Systems Biology Across Scales: A Personal View XXV. Waves in Biology: Excitable Media

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Turing's model for pattern formation is a specific example of

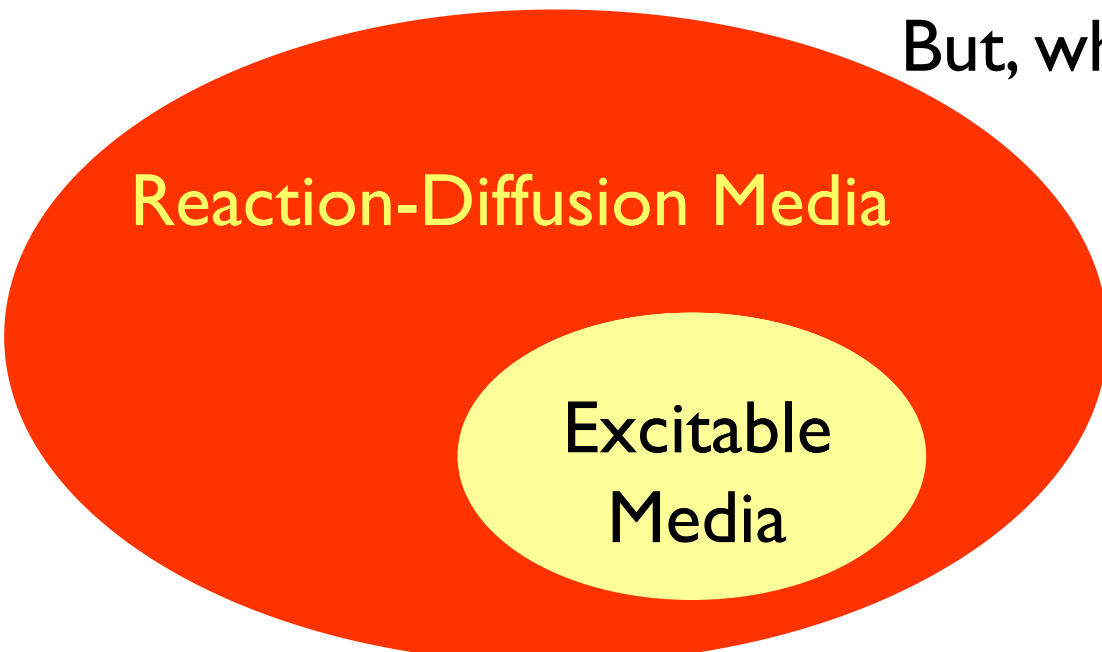
Reaction-Diffusion Equations

Activator: $\partial u/\partial t = D_u \Delta u + f(u,v)$

Inhibitor: $\partial v/\partial t = D_v \Delta v + g(u,v)$

For Turing patterns to occur, $D_u < D_v$

But, what if $D_u > 0$ and $D_v = 0$



Spatiotemporal Pattern formation in excitable media models

What is Excitable Media ?

… that biology should be mindful of it ?

- **pancreatic beta cells**
- **neurons**
- **cardiac myocytes**
- **pregnant uterus**

What is Excitable Media ?

Think of an excitable person

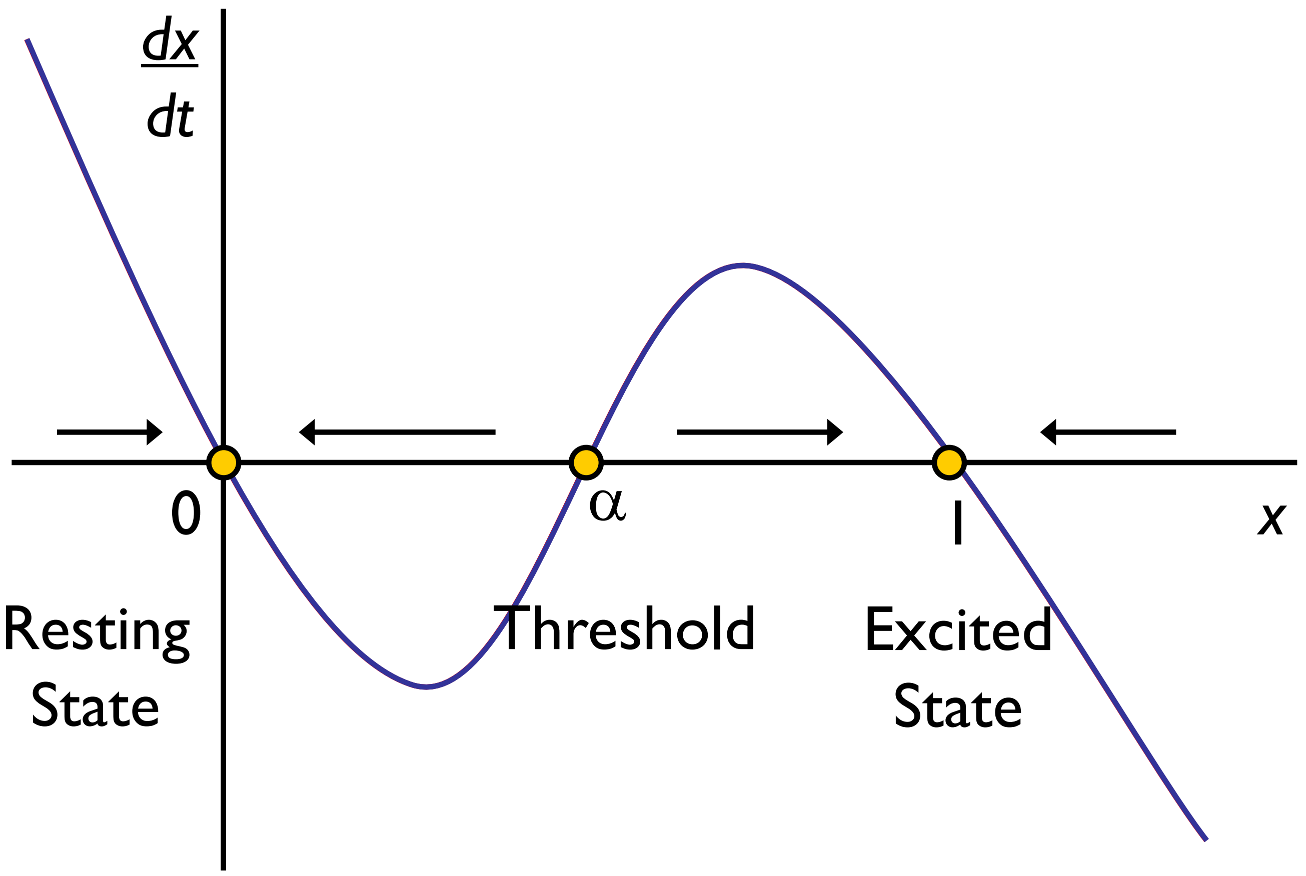
Resting State **Excited State**

Transition from resting to excited state if stimulation exceeds a threshold

Immediately after one excitation, the medium cannot be excited even by a very high stimulus for a resting (refractory) period

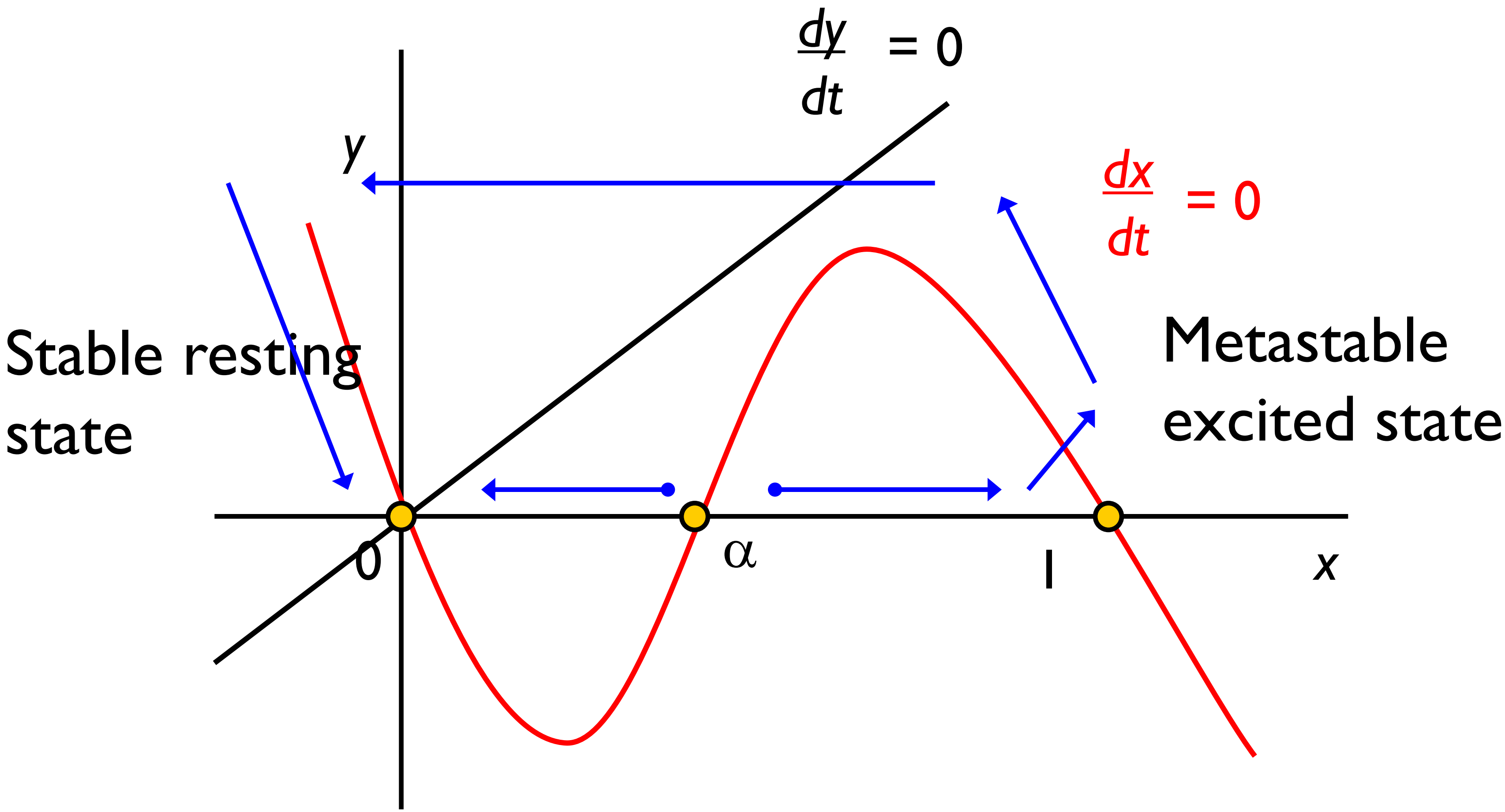
A simple model

$$\frac{dx}{dt} = f(x) = x(x - \alpha)(1 - x) \; - y$$



$$\frac{dy}{dt} = \varepsilon (k x - y)$$

Phase plane dynamics of the simple model



Below threshold → decays to resting state

Above threshold → excitation (large excursion from stable resting state).

This simple model is none other than the

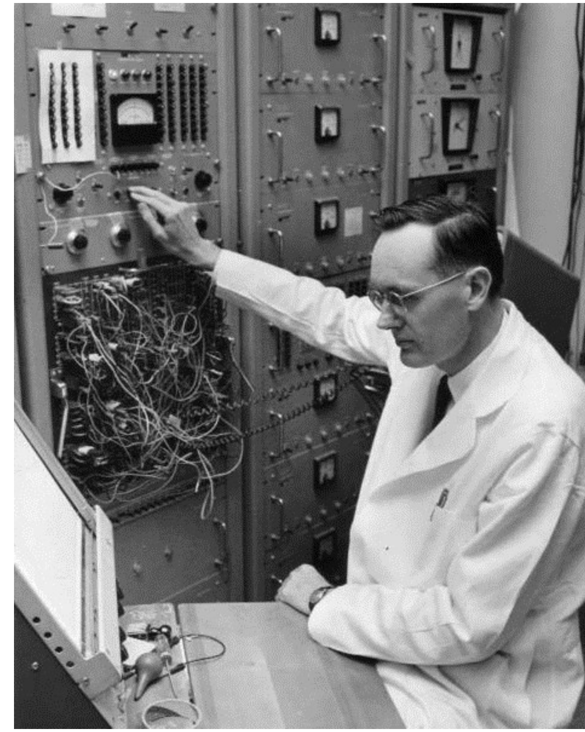
Fitzhugh-Nagumo model

$$\frac{du_e}{dt} = F_e(u_e, v) = Au_e(u_e - \alpha)(1 - u_e) - v,$$
$$\frac{dv}{dt} = \epsilon(u_e - v),$$

Developed by R Fitzhugh (1961) [who called it the Bonhoeffer-Van der Pol model] and J Nagumo (1962) to isolate the essential concepts of excitation propagation

Richard Fitzhugh: Simplified the Hodgkin-Huxley equations describing spike generation in squid giant axon

Jin-ichi Nagumo: built monostable multivibrator electronic circuit using tunnel (Esaki) diodes
Esaki diodes have cubic I-V curve similar to that used in Fitzhugh's eqn



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Spatial propagation of excitation waves

Example: Cardiac tissue

functions as a syncytium: constituent cells are electrically synchronized through specialized channels called gap junctions

Delay in spread of depolarization to neighboring cells via gap junctions … but usually the discrete nature of cardiac myocytes can be ignored and propagation of excitation assumed to be continuous.

Mathematically approximated as a **diffusion equation** yielding the partial differential equation

$$\frac{\partial V}{\partial t} = D\ \frac{\partial^2 V}{\partial x^2} - \frac{I_{ion}}{C_m}$$

with diffusion constant

$$D = \frac{G_i}{S_v C_m}$$

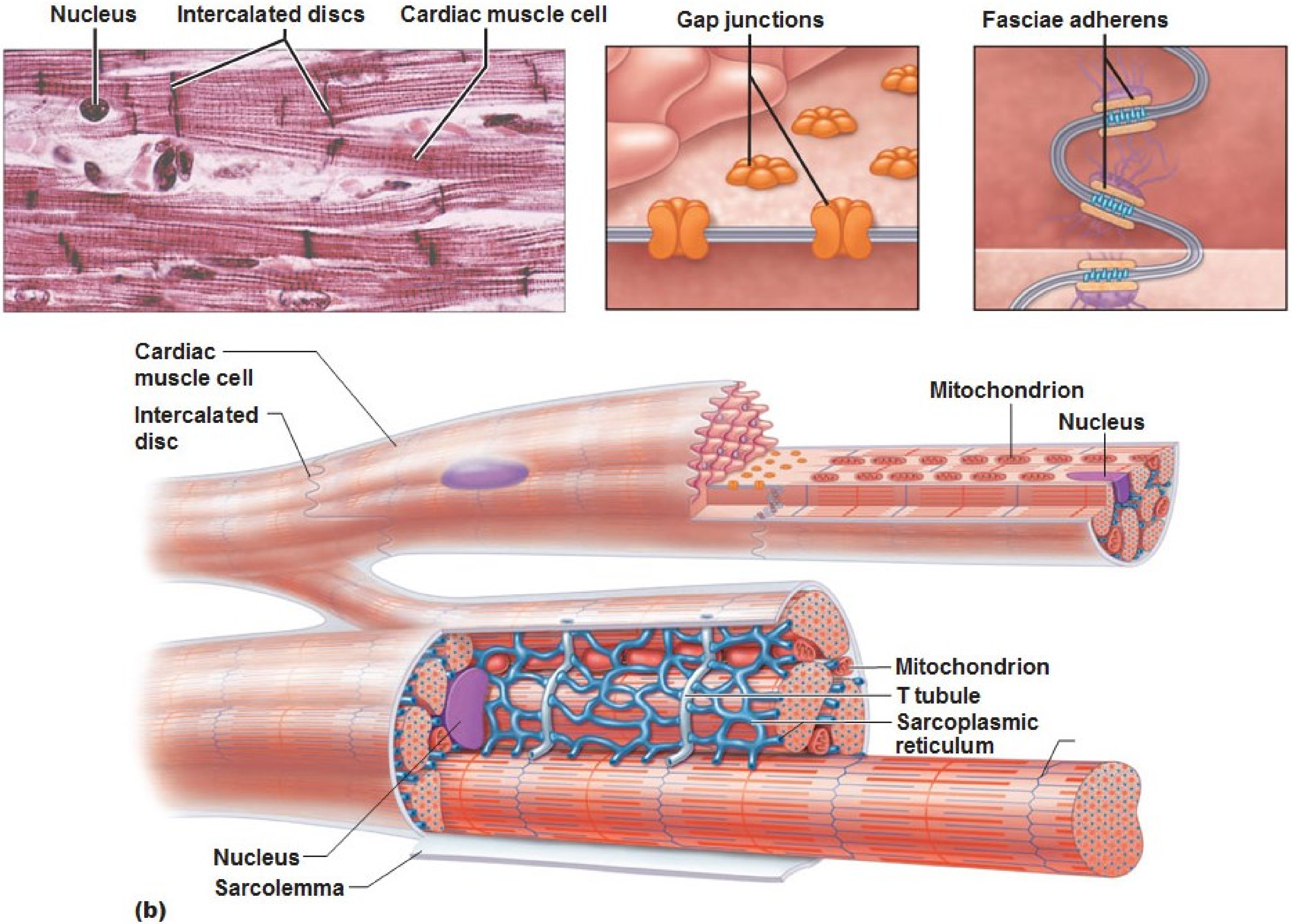
G_i: Bulk intracellular conductivity
S_v: Surface to volume ratio of cells
C_m: Membrane capacitance

Biological tissue is anisotropic $\Rightarrow$ D is a tensor

E.g., action potentials travel along the direction of muscle fibers much faster than transverse to it

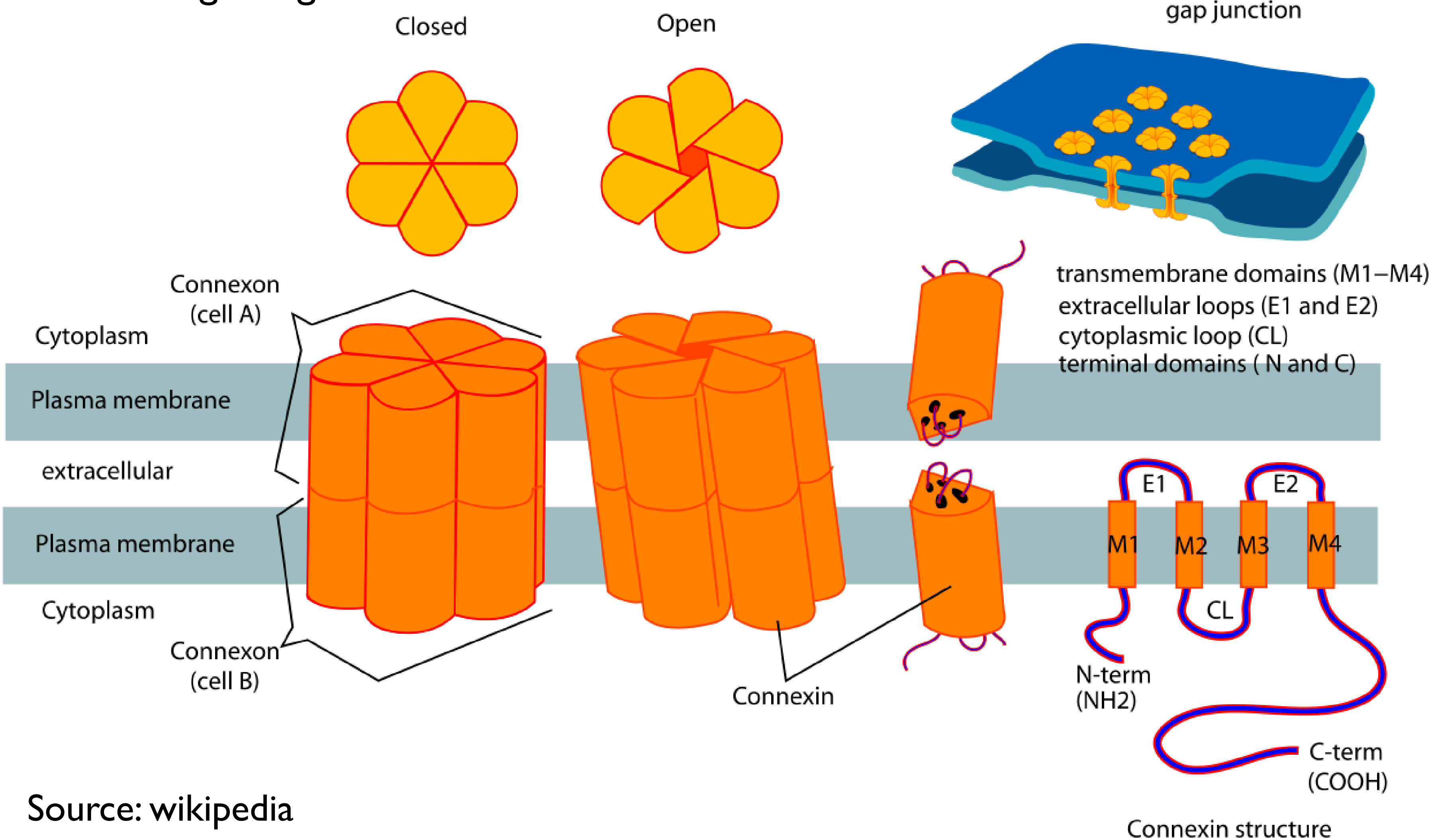
Microscopic anatomy of cardiac muscle

http://antranik.org/



Gap junctions formed by assembly of connexin proteins

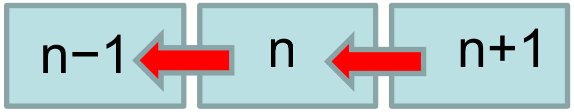
connexon: assembly of six connexin proteins forming the pore for a gap junction between cytoplasm of a pair of connected cells – allowing bidirectional flow of ions and signaling molecules



Source: wikipedia

Example: one-dimensional chain of cells

Nearest neighbors connected by gap junctions
V_n: transmembrane potential of n-th cell
I_n: current from the n-th to the (n−1)-th cell



The net current that passes through gap junctions of the n-th cell:

$$I_{junction} = I_n - I_{n+1} = g_{gap}(V_n - V_{n-1}) - g_{gap}(V_{n+1} - V_n)$$

where g_{gap}: gap-junction conductance

Using continuum approximation,

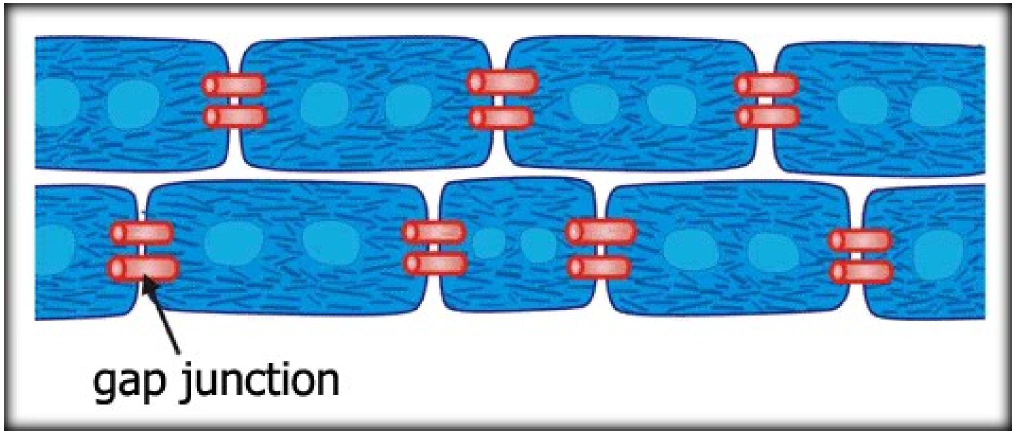
$$I_{junction} = -g_{gap}\frac{\partial^2 V}{\partial x^2}$$

yielding the partial differential equation describing spatial diffusion of excitation

$$C_m\frac{\partial V}{\partial t} = -I_{ion} - I_{junction} = g_{gap}\frac{\partial^2 V}{\partial x^2} - I_{ion}$$

Propagating Waves in Excitable Media

- Excited cells can excite their neighboring cells via diffusion



- The propagating excitation waves can collide and annihilate each other

… resulting in spontaneous pattern formation, such as single or multiple spiral waves