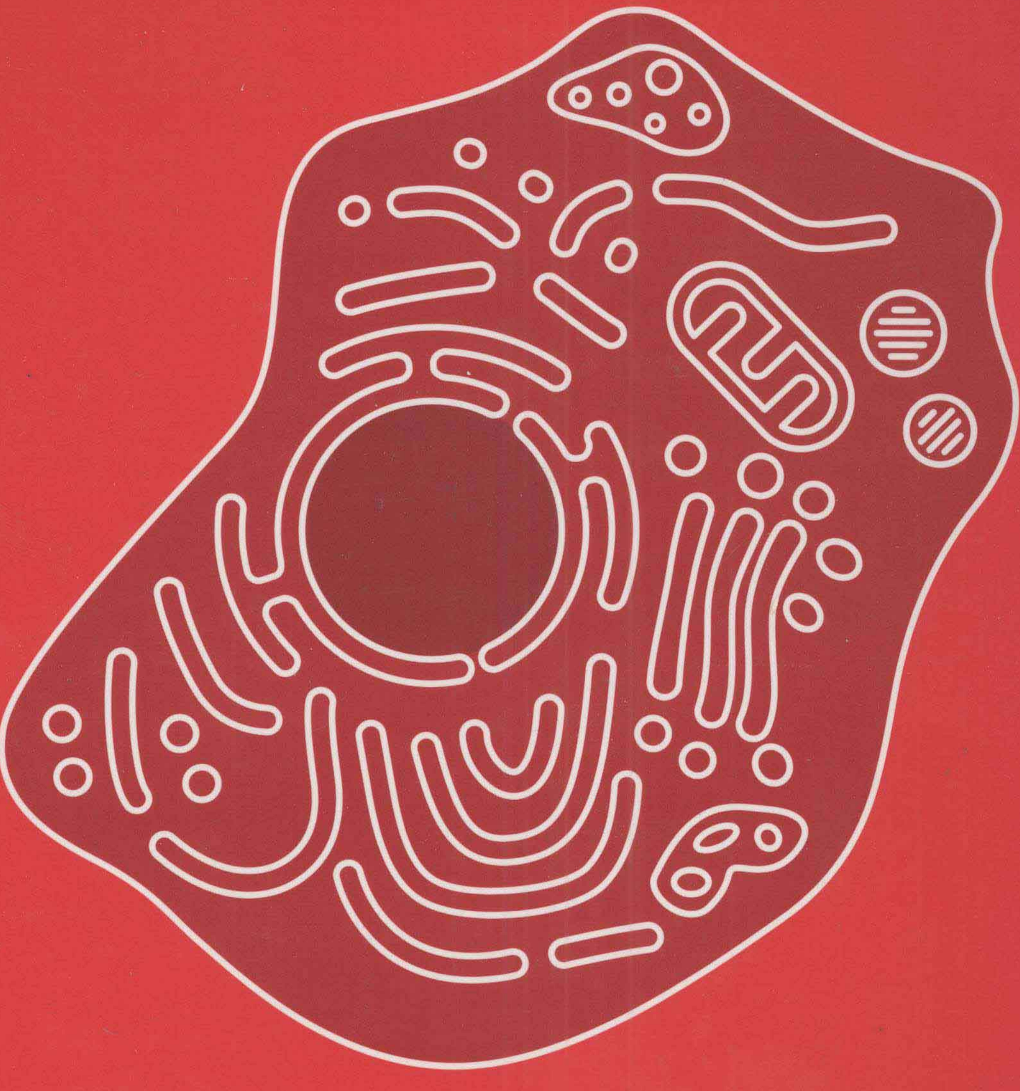
Molecular Biology of

THE CELL

Fifth Edition

The Problems Book



Also includes complete solutions to the end-of-chapter problems from *Molecular Biology of the Cell*, Fifth Edition

JOHN WILSON and TIM HUNT

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Tim Hunt received his Ph.D. from the University of Cambridge where he taught biochemistry and cell biology for more than 20 years. In the late 1970s and early 1980s he spent his summers teaching cell and molecular biology at the Marine Biological Laboratory, Woods Hole, Massachusetts. He left Cambridge in 1990 and moved to the Cancer Research UK Clare Hall Laboratories, just outside London, where he works on the control of the cell cycle. He shared the 2001 Nobel Prize in Physiology or Medicine with Lee Hartwell and Paul Nurse.

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Constants

SYMBOL	CONSTANT	VALUE
c	Speed of Light	3.0×10^{17} nm/sec
e	Charge on a Proton or an Electron	1.6×10^{-19} coulomb (C)
F	Faraday Constant	23 kcal/V mole
g	Earth's Gravitational Acceleration	9.81 m/sec^2
h	Planck's Constant	1.58×10^{-37} kcal sec/photon
k	Boltzmann Constant	1.38×10^{-23} J/K
N	Avogadro's Number	6.02×10^{23} molecules/mole
R	The Gas Constant	1.98×10^{-3} kcal/K mole

Variables

SYMBOL	UNITS	DEFINITION
ΔE_0	V	Standard electromotive potential (T = 298 K, all concentrations at 1 M)
ΔE	V	Electromotive potential
E_0	V	Standard reduction potential (T = 298 K, all concentrations at 1 M)
E	kcal/photon	Energy of a photon at a particular wavelength
$\Delta G°$	kcal/mole	Standard free-energy change (T = 298 K, all concentrations at 1 M)
ΔG	kcal/mole	Free-energy change
K	(variable)	Ratio of the molar concentrations of products to reactants at equilibrium
λ	nm	Wavelength
M_r	no units	Relative molecular mass (mass of molecule relative to $^1/_{12}$ mass of carbon atom)
n	no units	Number of electrons transferred during a redox reaction
v	sec^{-1}	Frequency
pH	no units	Negative $\log_{10}$ of molar concentration of H^+
pK	no units	The pH at which an ionizable group is half dissociated
T	K	Absolute temperature
V	V	Membrane potential
z	no units	Valence (charge) on solute

Units

SYMBOL	NAME	MEASURE OF	CONVERSION FACTORS
A	ampere	electrical current	1 C/sec
Å	Ångström	length	10^{-10} m, 0.1 nm
Bq	becquerel	radioactivity	1 disintegration/sec, 60 dpm
C	coulomb	electrical charge	1 A sec
°C	centigrade degree	temperature	K – 273
Ci	curie	radioactivity	3.7×10^{10} Bq, 2.22×10^{12} dpm
cm	centimeter	length	10^{-2} m, 10^{7} nm
cpm	counts/min	radioactivity	dpm × counting efficiency[a]
d	dalton	molecular mass	1.66×10^{-24} g
			($^{1}/_{12}$ mass of a carbon atom)
dpm	disintegrations/min	radioactivity	0.016 Bq, cpm/counting efficiency[a]
g	gram	mass	6.02×10^{23} daltons
J	joule	energy	1 kg m^2/sec^2, 10^7 ergs, 0.239 cal
K	Kelvin	temperature	°C + 273
kb	kilobase	nucleotides	1000 bases or base pairs
kcal	kilocalorie	energy	4.18 kilojoules
kd	kilodalton	molecular mass	1000 d
kJ	kilojoule	energy	0.24 kilocalories
L	liter	volume	1000 mL
m	meter	length	100 cm, 10^9 nm
M	molar	concentration	moles solute per liter of solution
µg	microgram	mass	10^{-6} g
min	minute	time	60 sec
mL	milliliter	volume	1 cm^3
mole	mole	number	6.02×10^{23} molecules
mV	millivolt	electrical potential	10^{-3} volts
N	newton	force	1 kg m/sec^2, 1 J/m, 10^5 dynes
nm	nanometer	length	10^{-9} m, 10 Å
Pa	pascal	pressure	1 N/m^2, 9.87×10^{-6} atm
S	siemens	electrical conductance	1 A/V
sec	second	time	3600 sec/hour; 86,400 sec/day
V	volt	electrical potential	1 W/A, 1 J/C, 1000 mV
W	watt	power	1 J/sec, 1 V A

[a]See table of radioactive isotopes (inside back cover) for efficiency of counting of specific isotopes.

Prefixes

SYMBOL	NAME	VALUE	SYMBOL	NAME	VALUE
d-	deci-	10^{-1}	da-	deca-	10^{1}
c-	centi-	10^{-2}	h-	hecto-	10^{2}
m-	milli-	10^{-3}	k-	kilo-	10^{3}
μ-	micro-	10^{-6}	M-	mega-	10^{6}
n-	nano-	10^{-9}	G-	giga-	10^{9}
p-	pico-	10^{-12}	T-	tera-	10^{12}
f-	femto-	10^{-15}	P-	peta-	10^{15}
a-	atto-	10^{-18}	E-	exa-	10^{18}
z-	zepto-	10^{-21}	Z-	zetta-	10^{21}
y-	yocto-	10^{-24}	Y-	yotta-	10^{24}

Geometric Formulas

FIGURE	AREA	SURFACE AREA	VOLUME
square	l^2		
circle	πr^2		
ellipse	$\pi r_1 r_2$		
cube		$6\,l^2$	l^3
cylinder		$2\pi r h + 2\pi r^2$	$\pi r^2 h$
sphere		$4\pi r^2$	$^4/_3\,\pi r^3$
cone			$^1/_3\,\pi r^2 h$

Radioactive Isotopes

ISOTOPE	EMISSION	HALF-LIFE	COUNTING EFFICIENCY[a]	MAXIMUM SPECIFIC ACTIVITY[b]
^{14}C	beta	5730 years	96%	0.062 Ci/mmol
^{3}H	beta	12.3 years	65%	29 Ci/mmol
^{35}S	beta	87.4 days	97%	1490 Ci/mmol
^{125}I	gamma, Auger, and conversion electrons	60.3 days	78%	2400 Ci/mmol
^{32}P	beta	14.3 days	100%	9120 Ci/mmol
^{131}I	beta and gamma	8.04 days	100%	16,100 Ci/mmol

[a]Maximum efficiency for an unquenched sample in a liquid scintillation counter. Most real samples are quenched to some extent.
[b]This value assumes one atom of radioisotope per molecule. If there are two radioactive atoms per molecule, the specific activity will be twice as great, and so on.

THE GENETIC CODE†

1st position (5′ end)	2nd Position: T	2nd Position: C	2nd Position: A	2nd Position: G	3rd Position (3′ end)
T	F	S	Y	C	T
	F	S	Y	C	C
	L	S	*	*	A
	L	S	*	W	G
C	L	P	H	R	T
	L	P	H	R	C
	L	P	Q	R	A
	L	P	Q	R	G
A	I	T	N	S	T
	I	T	N	S	C
	I	T	K	R	A
	M	T	K	R	G
G	V	A	D	G	T
	V	A	D	G	C
	V	A	E	G	A
	V	A	E	G	G

AMINO ACIDS		CODONS†			
A	Alanine	GCT	GCC	GCA	GCG
C	Cysteine	TGT	TGC		
D	Aspartic acid	GAT	GAC		
E	Glutamic acid	GAA	GAG		
F	Phenylalanine	TTT	TTC		
G	Glycine	GGT	GGC	GGA	GGG
H	Histidine	CAT	CAC		
I	Isoleucine	ATT	ATC	ATA	
K	Lysine	AAA	AAG		
L	Leucine	CTT	CTC	CTA	CTG
		TTA	TTG		
M	Methionine	ATG			
N	Asparagine	AAT	AAC		
P	Proline	CCT	CCC	CCA	CCG
Q	Glutamine	CAA	CAG		
R	Arginine	CGT	CGC	CGA	CGG
		AGA	AGG		
S	Serine	TCT	TCC	TCA	TCG
		AGT	AGC		
T	Threonine	ACT	ACC	ACA	ACG
V	Valine	GTT	GTC	GTA	GTG
W	Tryptophan	TGG			
Y	Tyrosine	TAT	TAC		
*	STOP	TAA	TAG	TGA	

† Codons are shown as DNA instead of RNA (Ts in place of Us) to facilitate the conversion of DNA sequences into protein sequences.

Molecular Biology of THE CELL

Fifth Edition

The Problems Book

For Lynda and Sofia
Mary, Celia, and Agnes

Preface

"You know, the proper method for inquiring after the properties of things is to deduce them from experiments"

Isaac Newton, 1672

The Problems Book aims to provide a running commentary for *Molecular Biology of the Cell, Fifth Edition* by Alberts et al. As we wrote in earlier prefaces, we would like to stimulate our readers to ask questions as well as to accept, digest, and learn the stories that 'the big book' tells. In real life, however, knowledge and understanding come from research, which entails curiosity, puzzlement, doubt, criticism, and debate. Groping one's way through the fog of uncertainty during a research project is a slow and often discouraging process; eureka moments (even if one is lucky) are few and far between. Nevertheless, those moments catch the essence of the drama, and we have tended to focus on them, where we have been able to cast them in the form of a problem. In this way, for student and teacher alike, we hope to encourage a questioning attitude to biology. Without curiosity there would be neither science nor scientists.

We have been making up problems together for more than twenty years, and the revision leading to this new edition of *The Problems Book* has taken us more than three years. There are several new things about this edition. We are proud to say that its 20 chapters now match the first twenty chapters of *Molecular Biology of the Cell,* which means that there are three entirely new chapters: on microscopy (Chapter 9), on the extracellular matrix and cell–cell interactions (Chapter 19) and on cancer (Chapter 20). Elsewhere, the organization of each chapter has undergone major revision besides minor modifications and additions to existing problems. As before, sections start by listing the terms in bold from *MBoC.* As a simple test of memory and comprehension, we have added a new type of problem, which we call "Definitions," where we ask the reader to identify these terms from a one-sentence description of their meaning. The following "True/False" section consists of a set of simple statements, whose truth the reader must judge and justify. Next come short questions we call "Thought Problems," modeled on the kinds of problems presented in *Essential Cell Biology* also by Alberts et al. Some of these are more challenging than others, some are playful, some are serious, but all are designed to make the reader think. After this comes a section called "Calculations," which is designed to help deal with quantitative aspects of cell biology. The calculations in this book are mostly very straightforward, usually involving no more than the interconversion of units, yet they provide a solid framework for thinking about the cell. Are cell-surface receptors sparse in the plasma membrane, or jam-packed? Do molecules diffuse across a cell slowly, or in the blink of an eye? Does chromatin occupy most of the nuclear volume, or just a tiny fraction? Numerical analysis of such questions is very important if one is to gain a feel for the molecular basis of cell biology. Last but not least, the "Data Handling" section contains research-based problems, which arguably form the most important part of the book. Our original brief was to compose problems based on experiments so as to allow readers to get a better feel for the way in which biological knowledge is obtained. It is tremendously important to keep asking, "How do we know that? What's the evidence?" or to wonder how one might go about finding something out. Often it's not at all obvious, often the initial breakthrough was a lucky chance observation, made while investigating some completely different business. In fact, it takes most of us years of research experience to grasp the idea of how one simple fact "can illuminate a distant area, hitherto dark" (Boveri, 1902). Seeing how these tiny shards of evidence give rise to the big picture often involves considerable imagination, as well as a certain discipline, to know how much weight the evidence will bear. We hope we have sometimes, at least, been able to capture the essence of how experiments lead to understanding. To do justice to the authors of the experiments we use in these problems, however, we strongly recommend recourse to the original papers, whose references we always provide.

We hope that the organization and classification of problems will help both student and teacher to find what they are looking for. As far as possible, the order of questions closely follows *Molecular Biology of the Cell.*

Another big change in this edition pleases us very much. For this edition, we have chosen to include the answers to every problem on the CD that comes with this book. We think this is a thoroughly good thing for readers. Many of these problems are difficult to answer, and are not really intended to be set as tests. Rather, we hope that readers will be intrigued (as we were) by the questions we ask, and after thinking a bit will want to see what the answer is, what form the discussion takes, how to get at thinking about this particular kind of a problem. Having used these problems ourselves, we know that even a problem with an answer can serve as the basis for a stimulating discussion in class. And if students are told in advance that a few problems from a larger set will be on an exam, they will be motivated to grapple with the reasoning behind *all* the answers—a lot of learning.

Another departure from previous editions is that a selection of questions from *The Problems Book* now appears in *Molecular Biology of the Cell* at the end of each chapter. We picked these problems in consultation with the authors of *MBoC* to highlight important issues in the text and to cover the range of problem styles. We are pleased with the final selections; they include some of our all-time favorites. The solutions to all these problems are printed in a separate section at the end of *The Problems Book.* We hope that many more readers of the main textbook will try working problems as a result of this change.

As always, we want to hear from our readers, for despite our best efforts, we do not always get things right. Please email John Wilson at jwilson@bcm.edu or Tim Hunt at tim.hunt@cancer.org.uk with your comments or queries, and we'll do our best to answer them.

Acknowledgments

We are slightly bemused to find that our rate of production, averaged over the history of this project, stands at about one chapter per year. But even this glacial progress would not have been possible without a tremendous amount of help from friends and colleagues whose names are recorded in previous editions of The Problems Book, which appeared in 1989, 1994 and 2002. The three new chapters in this fourth edition had special help from Ralph Baeirlein, who explained in terms we could understand why light slows down in glass, from Richard Peto, who explained how Richard Doll and his colleagues first found the connection between smoking and lung cancer, and from Robin Weiss for help with the cellular transmission of tumors in dogs and Tasmanian devils. Doug Sipp at the Center for Developmental Biology in Kobe provided reprints that were unavailable online. We are grateful to Martin Rees for explaining how to estimate the size of the known universe, to Russ Doolittle, who showed us how to construct simple phylogenetic trees based on protein sequences, and to Niles Eldridge and David Kohn, who helped us to understand Charles Darwin's first (theoretical) sketch of the tree of life. As has been the case from the very first edition, we owe a huge debt to Alastair Ewing of the Open University, who worked through almost all the problems, new and old, discovering embarrassing mistakes and finding better, clearer and more graceful ways of putting things. Denise Schanck has been a tower of strength, as always, and Emma Jeffcock a brilliant designer, coordinator and friend throughout this edition. Mike Morales helped to set up an instant home-away-from-home during meetings in California, and his cheerful humor was much appreciated. Adam Sendroff, who took care of publicity and gave us useful audience feedback, was unfailingly supportive. We are especially grateful to all the authors of *Molecular Biology of the Cell,* who have been extremely helpful in the selection and refinement of problems that appear in the main text. We thank them most warmly for their suggestions. Once again, Nigel Orme has been a great help with the illustrations, particularly in adding color to the selection of images that appear in *Molecular Biology of the Cell,* Fifth Edition.

A Couple of Things to Know

Avogadro's Number (6.02×10^{23} molecules/mole)

Avogadro's number (*N*) is perhaps the most important constant in molecular sciences, and it appears again and again in this book. Do you know how it was determined? We didn't, or had forgotten if we ever knew. How can one measure the number of molecules in a mole? And who did it first? You will not find this information in modern biology books, partly because it is ancient history, and partly because it was the business of physicists; some pretty good physicists too, as we shall see.

Amadeo Avogadro had no idea how many molecules there were in 22.4 L of a gas. His hypothesis, presented in 1811, was simply that equal volumes of all gases contained the same number of molecules, irrespective of their size or density. Not until much later, when the reality of molecules was more widely accepted and the microscopic basis for the properties of gases was being worked out, were the first estimates attempted. An Austrian high school teacher called Josef Loschmidt used James Clerk Maxwell's recently developed kinetic theory of gases to estimate how many molecules there were in a cubic centimeter of air. Maxwell had derived an expression for the viscosity of a gas, which is proportional to the density of the gas, to the mean velocity of the molecules, and to their mean free path. The latter could be estimated if one knew the size and number of the molecules. Loschmidt simply made the assumption that when a gas was condensed into a liquid, its molecules were packed as closely as they could be, like oranges in a display on a fruit stand, and from this he was able to get a pretty accurate value for Avogadro's number. Not surprisingly, in Austria they often refer to *N* as 'Loschmidt's number.' In fact, it wasn't until 1909 that the term 'Avogadro's number' was suggested by Jean Perrin, who won the 1926 Nobel prize for physics (his lecture is available on the Nobel web site, and his book on Atoms [Les Atomes, 1913, translated from the original French by D. Ll. Hammick, reprinted in 1990 by Ox Bow Press] is highly recommended—and accessible—reading. It has been called the finest book on physics of the 20th century).

You may be surprised to discover, as we were, that estimating Avogadro's number was an important topic of Albert Einstein's Ph.D. thesis. Abraham Pais's wonderful biography of Einstein, *Subtle is the Lord* (subtitled *The Science and the Life of Albert Einstein,* 1982 Oxford University Press) devotes Chapter 5, 'The Reality of Molecules,' to this period of the great physicist's life and work. Einstein found three independent ways to estimate *N*: from the viscosity of dilute sucrose solutions, from his analysis of Brownian motion, and from light scattering by gases near the critical point, including the blueness of the sky. Because the sky is five million times less bright than direct sunlight, Avogadro's number is 6×10^{23}. Isn't that romantic?

But Einstein's was not the last word on the subject. Indeed, according to Pais, he made an "elementary but nontrivial mistake" in his thesis that was later corrected, and it was really Perrin who brought the whole field together with his experiments on Brownian motion. The Nobel presentation speech contains this line:

"His [Perrin's] measurements on the Brownian movement showed that Einstein's theory was in perfect agreement with reality. Through these measurements a new determination of Avogadro's number was obtained."

For most methods of counting molecules, neither the physics nor the math is easy to follow, but two are simple to understand. The first comes from radioactive decay, and another Nobel prize-winning physicist, Ernest Rutherford. When radium decays, it emits alpha particles, which are helium nuclei. If you can count the radioactive decay events with a Geiger counter and measure the volume of helium emitted, you can estimate Avogadro's number. The second way is much more modern. You can see large proteins and nucleic acids with the aid of an electron microscope.

Calculations and Unit Analysis

Many of the problems in this book involve calculations. Where the calculations are based on an equation (for example, the Nernst equation or the equation for volume of a sphere), we provide the equation along with a brief explanation of symbols, and often their values. Many calculations, however, involve the conversion of information from one form into another, equivalent form. For example, if the concentration of a protein is 10^{-9} M, how many molecules of it would be present in a mammalian nucleus with a volume of 500 μm^3? Here, a concentration is given as M (moles/L), whereas the desired answer is molecules/nucleus; both values are expressed as 'number/volume' and the problem is to convert one into the other.

Both kinds of calculation use constants and conversion factors that may or may not be included in the problem. The Nernst equation, for example, uses the gas constant R (2.0×10^{-3} kcal/°K mole) and the Faraday constant F (23 kcal/V mole). And conversion of moles/L to molecules/nucleus requires Avogadro's number N (6.0×10^{23} molecules/mole). All of the constants, symbols, and conversion factors that are used in this book are listed inside the book covers (along with the standard genetic code, the one-letter amino acid code, useful geometric formulas, and data on common radioisotopes used in biology).

For each type of calculation, we strongly recommend the powerful general strategy known as unit analysis (or dimensional analysis). If units (for example, moles/L) are included along with the numbers in the calculations, they provide an internal check on whether the numbers have been combined correctly. If you've made a mistake in your math, the units will not help, but if you've divided where you should have multiplied, for example, the units of the answer will be nonsensical: they will shout 'error.' Consider the conversion of 10^{-9} M (moles/L) to molecules/nucleus. In the conversion of moles to molecules, do you multiply 10^{-9} by 6×10^{23} (Avogadro's number) or do you divide by it? If units are included, the answer is clear.

$$\frac{10^{-9}\ \text{moles}}{\text{L}} \times \frac{6 \times 10^{23}\ \text{molecules}}{\text{mole}} = \frac{6 \times 10^{14}\ \text{molecules}}{\text{L}} \qquad \textbf{YES}$$

$$\frac{10^{-9}\ \text{moles}}{\text{L}} \times \frac{\text{mole}}{6 \times 10^{23}\ \text{molecules}} = \frac{1.7 \times 10^{-33}\ \text{mole}^2}{\text{molecules L}} \qquad \textbf{NO}$$

Similarly, in the conversion of liters to nuclei, the goal is to organize the conversion factors to transform the units to the desired form.

$$\frac{6 \times 10^{14}\ \text{molecules}}{\text{L}} \times \frac{1\ \text{L}}{1000\ \text{mL}} \times \frac{\text{mL}}{\text{cm}^3} \times \frac{\text{cm}^3}{(10^4\ \mu\text{m})^3} \times \frac{500\ \mu\text{m}^3}{\text{nucleus}} = \frac{300\ \text{molecules}}{\text{nucleus}}$$

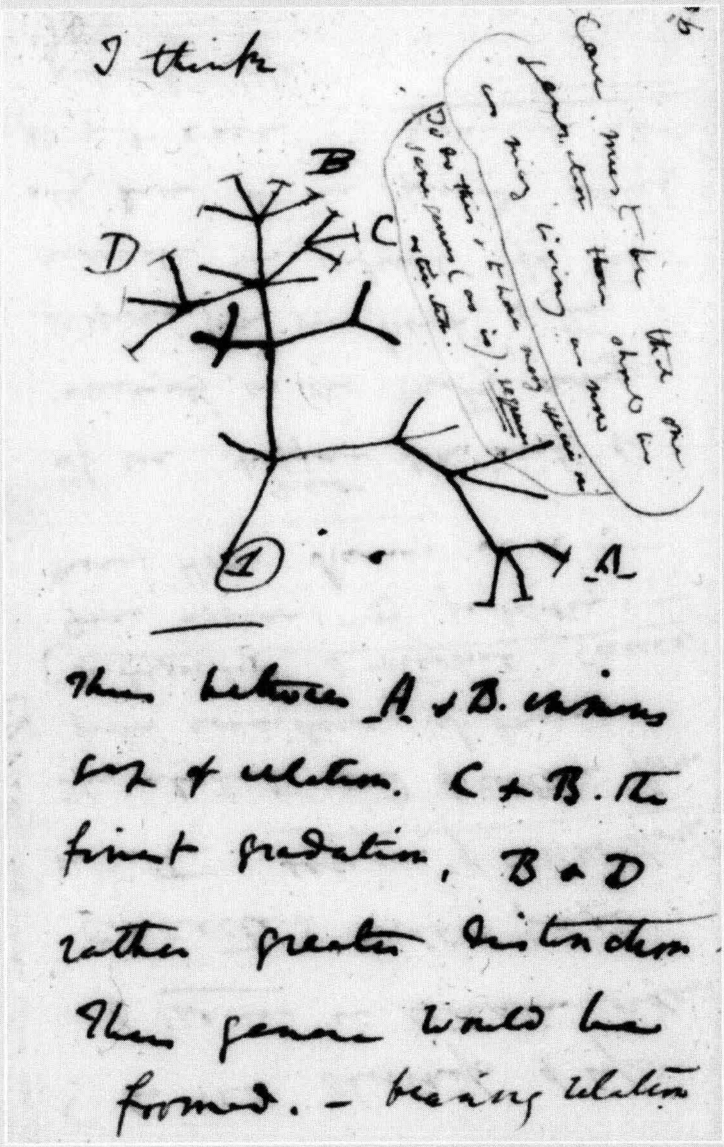
If you do this calculation with pure numbers, you must worry at each step whether to divide or multiply. If you attach the units, however, the decision is obvious. It is important to realize that any set of (correct) conversion factors will give the same answer. If you are more comfortable converting liters to ounces, that's fine, so long as you know a string of conversion factors that will ultimately transform ounces to μm^3.

There are a few simple rules for handling units in calculations.

1. Quantities with different units cannot be added or subtracted. (You cannot subtract 3 meters from 10 kcal.)
2. Quantities with different units can be multiplied or divided; just multiply or divide the units along with the numbers. (You can multiply 3 meters times 10 kcal; the answer is 30 kcal meters.)
3. All exponents are unitless. (You can't use $10^{6\ \text{mL}}$.)
4. You cannot take the logarithm of a quantity with units.

Throughout this book, we have included the units for each element in every calculation. If the units are arranged so that they cancel to give the correct units for the answer, the numbers will take care of themselves.

Problems



Darwin's first known (July 1837) sketch of the tree of life.
The writing reads:
"I think"
"Thus between A & B enormous gap of relation. C + B. The finest gradation, B + D rather greater distinction Thus genera would have formed. - bearing relation"

In the bubbles, added later (probably in 1839):
"Case must be that one generation then should be as many living as now"
"To do this & to have many species in same genus (as is) requires extinction."

See Charles Darwin's Notebooks (1836–1844): Geology, Transmutation of Species, Metaphysical Enquiries. Edited with Paul Barrett, Peter Gautrey, Sandra Herbert and Sydney Smith. Ithaca: British Museum (Natural History), Cornell University Press, and Cambridge University Press, 1987. Thanks to David Kohn for the image and helpful comments on its significance.

Contents