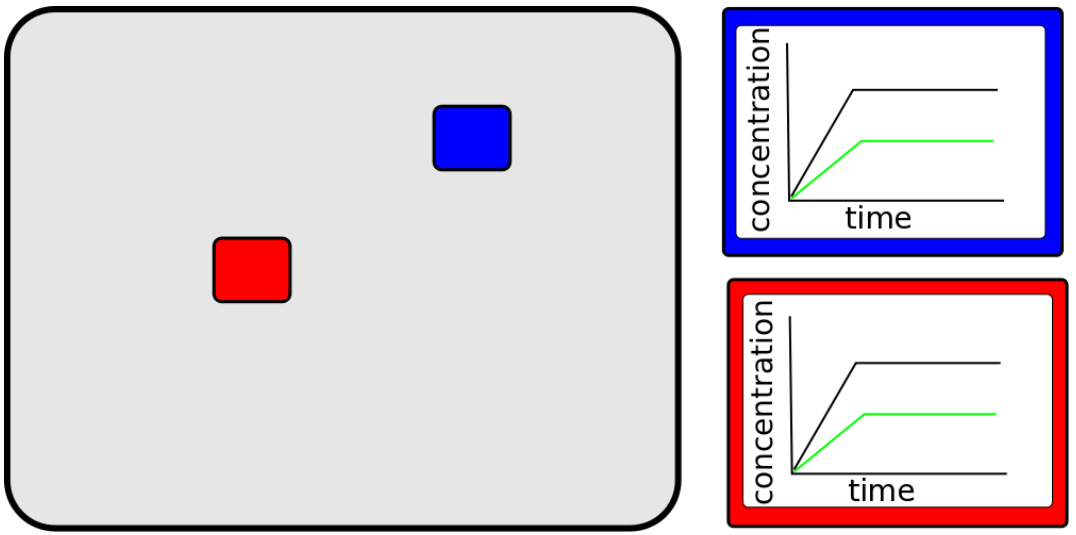
Chapter 10
Spatial patterns

Chapter goals

- explain why we get spatial patterns in biology
- illustrate patterns of different space and timescales
- illustrate dynamic wave patterns and stationary patterns
- explain how we can model spatial processes: PDEs and CAs

Patterns in space

Homogeneous situation:
the same things happen at the same time everywhere
happens for well mixed systems: differences disappear fast



we can describe what happens everywhere by describing the dynamics in a single point: no need to include space in model

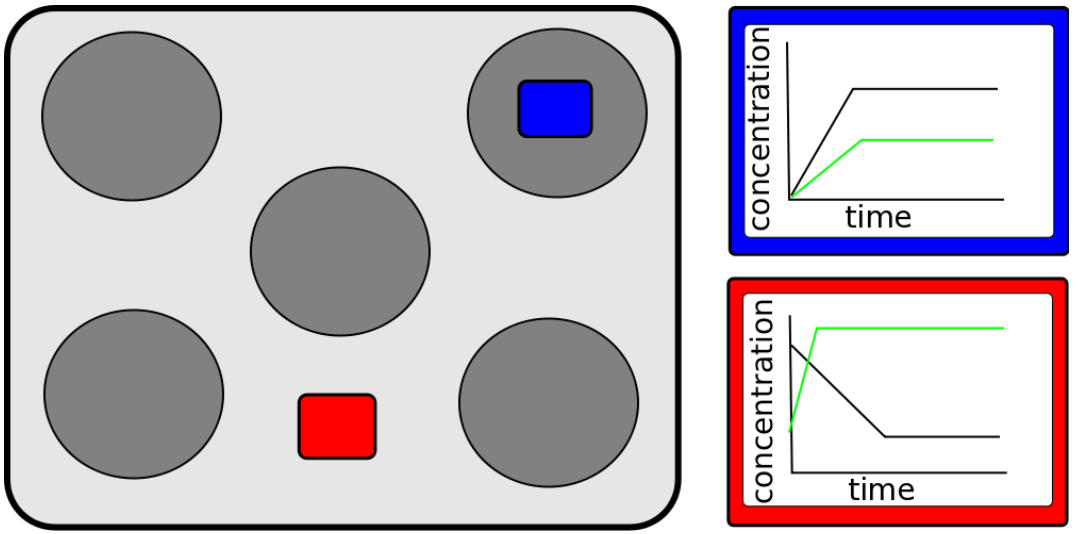
But.....

Biological systems are rarely homogeneous.
Often just used as a simplifying assumption.

Examples:
- Cells: reactions occur on membrane, in cytoplasm or organelle
- Populations: more likely to mate with neighbour than distant other

Patterns in space II

Patterned situation:
at different points in space different things happen
but dynamics in different points are co-dependent
(due to diffusion, migration, flow, etc between points)



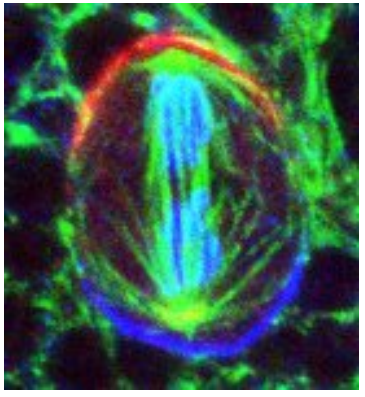
- system dynamics $\neq$ single point dynamics
- system dynamics $\neq$ independent dynamics in two points

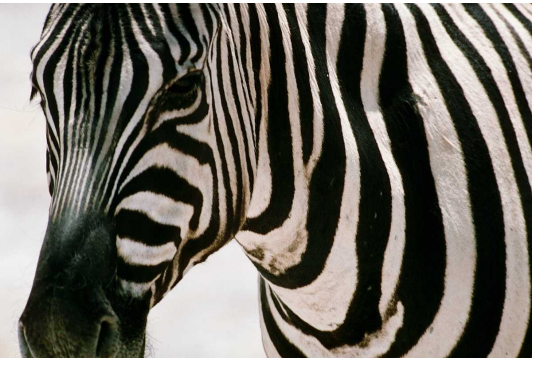
$\rightarrow$ need to describe dynamics in all points
$\rightarrow$ need to include how local points affect each other

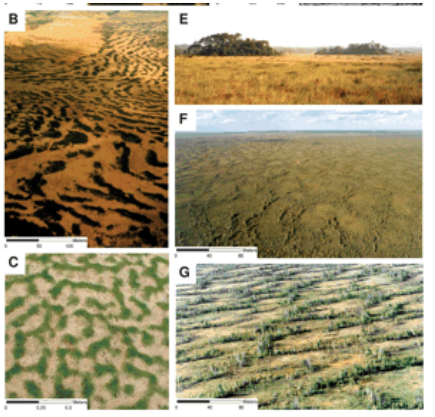
Biological patterns

Patterns occur on very different space and timescales:

Cell polarization, skin pigmentation, ecosystem patterns:



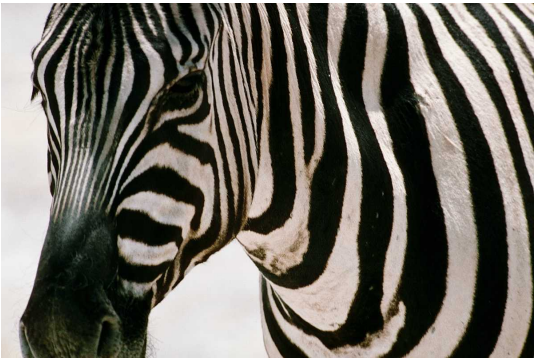




Biological patterns II

Patterns can vary dynamically: wave patterns

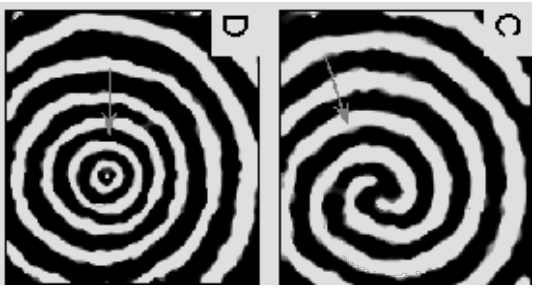
Patterns can be stationary (after initialisation)



Biological patterns III

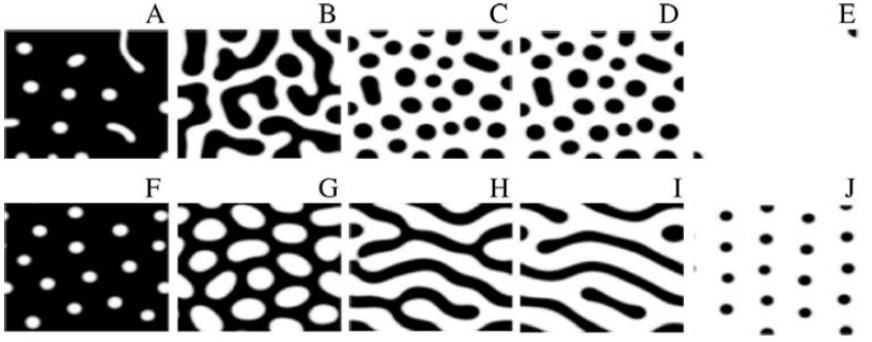
Patterns can have all kinds of shapes:

Dynamic patterns are often waves or spirals



From: hopf.chem.brandeis.edu/.../ResearchAreas.htm

Stationary patterns are often spots or stripes



From: Kefi *et al*, Theoretical Ecology 2009

Including space in models

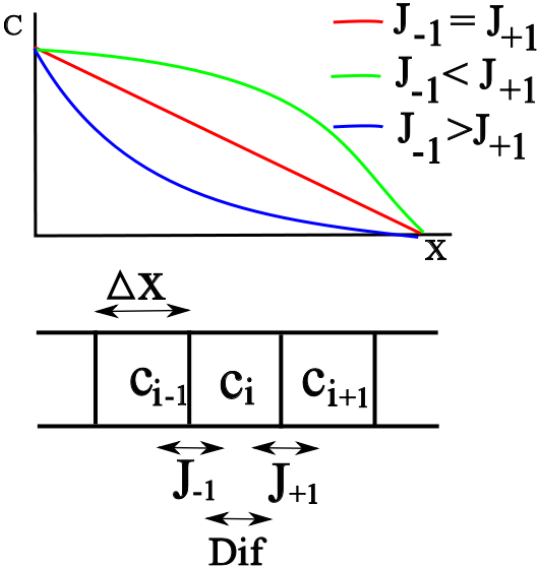
To include space in models we need to
- model the dynamics in **each individual point** in space
- and **couple** the dynamics of variables in nearby points

Simplest spatial coupling:
Diffusion: flow of particles from high to low concentrations

Note:
We can use diffusion term also to model migration of animals

How to model diffusion

Assume a 1D cable of points with a concentration gradient:



$$J_{-1} = D\frac{c_{i-1}-c_i}{\Delta x} = D\frac{\Delta c}{\Delta x}$$

$$J_{+1} = D\frac{c_i-c_{i+1}}{\Delta x} = D\frac{\Delta c}{\Delta x}$$

$$Dif = \frac{J_{-1}-J_{+1}}{\Delta x} = \frac{\Delta J}{\Delta x} = \frac{\Delta \frac{D\Delta c}{\Delta x}}{\Delta x} = D\frac{\Delta^2 c}{\Delta x^2}$$

So to model diffusion we need second derivative of concentration to space

ODE's and PDE's

ODE: ordinary differential equation:

$$\frac{dN}{dt} = f(N)$$

we assume that N depends on t but not x

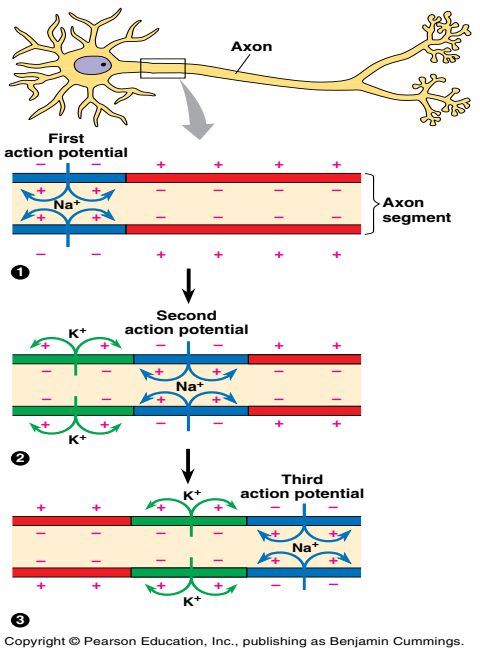
PDE: partial differential equation:

$$\frac{\partial N}{\partial t} = f(N) + D\frac{\partial^2 N}{\partial x^2}$$

N depends on both t and x
equation is applied per point in space
diffusion term couples different locations
so partial rather than normal derivates

Example of a spatial model

Action potential propagation along axon:
$\partial V/\partial t = -V(V-a)(V-1) - W + D\partial^2 V/\partial x^2$
$\partial W/\partial t = c(V - bW)$



only voltage (i.e. ions) diffuses

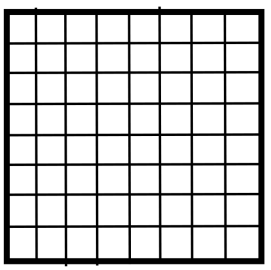
Alternative spatial models

PDE models assume that variables, space and time are all **continous**. This is appropriate if numbers are high and processes are regular.

Biology often deals with a **finite number** of **discrete** organisms / cells /molecules occupying distinct positions and moving / replicating / etc at distinct time points. **Cellular automata models** (CAs) are very suitable for studying such dynamics.

CA model ingredients:

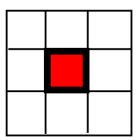
grid



variable states

□ 0 dead
■ 1 alive

neigborhood



□ neighbor
■ individual

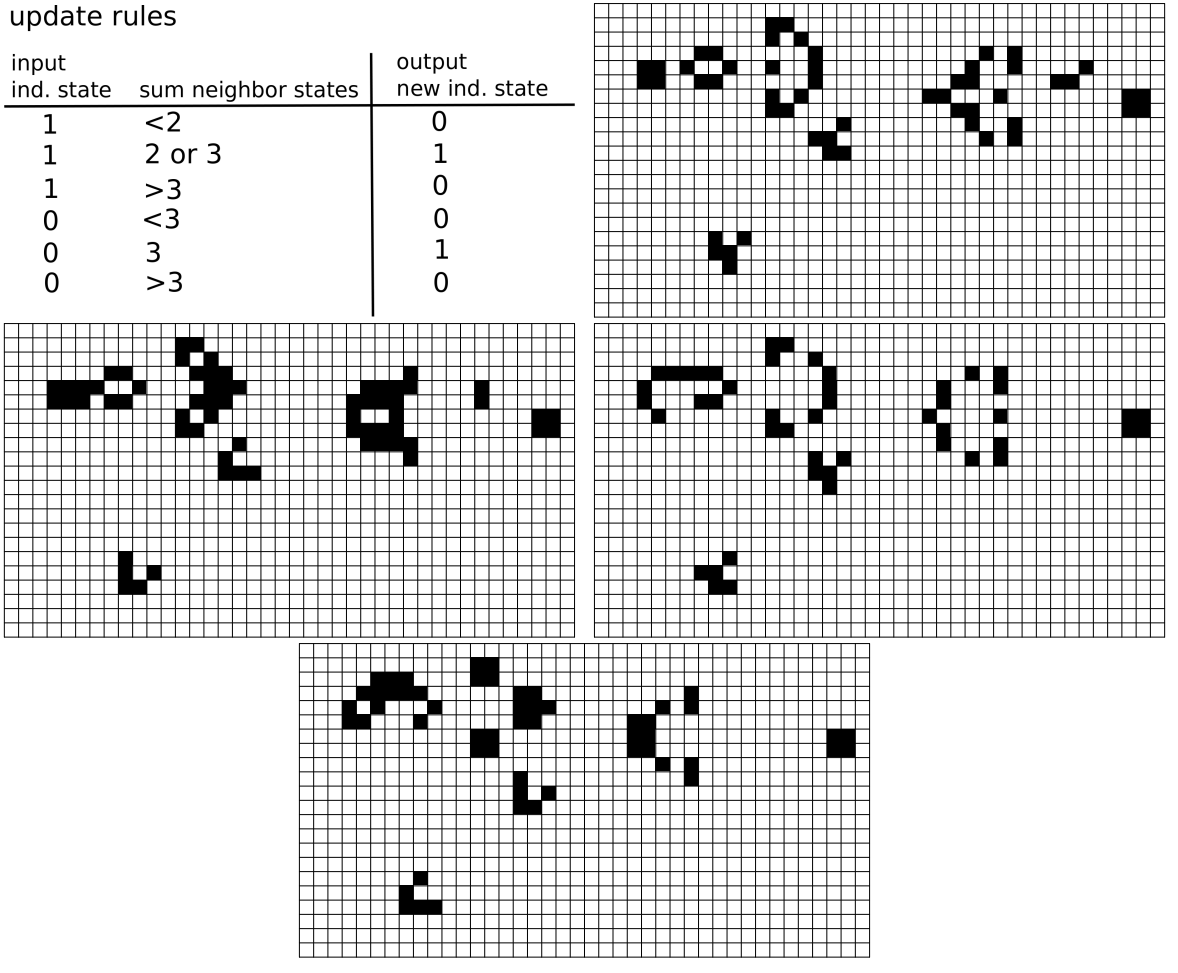
update rules

input ind. state	sum neighbor states	output new ind. state
1	<2	0
1	2 or 3	1
1	>3	0
0	<3	0
0	3	1
0	>3	0

Game of Life

update rules

input ind. state	sum neighbor states	output new ind. state
1	<2	0
1	2 or 3	1
1	>3	0
0	<3	0
0	3	1
0	>3	0

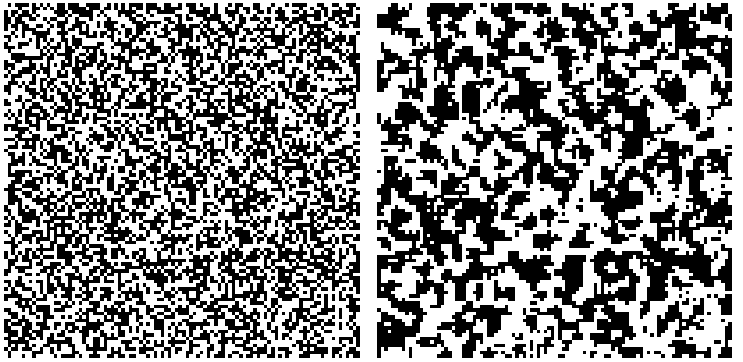


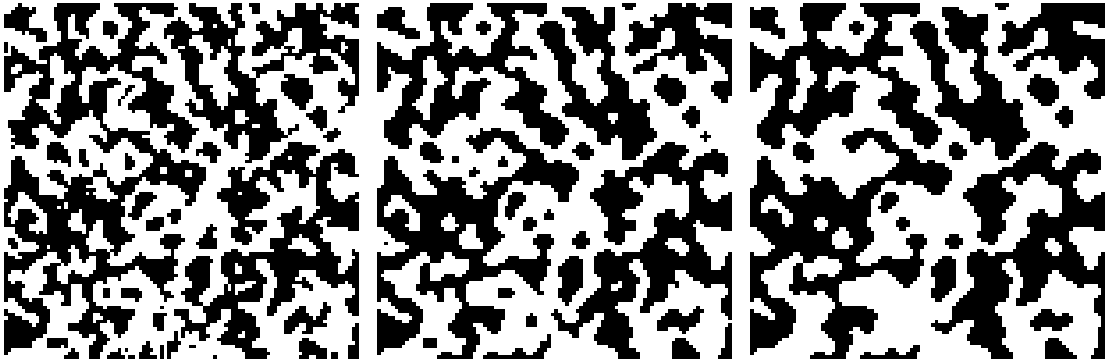
Illustrates how simple rules can lead to complex processes!

Majority Voting

update rules

input ind. state	sum neighbor states	output new ind. state
1	<=3	0
1	> 3	1
0	<=4	0
0	>4	1
i.e. if sum <=4		0
i.e. if sum >4		1





Do what majority around you does: patch formation.
Resembles certain vegetation pattern dynamics.

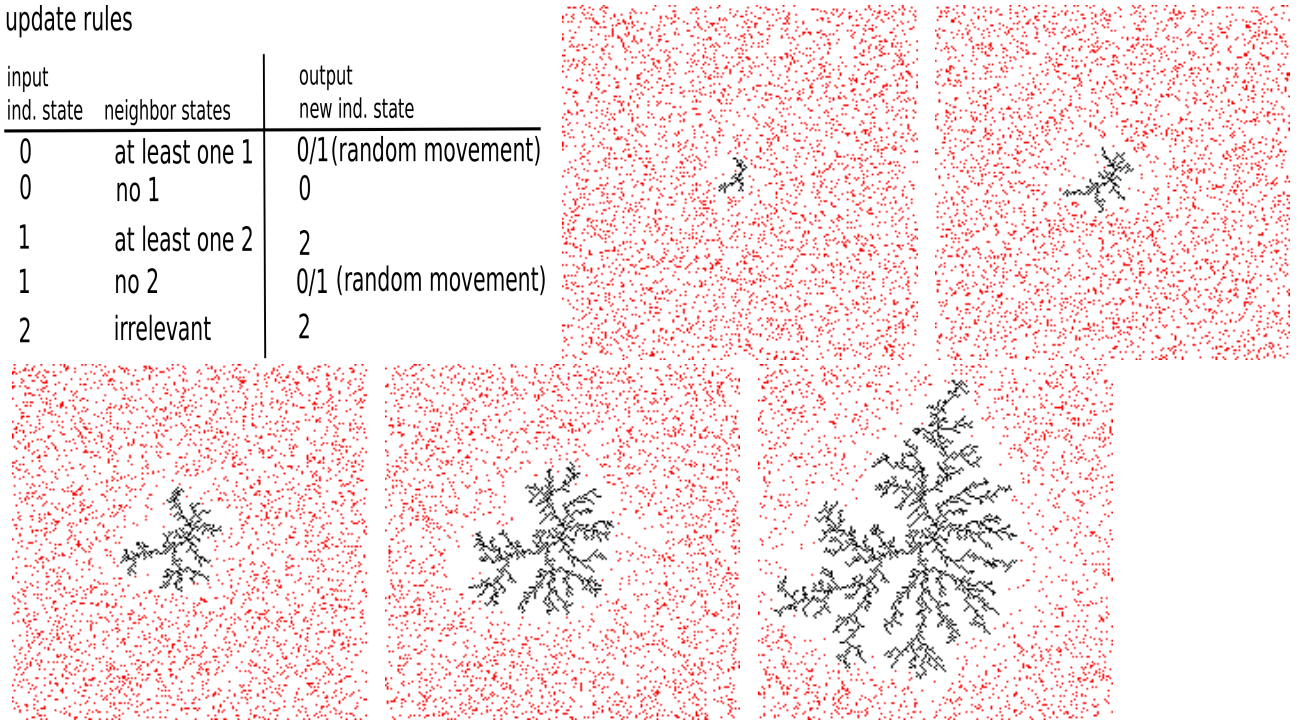
Diffusion Limited Aggregation

variable states

- 0 empty
- 1 moving
- 2 frozen

update rules

input ind. state	neighbor states	output new ind. state
0	at least one 1	0/1(random movement)
0	no 1	0
1	at least one 2	2
1	no 2	0/1 (random movement)
2	irrelevant	2

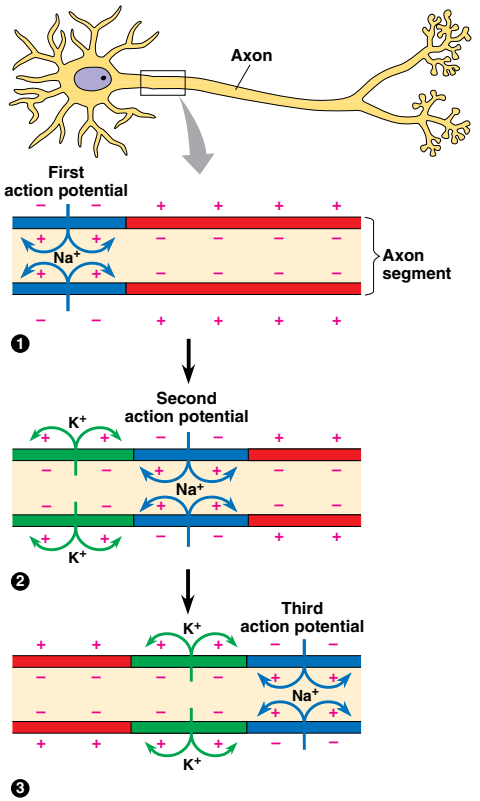


Freeze if one of your neighbors if frozen.
Resembles growth of minerals, snowflakes and corals

Chapter 11

Dynamic spatial patterns: waves and spirals

Action potential propagation



Excitable media

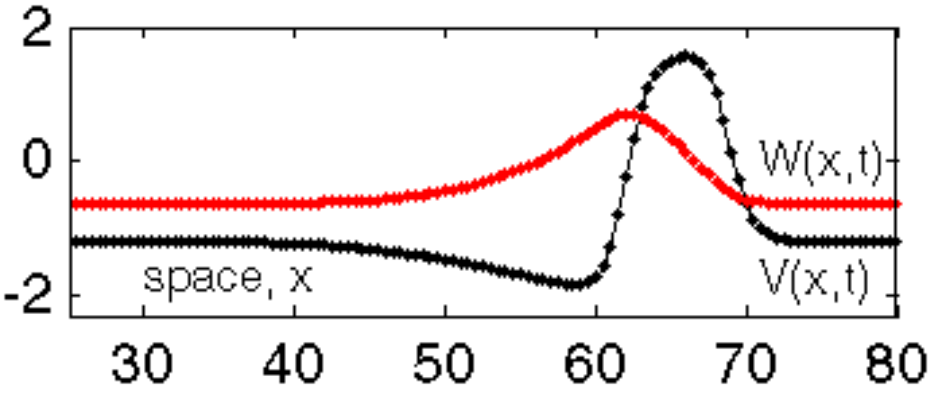
A neuron is an example of an excitable medium.

General excitable medium properties:
- threshold
- all or none response
- refractoriness
- **wave propagation**

Wave propagation results from:
- *passive* spread of activation to nearby spot
- exceeding of the threshold at this spot
- generation of new *active* response
- refractoriness prevents immediate return

Model wave propagation in excitable medium

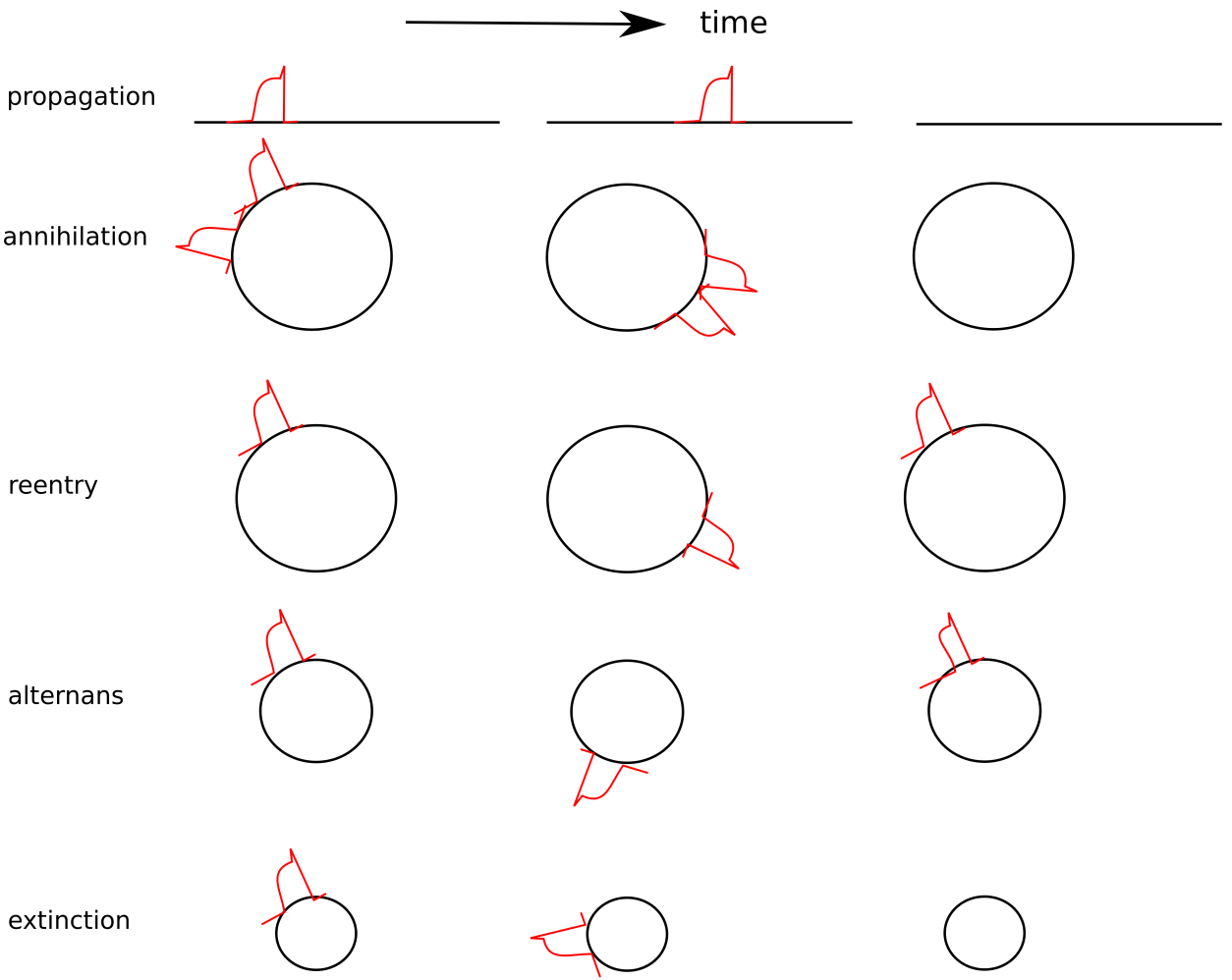
Add diffusion to the FHN-model:
$\partial V/\partial t = -V(V-a)(V-1) - W + D\partial^2 V/\partial x^2$
$\partial W/\partial t = c(V - bW)$



- activating wavefront
- refractory wavetail

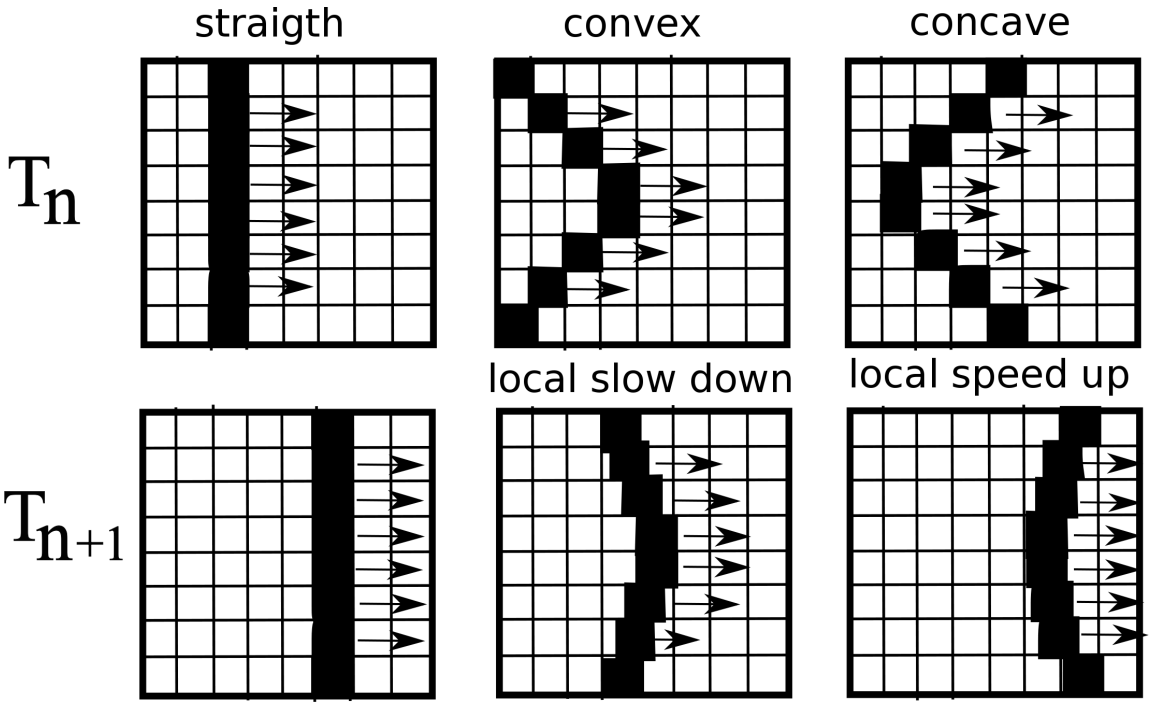
http://www.scholarpedia.org/article/FitzHugh-Nagumo_model

Wave propagation in 1D



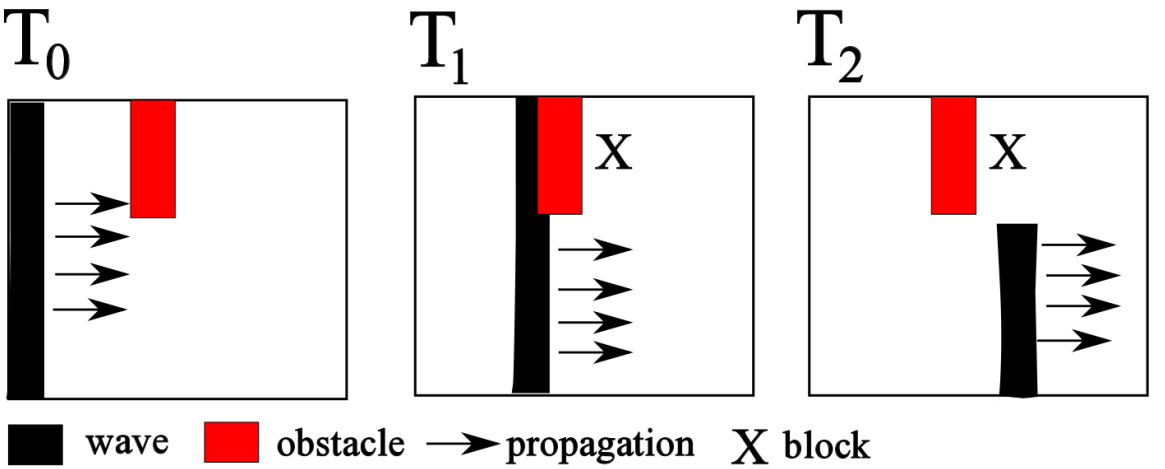
Wave propagation in 2D: Curvature

$$\partial V/\partial t = -V(V-a)(V-1) - W + D(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2})$$
$$\partial W/\partial t = c(V - bW)$$



Curvature affects the *local propagation speed* of waves.
Net effect of this is the *straigthening* of wavefronts.

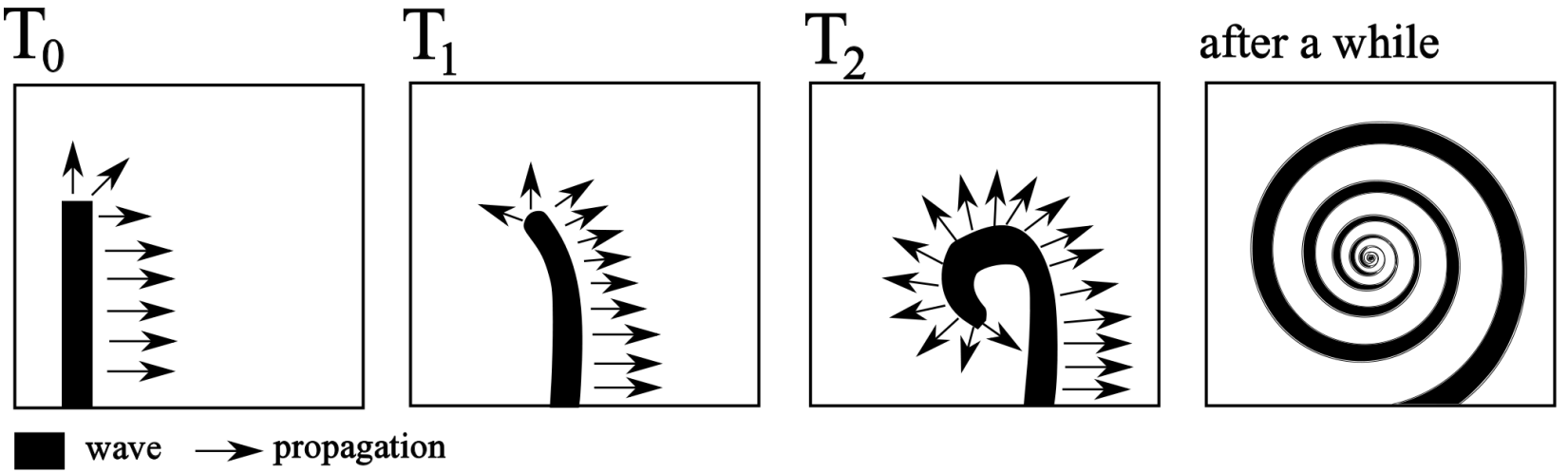
Wave propagation in 2D: Wave break and free ends



Presence of **inexcitable obstacle or refractory region** cause the wave to break and produce a free wave end.

Wave propagation in 2D: Spiral Formation

So what happens next if we have a free wave end?

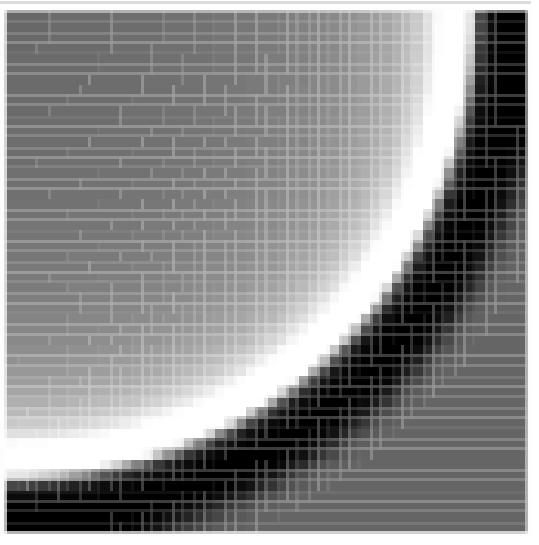


Curvature at free wave end locally slows propagation, causing **curling back of the wave and spiral wave formation**

Note the direction of curling and wave propagation!

Wave propagation in 2D: waves, spirals and turbulence

target waves | spirals | turbulence



propagation | reentry | alternans

Planar waves: single trigger produces single wave: **terminates**
Spirals and turbulence: reentry allows for reexcitation: **perpetual**

CA instead of PDE model

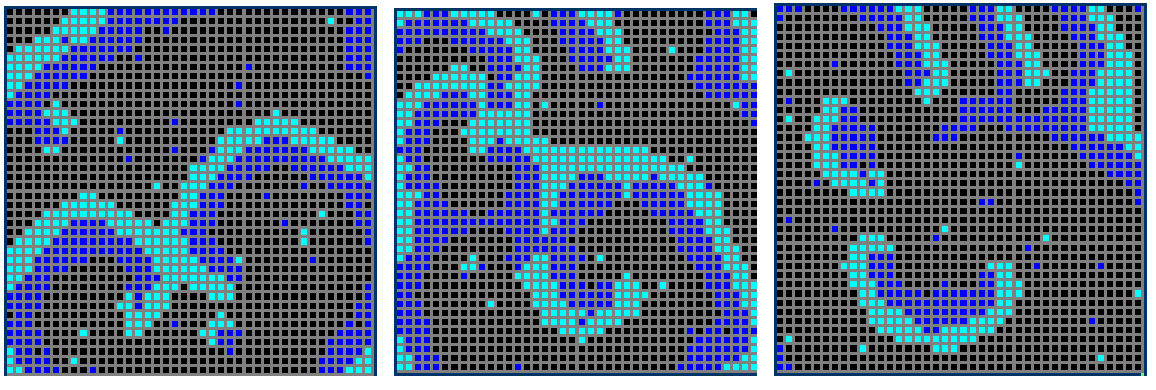
We can model an excitable medium also with a CA:

variable states

- 0 rest
- 1 excited
- 2 refractory

update rules

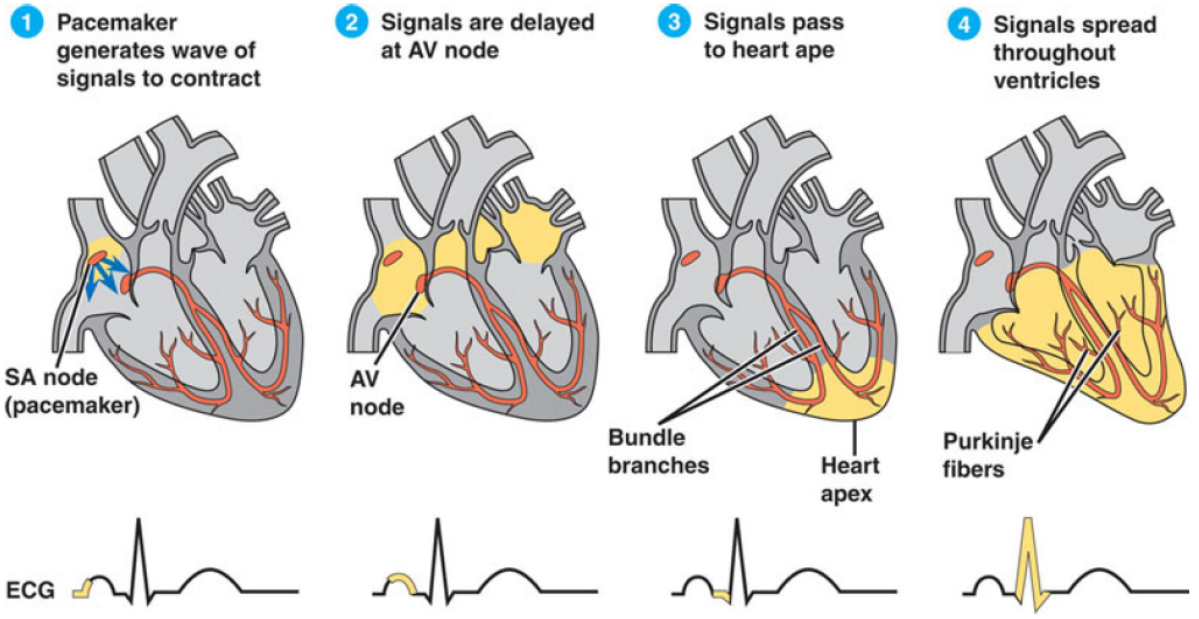
input ind. state	duration own state neighbor states	output new ind. state
0	3 or more 1's	1
0	less than 3 1's	0
1	5 steps	2
1	less than 5 steps	1
2	4 steps	0
2	less than 4 steps	2



From: http://www.cnd.mcgill.ca/bios/bub/CAs.html

Cardiac tissue

The heart is an electro-mechanical pump:
Cells generate and conduct action potentials
Cells contract in response to action potentials

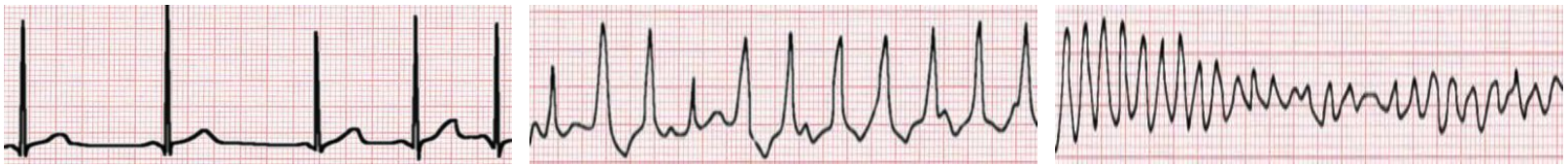


Fast wave propagation ensures timed, coordinated contraction

Cardiac arrhythmias

Arrhythmias: abnormalities in *rate* and / or *coordination* of cardiac contraction, caused by abnormality of the **excitation wave**.

normal sinus rhythm ventricular tachycardia ventricular fibrillation

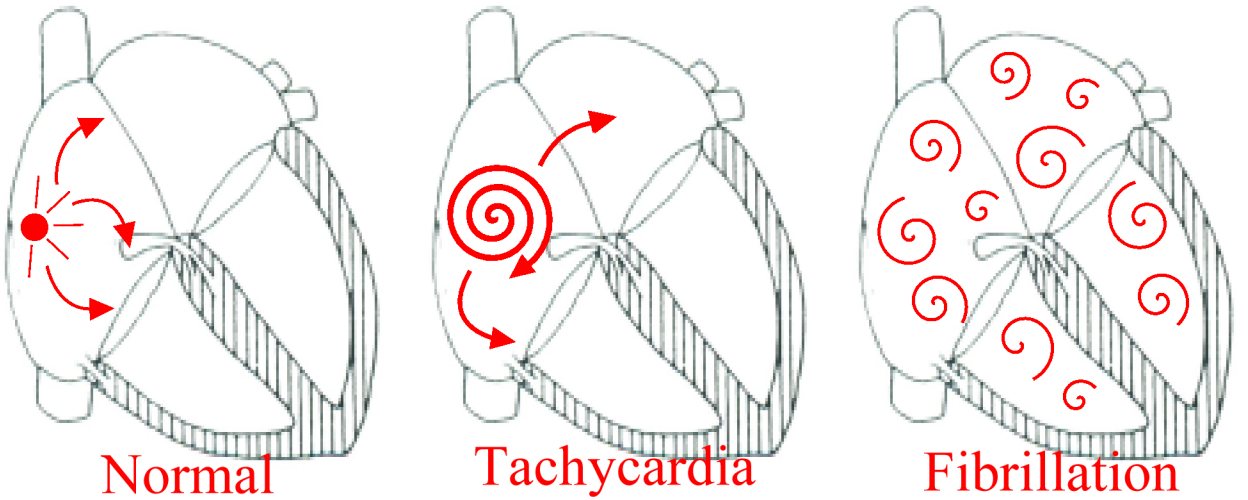


Tachycardia: increased contraction rate, incomplete filling with blood, less efficient pumping

Fibrillation: increased rate, no coordination, hardly any pumping, lethal within minutes

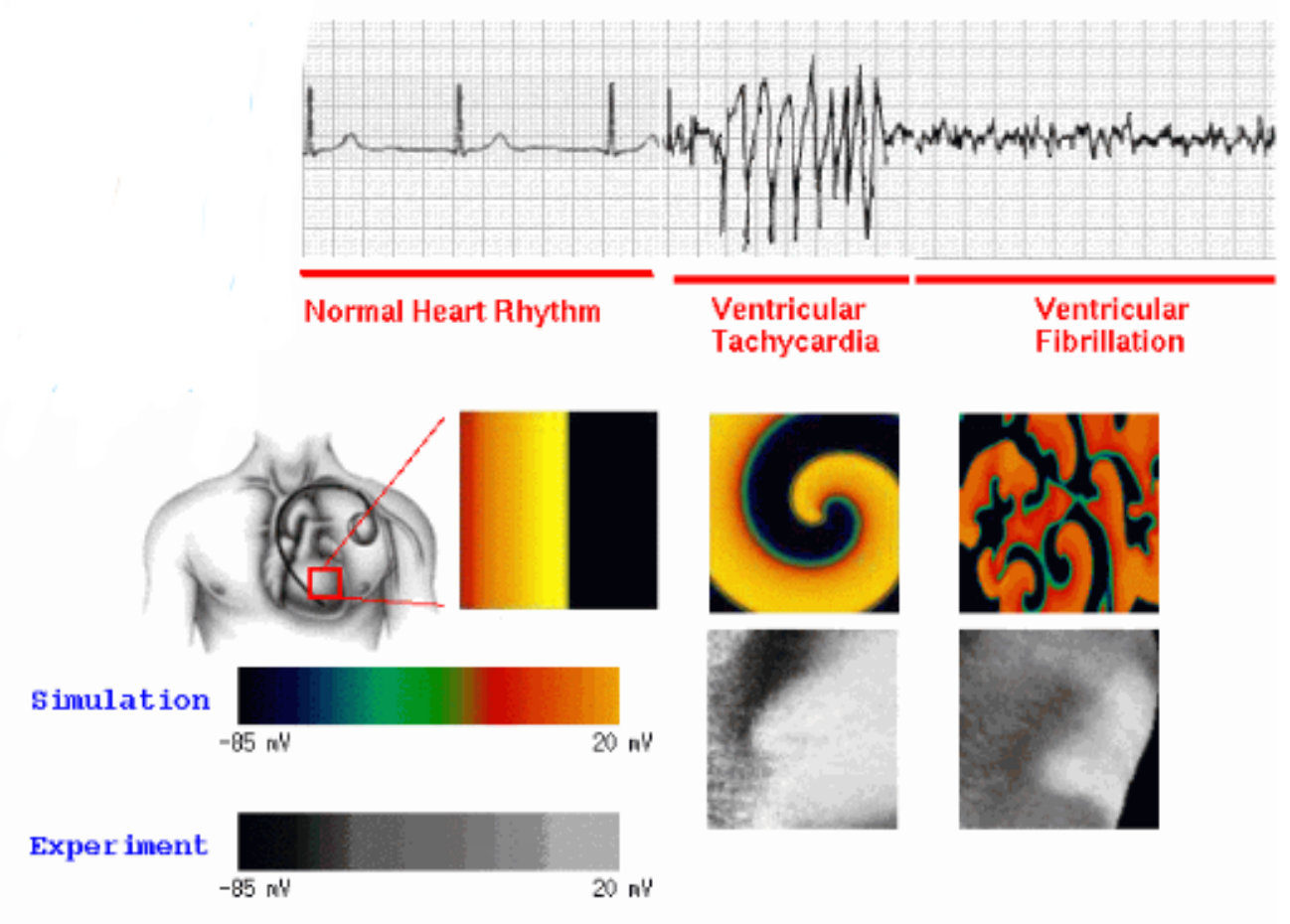
Cardiac arrhythmias - Hypothesis

Spiral waves and turbulence (multiple spirals) underlying arrhythmias



Experimental proof of hypotheses

http://www.vet.cornell.edu/news/FentonCherry/Media/main.html



Curing Fibrillation: Using our knowledge

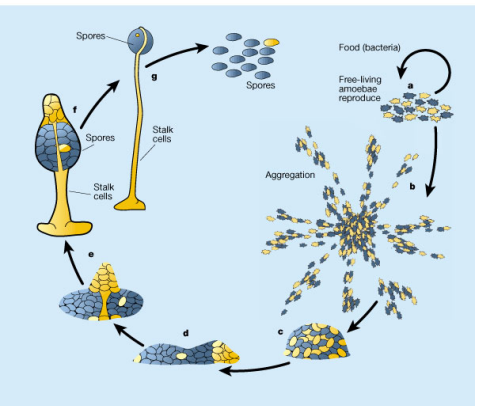
Use knowledge about excitable media to:
- invent new cures
- understand existing ones

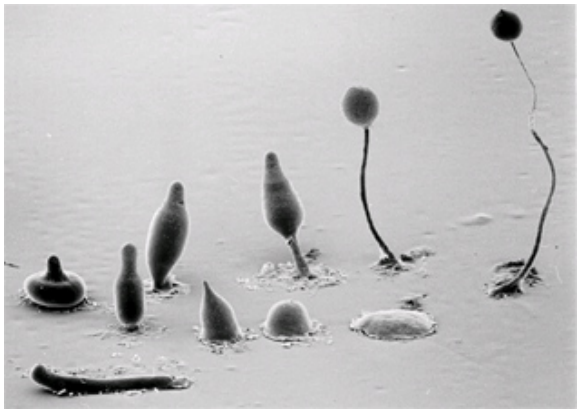
We are going to do this in werkcollege

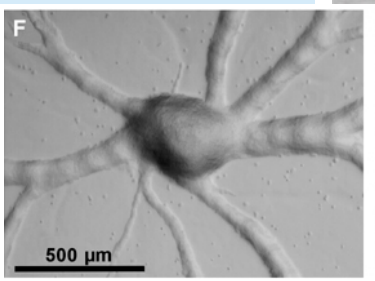
Other excitable media: Dictyostelium discoidum

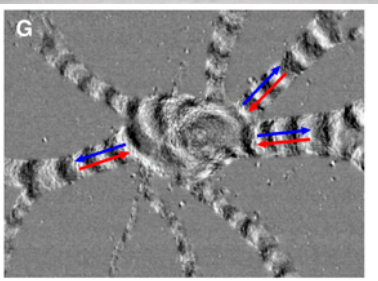
Cellular signalling system:

- c-AMP produced in response to stress by cells
- c-AMP acts as a chemoattractant for other cells
- c-AMP makes cells produce more c-AMP
- c-AMP production becomes refractory





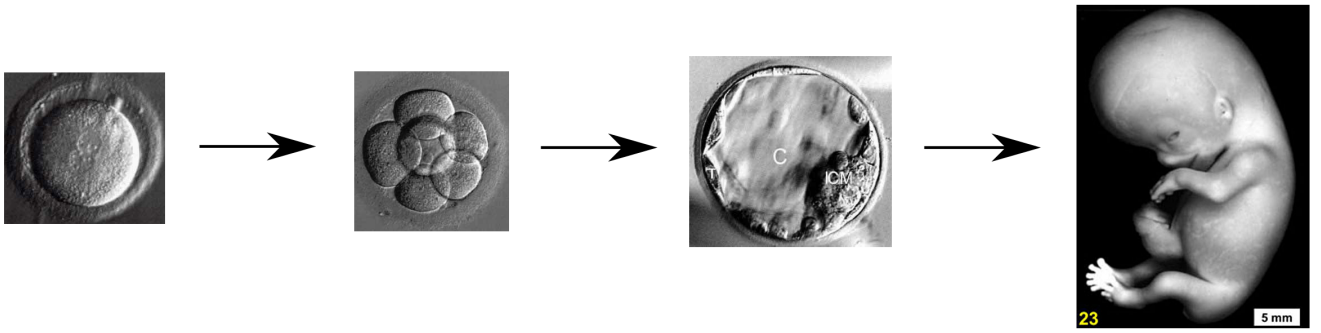




Chapter 12

Stationary spatial patterns: spots, stripes and colors

Development

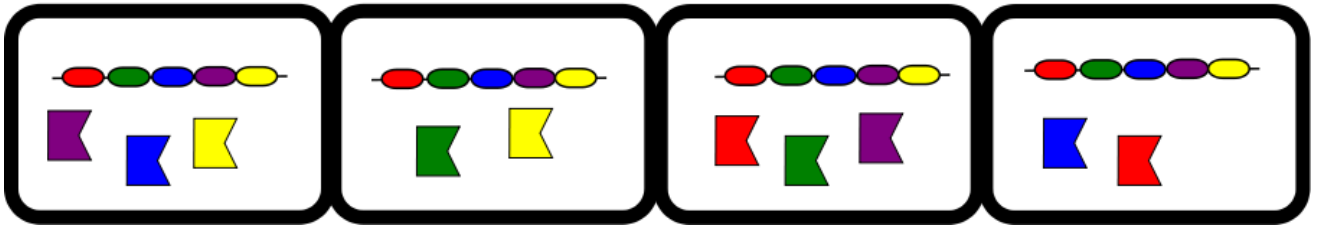


How do the different cells know which celltype to become?

Cell differentiation

- All cells in the body have the same DNA, the same genes.
- Cellular properties are mainly determined by proteins.
- Cells can thus differentiate by expressing different gene subsets.

Same genes, different proteins, different celltypes



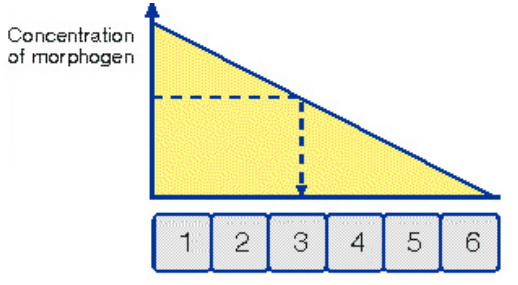
How does a cell know which genes to express?

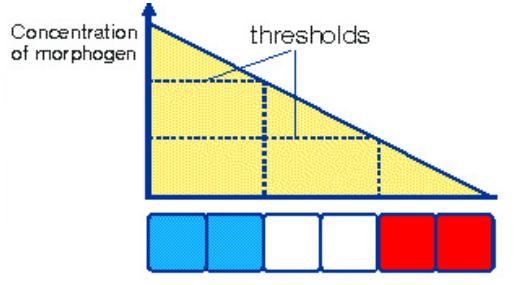
Should be:
- not too static: different cells should express different genes.
- not too dynamic: a celltype should maintain its typical expression.

This requires:
- mechanisms generating differences: patterning mechanisms
- mechanisms maintaing different states: alternative attractors

Patterning: The French Flag model

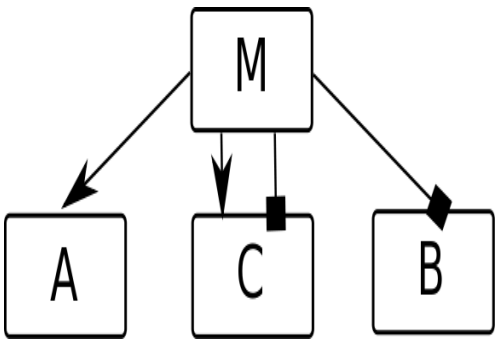
How a morphogen gradient can lead to multiple domains.
First proposed by L. Wolpert in the 1960's

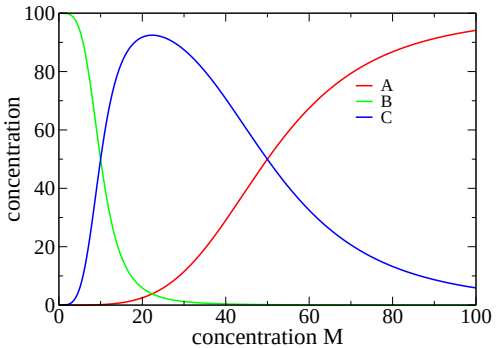


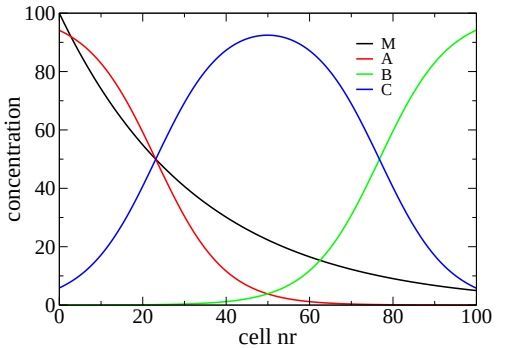


Key ingredient:
different concentration thresholds defining a different cellular response.

Patterning: The French Flag model 2







$$
\begin{aligned}
M(x) &= M_{max} e^{-bx} \\
\frac{dA}{dt} &= a \frac{M^4}{M^4 + T_h^4} - dA \\
\frac{dB}{dt} &= a \frac{T_l^4}{M^4 + T_l^4} - dB \\
\frac{dC}{dt} &= a \frac{M^4}{M^4 + T_l^4} \frac{T_h^4}{M^4 + T_h^4} - dC
\end{aligned}
$$

Note: implicit diffusion of M, and $T_h > T_l$

Patterning: The French Flag model 3

How do we get these concentration and spatial profiles?

$\frac{dA}{dt} = 0$ gives us:
$A = \frac{a}{d}\frac{M^4}{M^4+T_h^4}$

likewise $\frac{dB}{dt} = 0$ gives us:
$B = \frac{a}{d}\frac{T_l^4}{M^4+T_l^4}$

and $\frac{dC}{dt} = 0$ gives us:
$C = \frac{a}{d}\frac{M^4}{M^4+T_l^4}\frac{T_h^4}{M^4+T_h^4}$

To get concentrations for x position rather than M concentration:
1) $M(x) = M_{max}e^{-bx}$: produces M concentration from x value
2) above equations: produces A,B,C from M concentration

Multiple attractors: Positive feedback, cooperativity and saturation

Assume gene A stimulates it's own expression: **positive feedback**

$$\frac{dA}{dt} = bA - dA$$

Single equilibrium $A = 0$ even if $b >> a$

Now assume A stimulates itself non-linearly: **cooperativity**

$$\frac{dA}{dt} = bA^2 - dA$$

Two equilibria $A = 0$ and $A = d/b$, only $A = d/b$ is stable

Next assume A stimulates itself in **saturating** fashion:

$$\frac{dA}{dt} = a\frac{A}{A+h} - dA$$

Two equilibria $A = 0$ and $A = (a - dh)/d$, only $A = (a - dh)/d$ is stable

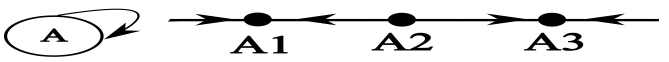
So, not sufficient for multiple attractors and hence celltypes

Multiple attractors: Positive feedback, cooperativity and saturation

Finally, **combine positive feedback, cooperativity and saturation**:

$$\frac{dA}{dt} = a\frac{A^2}{A^2 + h^2} - dA$$

Three equilibria: $A = 0$, $A = \frac{\frac{a}{d} - \sqrt{\frac{a}{d}^2 - 4h^2}}{2}$ and $A = \frac{\frac{a}{d} + \sqrt{\frac{a}{d}^2 - 4h^2}}{2}$



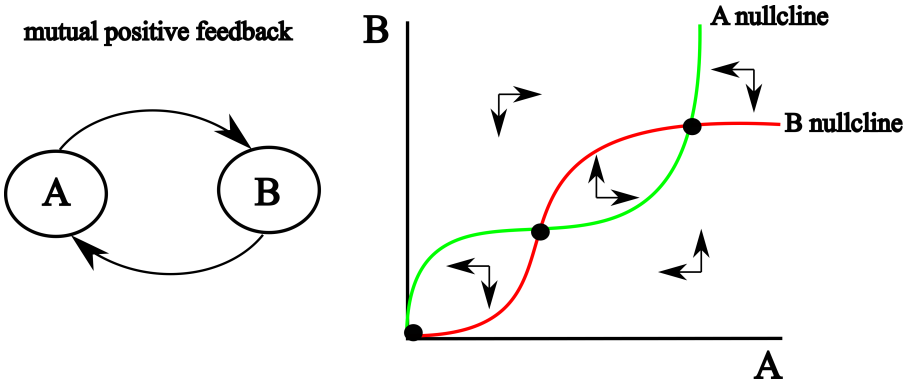
First and last equilibrium stable: bistability!
Initial conditions (French Flag!) determine final state

Alternative attractors: Positive feedback and cooperativity (2)

Assume genes A and B stimulate each others expression cooperatively:

$$\frac{dA}{dt} = a\frac{B^2}{B^2+h^2} - dA$$
$$\frac{dB}{dt} = a\frac{A^2}{A^2+h^2} - dB$$

Equilibria not easy to solve, but we can draw nullclines:
$A = \frac{a}{d}\frac{B^2}{B^2+h^2}$ and $B = \frac{a}{d}\frac{A^2}{A^2+h^2}$



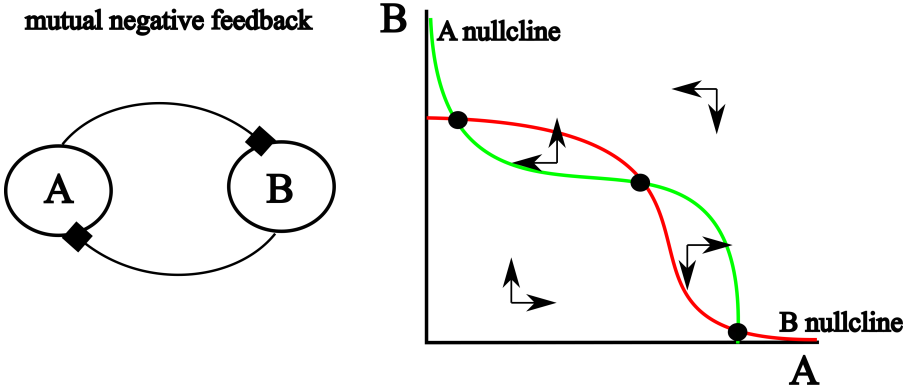
Also results in bistability!
One state: A and B both not expresssed
Other state: A and B both expressed

Alternative attractors: Positive feedback and cooperativity (3)

Assume genes A and B repress each others expression cooperatively:

$$\frac{dA}{dt} = a\frac{h^2}{B^2+h^2} - dA$$
$$\frac{dB}{dt} = a\frac{h^2}{A^2+h^2} - dB$$

Equilibria not easy to solve, but we can draw nullclines:
$A = \frac{a}{d}\frac{h^2}{B^2+h^2}$ and $B = \frac{a}{d}\frac{h^2}{A^2+h^2}$



Also results in bistability!
One state: A expressed B not
Other state: B expressed A not

Pattern initialisation and maintenance

In development different cell types:
- have to be initialized
- have to be maintained

So to model this we need to incorporate:
- a morphogen initializing differences
- alternative attractors maintaining them

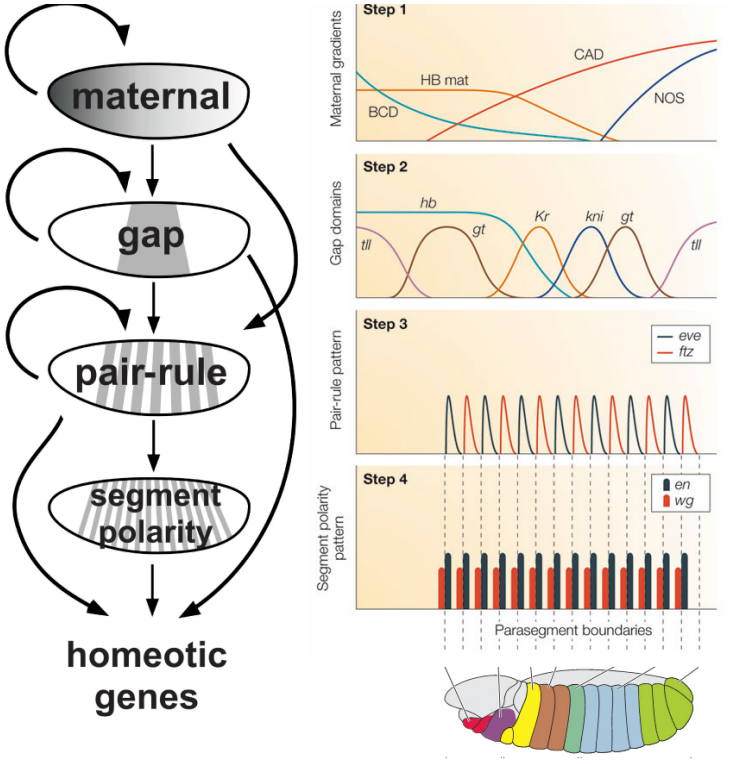
$$
\begin{aligned}
M(x) &= M_{max} e^{-bx} \\
\frac{dA}{dt} &= max(a\frac{M^2}{M^2+h^2}, \frac{h^2}{B^2+h^2}) - dA \\
\frac{dB}{dt} &= a\frac{h^2}{M^2+h^2} \times \frac{h^2}{A^2+h^2} - dB
\end{aligned}
$$

Note input integration difference:
- A: max: M **or** not-B sufficient to locally express A
- B: $\times$: M **or** A sufficient to locally supress B

Not so easy to analyse!, so do it in phases:
- in beginning A and B 0, M not
- at end A and B not 0, M 0

Drosophila development

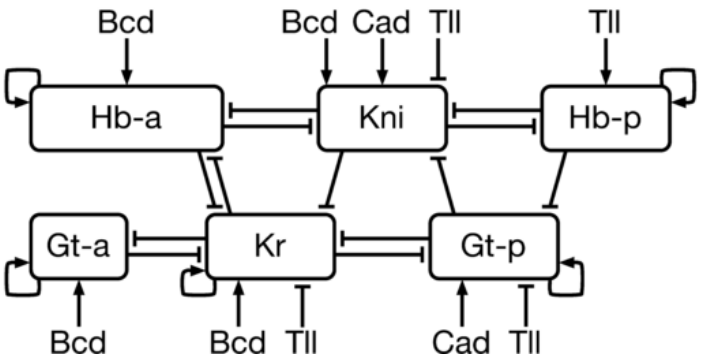
Patterning of the anterior-posterior axis in the drosophila embryo.

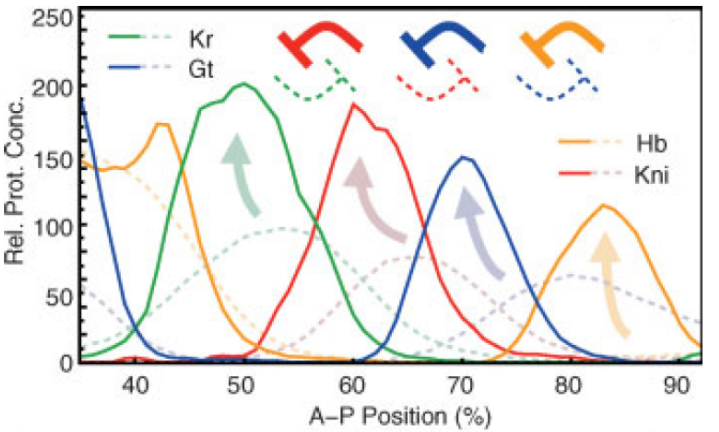


Entangled hierarchy of different regulatory gene classes.
Results in a body plan that is both segmented and differentiated.
First step is morphogen gradient based.

Drosophila development 2

Unravelling of this first step produced:





Indeed:

- morphogen (Bcd, Cad) initializes differences
- mutual repression maintains differences

Wrap up

On Monday very nice guest lecture by Prof. Paulien Hogeweg.
Content of this lecture is also part of course and can be asked in exam.

After the lecture is the last werkcollege to obtain your bonuspoint.
There is also time to ask me and assistents general questions about all parts of the course.