Biophysics and Physiological Modeling

IPLS – the physics that life-science students want and need

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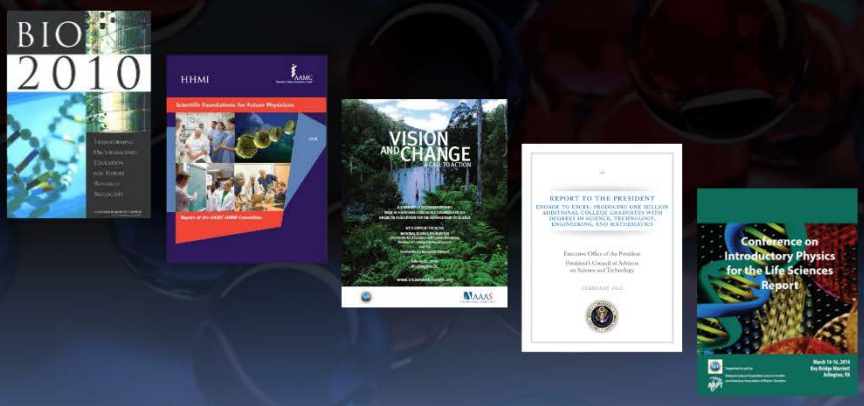
circle4.com/biophysics
AAPT Virtual Winter Meeting, January 9-12, 2021

Background and motivation

There is a growing movement within STEM to transform the undergraduate curriculum for life science majors…



AAPT IPLS recommendations

- Include stochastic processes
  - Diffusion
  - Osmosis
  - Radioactive decay (drug elimination)
  - Make thermodynamics relevant to life-science students
- Reduce or eliminate topics…
  - 2D and 3D Kinematics
  - Complex rotations and dynamics
  - Heat engines
  - …

Things that life-science students care about

- Physiology and Biophysics
  - Diffusion
  - O_2 uptake and distribution
  - Osmosis and volume regulation
  - Temperature regulation
  - Drug elimination
  - Radioactive decay – PET scans
- Biochemistry and Molecular Biology
  - Ligand binding etc.
- Neuroscience & electrophysiology
  - Membrane potentials etc.
  - The action potential
- Biomechanics (not the focus of this talk)
  - Newton's laws, levers, pulleys, torque etc. – see BPM Chapter 13
- COVID-19 and epidemiology (see poster)

Things that life-science students need

- Excel skills – the marble game
- Algorithmic thinking – kinetic Monte Carlo simulation
- Modeling change – finite difference methods (any differential model)
- Model validation – curve fitting and data analysis
- Thermodynamics for life sciences (and biochemistry)
  - using chemical potential (P_{O_2}) for O_2 concentration in blood and air
  - osmosis and osmotic pressure – the chemical potential of water
  - entropy and multiplicity – distribution of states
  - Boltzmann factor and the Boltzmann distribution
  - phase changes – evaporative cooling
  - ligand binding – biochemistry
- Random walks and molecular diffusion
- Membrane voltage and equivalent circuits
  - ion channels and membrane voltage – the Nernst potential
  - cell membrane as a capacitor
  - Ion channels – current, conductance and resistance
  - equivalent circuit models of ion channels – batteries and RC circuits
  - the action potential

Pedagogical approach

- Guided-inquiry self-study guides – ideal for online
  - flipped classroom – interactive HW in class time
- Active learning
  - student activities using preformatted spreadsheets
- Emphasis on skills
  - reading and interpreting graphs
    - semi-log graphs
  - fitting models to real data
    - linear regression and non-linear least-squares
    - residual analysis
  - FD models of rate of change
    - simple and realistic systems
- Thermodynamics from kinetics

Figures from
Biophysics and Physiological Modeling
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Ch.1 Introduction – marble game

Figure 1.3 Photo of the marble game. It has ten marbles that can jump between two boxes. A ten-sided die is used to pick which marble jumps next.

Note: Chapters 1, 2, 3, 5 and 12 are available for free at http://circle4.com/biophysics/chapters/. There are also instructional videos and instructor guides. Visit http://circle4.com/biophysics/

- GlowScript Brownian motion simulation of the Marble Game

Instructions for using Excel start with the basics

	A	B
1	Turn	
2		
3		

Figure 1.6 Screenshot from Excel 2016.

	A	B	C
1	Turn	*r*	N_1
2	0		3
3	=A2+1		
4			
5			

	A	B	C
1	Turn	*r*	N_1
2	0		3
3	1		
4			
5			

Figure 1.7 Screenshots from Excel 2016, before and after hitting ENTER (see text).

Ch.2 Algorithms and pain relief

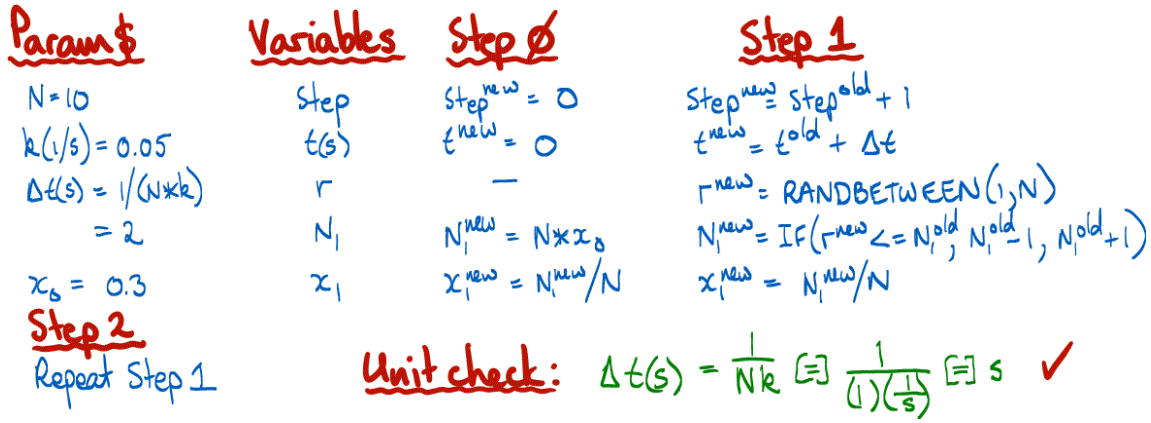


Figure 2.2 Algorithm for the marble game kMC sim shown in Figure 2.1.

Ch.3 Finite difference method and O_2

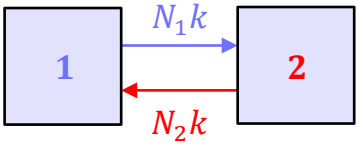


Figure 3.2 Finite difference (FD) diagram of the two-box marble game.

$$\delta N_1 = -N_1 k \delta t + N_2 k \delta t \tag{3.1}$$

which rearranges to

$$\delta N_1 = (N_2 - N_1) k \delta t \tag{3.2}$$

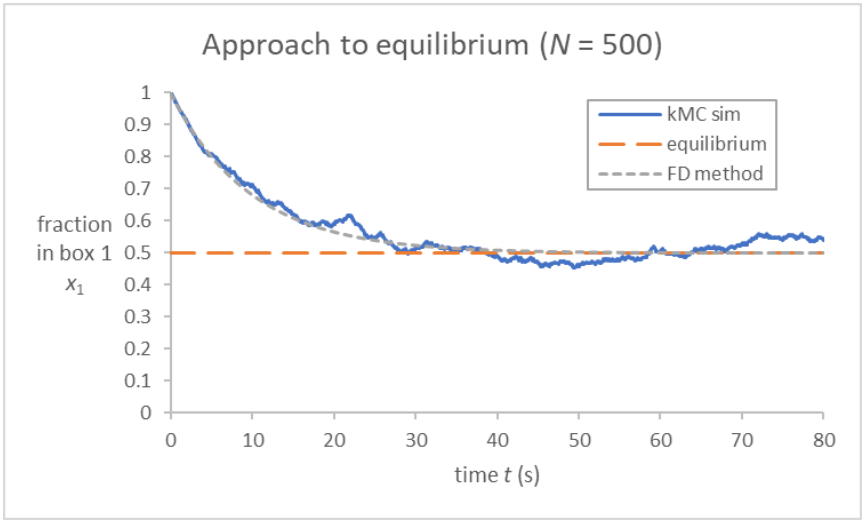


Fig.A3.1 Excel 2016 chart of the two-box marble game. Comparing kMC simulation with the FD method for a system with $N = 500$, $k = 0.05\ s^{-1}$ and $x_0 = 1$. **Note:** The mean residence time is $\tau = 1/k = 20$ s and the system is close to equilibrium at $t = 2\tau = 40$ s.

Ch.4 Model validation and penicillin

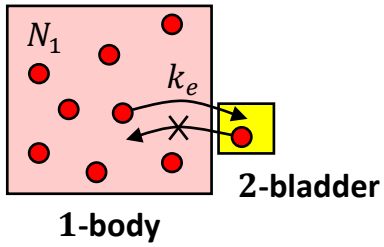


Fig.4.1 Marble game representation of the two-box model of drug elimination (same as Fig.2.8).

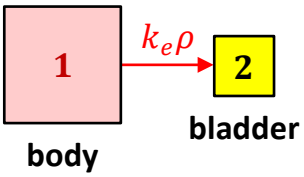


Fig.4.2 FD diagram of the two-box model of drug elimination.

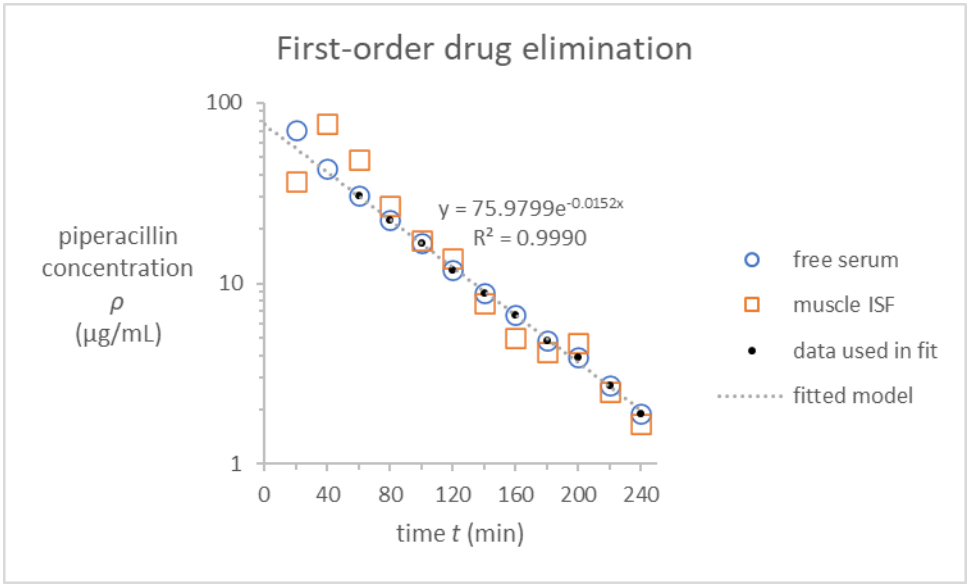


Fig.A4.3 (modified) Excel 2016 chart showing a fit to *only* the free serum data from $t = 60$ min to $t = 240$ min (small black dots).

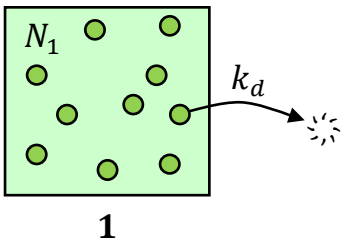


Fig.4.5 Marble game representation of radioactive decay.

Ch.13 Newtonian mechanics – Bugatti physics

Fig.13.1 Captain Slow drives the world's fastest production car!

Euler's method (FD equations) defines velocity and acceleration

$$\delta x = v\delta t \tag{13.1}$$

$$\delta v = a\delta t \tag{13.4}$$

The FD definition of **velocity** is

$$v \equiv \frac{\delta x}{\delta t} \tag{13.61}$$

The FD definition of **acceleration** is

$$a \equiv \frac{\delta v}{\delta t} \tag{13.32}$$

Midpoint algorithm – improves Euler's method

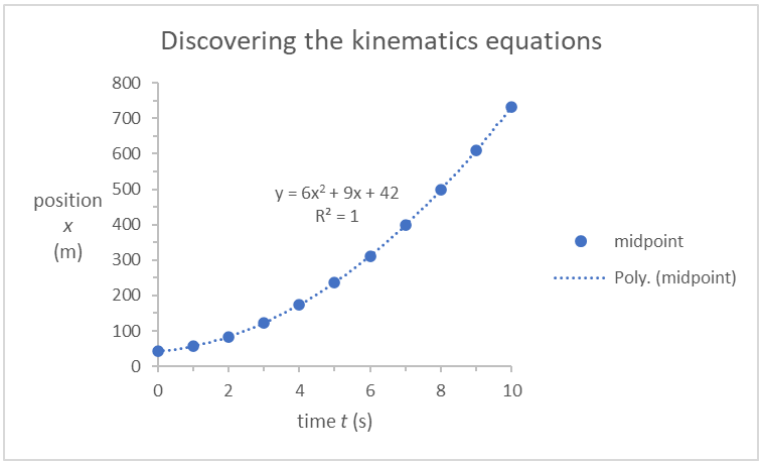


Fig.A13.2 Excel 2016 chart of Captain Slow's progress shown as a position-time graph. In the fitted equation, **y** represents position x, **6** is $a/2$, **x²** is t^2, **9** is the initial velocity v_0, **x** is time t, and **42** is the initial position x_0.

Newton II

$$a = \frac{F^{\text{net}}}{m} \tag{13.25}$$

Work-energy theorem and kinetic energy *K*

$$F^{\text{net}}\delta x = mv\delta v \tag{13.34}$$

or

$$\delta W^{\text{net}} = \delta K \tag{13.36}$$

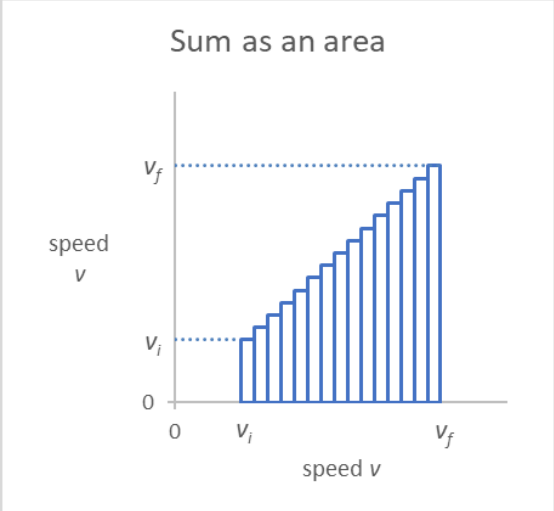


Fig.13.6 Plot of speed v vs speed v. The area under each step is area = height × width = $v\delta v$. According to equation (13.41), the sum of the areas under the steps is $\Delta K/m$. As the number of steps becomes large this shape approaches a right trapezoid.

The area under a graph (Fig.13.6) can be calculated using a sum or an integral

$$\lim_{\delta v \to 0} \sum_{v=v_i}^{v=v_f} v\delta v = \int_{v=v_i}^{v=v_f} v\mathrm{d}v = \frac{1}{2}\left(v_f^2 - v_i^2\right) \tag{13.59}$$

$$\Delta K = \sum_{v=v_i}^{v=v_f} mv\delta v = \frac{1}{2}mv_f^2 - \frac{1}{2}mv_i^2 \tag{13.40}$$
$$\tag{13.62}$$

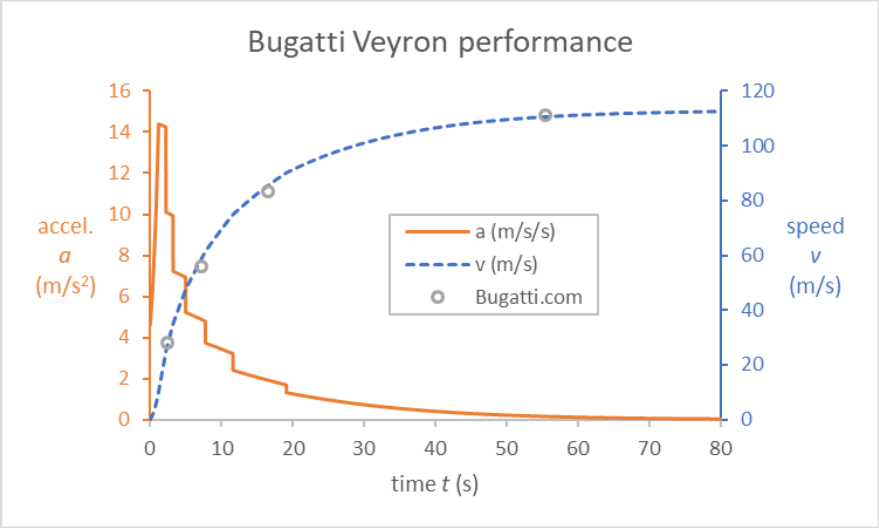


Fig.13.8 Excel 2016 chart comparing the FD model with reported Bugatti Veyron performance. The FD model includes a seven-speed transmission and air resistance. The only fitted parameter in the model is the *b*-parameter in equation (13.58). The solid line is the predicted acceleration. The dashed line is the predicted speed. The open circles are data from the Bugatti.com website (2014) namely 2.5, 7.3, 16.7 and 55.6 seconds to reach 100, 200, 300 and 400 km/h, respectively.

Ch.5 A new model of osmosis

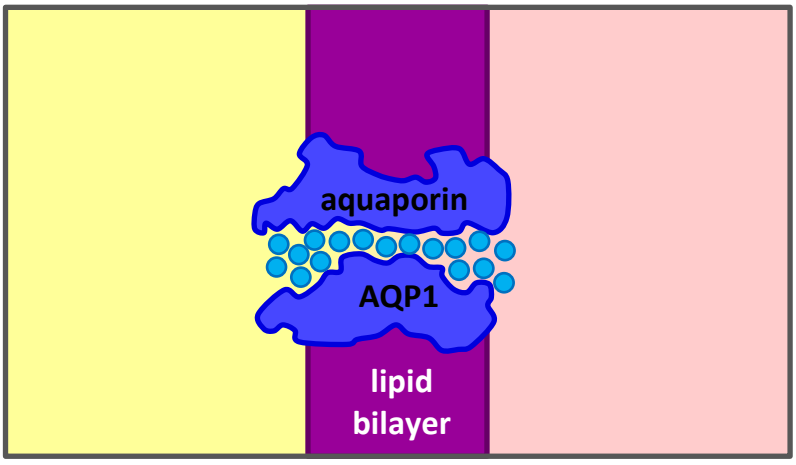


Fig.5.2 Schematic diagram of an AQP1 aquaporin protein (water channel) imbedded in a lipid bilayer membrane separating two solutions with differing effective water concentrations (after Murata *et al.* [2000]). The aquaporin provides a single-file pathway (shown in cross-section) for water molecules (circles) that makes the membrane semipermeable because only water molecules can pass through.

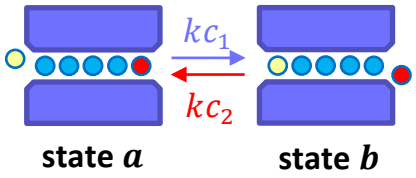


Fig.5.3 Schematic diagram of an AQP1 aquaporin selectivity filter showing the knock-on jump

summary of single-file water permeation. The diagram shows two states (a and b) of the *same* AQP1 aquaporin. For the jump from state $a \rightarrow b$, the water molecule entering from box 1 is highlighted in yellow (lighter) and the water molecule knocked-on into box 2 is highlighted in red (darker). In the reverse $b \rightarrow a$ jump, the red water molecule enters from box 2 and the yellow water molecule is knocked-on into box 1.

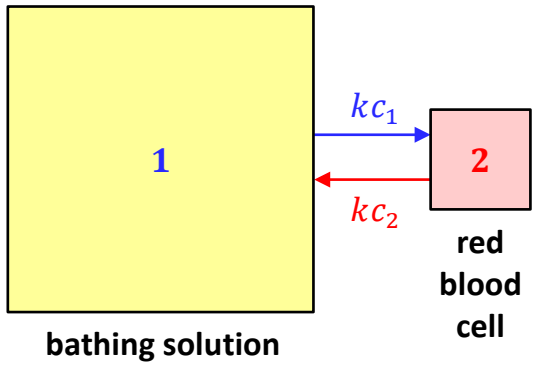


Fig.5.4 FD diagram of a red blood cell (box 2) floating in a large bathing solution (box 1). The water in the red blood cell has an effective concentration c_2 and the bathing solution has a constant effective water concentration c_1.

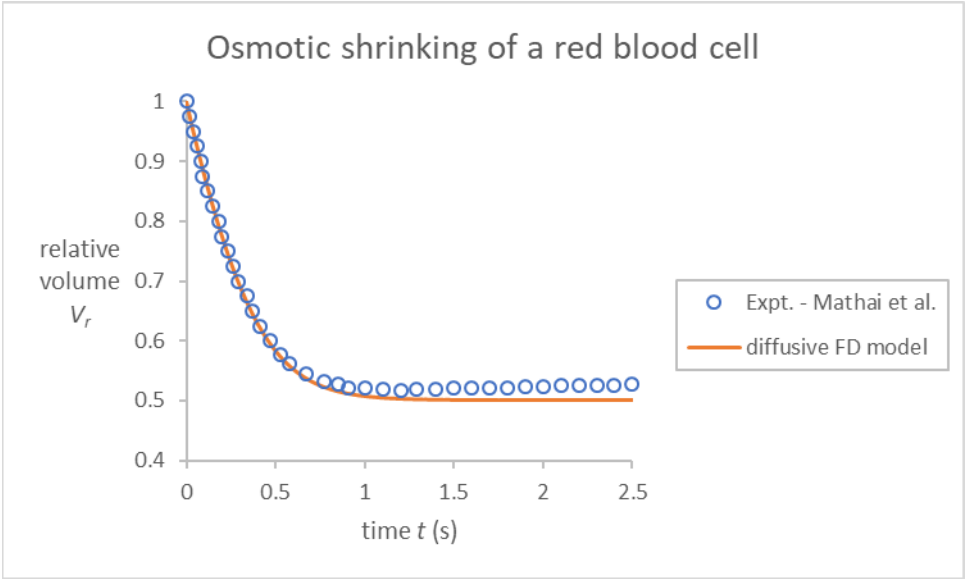


Fig.5.7 Excel 2016 chart showing the control (+/+) data from Fig. 5*A*. of Mathai *et al.* [1996] for the osmotic shrinking of a red blood cell, together with the diffusive model of osmosis calculated using FD equation (5.14). The experimental data were obtained by digitizing Fig. 5*A* and are reproduced here with permission from Mathai *et al.* [1996]).

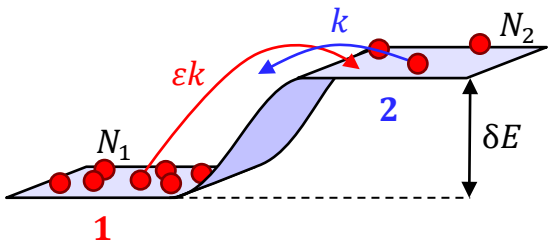


Fig.5.17 Schematic representation of the gravity marble game. The jump rate constant in the uphill direction is εk and k is the jump rate constant in the downhill direction. The gravitational potential energy difference is $\delta E = mg\delta y$, where the marbles each have mass m and the two boxes are separated by height δy in a gravitational field of magnitude g (based on Fig.5.8).

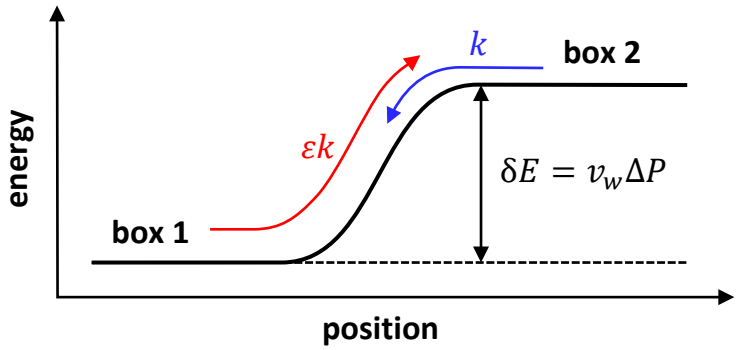


Fig.5.14 Simplified schematic energy diagram of osmosis with a (hydrostatic) pressure difference ΔP. The diagram shows a situation where box 2 has a higher pressure P_2 than box 1 with the difference given by $\Delta P = P_2 - P_1$. The water molecules each have volume v_w and the pressure difference ΔP raises the marble's potential energy by $\delta E = v_w \Delta P$ when it moves from box 1 → 2. The uphill jump rate is reduced by a factor $\varepsilon = 1 - \delta\psi$, where the small dimensionless energy step is $\delta\psi = \delta E/(k_B T)$.

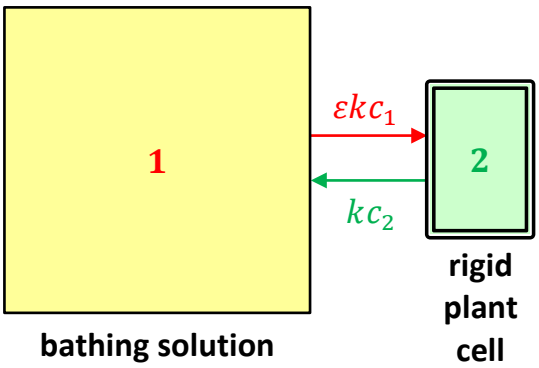


Fig.5.15 FD diagram of a rigid plant cell (box 2) in contact with a large bathing solution (box 1) within the **Helmholtz ensemble** (constant T, V). The water in the rigid plant cell has an effective water concentration c_2 and the bathing solution has a constant effective water concentration c_1. There is also a hydrostatic pressure difference $\Delta P = P_2 - P_1$ between the boxes that is maintained by the rigid cell wall of the plant cell. ΔP determines the value of the energy factor ε (5.44).

The new **diffusive model of osmosis** predicts the van't Hoff equation

$$\Delta\pi = \Delta sRT = -\Delta cRT \tag{5.68}$$

where $\Delta c = c_2 - c_1$ is the effective water concentration difference and $\Delta s = s_2 - s_1 = -\Delta c$ is the osmolarity difference.

Ch.6 Ligand binding and least-squares fits

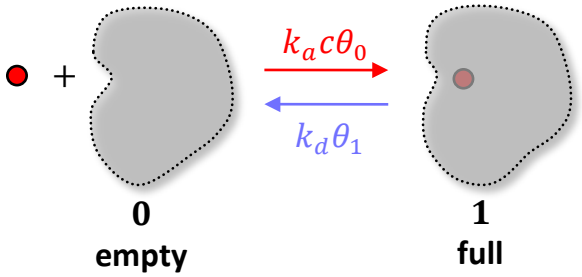
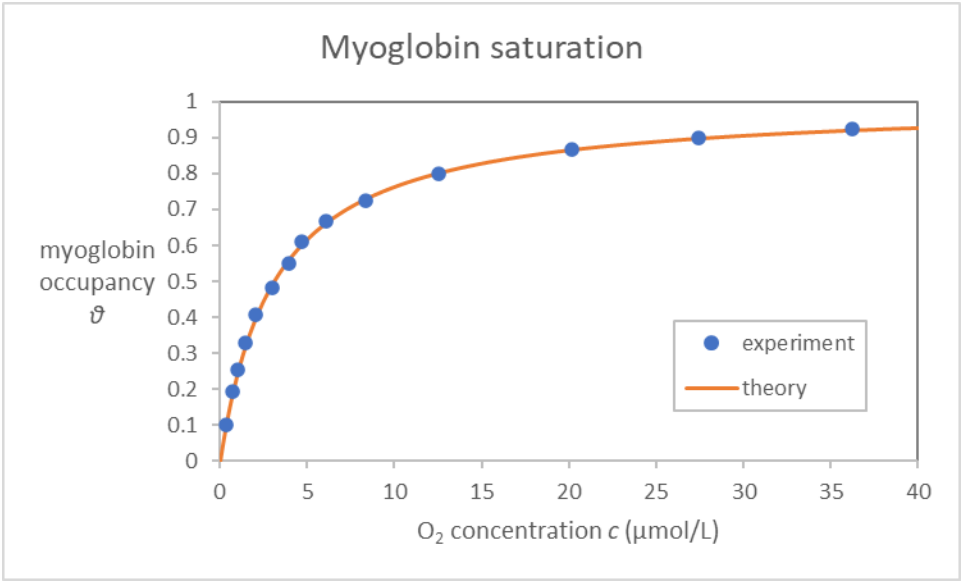


Fig.6.1 Schematic FD diagram of the single-occupancy binding model for an O_2 molecule (red circle) binding to a myoglobin molecule.

Least-squares fits

$$Q = \sum_i r_i^2 \tag{6.11}$$



Q.6.25 Excel 2016 chart comparing the experimental data at 37 °C with the model prediction of equation (6.4) using the dissociation constant obtained by least-squares fit. Experimental data from Schenkman et al. (1997) *J. Appl. Physiol.* **82**:86-92.

Ch.7 Diffusion – spread it around

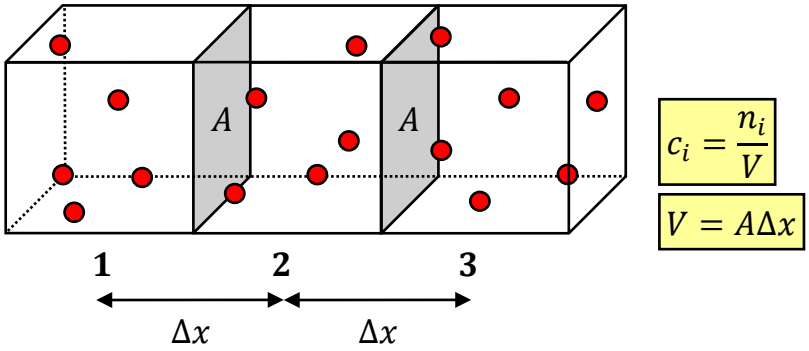


Fig.7.16 Three-dimensional schematic representation of three adjacent boxes in a diffusion analysis. Each box has the same width Δx and volume V. They are connected by area A.

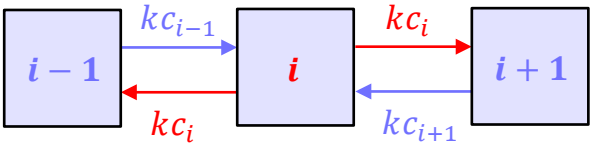


Fig.7.8 FD diagram of three boxes in the middle of a diffusion problem.

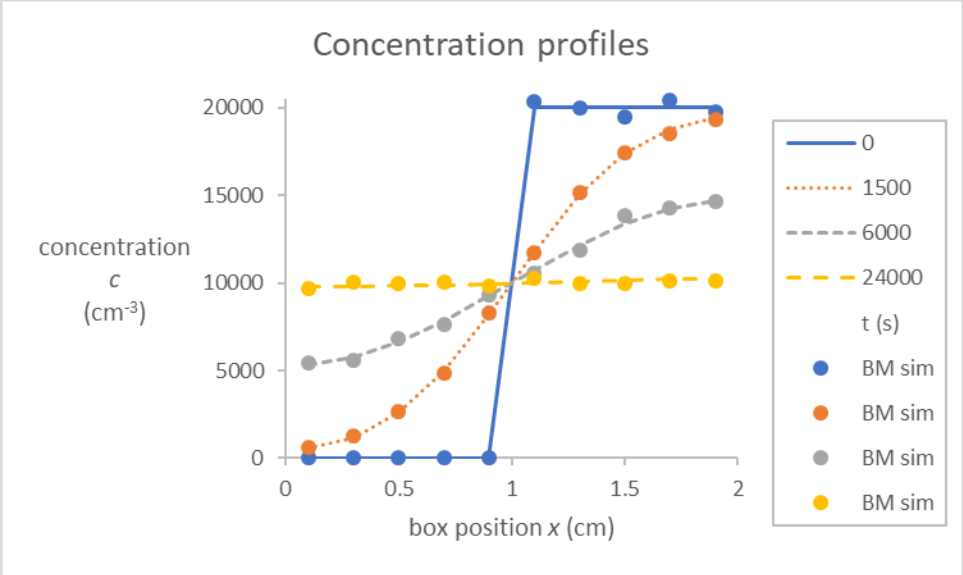


Fig.7.14 Excel 2016 chart of concentration profiles measured during a 20000-marble Brownian motion simulation of diffusion. Symbols (circles) are data from the BM sim and lines represent the corresponding FD model of diffusion. All that's needed to make the comparison is the diffusivity D, but how can we estimate it?

- GlowScript Brownian motion simulation of the Marble Game

Ch.8 Equilibrium distributions & entropy

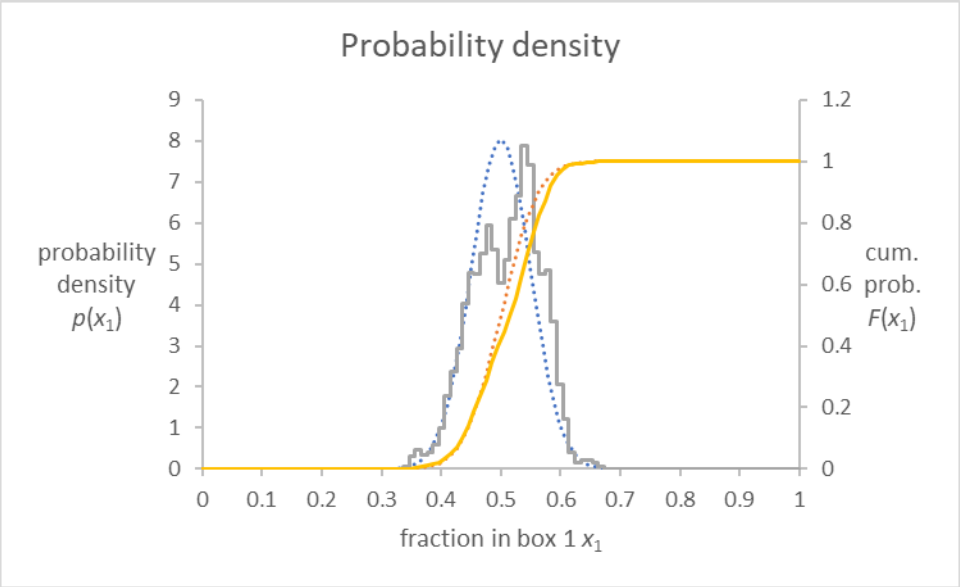


Fig.8.11 Excel 2016 chart of the observed (sim) and expected (binomial) values of the probability density $p(x_1)$ and cumulative probability $F(x_1)$ for a marble game with $N = 100$ marbles and $N_{steps} = 2000$.

Ch.9 Energy and the Boltzmann factor

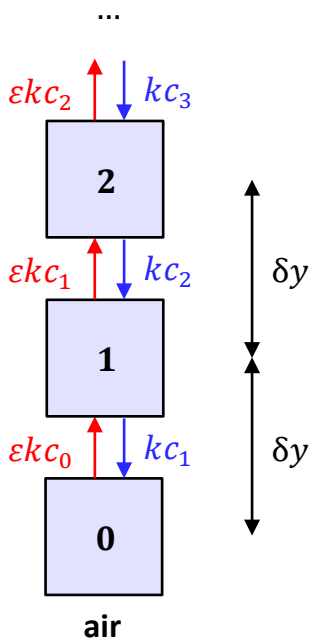


Fig.9.2 FD diagram of the isothermal atmosphere.

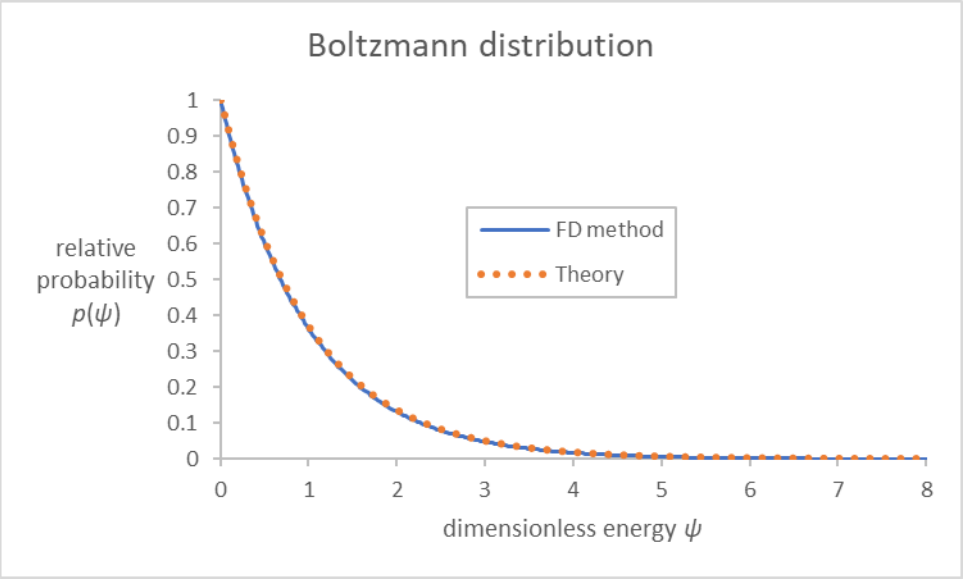


Fig.9.3 Excel 2016 chart showing the relative probability of finding a molecule at a particular dimensionless energy as a function of the dimensionless energy. The line shows the prediction of the FD model for the isothermal atmosphere and the dotted line shows the prediction of equation (9.18). As we'll discover, this graph represents one of the most important ideas in molecular science – the **Boltzmann distribution**.

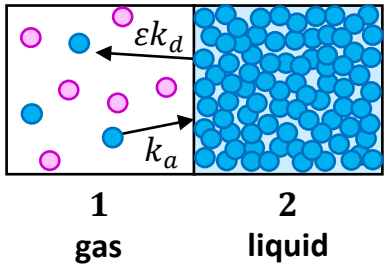


Fig.9.6 Marble game representation of the two-box model of liquid water in contact with the atmosphere (a gas mixture). The small blue (darker) circles represent water molecules that can dissociate (evaporate) from the surface. Water molecules in the gas can associate with (condense on) the liquid surface of the liquid. The pink (lighter) circles in box 1 represent gas molecules such as nitrogen and oxygen that we're assuming are insoluble in the liquid water. The two-box system is held at constant total pressure P, which means that the volume of the boxes can change.

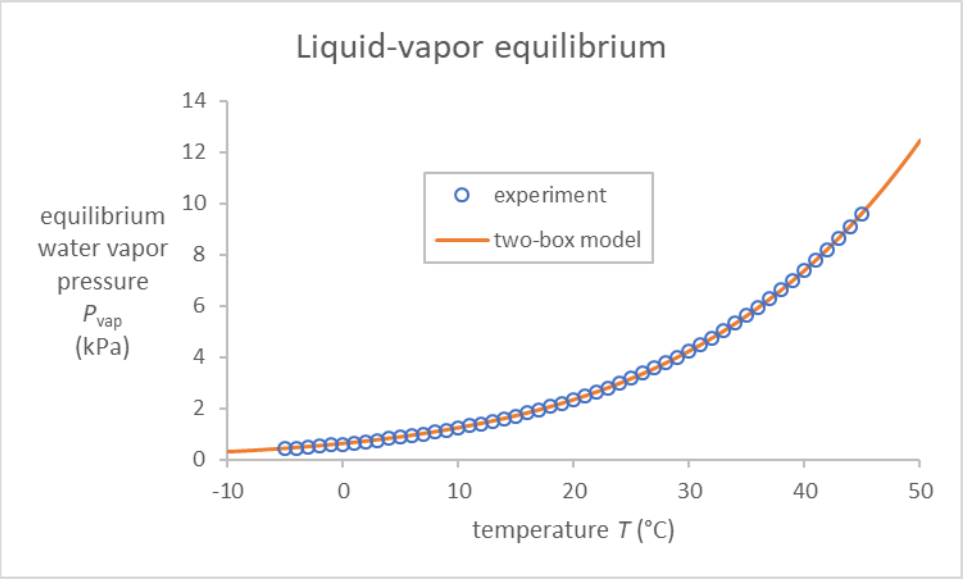


Fig.9.9 Excel 2016 chart showing the fit between experimental data from Monteith and Unsworth (2008) and the two-box model prediction of equation (9.36).

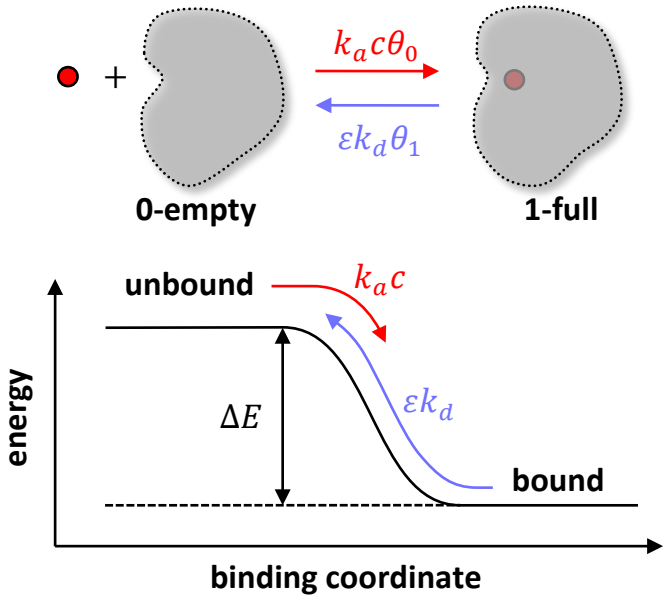


Fig.9.10 Schematic FD diagram of an O_2 molecule binding to myoglobin (upper) and energy diagram as a function of binding coordinate (lower). The energy difference $\Delta E \approx E_b$ is the binding energy, the energy required to remove a O_2 molecule from the Mb molecule's grasp.

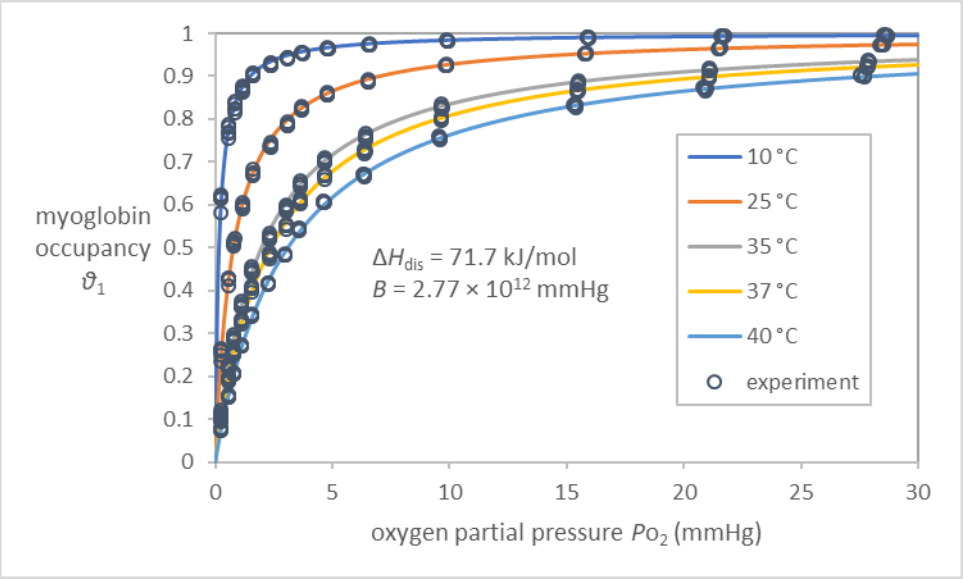


Fig.9.11 Excel 2016 chart comparing equation (9.60) of our model with experimental Mb-O_2 saturation data. Theoretical curves (solid lines) were fitted to equation (9.60) using nonlinear least-squares analysis (in Excel) resulting in $\Delta H_{dis} = 71.7$ kJ/mol and $B = 2.77 \times 10^{12}$ mmHg. Experimental data (symbols) reproduced (with permission) from Schenkman *et al.* [1997].

Ch.10 Random walks cause diffusion

Single random walker

i walk a lonely road
the only one that i have ever known
don't know where it goes…

…sometimes i wish someone out
there will find me
'til then i walk alone…

…i walk alone, i walk alone…♪

♪Green Day, 2004, *Boulevard of Broken Dreams*

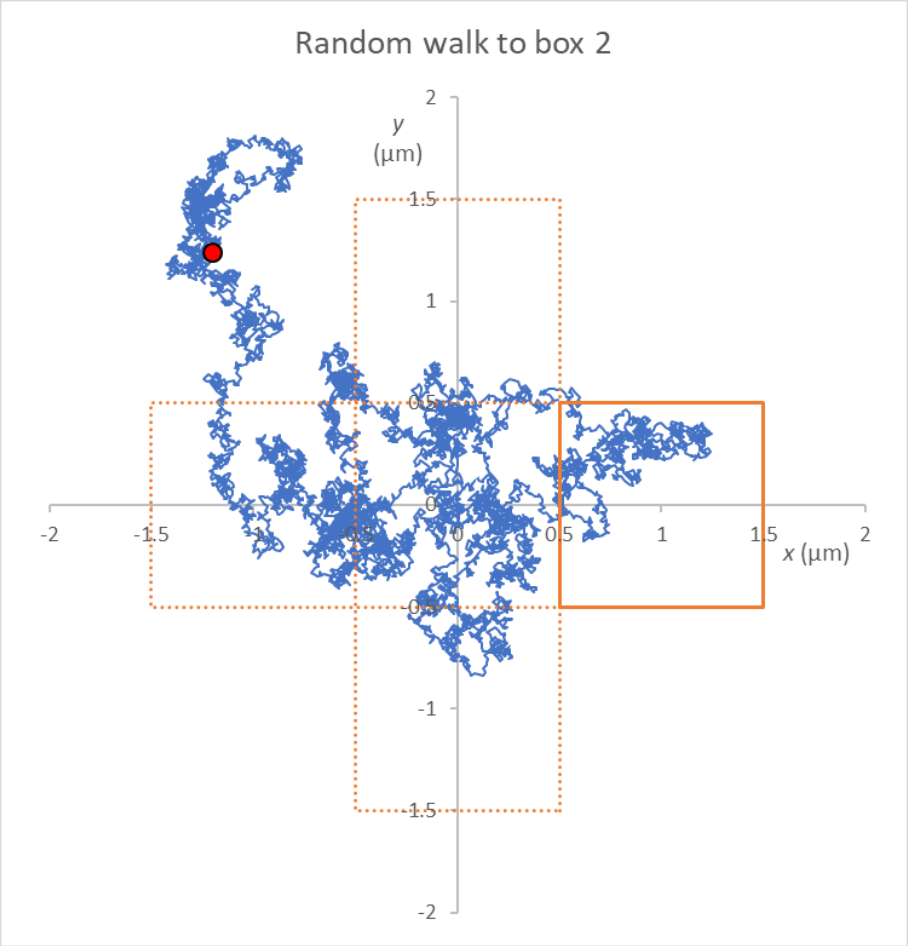


Fig.10.3 Excel 2016 (x, y) snail-trail chart of a 9600-step random walk that entered box 2.

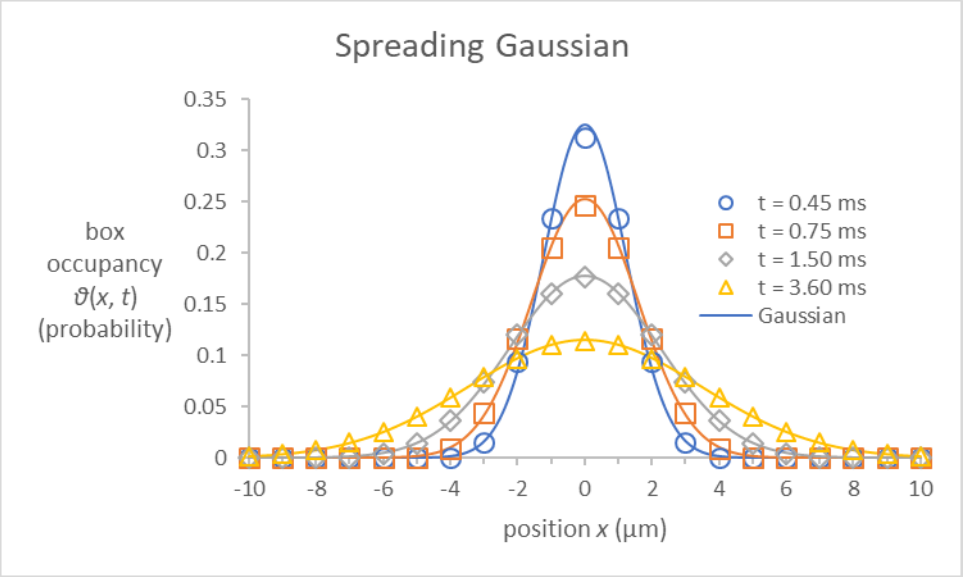


Fig.10.13 Excel 2016 chart of a spreading Gaussian for the probability of finding a random walker ($D = 5/3\ \mu m^2 \cdot ms^{-1}$) in 1 μm^3 boxes at the times indicated. Lines – calculus prediction from equation (10.37). Symbols – prediction- from the FD formulation with $\Delta x = 1\ \mu m$ and $\delta t = 0.15$ ms ($\varphi = 0.25$). The Gaussian has the same shape as a normal distribution.

Ch.11 Membrane voltage and equivalent circuits

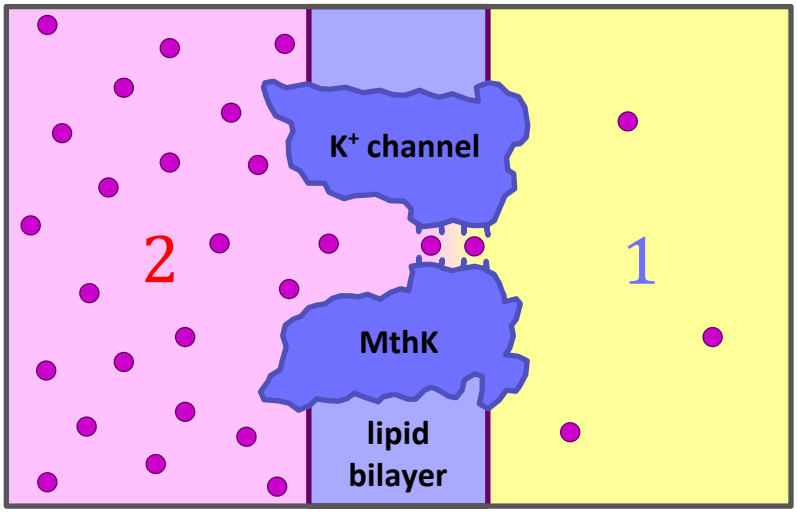


Fig.11.01 Schematic diagram of an open MthK potassium channel protein imbedded in a lipid bilayer membrane separating two solutions with differing K^+ ion concentrations (after Jiang *et al.* [2002]). The K^+ channel provides a single-file pathway (shown in cross-section) for potassium ions (circles) that makes the membrane semipermeable because only K^+ ions can pass through. **Note:** According to **the physiological convention**, box 2 (inside the cell) is on the left and box 1 (outside) is on the right.

Barrierless knock-on model

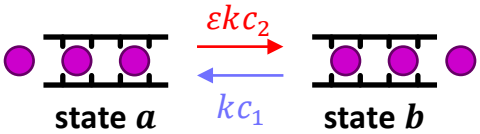


Fig.11.27 Hodgkin and Keynes knock-on mechanism. Permeation through the selectivity filter of an ion channel is modeled as a single *diffusive* jump. The energy factor in the outward direction from box 2 → 1 reflects the barrierless energy diagram Fig.11.06 (modified from Fig.11.02).

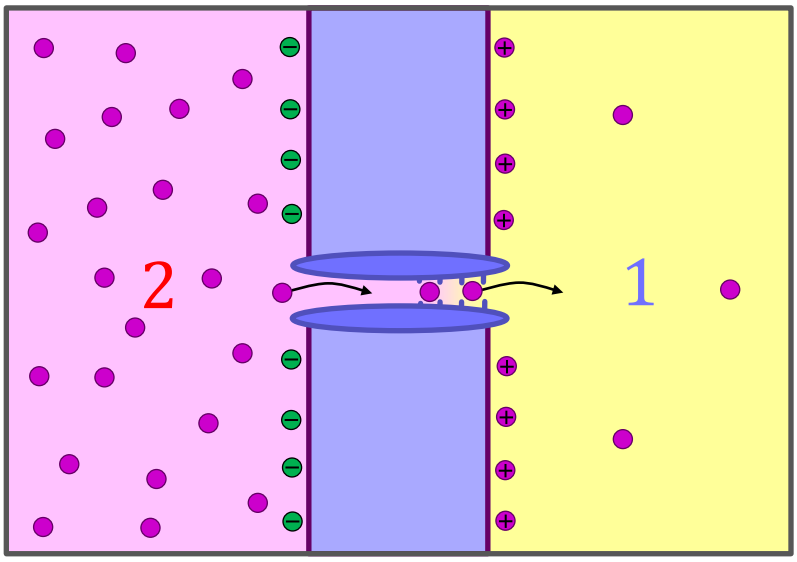


Fig.11.05 Schematic diagram of a cell membrane containing an open K^+ channel. K^+ ions have diffused from high to low concentration (box 2 → 1). The excess positive charges (shown as circles with a plus sign) have accumulated on the outside of the cell (box 1). They are attracted back towards their negative counter ions (shown as circles with a minus sign) that they left behind inside the cell. The charge separation produces a voltage difference ΔV because the attraction between the separated charges stores electric potential energy. I.e. the membrane acts like a **capacitor** (**SECTION 11.4**).

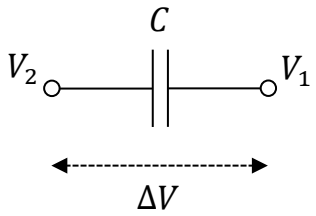


Fig.11.11 Equivalent circuit diagram of a cell membrane separating two solutions. The two open circles represent the inner (2) and outer (1) solutions that have a voltage difference $\Delta V = V_2 - V_1$. The **capacitor** (parallel lines symbol) has **capacitance** *C*.

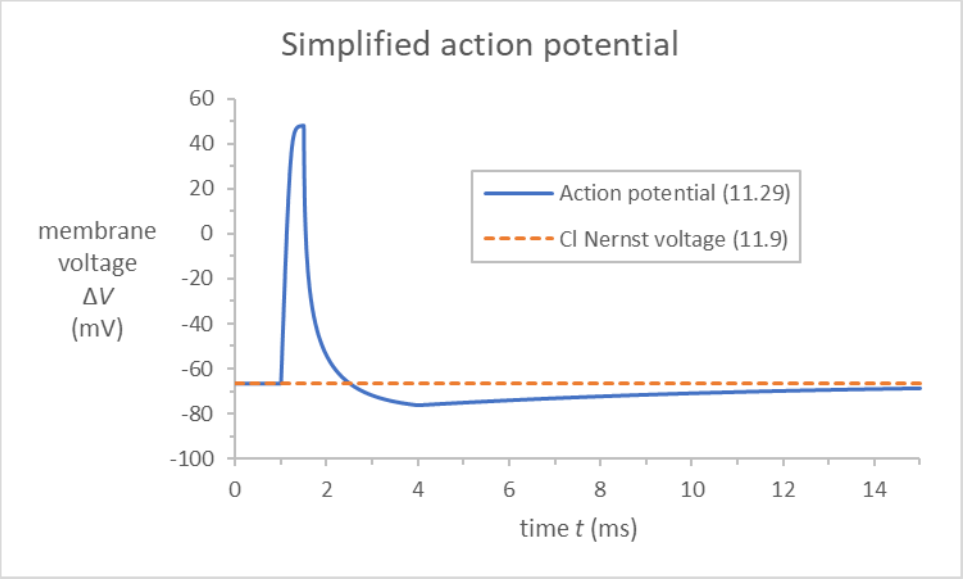


Fig.11.14 Excel 2016 chart showing a **simplified action potential** based on opening and closing Na^+ and K^+ channels "by hand" – see text. The graph begins with Cl^- channels open and the membrane voltage at about -70 mV, the Nernst voltage (11.9) for Cl^- ions, shown as a dashed line. The Cl^- channels always stay open throughout the graph. At time $t = 1$ ms, Na^+ channels open and the membrane voltage rapidly rises to about 50 mV. At time $t = 1.5$ ms, Na^+ channels close and K^+ channels open and the voltage drops down to about -80 mV. At time $t = 4$ ms, K^+ channels close leaving only the Cl^- channels open and the voltage slowly rises back to about -70 mV the Nernst voltage (11.9) for Cl^- ions.

Equivalent circuit for an ion channel in a membrane

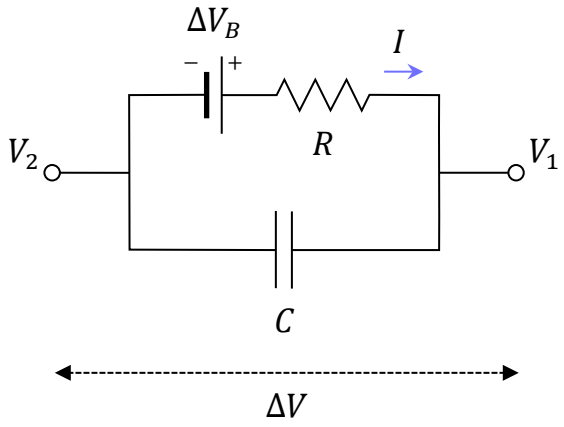


Fig.11.24 Equivalent circuit diagram of an open K^+ channel imbedded in a cell membrane separating two K^+ ion solutions with differing concentrations. The two open circles represent the inner (2) and outer (1) solutions in boxes 2 and 1 that have a voltage difference $\Delta V = V_2 - V_1$. The resistor has a voltage drop of $\Delta V_R = IR$ (11.63). The magnitude of the voltage across the battery is $\Delta V_B = -\Delta V_K$. The capacitor has a voltage difference of $\Delta V_C = \Delta V = IR - \Delta V_B$ (11.64). According to **the physiological convention**, positive current flows through the resistor R in the outward direction as indicated by the arrow labelled I.

Ch.12 COVID-19 and epidemiology

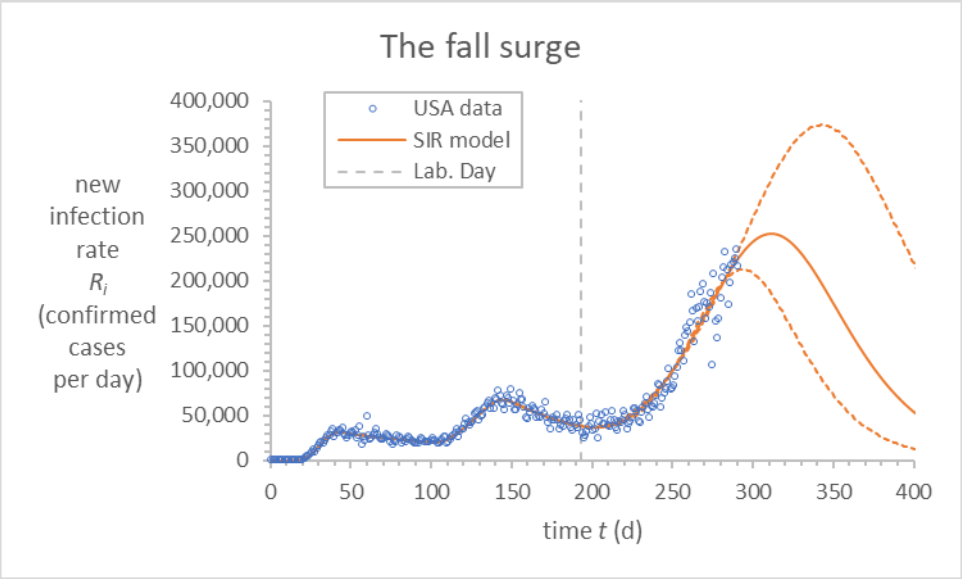


Fig.12.IPLS Excel 2016 chart showing the predictions of the SIR model (Fig.12.11) when fitted to five different periods. The open circles show the USA data reported as confirmed cases per day by the ECDC up to December 13, 2020. Sold orange line is with model population being 25% of the actual population. Dashed lines represent 15% and 50% (see poster "Modeling the coronavirus pandemic in the United States").

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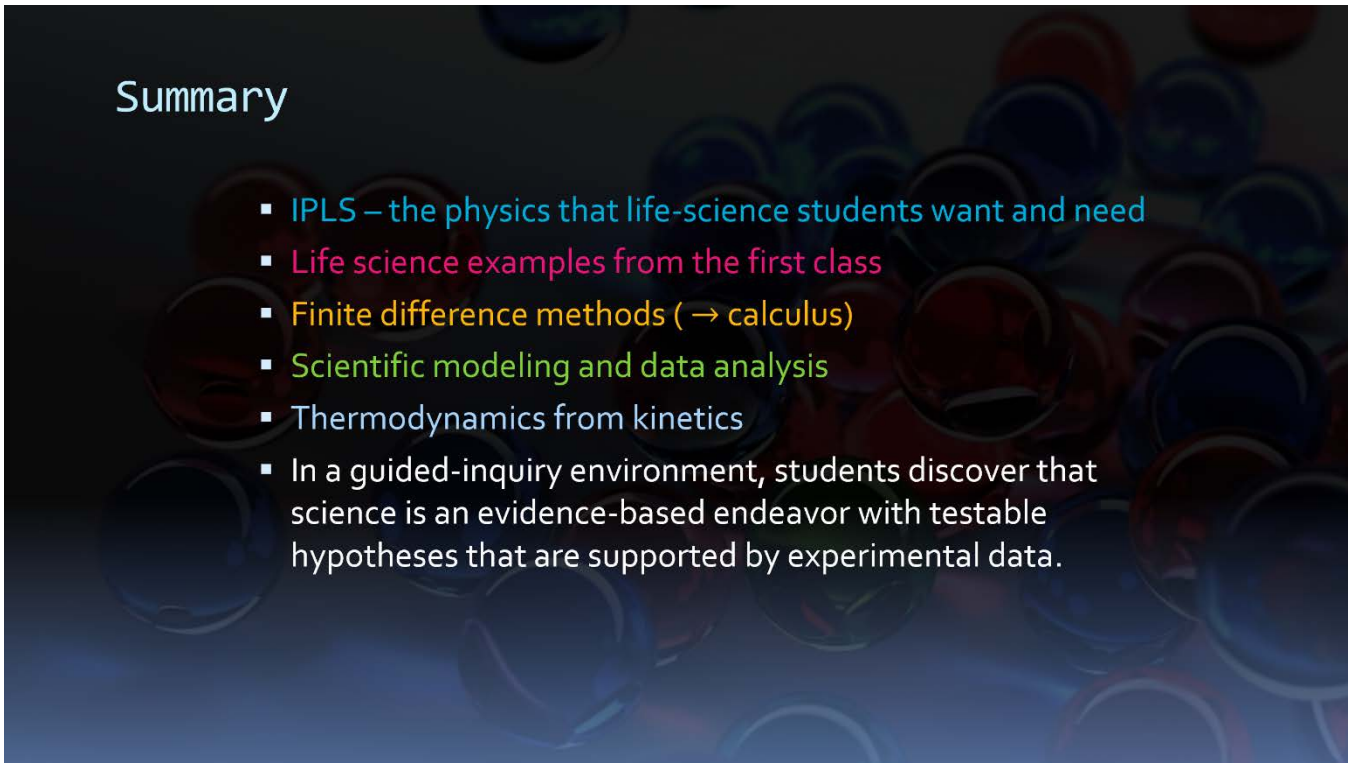

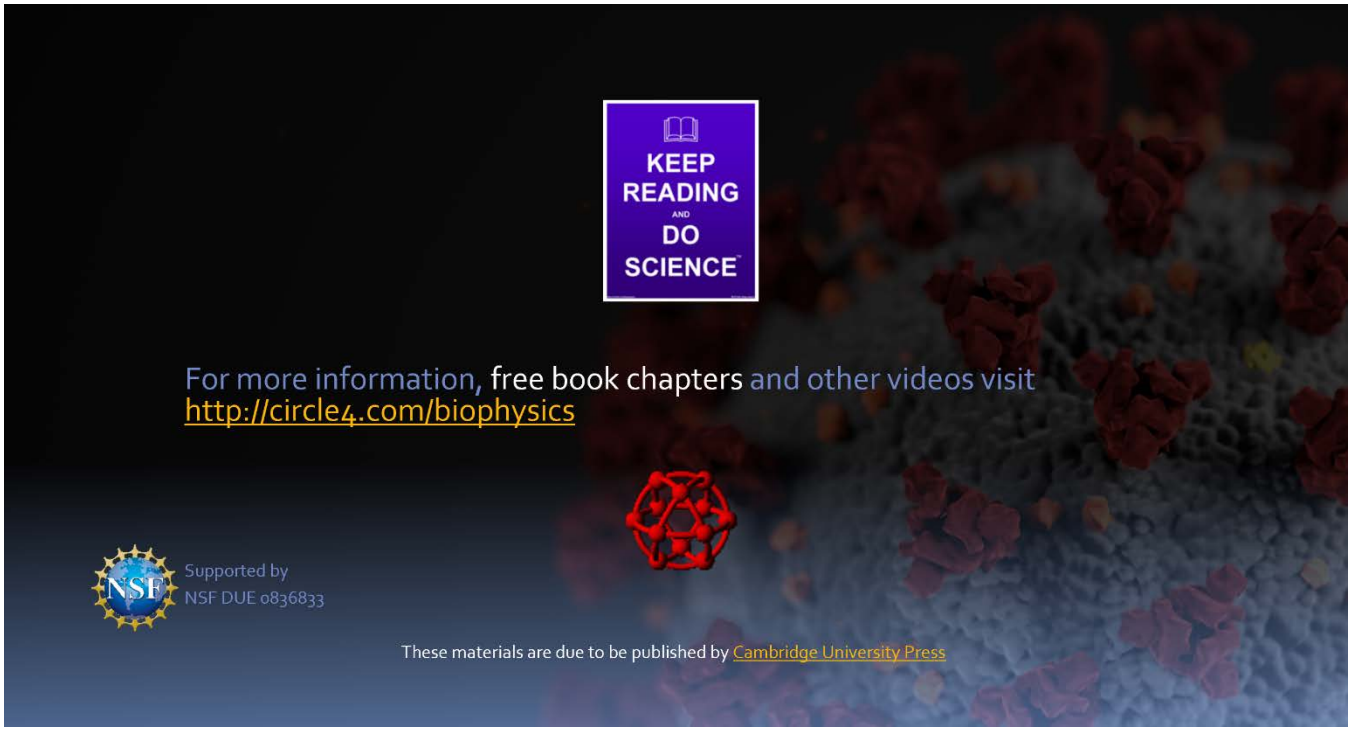

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