## **CONTENTS**

1	Intro	duction: viruses, immunity, equations	1
_		Viruses	ī
	1.2	Immunity	
		1.2.1 B cells	3
		1.2.2 T cells	4
	1.3	Mathematical biology	6
		Further reading	9
2	HIV		10
	2.1	Discovery	10
	2.2	Some basic facts about HIV	11
	2.3	Treatment	13
	2.4	Origins of HIV	14
	2.5	Further reading	15
3	The basic model of virus dynamics		16
	3.1	The model	17
	3.2	Dynamics	18
	3.3	Equilibrium	21
	3.4	The primary phase of HIV and SIV infection	21
		3.4.1 Estimating $R_0$	24
		3.4.2 Vaccination to reduce $R_0$	25
	3.5	Further reading	26
4	Anti-viral drug therapy		27
	4.1	Theory	30
		4.1.1 HIV: reverse transcriptase inhibitors	30
		4.1.2 HIV: protease inhibitors	32
		4.1.3 Rise of uninfected cells	34
		4.1.4 Long-lived infected cells	34
	4.2	Experiment	36
		4.2.1 Short-term decay	36
		4.2.2 CD4 cell increase	38
		4.2.3 Long-lived infected cells	39
		4.2.4 Virion turnover	40
		4.2.5 Triple-drug therapy	41
		4.2.6 Eradication	42
	4.3	Further reading	43

x Contents

5	Dyna	mics of hepatitis B virus	44
	5.1	Theory	45
		Experiment	46
		Comparing HBV and HIV	50
	5.4	Further reading	51
6	Dyna	mics of immune responses	52
	6.1	A self-regulating CTL response	53
		6.1.1 Persistent infection or clearance	55
		6.1.2 Variation in CTL responsiveness leads to a negative	
		correlation between virus load and the magnitude of	
		the CTL response	56
		Other self-regulating immune responses	56
	6.3	real fraction from the first that th	58
		6.3.1 Virus load reduction	59
		6.3.2 Variation in immune responsiveness	59
	6.4	4	61
		Dynamic elimination	63
	6.6	The simplest models of immune response dynamics	63
		6.6.1 Variation in immune responsiveness	66
		Experimental observations: HTLV-1 and HIV-1,2	66
	6.8	Further reading	67
7	The state of the s		69
	7.1		71
	7.2	<b>3</b>	74
		7.2.1 Model 1	75
		7.2.2 Model 2	76
		Virus decay slopes	77
		Comparing HIV and HBV	80
	7.5	Further reading	81
8			82
	8.1	More than atoms in our universe	83
	8.2	Quasispecies live in sequence space	84
	8.3	Quasispecies explore fitness landscapes	84
	8.4	The mathematics of quasispecies	85
	8.5	Error-thresholds	86
	8.6	Some fancier quasispecies maths	87
	8.7	Viral quasispecies	88
	8.8	Antigenic escape and optimum mutation rate	89
	8.9	Further reading	89

Contents xi

9		requency of resistant mutant virus	
	befor	e anti-viral therapy	90
	9.1	Wild-type and mutant differ by 1-point mutation	91
	9.2	Wild-type and mutant differ by 2-point mutations	92
	9.3	Wild-type and mutant differ by $n$ -point mutations	93
	9.4	Some practical implications	95
	9.5	Further reading	96
10	Emergence of drug resistance		97
	10.1	The basic model	100
	10.2	Emergence of resistance during drug treatment	101
		10.2.1 Equilibrium properties	102
		10.2.2 Total gain of CD4 cells and total reduction of virus load	
		are independent of inhibition of sensitive virus	103
		10.2.3 A stronger drug selects for faster emergence of	
		resistance	105
	10.3	The probability of producing a resistant mutant during	
		therapy	105
	10.4	•	108
	10.5	Further reading	109
11	3		110
	11.1	•	110
	11.2		116
		11.2.1 The probability of producing replication	
		competent provirus	117
	11.3	•	121
	11.4	Further reading	121
12	Simp	le antigenic variation	123
	12.1		125
	12.2		129
	12.3		133
	12.4	Further reading	136
13			137
	13.1	Immune response can select for or aganist antigenic diversity	138
		13.1.1 Cross-sectional comparisons	142
	13.2		143
		13.2.1 Cross-sectional comparisons	146
		Comparison with data	147
	13.4	Further reading	148
14	··-·-		
	14.1	Experimental evidence	153
	14.2	The simplest multiple epitope model	155

xii Contents

	14.3	Different parameters for different mutants	157
		14.3.1 What determines immunodominance?	161
	14.4	Activated CTLs arise from inactivated precursors	162
		14.4.1 The neutral case: all mutants have the same	
		replication rates	163
		14.4.2 The mutants have different replication rates	164
		14.4.3 The limit of large $\eta$	167
	14.5	The $2 \times 1$ case	167
		14.5.1 $\eta = 0$	167
		14.5.2 $\eta > 0$	169
		14.5.3 The limit of large $\eta$	174
	14.6	Cross-reactivity within the variants of a given epitope	174
	14.7	Immunogenicity and intracellular competition	175
	14.8	Immunotherapy	177
	14.9	Summary	179
	14.10	Further reading	181
15	Every	thing we know so far and beyond	182
	15.1	The mechanism of HIV-1 disease progression	182
	15.2	How to overcome HIV	186
	15.3	A quantitative immunology and virology	187
	15.4	Further reading	187
Ap	pendix A	A: Dynamics of resistance in different types of infected cells	188
Ap	pendix l	B: Analysis of multiple epitope dynamics	196
	B.1	An invariant of motion	196
	<b>B.2</b>	Local dynamics of a multiple epitope equation	197
	B.3	The $2 \times 2$ system	200
		B.3.1 $\eta = 0$	200
		B.3.2 $\eta > 0$	202
		B.3.3 The limit of large $\eta$	204
	B.4	Intracellular competition between epitopes	207
References			209
Index			233