Lecture 2
Diffusion in Biological Systems

Lecture Summary

What is diffusion?

How do we describe it mathematically?

What does diffusion look like in real tissues, and can we characterize that?

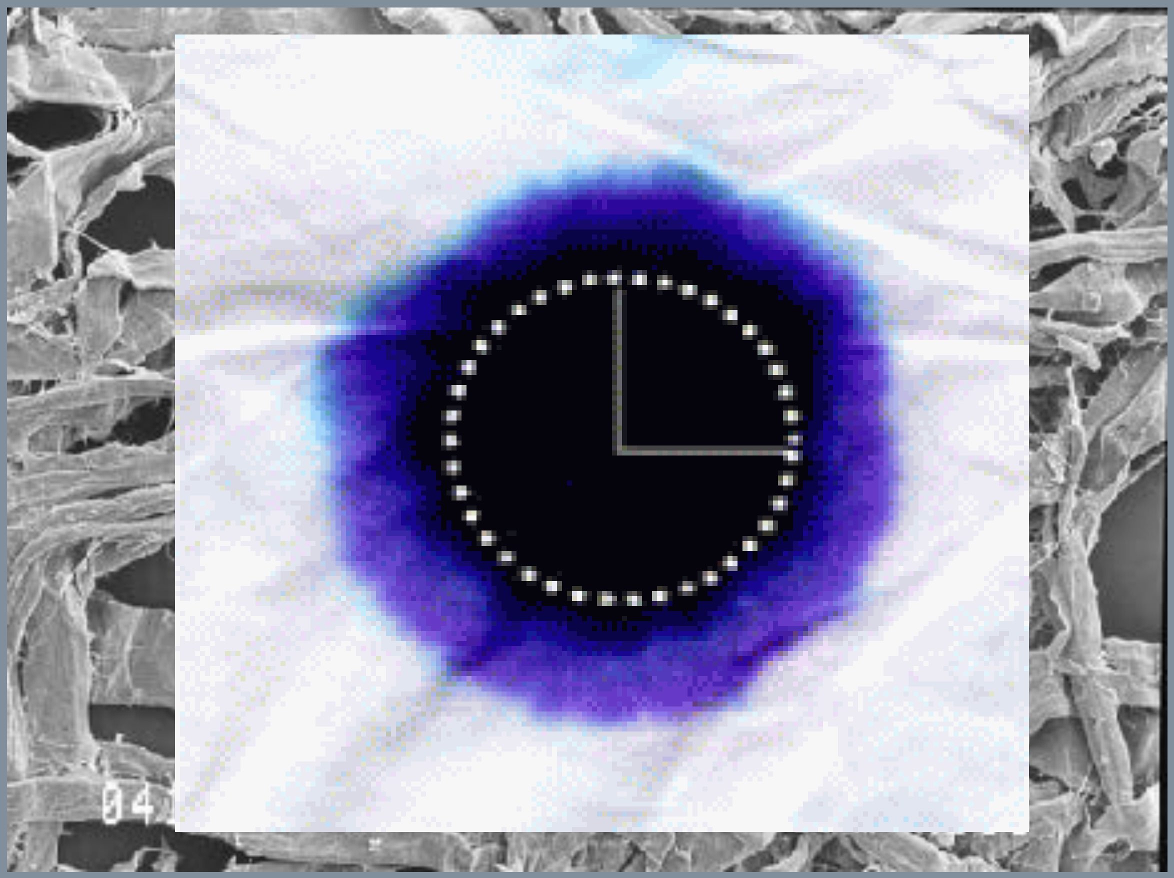
What is diffusion and why do we care about it?

Self-diffusion is the thermally driven random motions of molecules that occurs in the absence of a concentration gradient

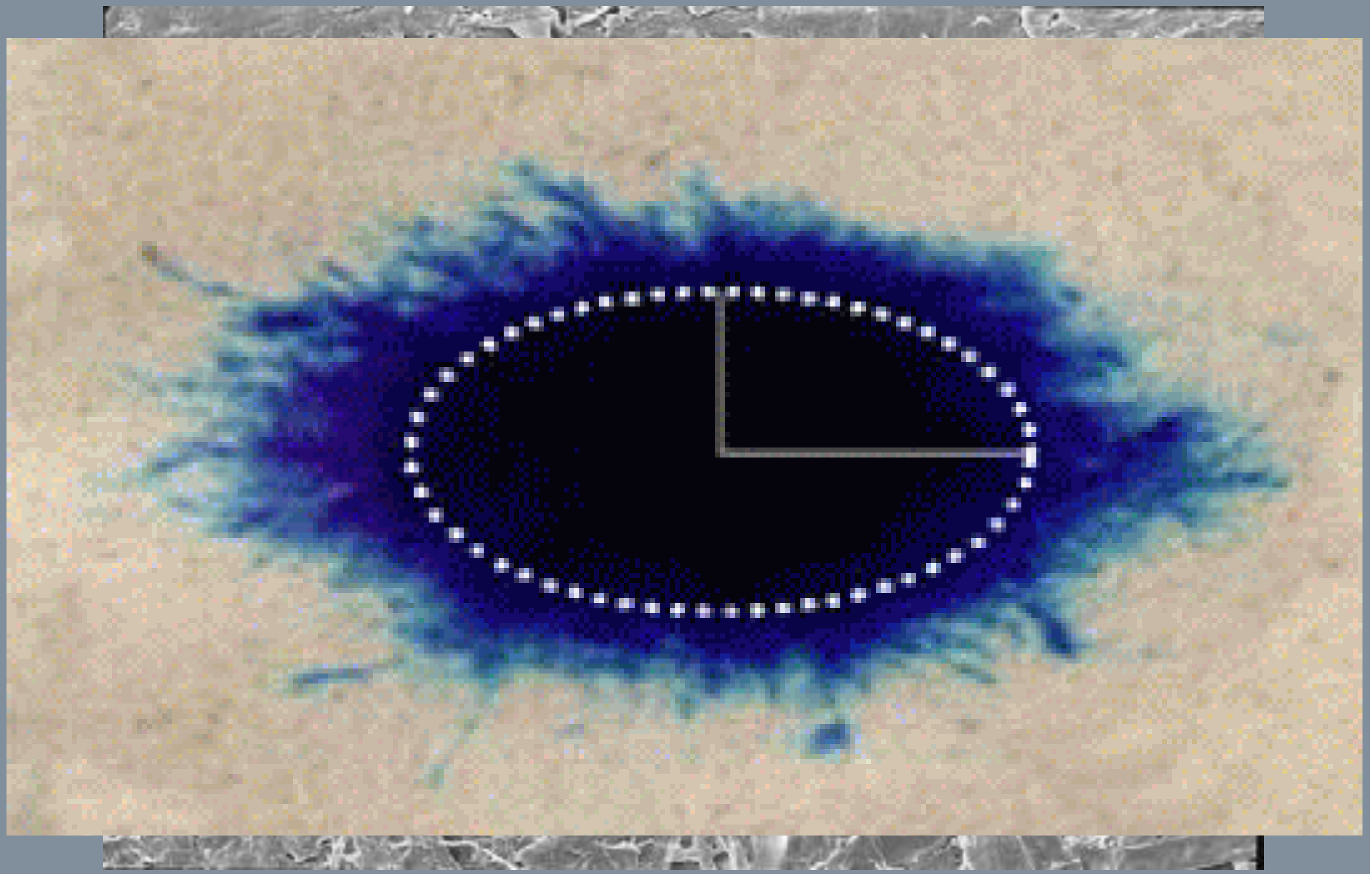
The self-diffusion of water is ongoing in the human body and its characteristics depend on the local tissue architecture and physiology

Therefore the ability to measure self-diffusion offers the possibility of non-invasively measuring tissue structure and physiology

Imaging Tissue Microstructure



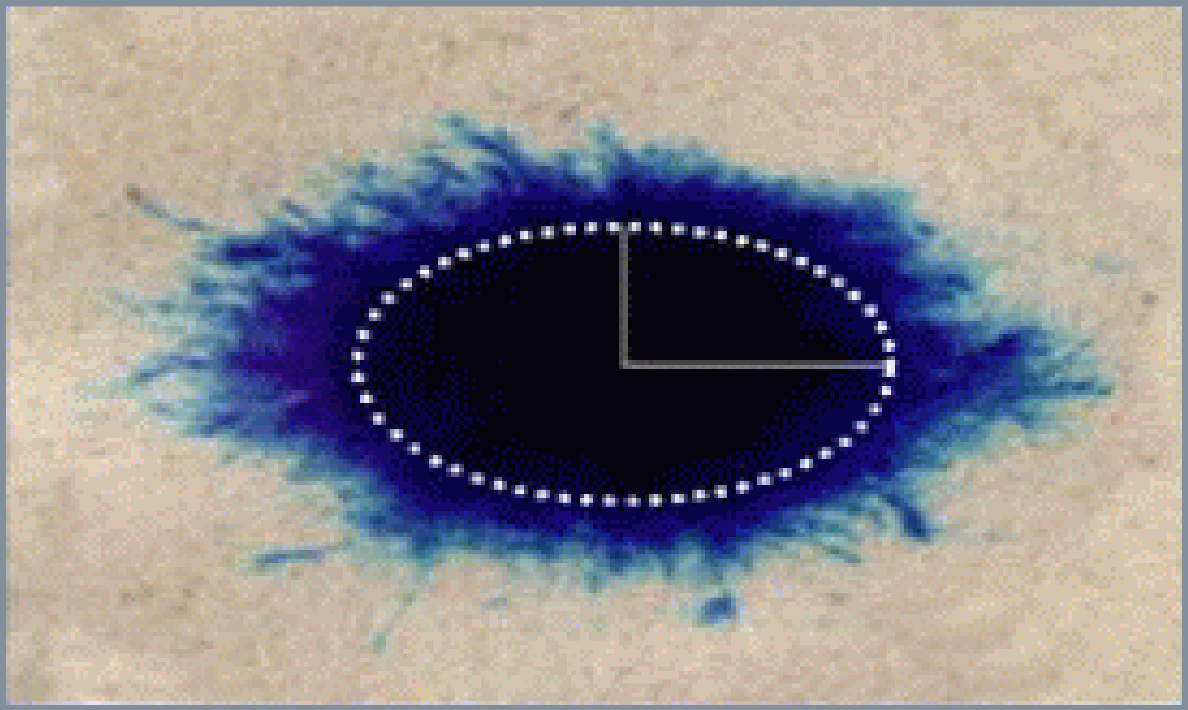
tissue paper
(isotropic diffusion)

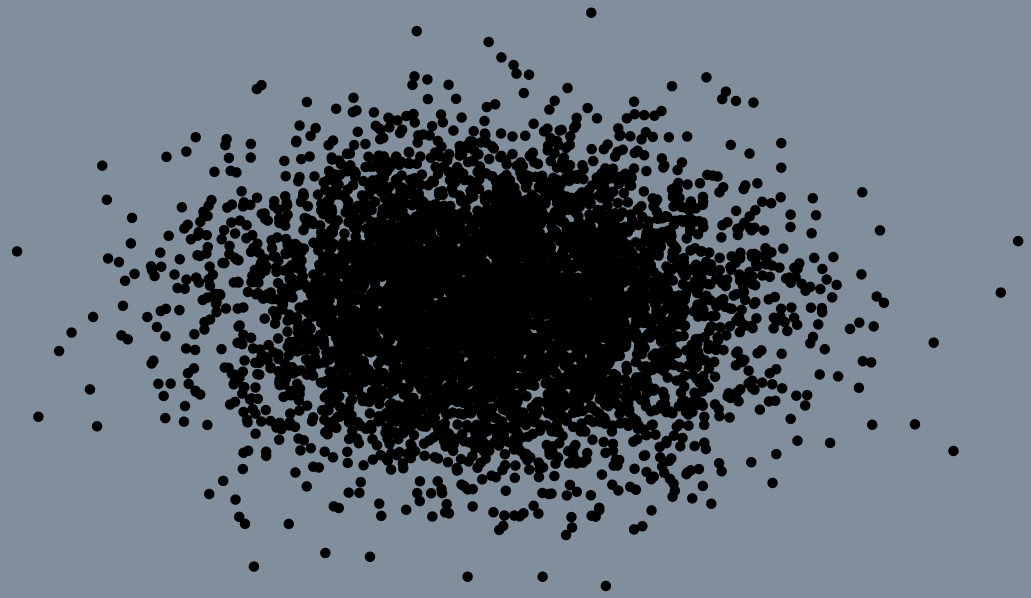


newspaper
(anisotropic diffusion)

Diffusing Ink on Paper

Random Motions





How do we describe this?

A Brief History of Diffusion Measurement

Lucretius (ca. 99 BC-55 BC)

– Roman philosopher and poet

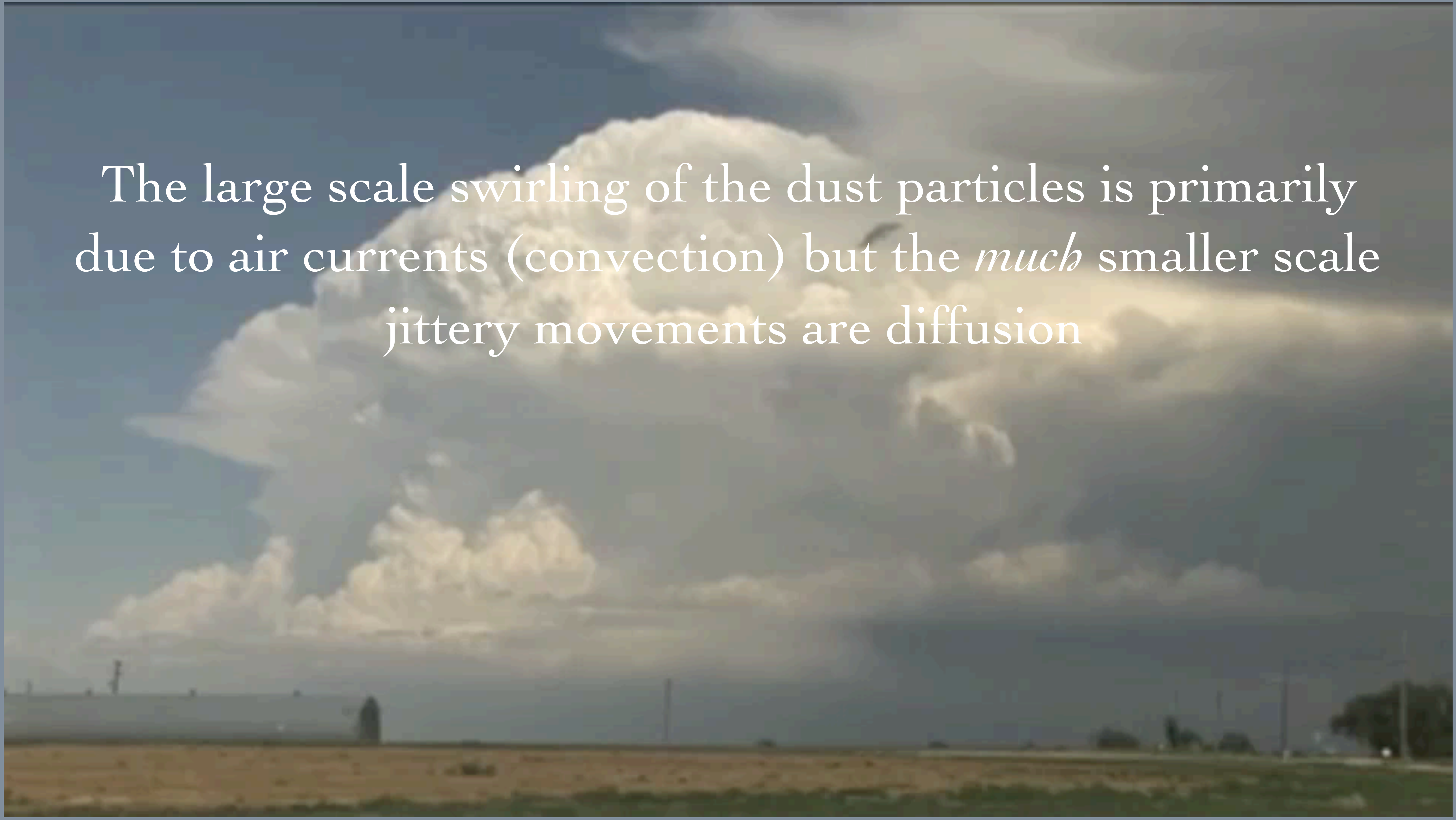
"Observe what happens when sunbeams are admitted into a building and shed light on its shadowy places.

You will see a multitude of tiny particles mingling in a multitude of ways...

their dancing is an actual indication of underlying movements of matter that are hidden from our sight...

http://www.youtube.com/eYeFractal

Convection vs Diffusion
A Cautionary Note



Convection

A Brief History of Diffusion Measurement

Jan Ingenhousz (1730 – 1799)
Dutch botanist and physiologist

Described the “irregular movements” of coal dust on the surface of alcohol

A Brief History of Diffusion Measurement

"Brownian Motion"

Robert Brown (1773 – 1858)
British botanist and surgeon

Observation:
irregular movement of pollen granules in water

Brown's hypothesis: They're alive

Experiment: Repeat pollen experiment using tiny shards of window glass

Result: Same!

Conclusion: Not alive

Theory: ???

Fat droplets in water

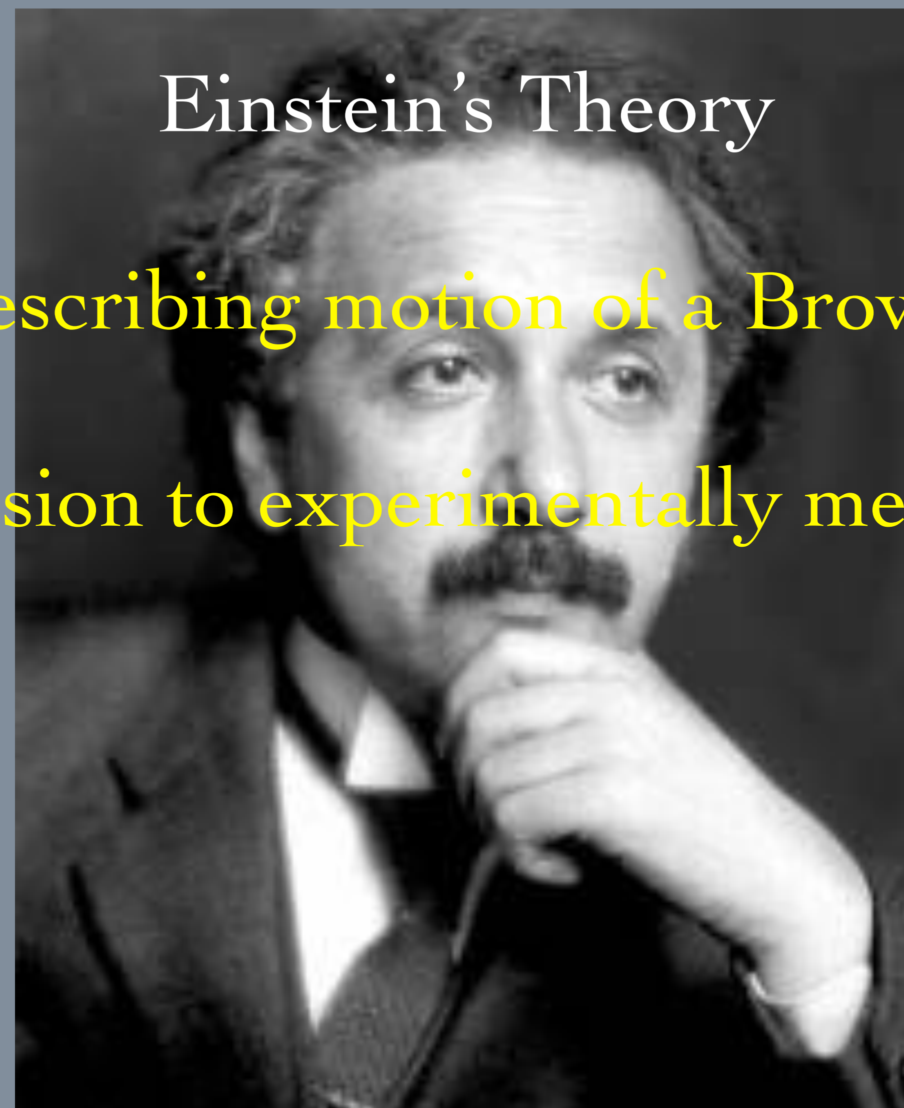
http://www.microscopy-uk.org.uk

Einstein's Theory of Brownian Motion

Einstein's Theory

Part 1: Equation describing motion of a Brownian particle

Part 2: Relate diffusion to experimentally measurable quantities



Albert Einstein (1879 – 1955)
German physicist

Einstein Theory of Brownian Motion
Part I

The particle density $\rho(x,t)$ at a position x at time t obeys

$$\frac{\partial \rho}{\partial t} = \boxed{D} \frac{\partial^2 \rho}{\partial x^2}$$

change with time

diffusion coefficient

change with space

The Diffusion Equation

Einstein Theory of Brownian Motion
Part I

The solution to the Diffusion Equation
for particles initially at location x_0

$$\rho(x,t) = \frac{1}{\sqrt{4\pi D t}}\, e^{-(x-x_0)^2/4Dt}$$

This is a Gaussian (or Normal) distribution
with mean position

$$\bar{x} = x_0$$

and variance in the position

$$\sigma_x^2 = \overline{(x-x_0)^2} = 2Dt$$

Einstein Theory of Brownian Motion
Part I

What does this mean?

$$\bar{x} = x_0$$

implies that, on *average*,
the particles do not move from their initial position

$$\sigma_x^2 = 2Dt$$

implies that the *variance* of a Brownian particle's position is proportional to the diffusion coefficient D and time t

Einstein Theory of Brownian Motion
Part I

Einstein argued that the *displacement* of a Brownian particle is thus the RMS distance

$$\Delta x = \sqrt{\overline{(x - x_0)^2}} = \sqrt{2Dt}$$

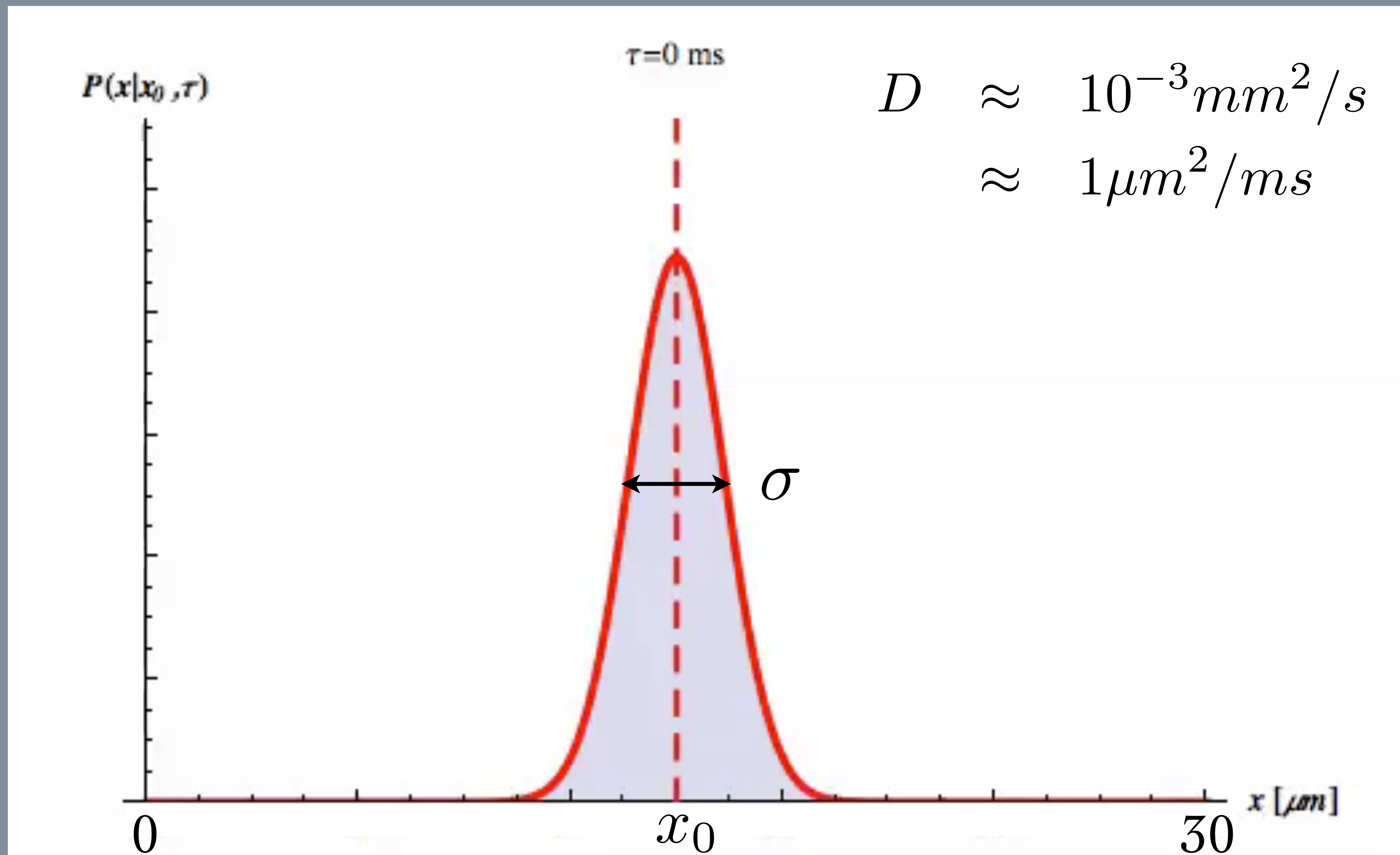
and thus *not* linearly proportional to time (like flow), but to the *square root of time*

<u>Diffusion in Brain Tissue</u>:

D ≅ 1 μ^2/ ms = (0.001 mm^2/s)

For t=100 msec, Δx ≅ 14 μ

Gaussian Diffusion



$$P(x|x_o,\tau) = \frac{1}{\sqrt{4\pi D\tau}}\, e^{-\frac{(x-x_o)^2}{4\pi D\tau}}$$

$$\boxed{\sigma = \sqrt{2D\tau}}$$

Einstein Theory of Brownian Motion
Part I

Diffusion vs Flow

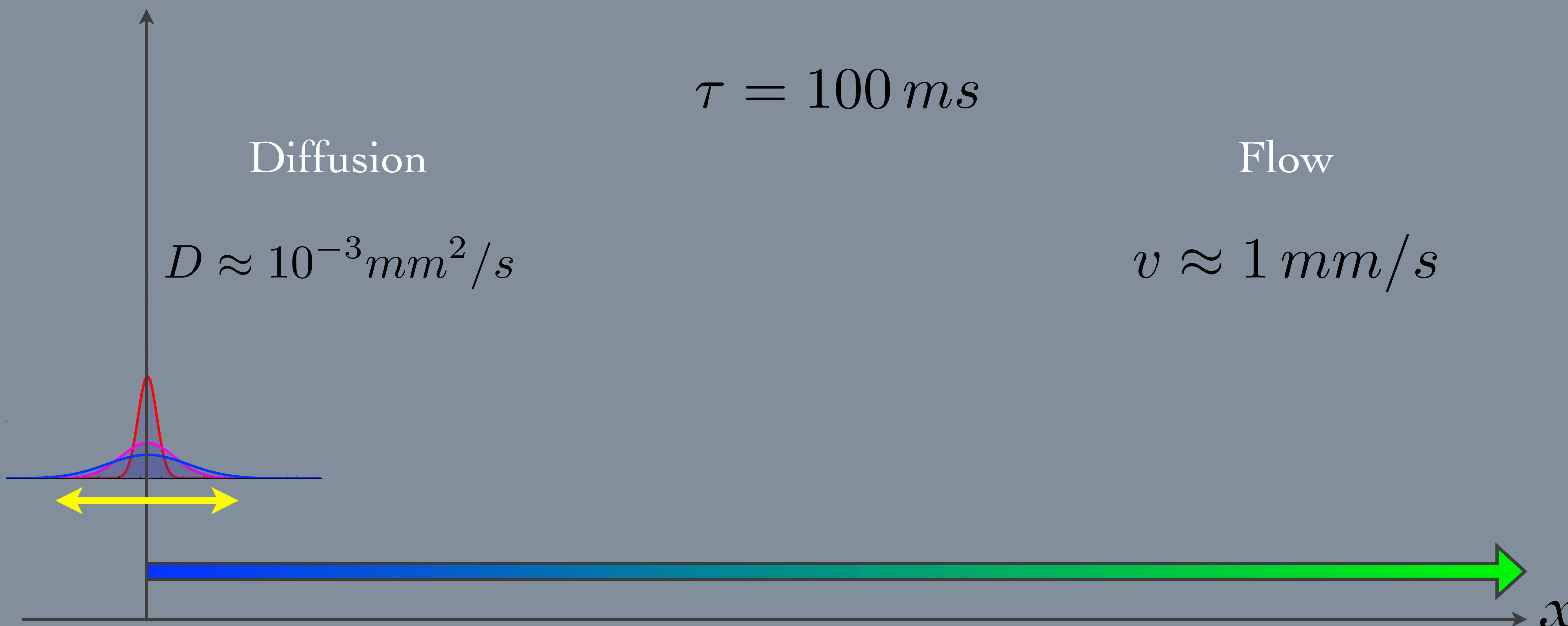
$$\tau = 100\, ms$$

Diffusion

$$D \approx 10^{-3} mm^2/s$$

Flow

$$v \approx 1\, mm/s$$



$$\Delta x \approx 14\, \mu m$$

$$\Delta x \approx 100\, \mu m$$

Einstein Theory of Brownian Motion
Part II

The diffusion coefficient is

$$D = \alpha \frac{T}{\eta r}$$

where

T = temperature

η = viscosity

r = particle radius

$$\alpha = \text{constant} = \frac{R}{6\pi N}$$

gas constant

Avogadro's number

Diffusion coefficient goes up with temperature and down with viscosity and particle radius

It's sensitive to the local environment!

Diffusion

Definition of Diffusion

The random migration of molecules due to motion induced by thermal energy

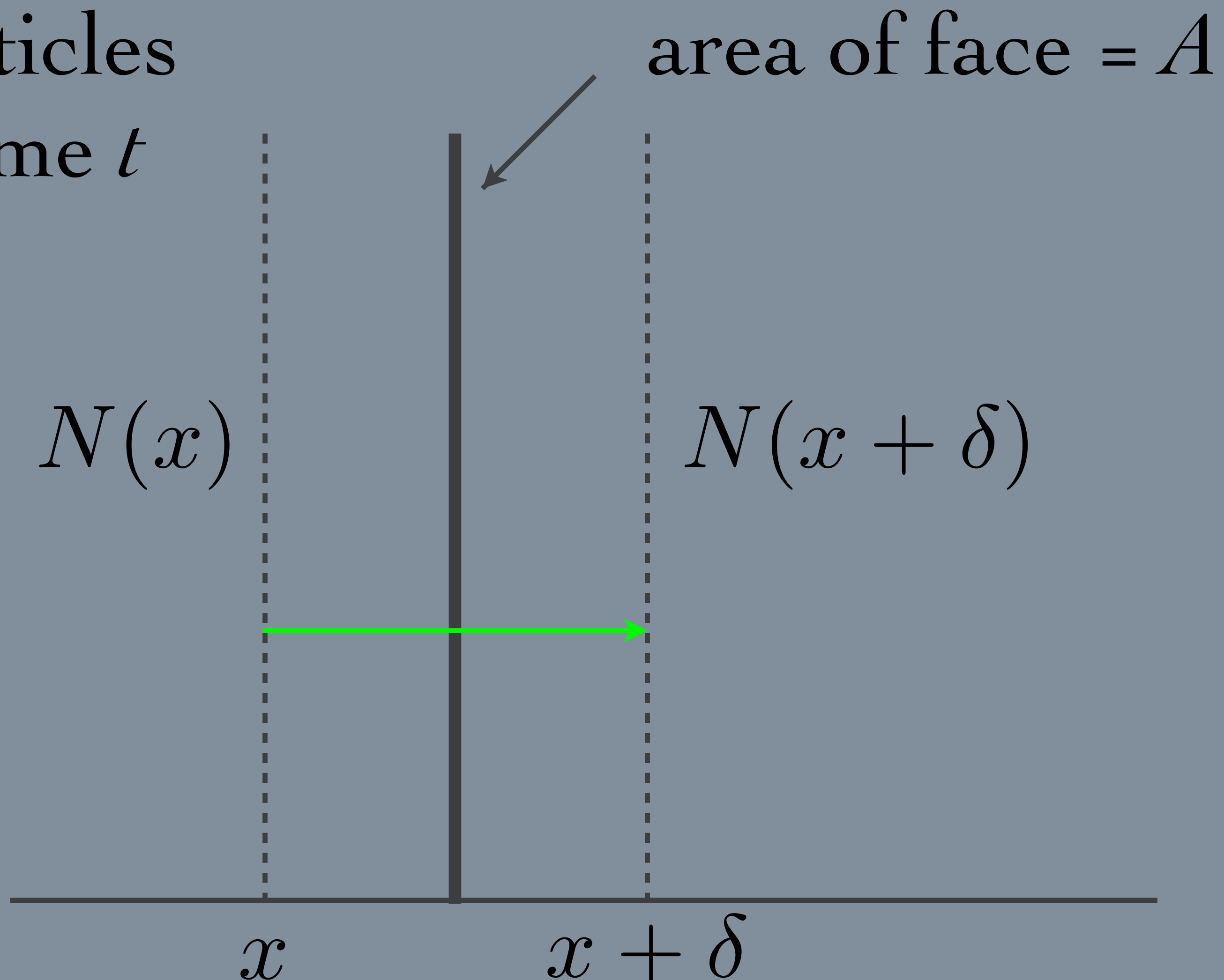
Macroscopic Theory of Diffusion

The Diffusion Equation

What you probably had in chemistry class …

Flux and Random Walk

N=number of particles along x axis at time t



How many particles will move across the face from x to x+δ in unit time?

That is, what is the *flux* J_x

Flux and Random Walk

Net number

$$-\frac{1}{2}[N(x+\delta)-N(x)]$$

So for area A and time τ

$$J_x = -\frac{1}{2}[N(x+\delta)-N(x)]/A\tau$$

Flux and Random Walk

$$J_x = -\underbrace{\frac{\delta^2}{2\tau}}_{D}\frac{1}{\delta}\left[\underbrace{\frac{N(x+\delta)}{A\delta}}_{C(x+\delta)} - \underbrace{\frac{N(x)}{A\delta}}_{C(x)}\right]$$

diffusion coefficient concentration at $x+\delta$ concentration at x

$$J_x = -D\frac{1}{\delta}[C(x+\delta) - C(x)]$$

Fick's First Law

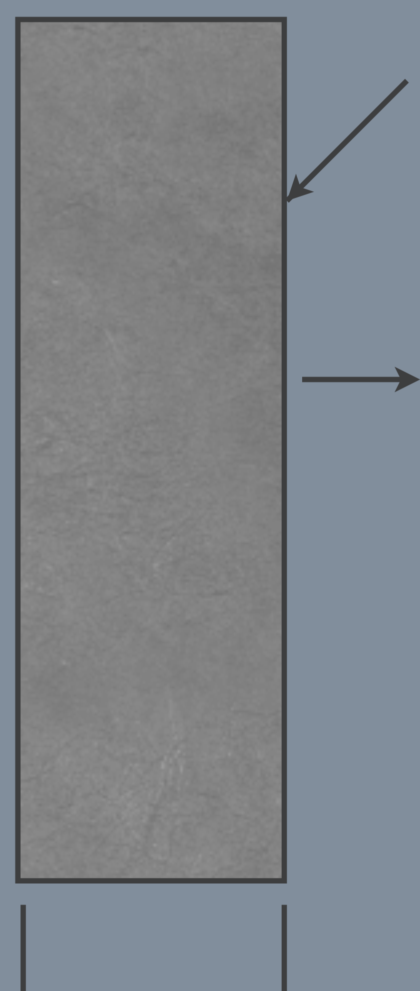
$$J_x = -D\frac{1}{\delta}[C(x+\delta) - C(x)]$$

$$\delta \to 0$$

$$\boxed{J_x = -D\frac{\partial C}{\partial x}}$$

Continuity Equation

Particle conservation gives the continuity equation



In time τ, $J_x(x)A\tau$ enter from left and $J_x(x+\delta)A\tau$ leave from right

Continuity Equation

Particle conservation means change in concentration must equal the flux per unit volume

$$
\begin{aligned}
\frac{1}{\tau}[C(t+\tau) - C(t)] &= -\frac{1}{\tau}[J_x(x+\delta) - J_x(x)]A\tau/A\delta \\
&= -\frac{1}{\delta}[J_x(x+\delta) - J_x(x)]
\end{aligned}
$$

$$\tau \rightarrow 0 \qquad \delta \rightarrow 0$$

$$\boxed{\frac{\partial C}{\partial t} = -\frac{\partial J_x}{\partial x}}$$

Continuity Equation (1D)

change in flux with location

change in concentration with time

$$\boxed{\frac{\partial J}{\partial x} = -\frac{\partial C}{\partial t}}$$

The continuity equation describes *conservative transport*

$$\begin{aligned} J &= \text{flux} \\ C &= \text{concentration} \\ x &= \text{spatial location} \\ t &= \text{time} \end{aligned}$$

Fick's Second Law

Fick's 1st Law

$$\boxed{J_x = -D\frac{\partial C}{\partial x}}$$

continuity

$$\boxed{\frac{\partial C}{\partial t} = -\frac{\partial J_x}{\partial x}}$$

$$\boxed{\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}}$$

The diffusion equation

Microscopic Theory of Diffusion

A particle at absolute temperature T
has a kinetic energy along each axis of $kT/2$ where
k is Boltzmann's constant.

This is independent of size of particle (Einstein, 1905)

So, for a particle of mass m and velocity v_x

$$\frac{1}{2}mv_x^2 = \frac{1}{2}kT$$

Microscopic Theory of Diffusion

The velocity fluctuates, but on average

$$\langle v_x^2 \rangle = kT/m$$

Thus, root-mean-squared (rms) velocity is

$$\langle v_x^2 \rangle^{1/2} = (kT/m)^{1/2}$$

Microscopic Theory of Diffusion

<u>Example</u>

If molecular weight = 1 kg, then molecule has mass

$$m = 1\text{kg/mole} = 1000\text{g}/6 \times 10^{23}\text{molecules} = 1.67 \times 10^{-21}\text{g}$$

$$kT \text{ at } 300^\circ K(27^\circ C) = 4.14 \times 10^{-14} \text{ g-cm}^2/\text{sec}^2$$

$$\langle v_x^2 \rangle^{1/2} = (kT/m)^{1/2} \approx 50 \text{ m/sec}$$

Fast!

Microscopic Theory of Diffusion

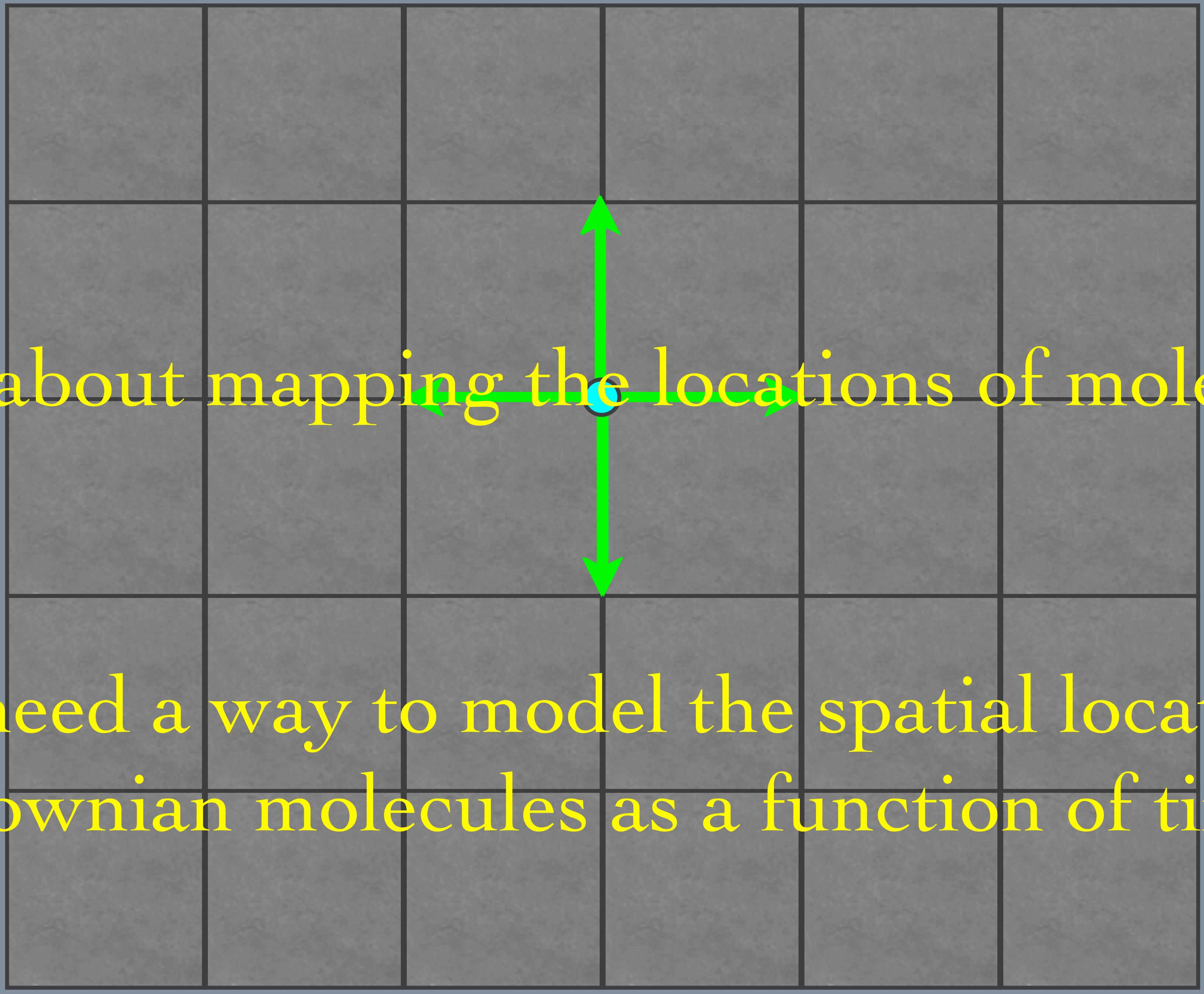
But molecule is immersed in a complex (water) environment, and so is constantly hitting and bouncing off of other molecules

It thus exhibits a *random walk*

A collection of such particles initially confined to a small area that undergo *random walks* eventually spread out in space.

This is called *diffusion*

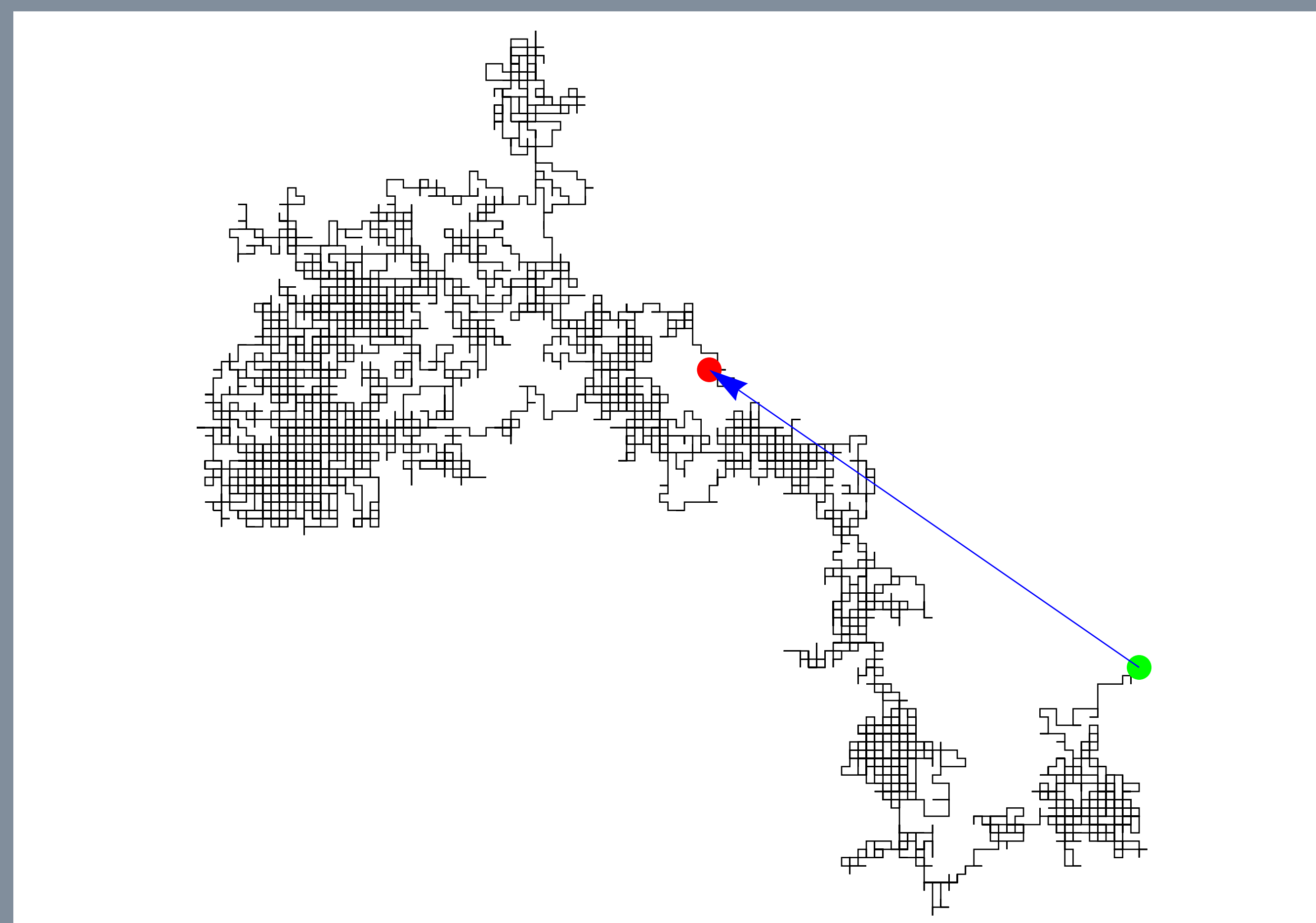
Modeling diffusion: Random Walk



MRI is all about mapping the locations of molecules ...

... we need a way to model the spatial locations of Brownian molecules as a function of time

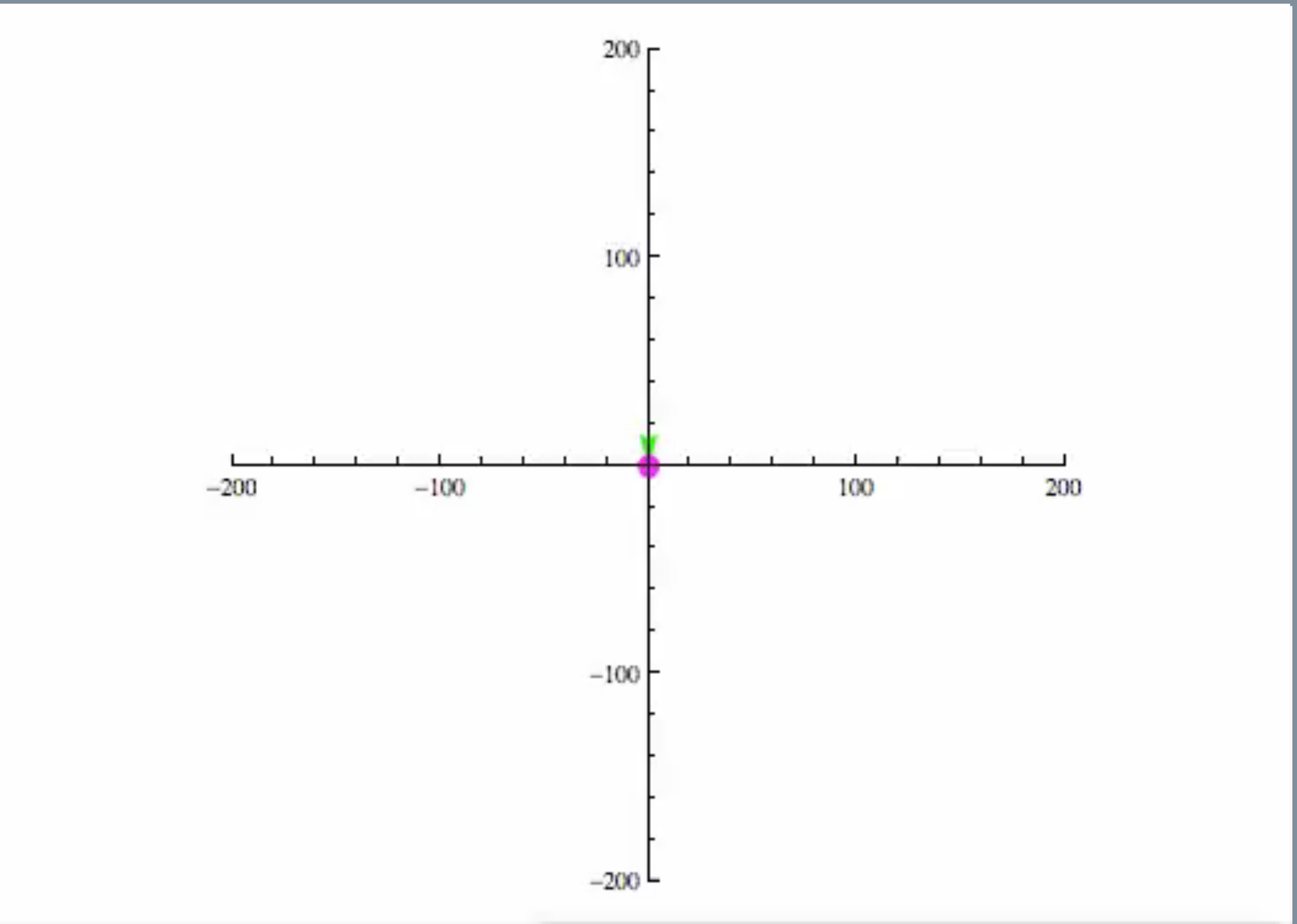
The Random Walk



start

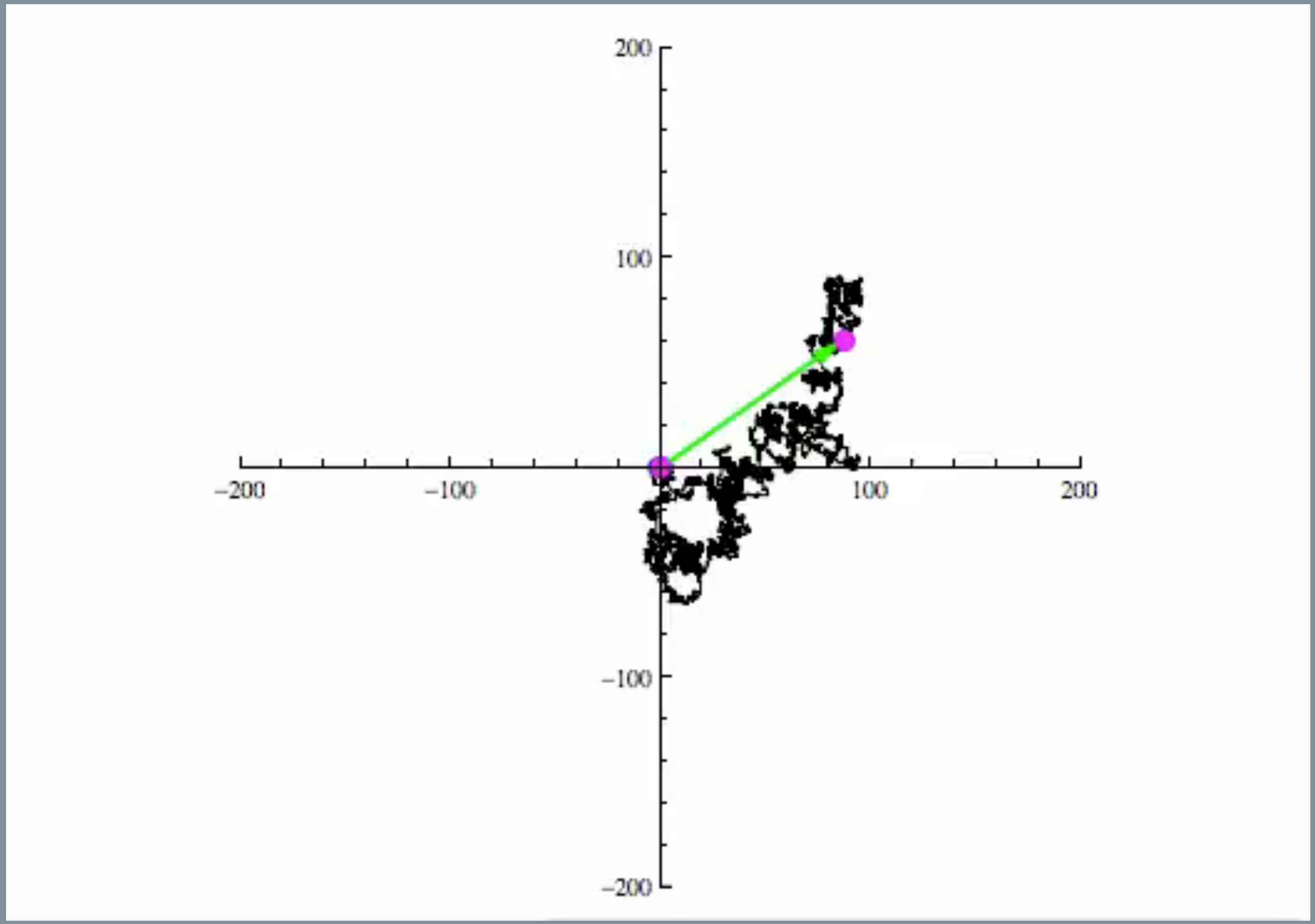
end

Modeling diffusion: Random Walk



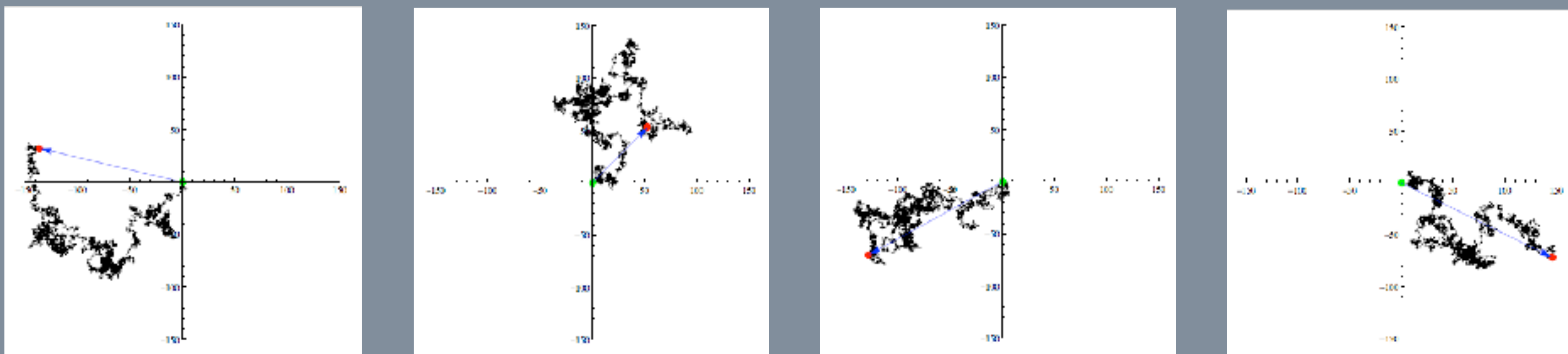
$$\tau = \text{constant}$$

Modeling diffusion: Random Walk



$$\tau = \text{constant}$$

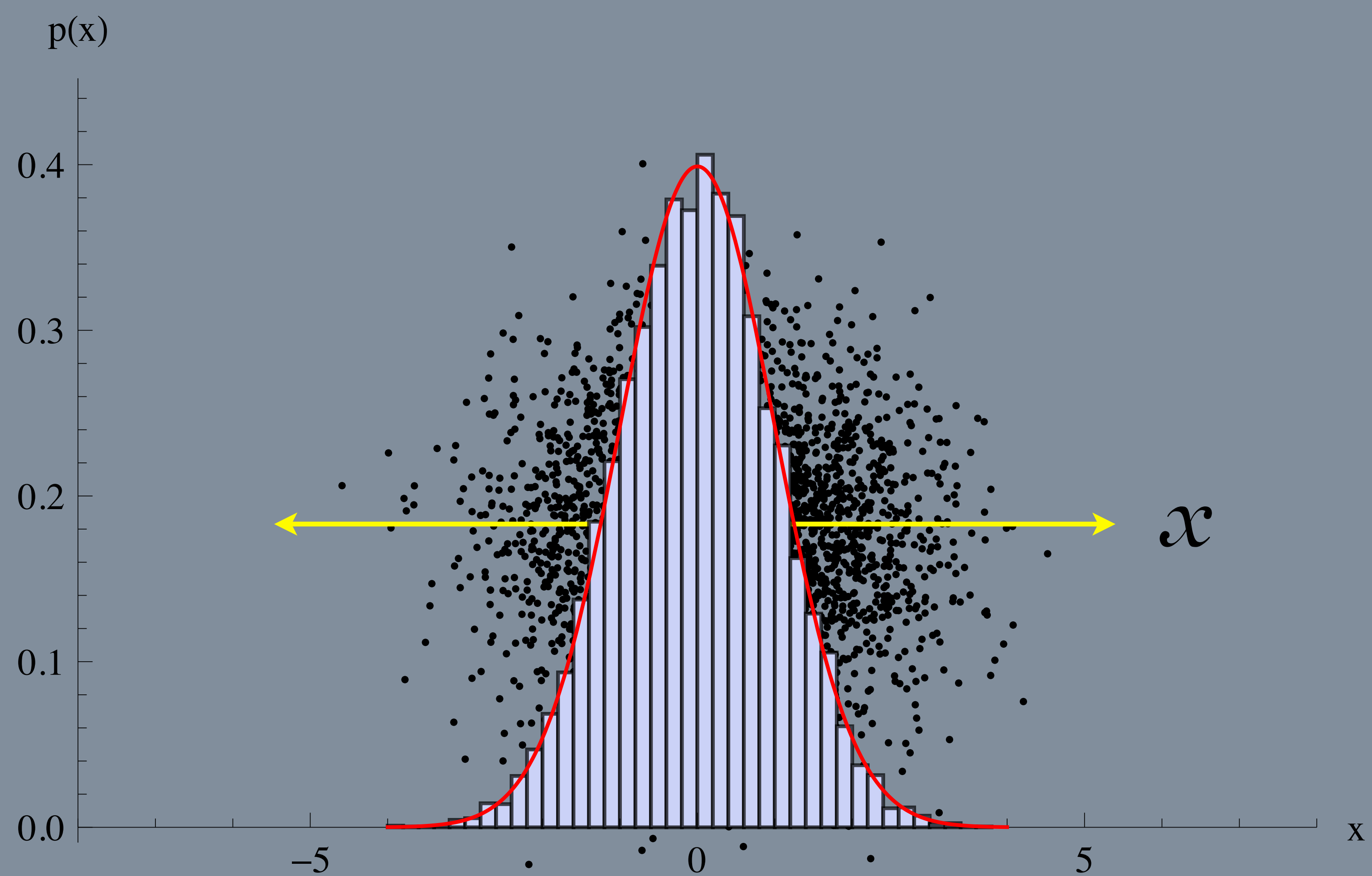
The Random Walk



What is the average distance $\langle r \rangle$ travelled?

What is the variance $var(r) = \langle r^2 \rangle - \langle r \rangle^2$ of the distances travelled?

The distribution of particles after a time τ



GAUSSIAN DIFFUSION

$$P(x|x_0,\tau) \propto N(x_0,\sigma^2)$$

$$P(x|x_0,\tau) = \frac{1}{\sqrt{4\pi D\tau}}\, e^{-\frac{(x-x_o)^2}{4\pi D\tau}}$$

Random Walk

the walker's position is distributed according to a *normal distribution* which depends only on the *variance* of the individual displacements:

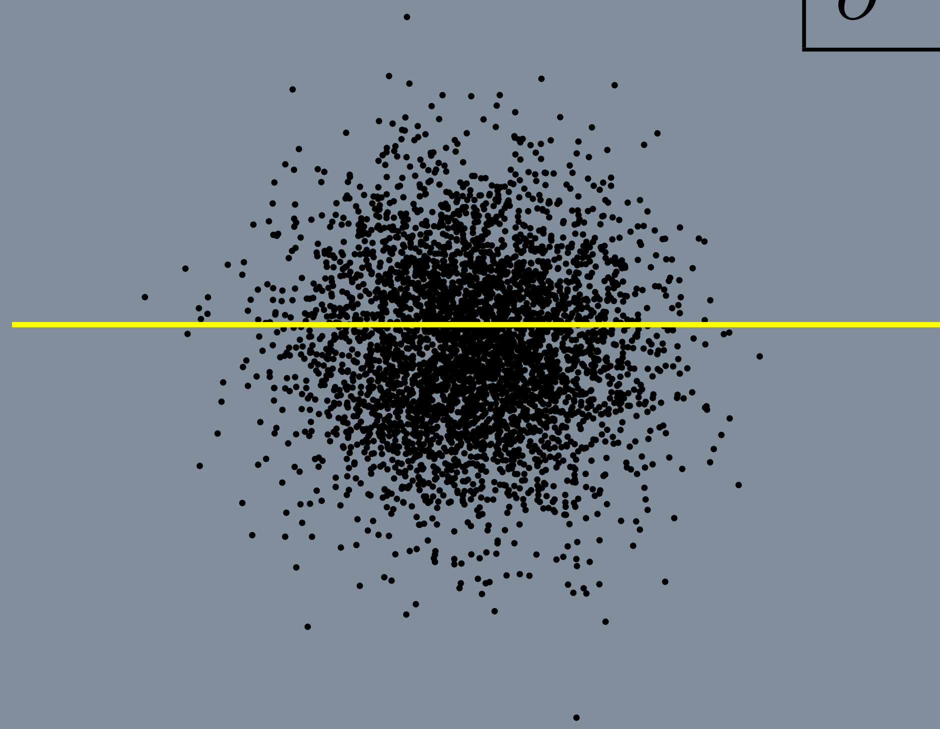
$$\langle r \rangle = 0$$

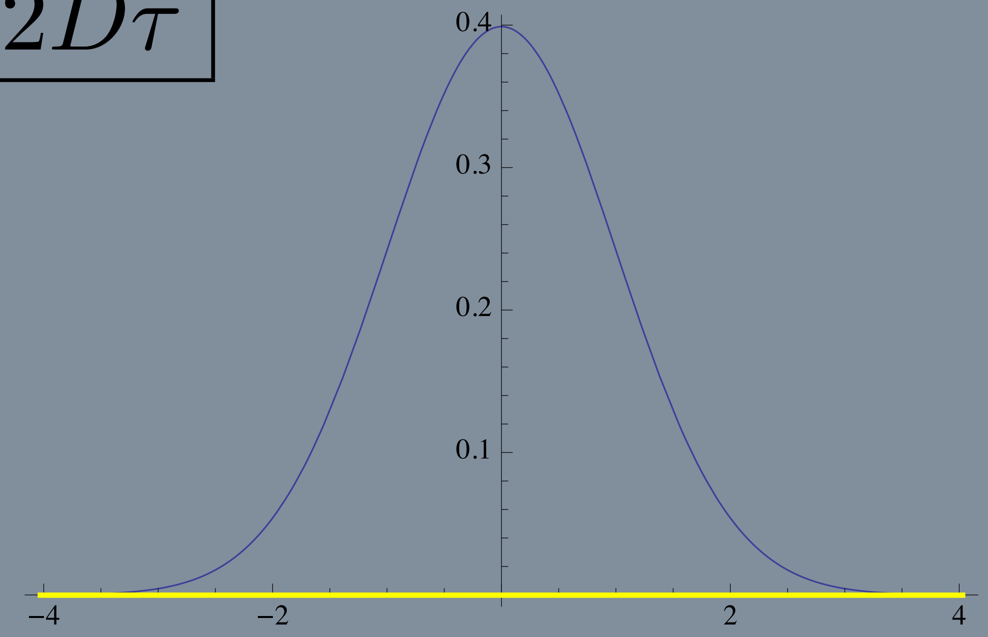
$$var(r) = \langle r^2 \rangle = 2\xi Dt \quad (\xi = \text{dimension})$$

The Random Walk in 1D

$$P(x) = \frac{1}{(2\pi\sigma^2)^{1/2}} \exp\left[-\frac{1}{2\sigma^2}(x-\mu)^2\right]$$

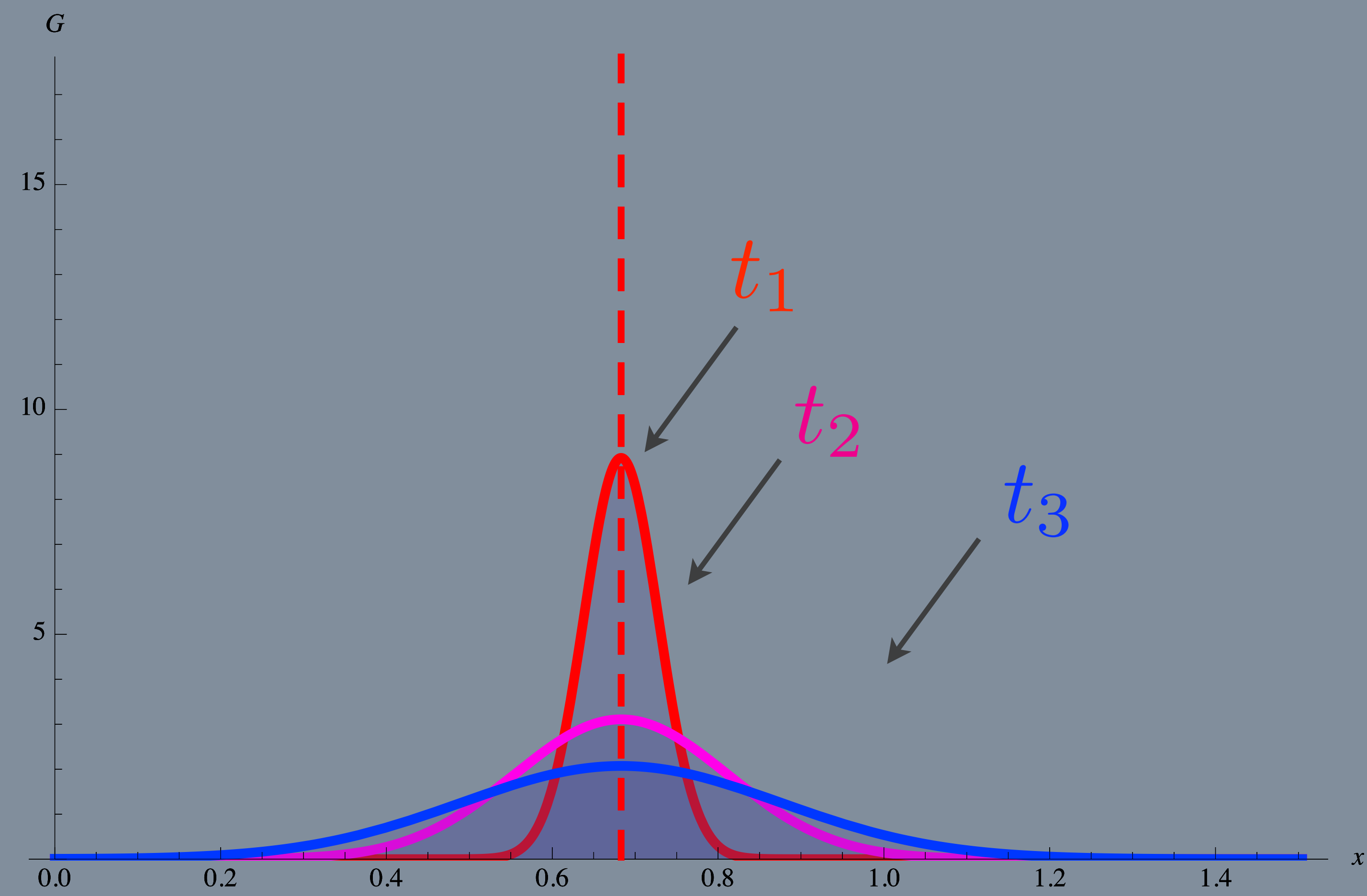
$$\boxed{\sigma^2 = 2D\tau}$$



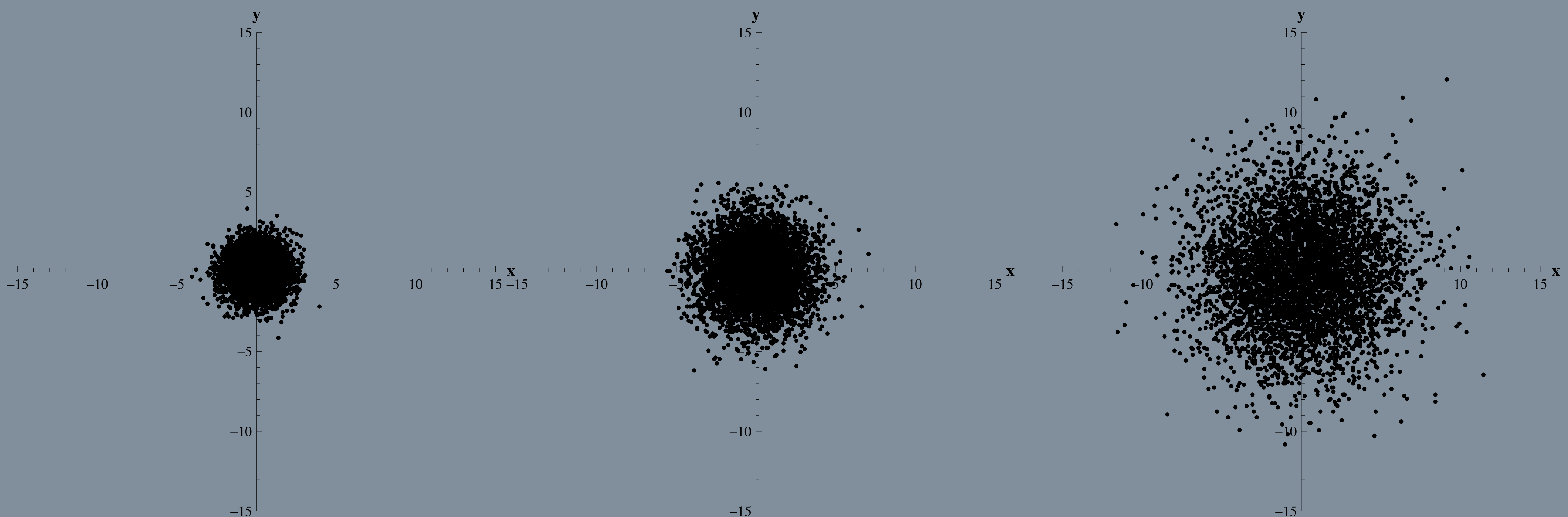


Diffusion Equation (1D) solution
Distribution of particles

$$P(x) = \frac{1}{(4\pi D\tau)^{1/2}} \exp\left[-\frac{(x-\mu)^2}{4D\tau}\right]$$

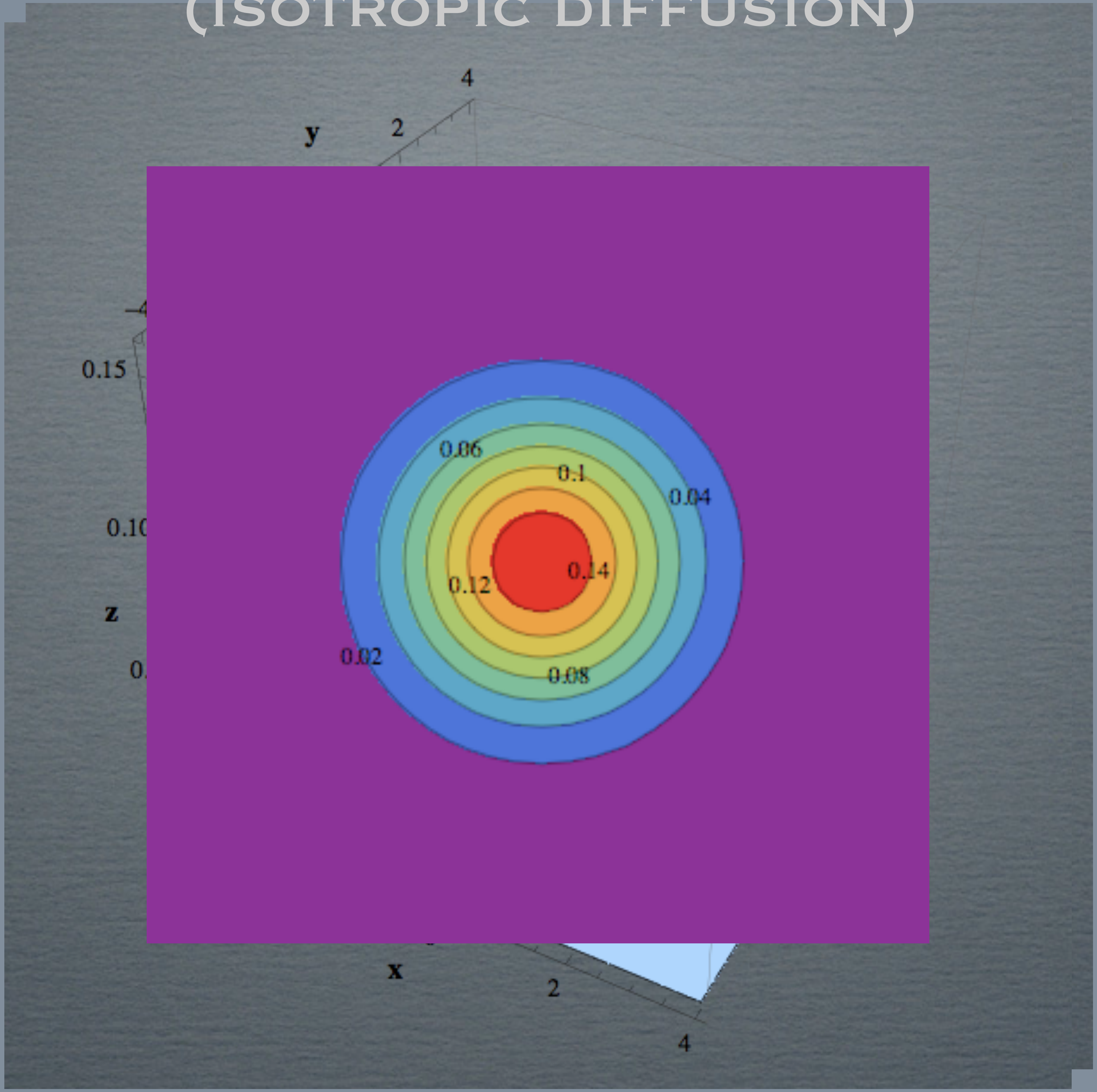


ISOTROPIC DIFFUSION IN 2D



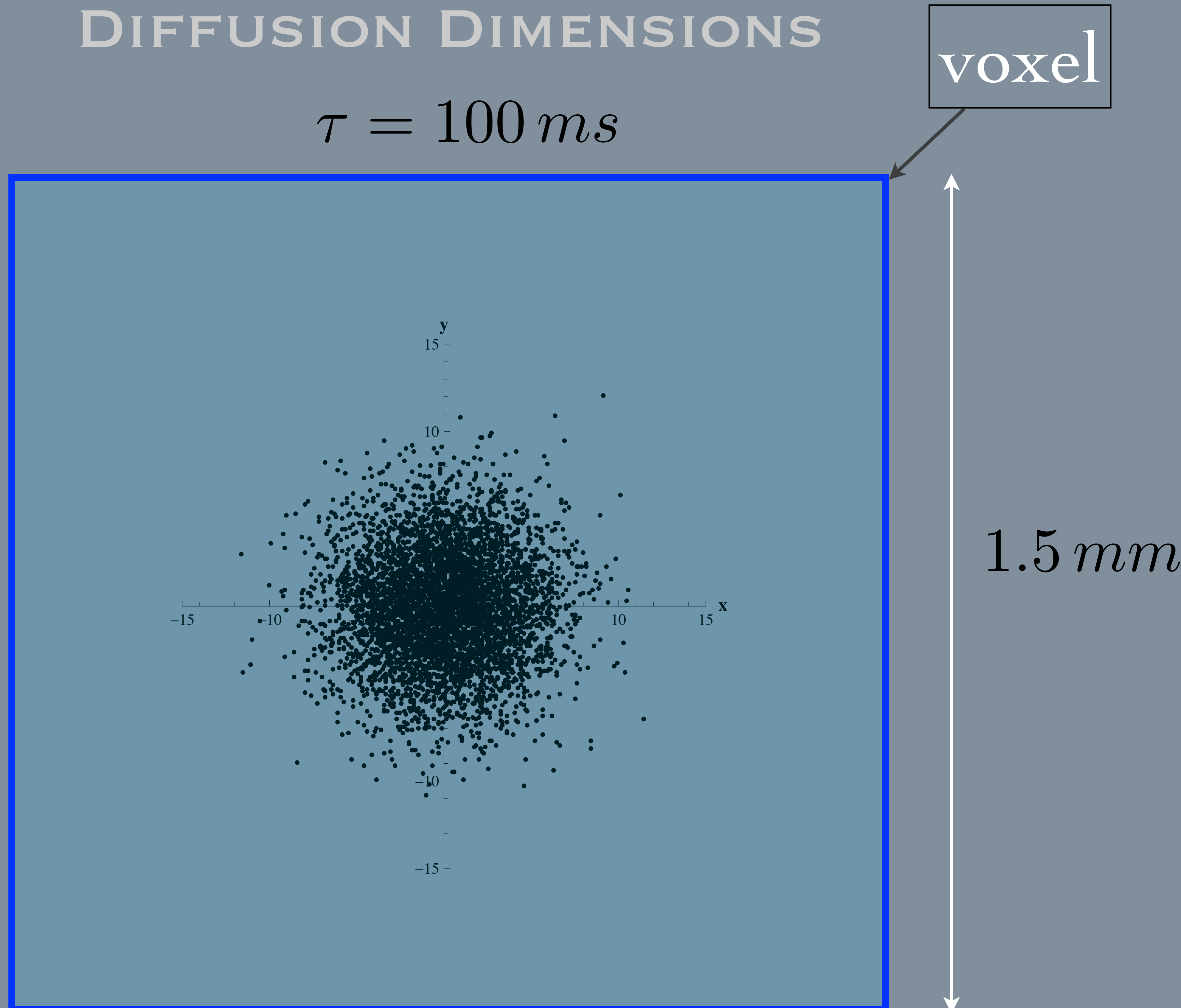
$\tau = 1\,ms$ $\tau = 10\,ms$ $\tau = 100\,ms$

Probability Contours (isotropic diffusion)



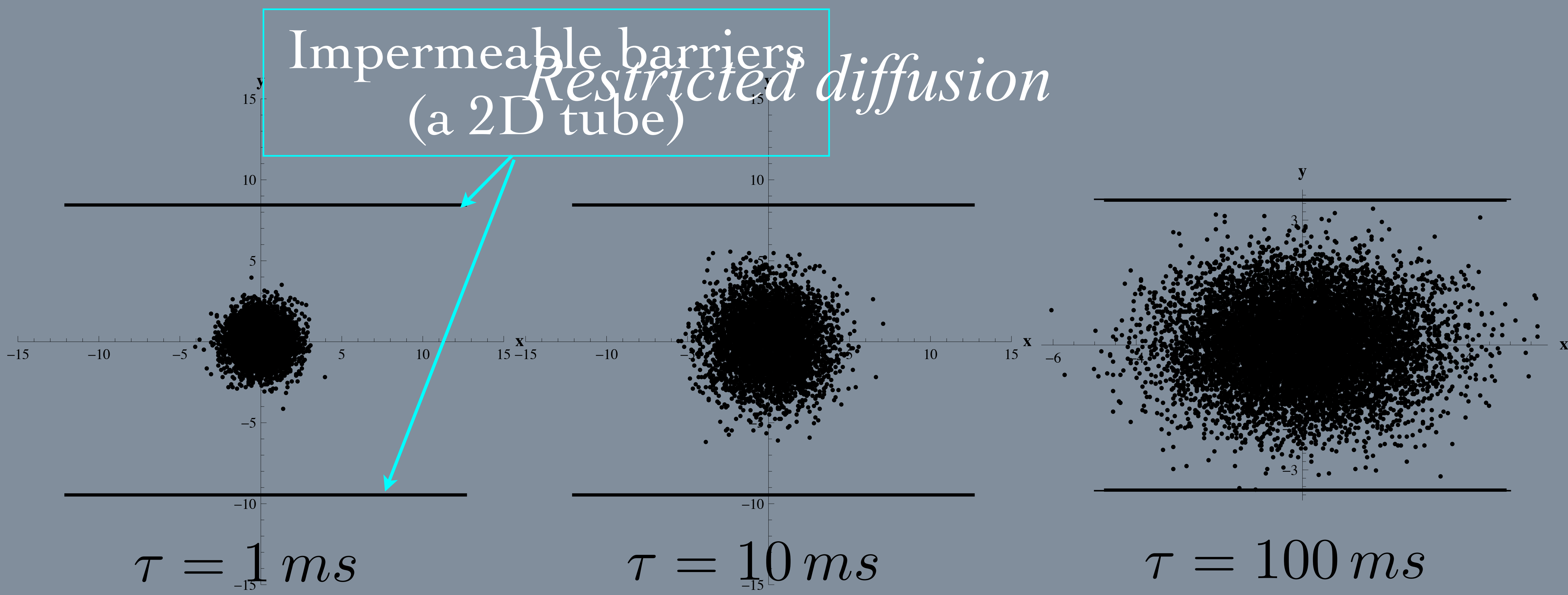
Diffusion Dimensions

$\tau = 100\, ms$



$\Delta x \approx \left(\frac{1}{1000}\right)$ a typical imaging voxel dimension

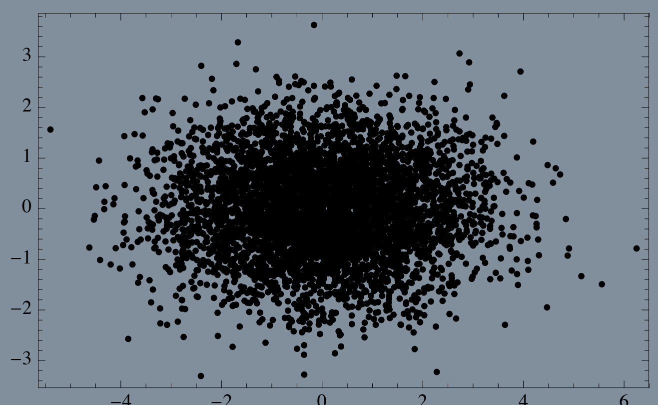
Anisotropic diffusion in 2D

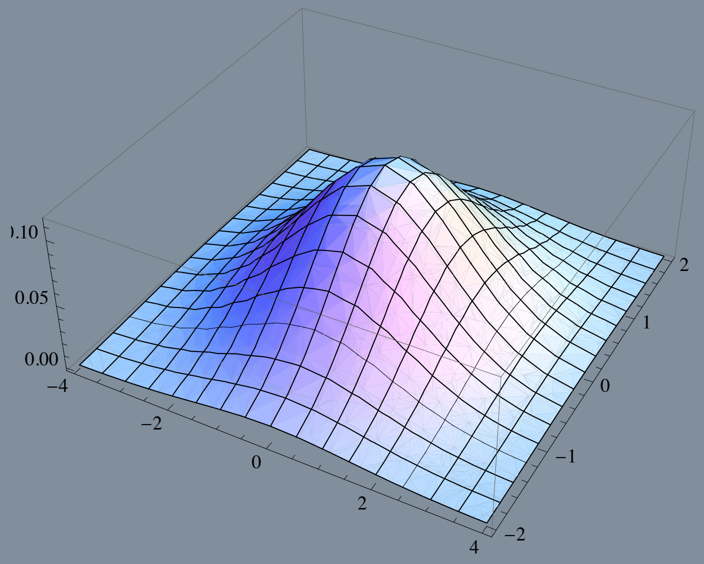


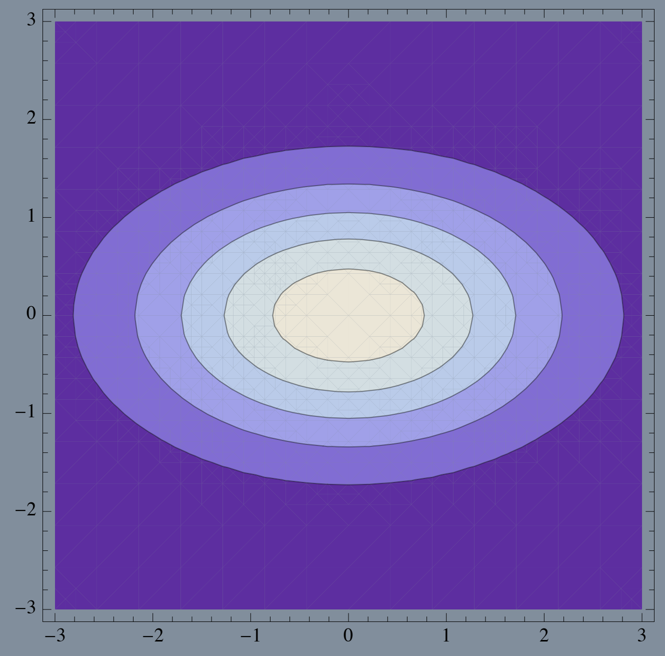
1. Anisotropy induced by local geometry
2. Sensitivity to geometry depends upon diffusion time τ
3. While the D of the liquid may be a constant, there is an *apparent diffusion coefficient* (ADC) that varies with direction

The Random Walk in 2D

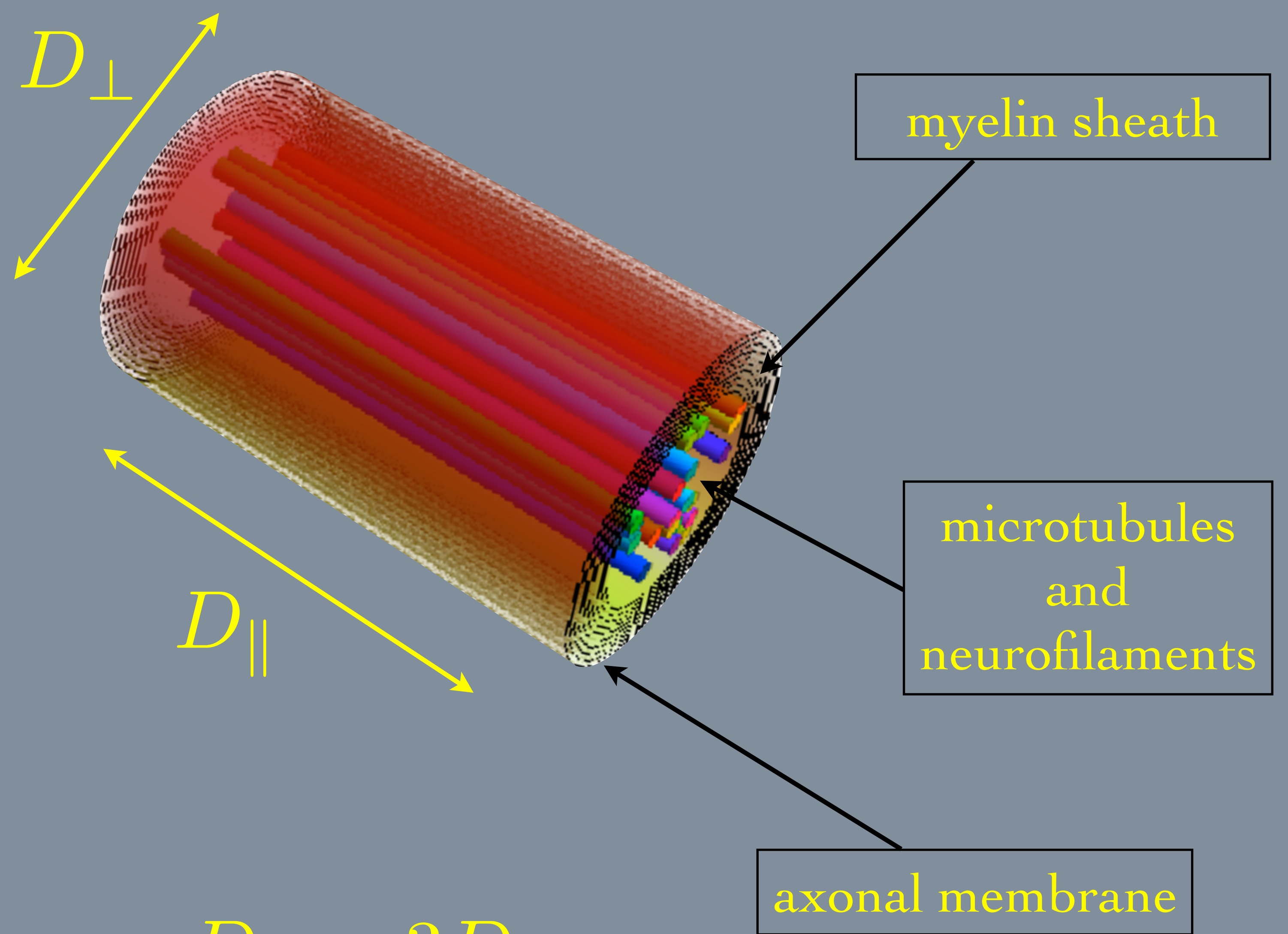
$$P(\boldsymbol{x}) = \frac{1}{2\pi|\boldsymbol{D}|^{1/2}} \exp\left[-\frac{1}{2}(\boldsymbol{x}-\boldsymbol{\mu})^t \boldsymbol{D}^{-1}(\boldsymbol{x}-\boldsymbol{\mu})\right]$$







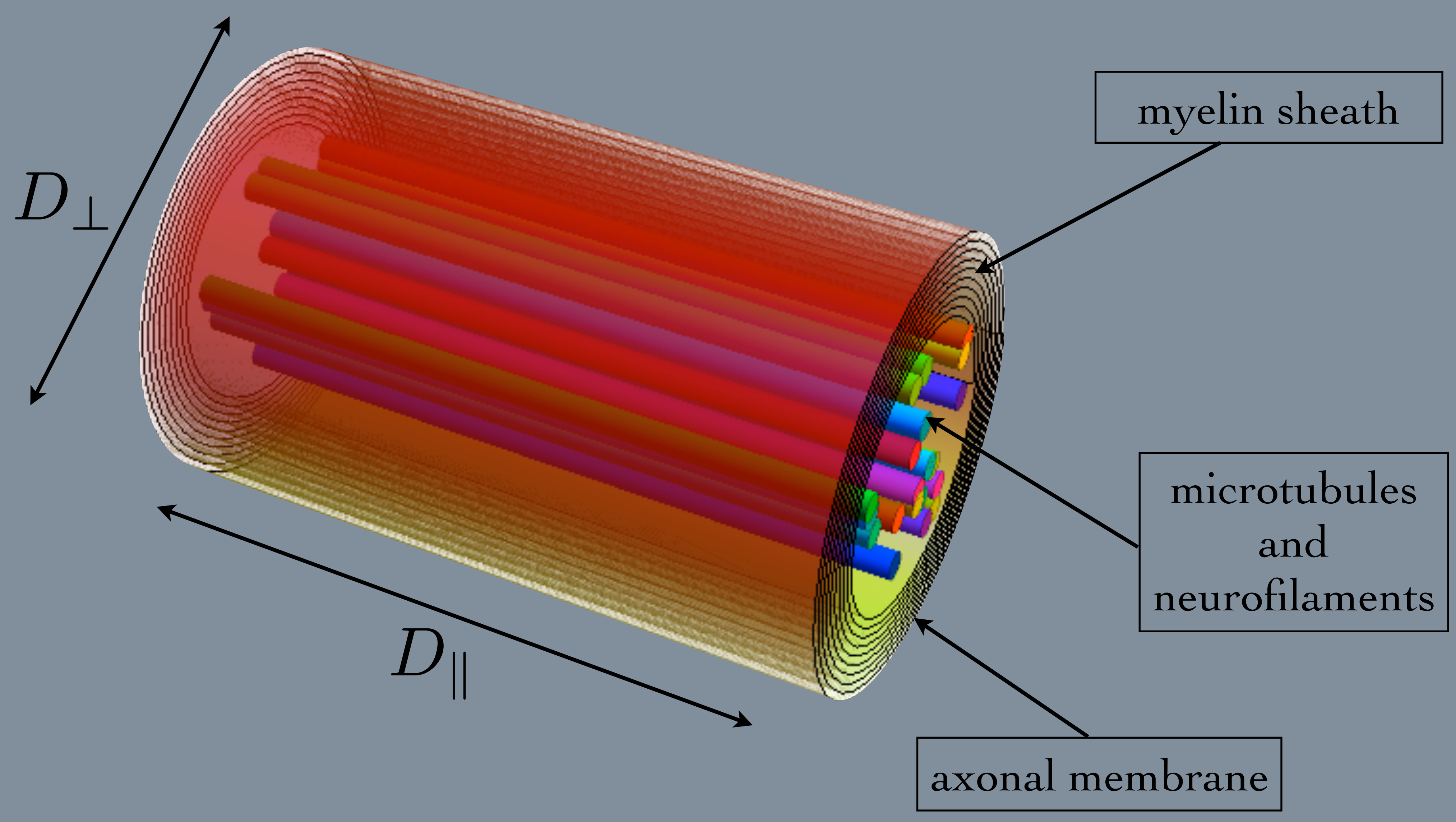
Diffusion Anisotropy in neural tissues



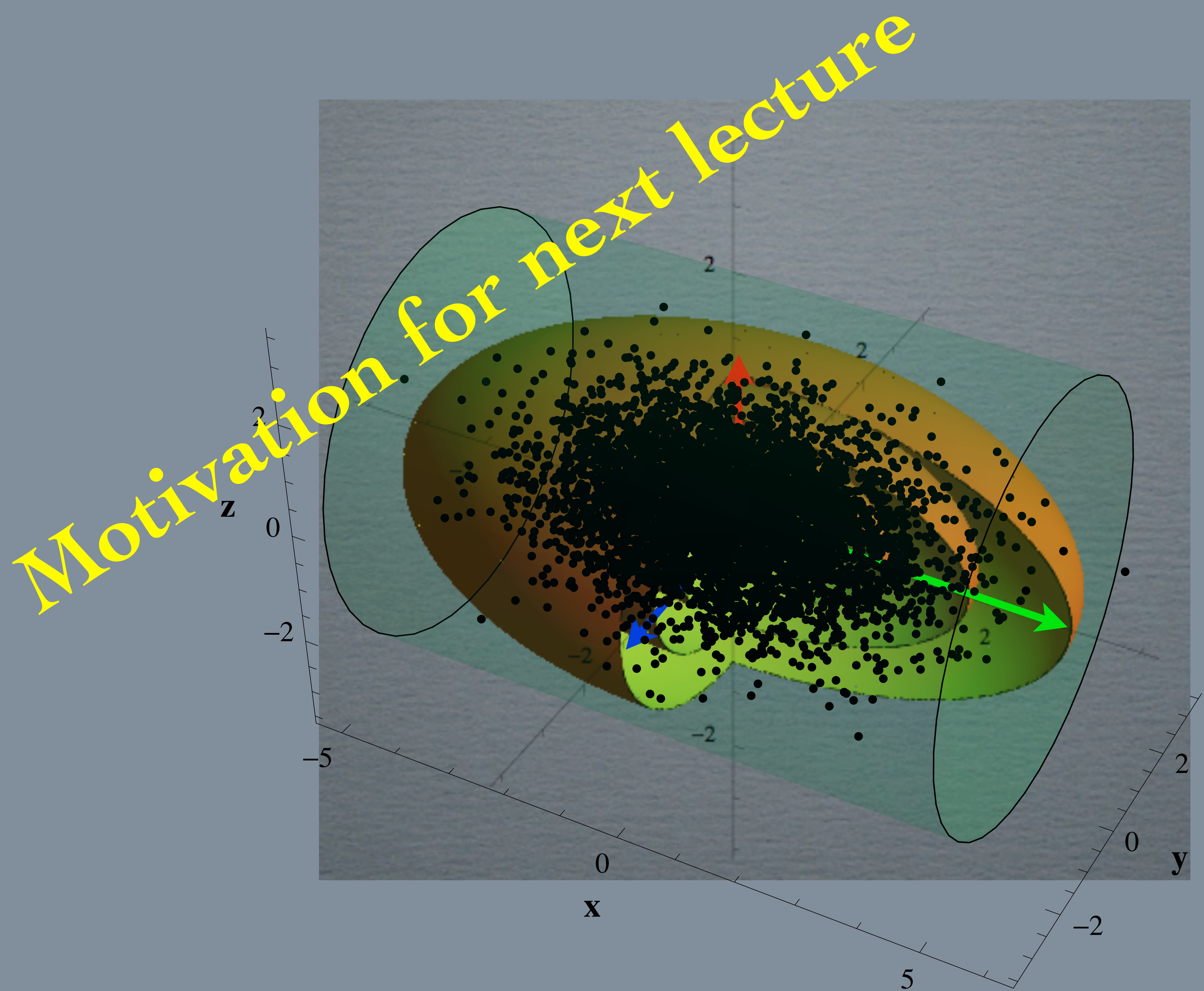
$$D_\parallel \approx 3D_\perp$$

$$(1.2\mu^2/ms) \qquad (0.4\mu^2/ms)$$

Myelinated Neural Fibers

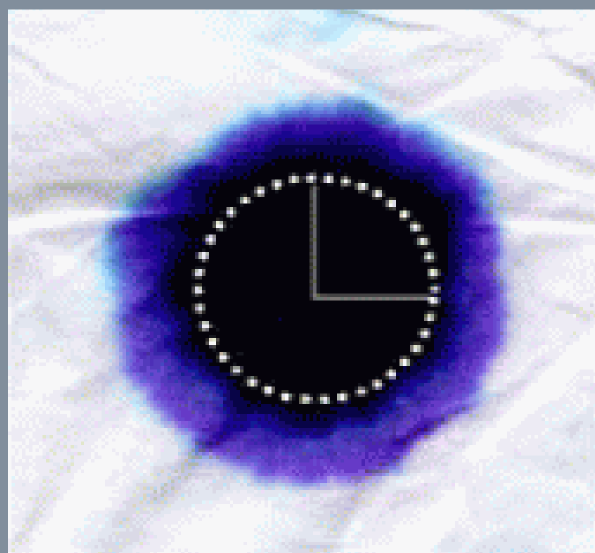


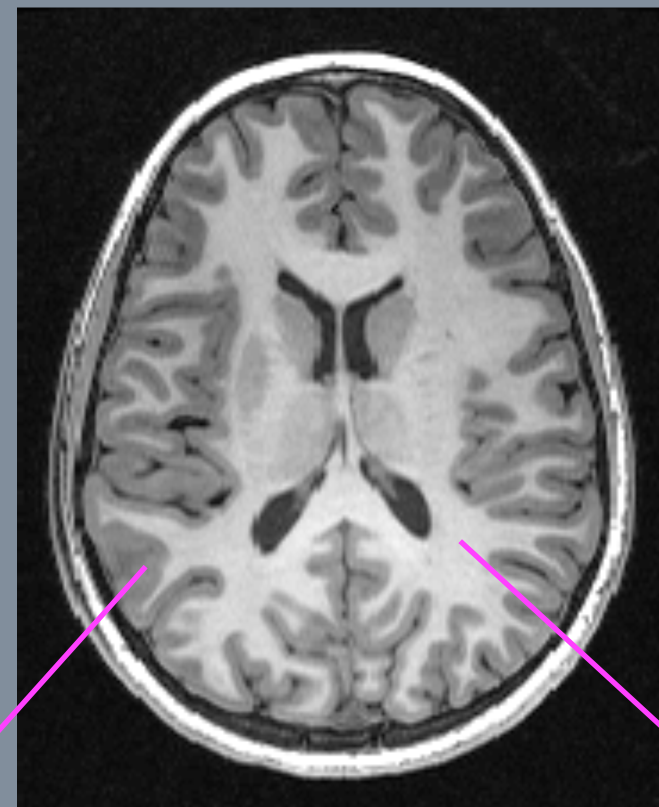
Diffusion Anisotropy in 3D

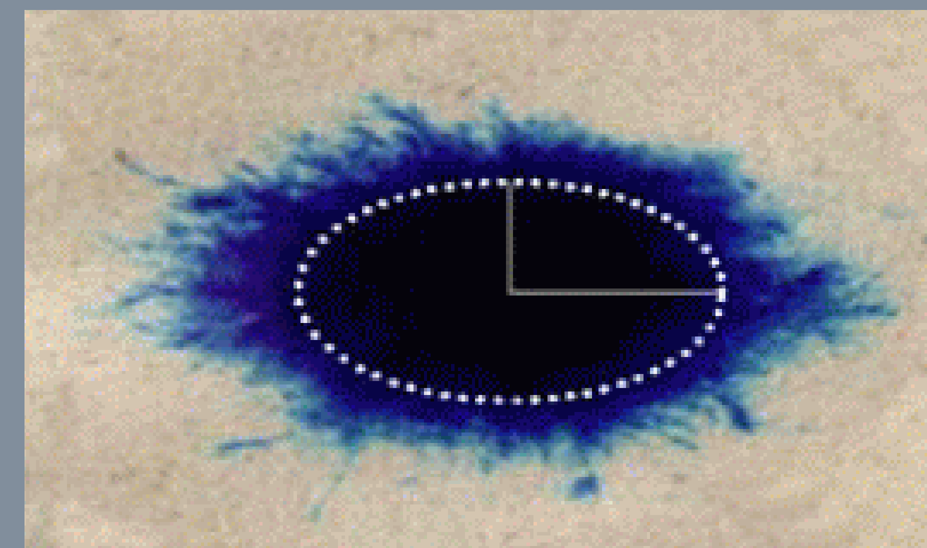


probability contours in 3D

Restricted Diffusion in Brain Tissues

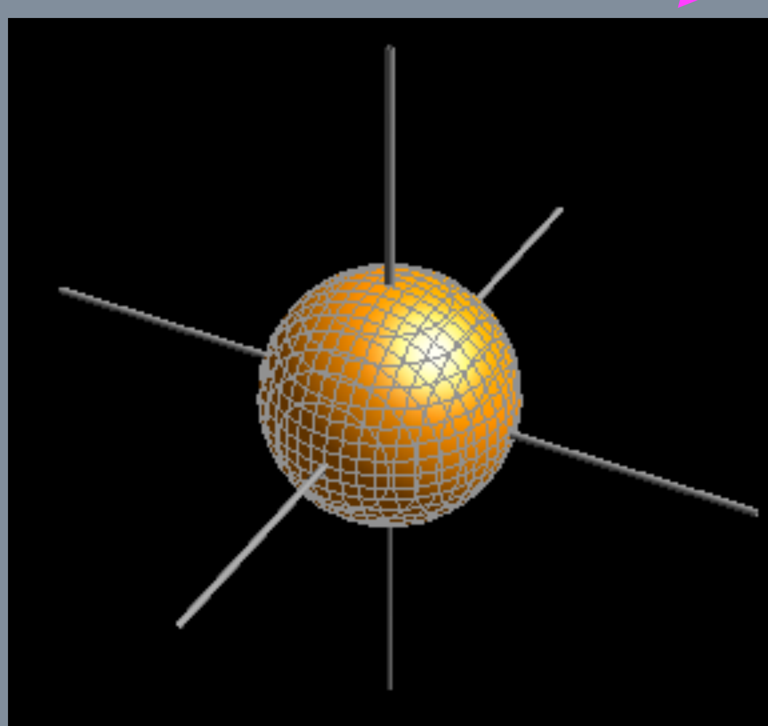




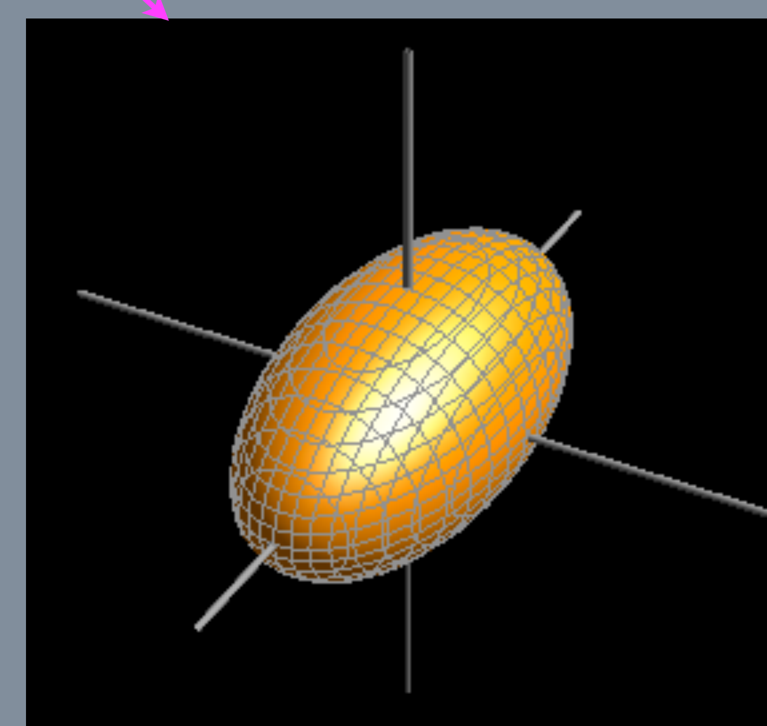


Gray Matter
(isotropic)

White Matter
(anisotropic)

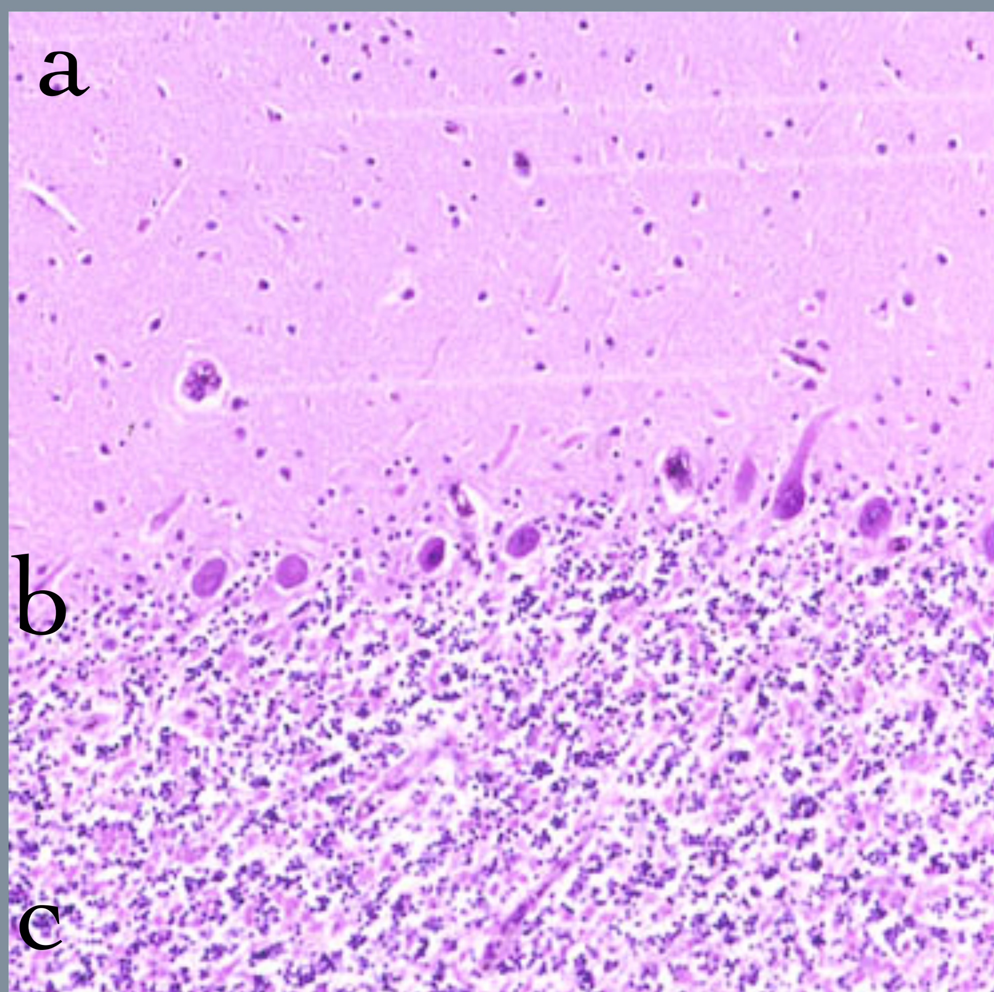


shape of diffusion
respresents underlying
tissue structure

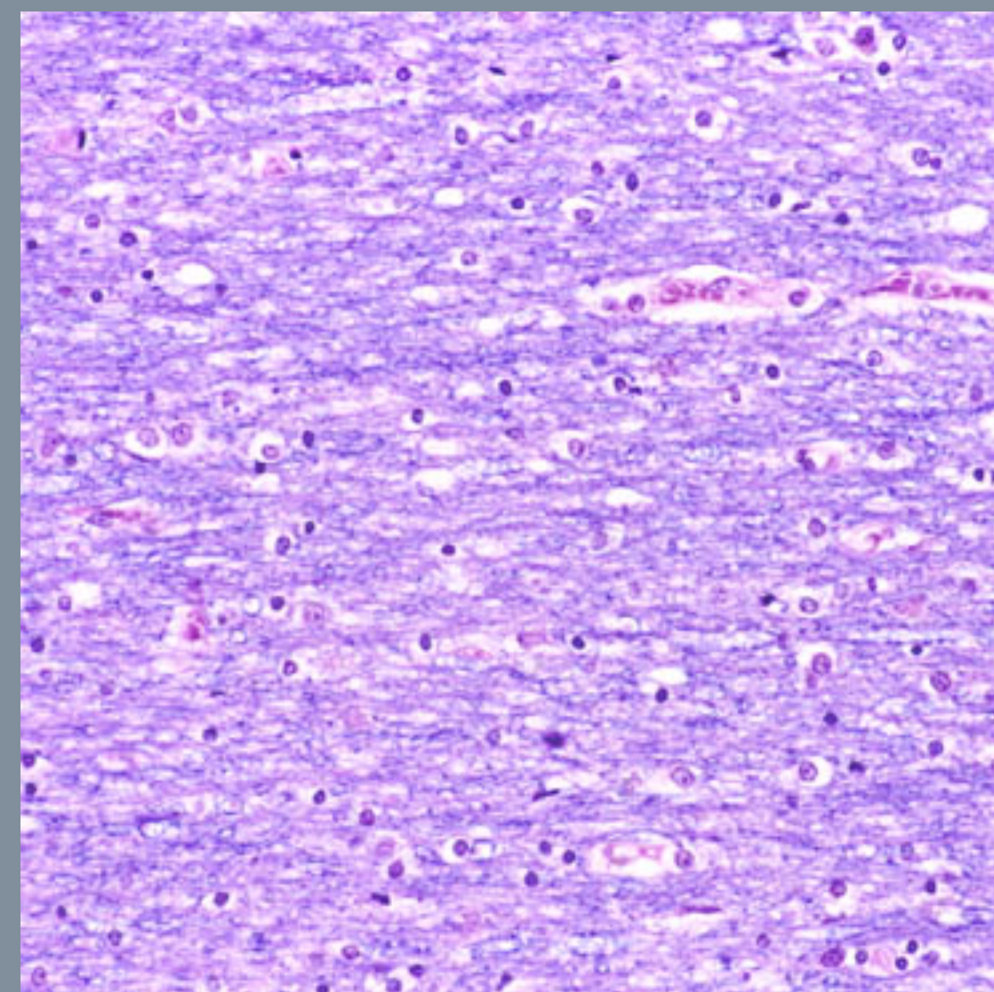


Histology

Gray matter



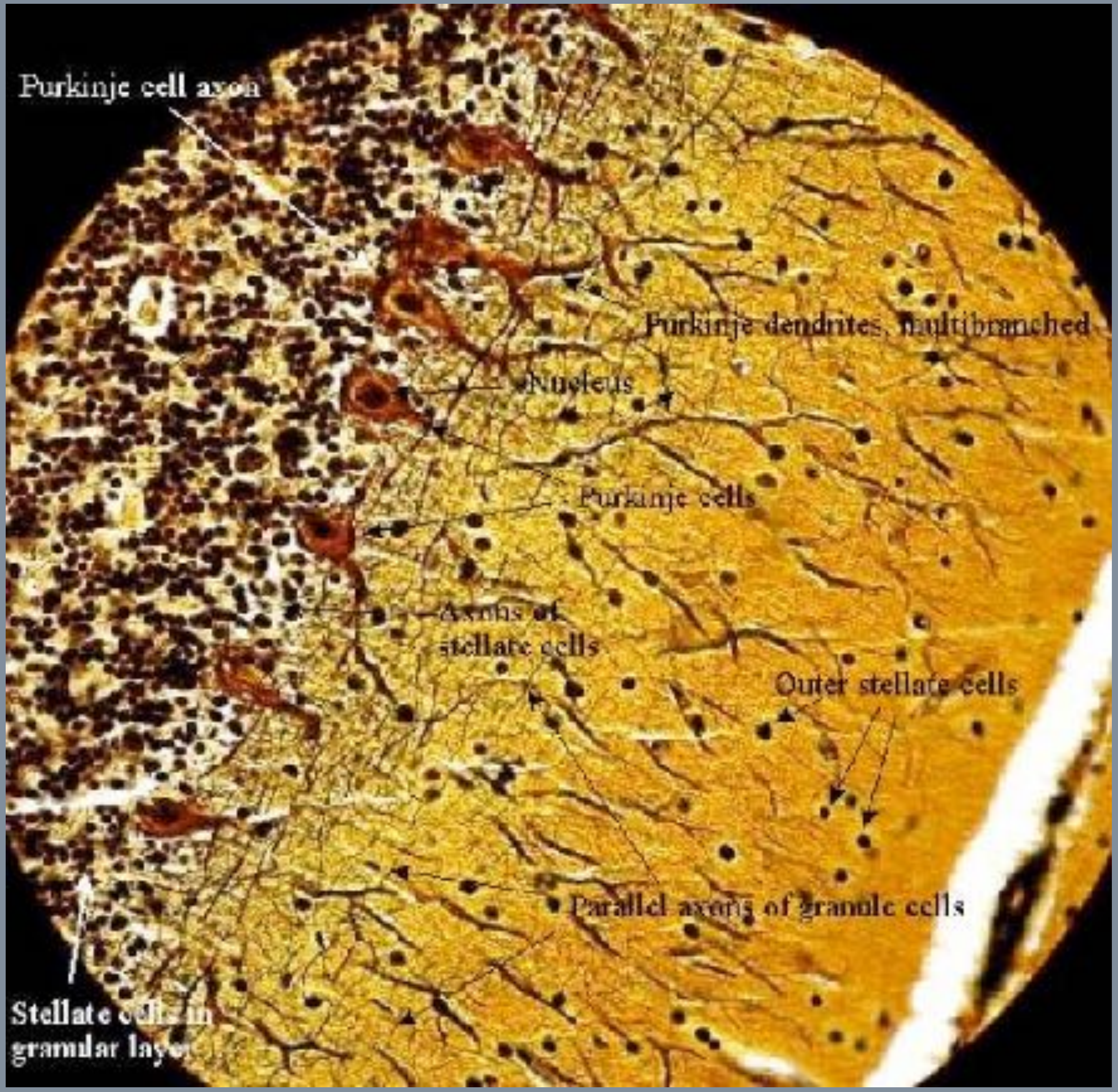
White Matter



a: granular layer
b:Purkinje cell layer
c: granular layer

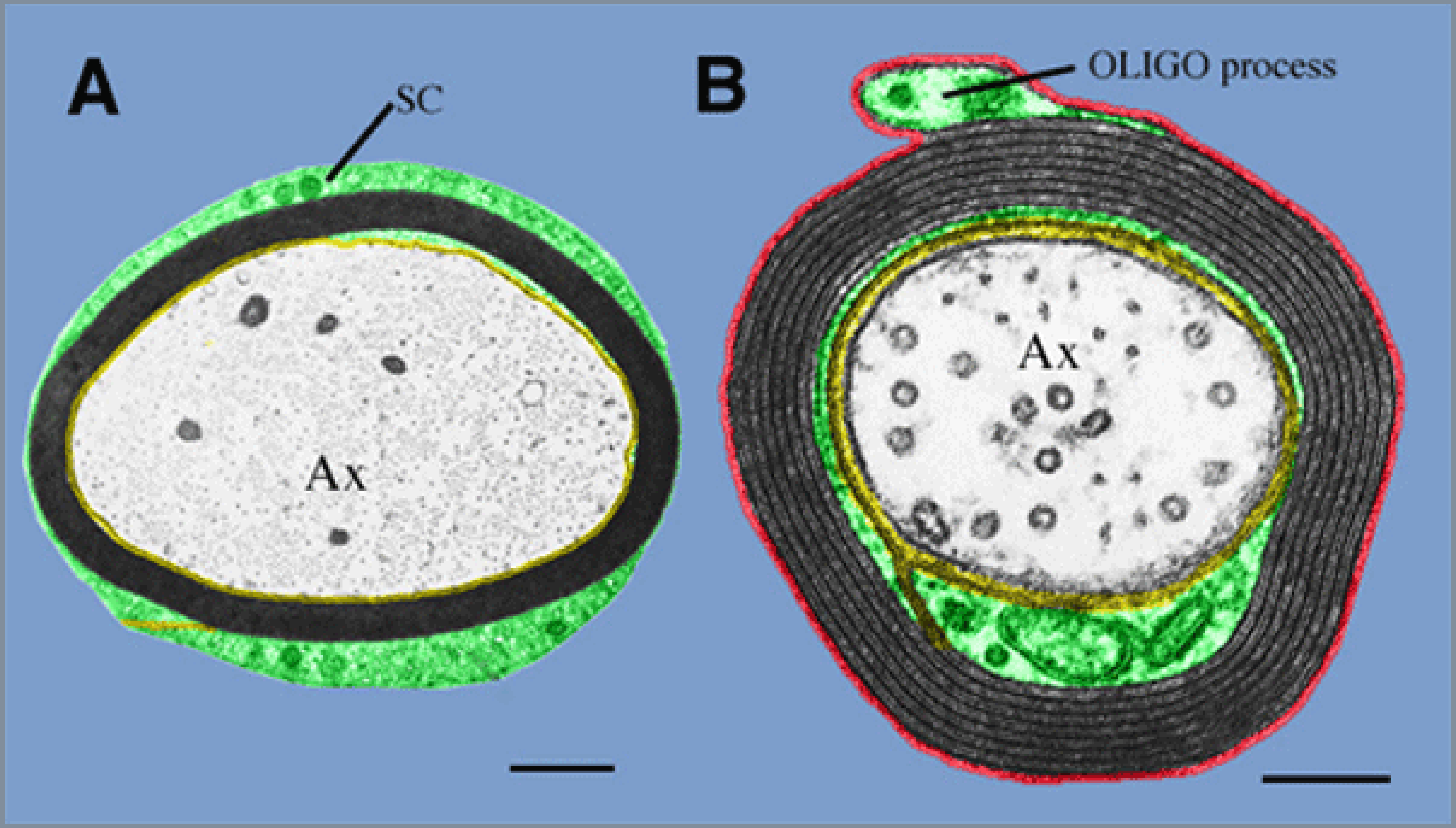
Histology of the Cerebellum

100x



400x

Myelinated Neural Fibers



Peripheral nervous system

Central nervous system

What is a realistic model for Diffusion?

DiffSim
DWI Simulation Environment

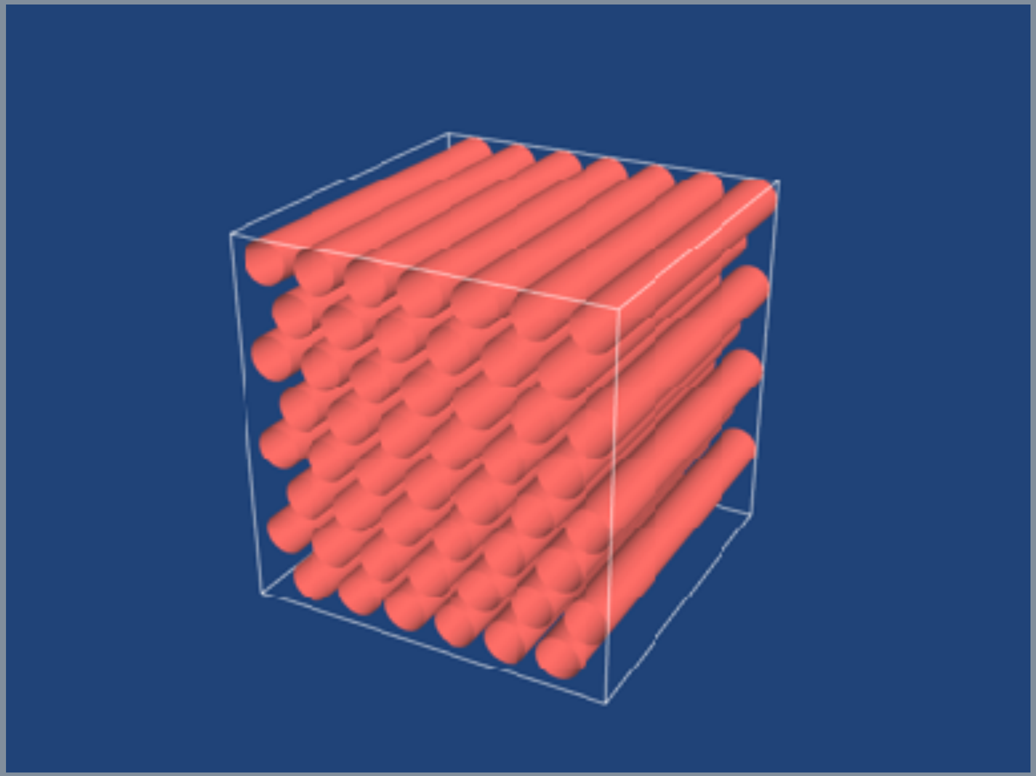
Spins diffusing in a Monte Carlo random walk within a user-defined geometry.

MCell (Bartol & Sejnowski)

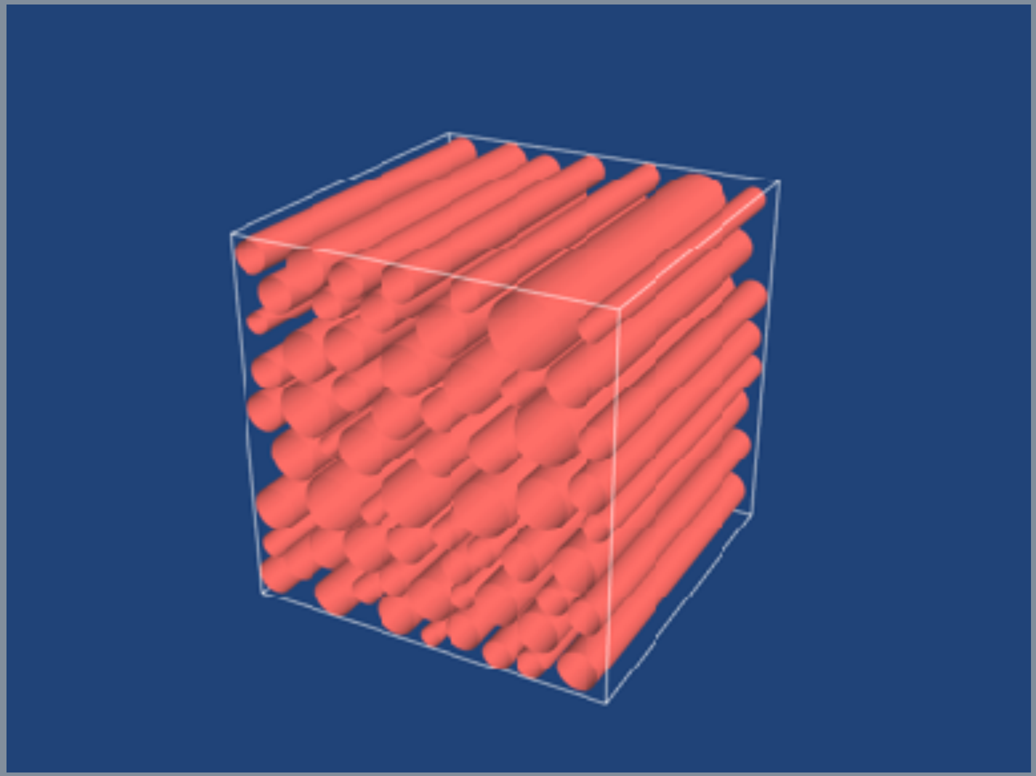
and are theoretically intractable.

DiffSim
Cylinders in a voxel

A 200 μm^3 voxel

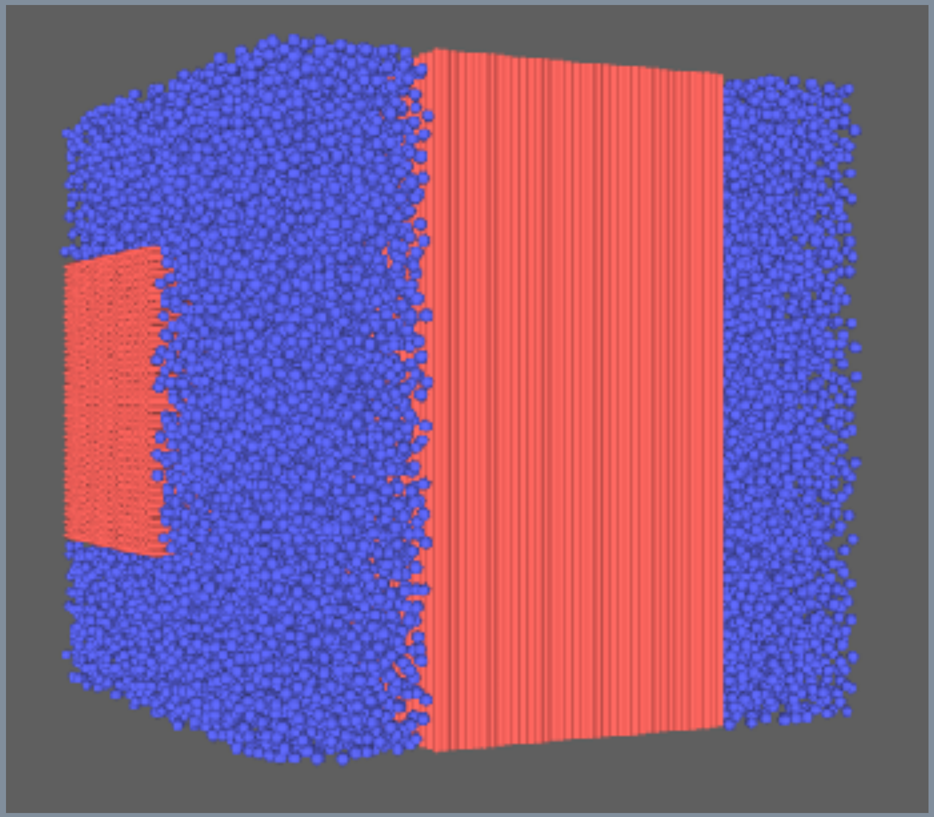


hexagonally packed fibers with a radius of 12 μm. Volume fraction filled is 0.54.



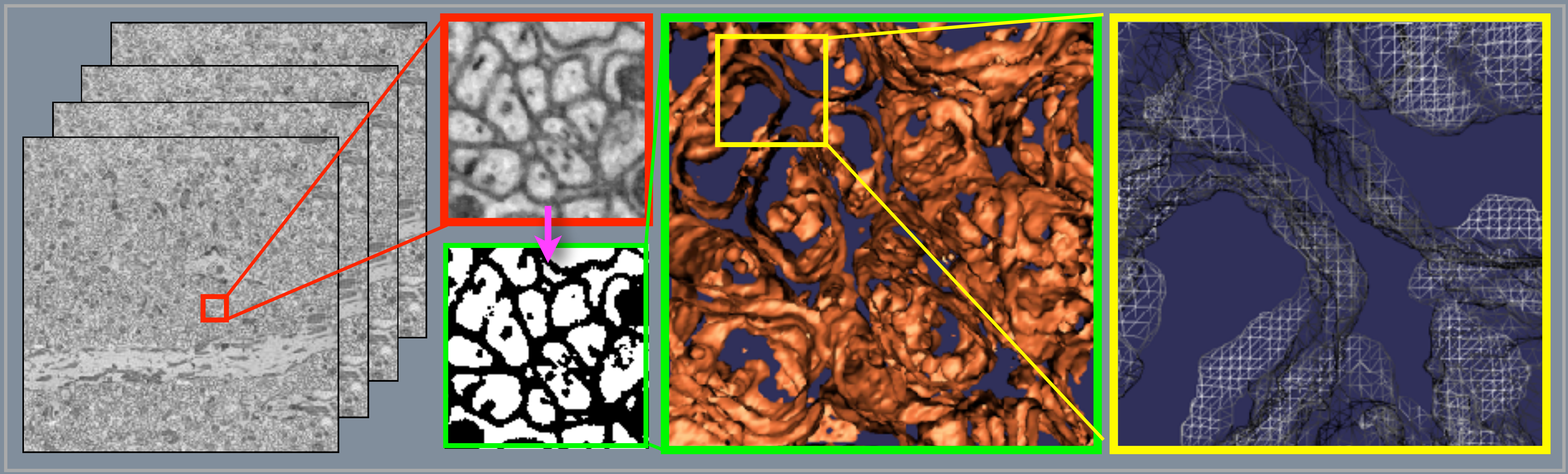
randomly packed fibers with a mean radius of 12 μm and a standard deviation of 2 μm. Volume fraction filled is 0.57.

DiffSim
Fibers and Cells



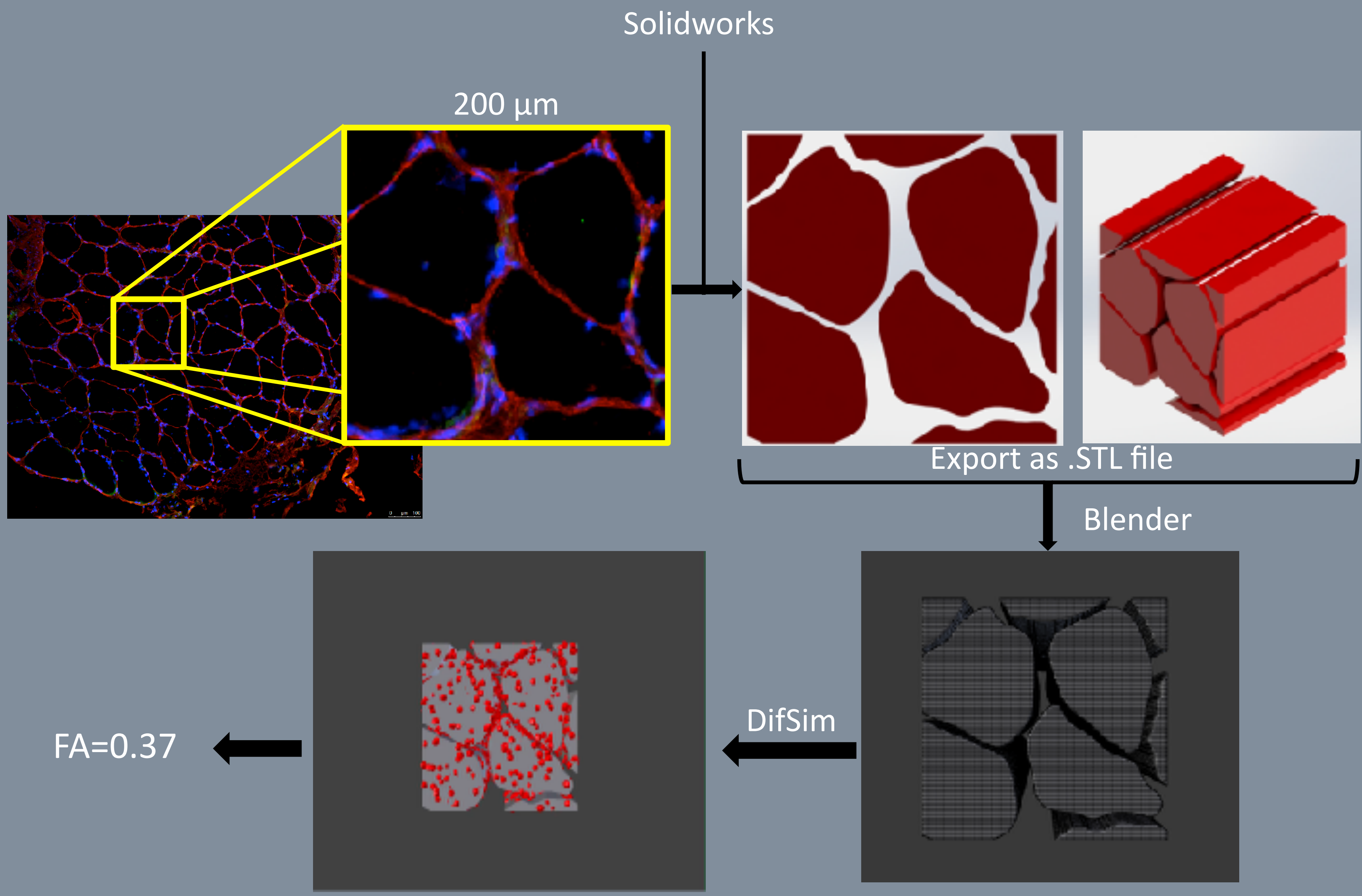
Two fiber bundles with randomly oriented ellipsoidal cells with an average diameter of 2.0 μm.

DiffSim for Realistic Tissues



Building computational models for diffusion in realistic tissues

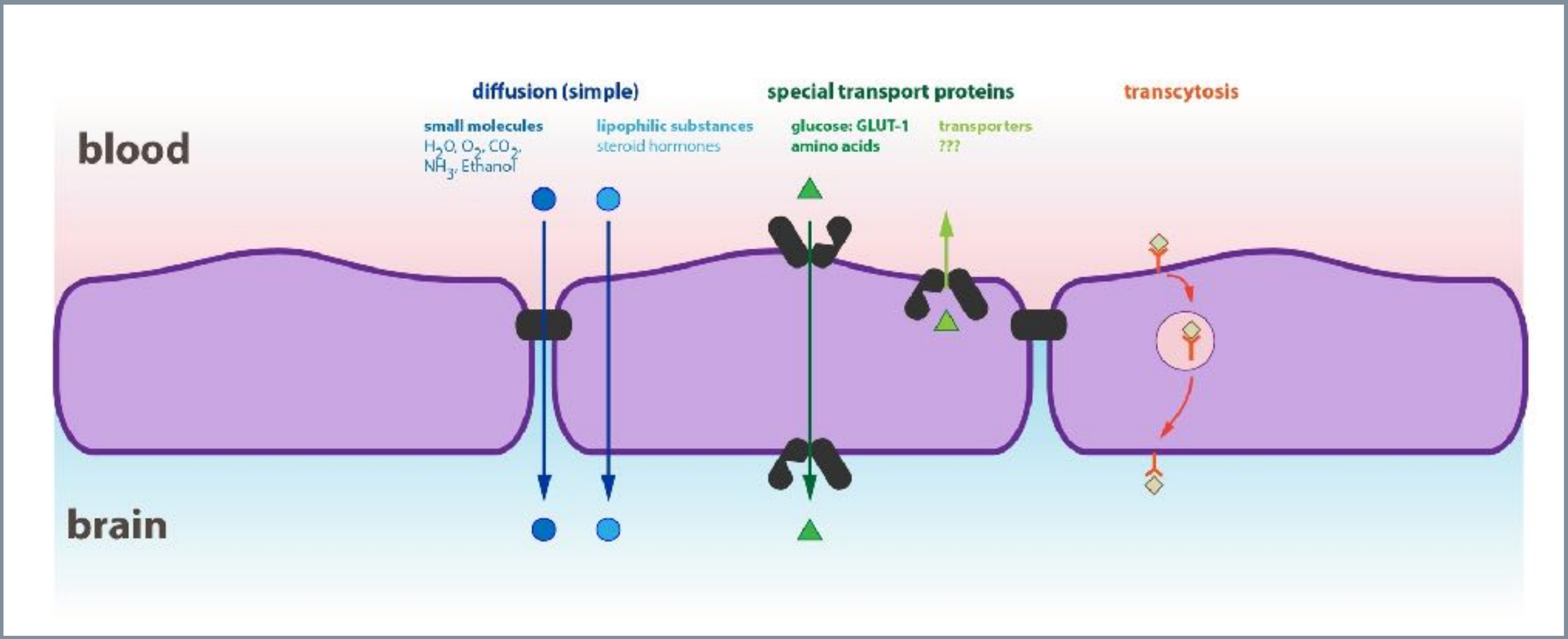
DiffSim for Realistic Tissues



Computational model for diffusion in muscle

David Berry, Ward Lab, UCSD
Ben Regner, CNL & CSCI, UCSD

Different ways water moves



Active transport of water