PK/PD
Antibiyotik Duyarlılık Eşiği

Haluk VAHABOĞLU

STATE-OF-THE-ART CLINICAL ARTICLE

Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men

William A. Craig

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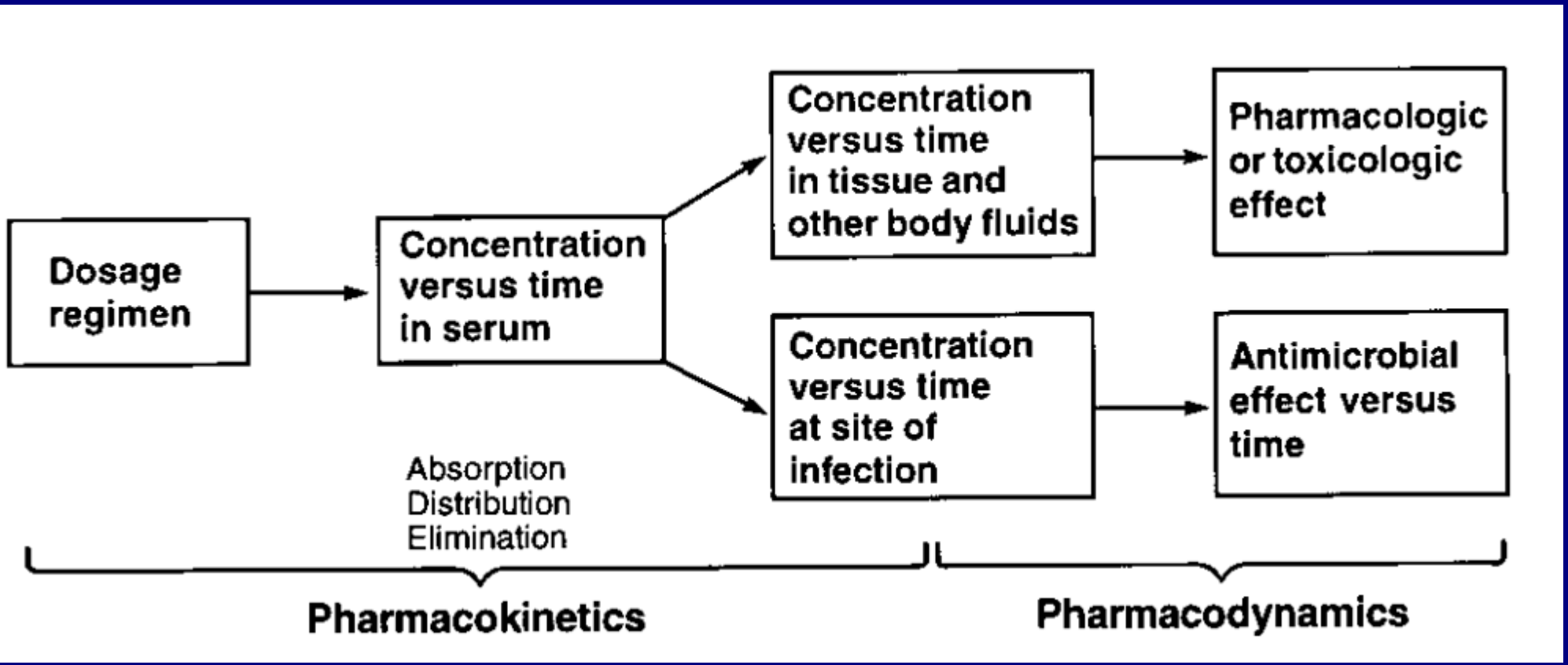
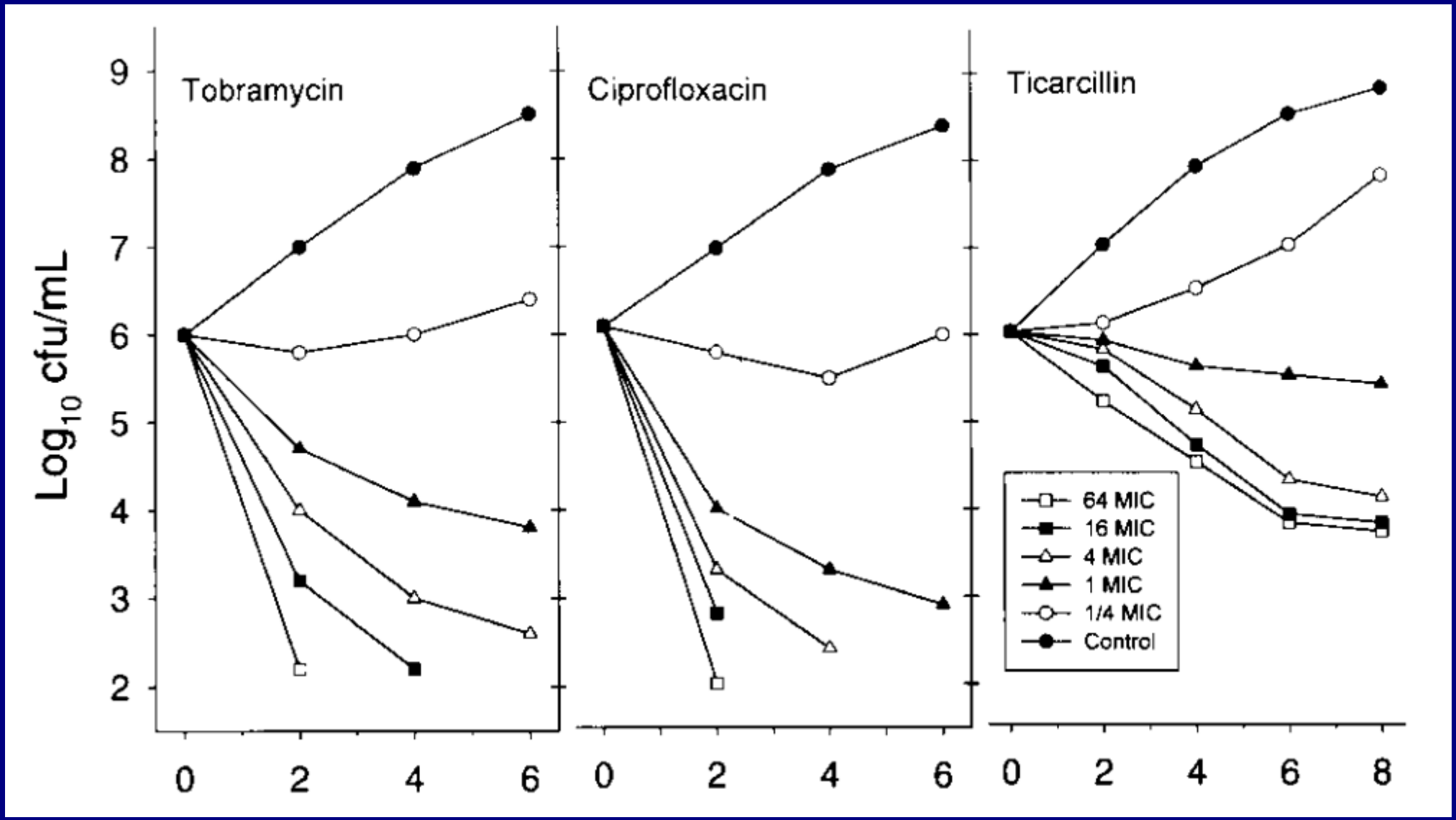
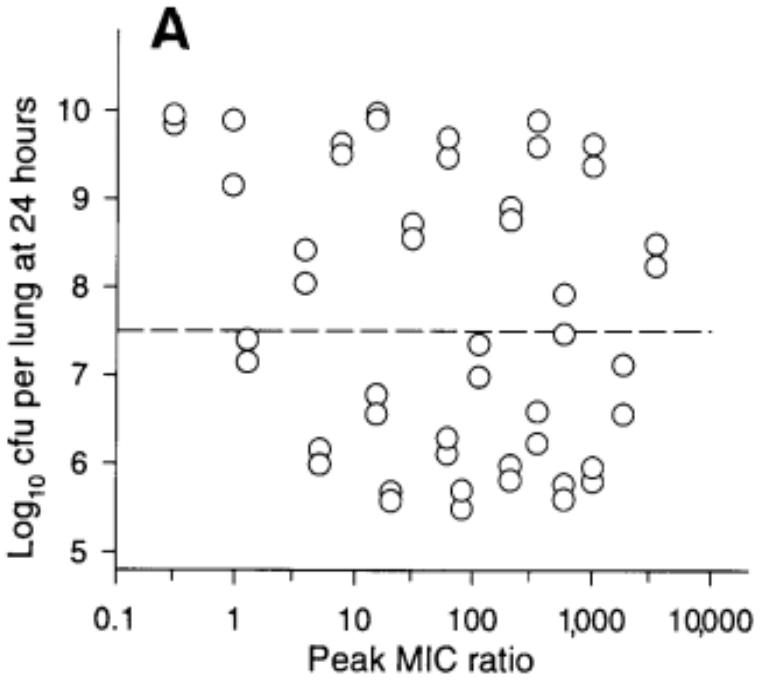
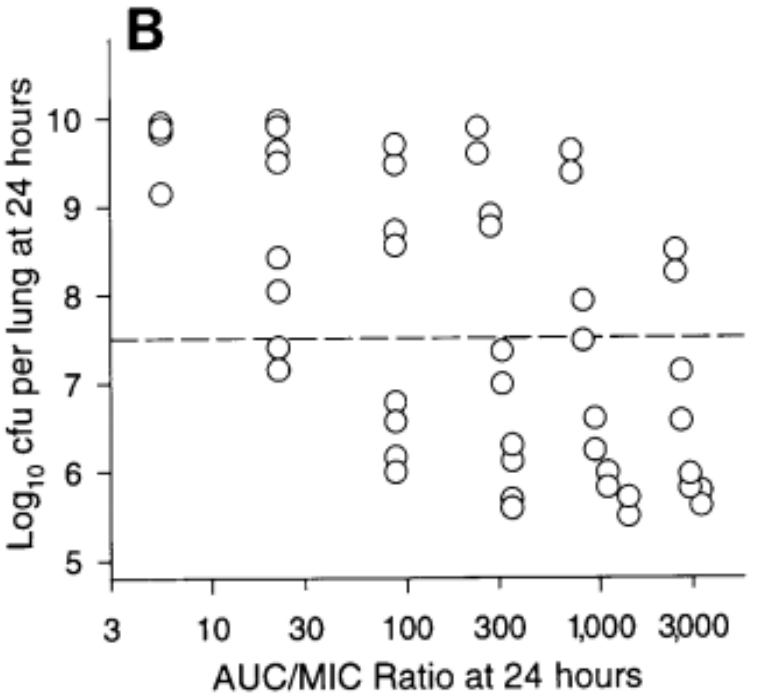

Dosage regimen
Concentration versus time in serum
Concentration versus time in tissue and other body fluids
Pharmacologic or toxicologic effect
Concentration versus time at site of infection
Antimicrobial effect versus time
Absorption
Distribution
Elimination
Pharmacokinetics
Pharmacodynamics


Tobramycin
Ciprofloxacin
Ticarcillin
Log10 cfu/mL
9
8
7
6
5
4
3
2
0
2
4
6
0
2
4
6
0
2
4
6
8
64 MIC
16 MIC
4 MIC
1 MIC
1/4 MIC
Control





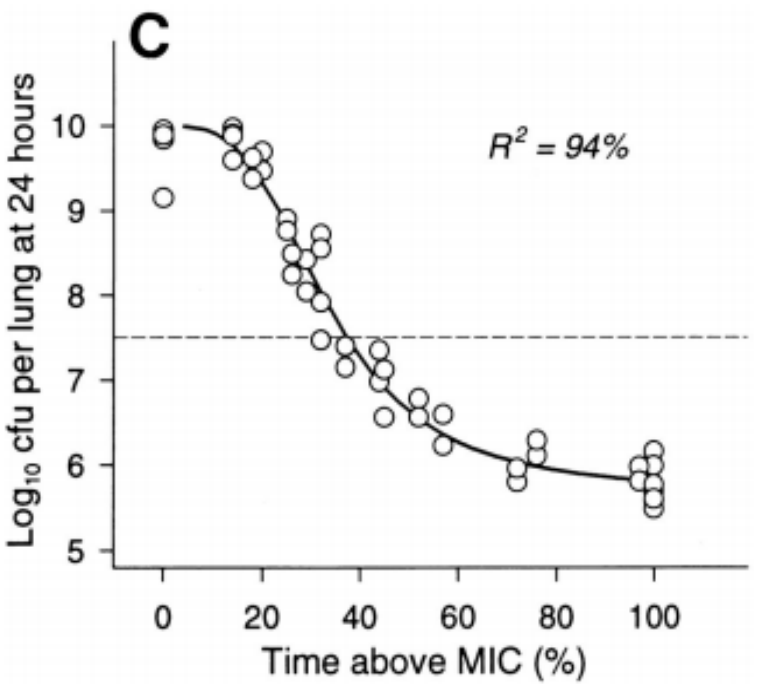
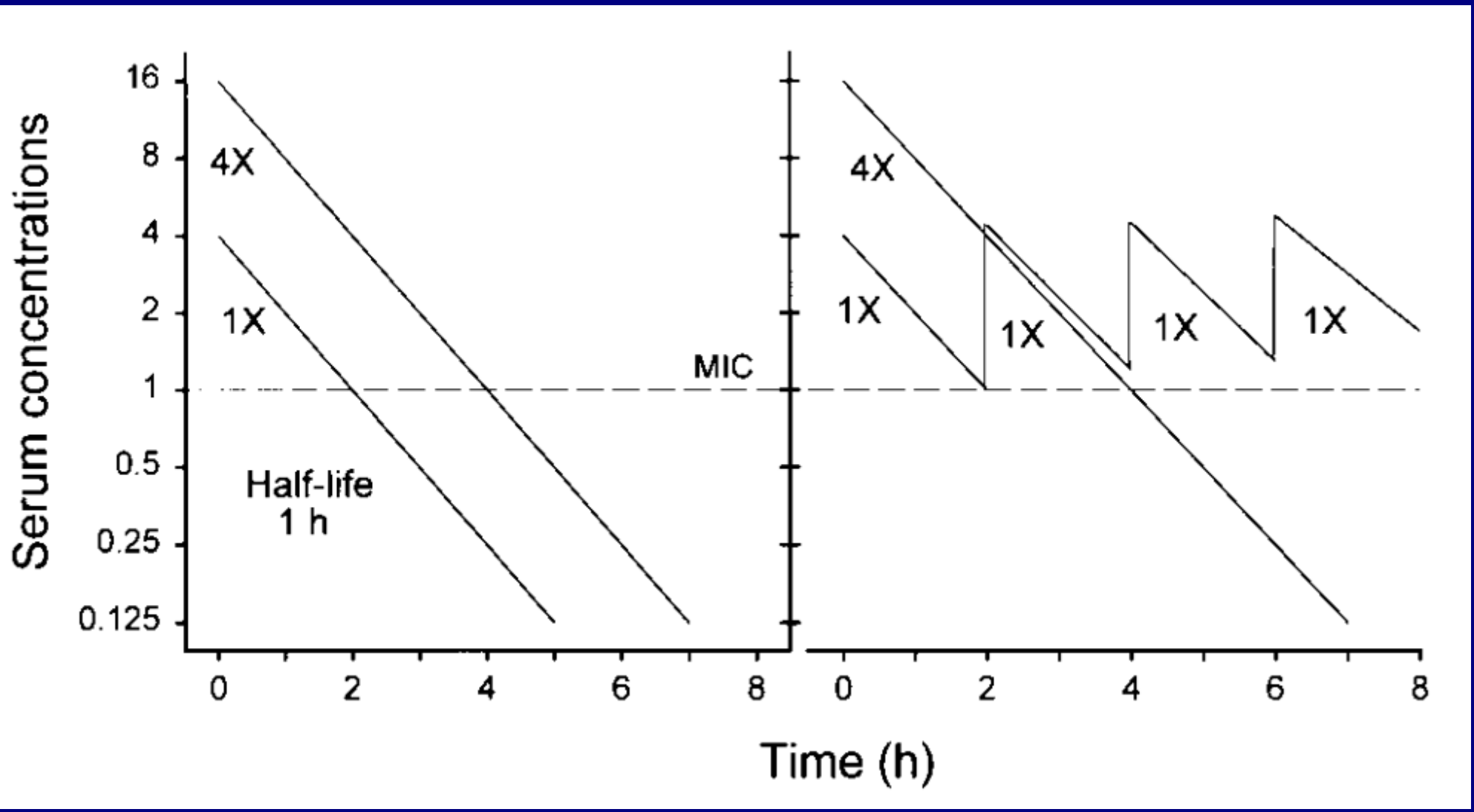


Figure 4. Relationship between three pharmacodynamic parameters ([*A*] peak/MIC ratio; [*B*] 24-hour AUC [area under the concentration-vs.-time curve]/MIC ratio; and [*C*] percentage of time that serum levels exceed the MIC) and the number of *Klebsiella pneumoniae* ATCC (American Type Culture Collection) 43816 in the lungs of neutropenic mice after 24 hours of therapy with cefotaxime. Each point represents data for one mouse. The dotted line reflects the number of bacteria at the beginning of therapy. The R^2 value in *C* represents the percentage of variation in bacterial numbers that could be attributed to differences in the time above the MIC. Reprinted with permission from *Diagnostic Microbiology and Infectious Diseases* [25].

Table 1. Pharmacokinetic and pharmacodynamic parameters correlating with antibacterial efficacy in animal infection models.

Parameter	Drugs
Time above the MIC	Penicillins, cephalosporins, carbapenems, aztreonam, macrolides, and clindamycin
24-hour AUC/MIC	Aminoglycosides, fluoroquinolones, azithromycin, tetracyclines, vancomycin, and quinupristin/dalfopristin
Peak/MIC	Aminoglycosides and fluoroquinolones

NOTE. AUC = Area under the concentration-vs.-time curve.


Serum concentrations
16
8
4
2
1
0.5
0.25
0.125
4X
1X
Half-life
1 h
MIC
4X
1X
1X
1X
1X
0
2
4
6
8
0
2
4
6
8
Time (h)

CLSI M100-S20 (2010) Cephalosporin and Aztreonam Breakpoint Revisions Fact Sheet

MIC breakpoints (µg/ml):

Agent	Old (M100-S19)			Revised (M100-S20)		
	Susc	Int	Res	Susc	Int	Res
Cefazolin	≤8	16	≥32	≤1	2	≥4
Cefotaxime	≤8	16-32	≥64	≤1	2	≥4
Ceftizoxime	≤8	16-32	≥64	≤1	2	≥4
Ceftriaxone	≤8	16-32	≥64	≤1	2	≥4
Ceftazidime	≤8	16	≥32	≤4	8	≥16
Aztreonam	≤8	16	≥32	≤4	8	≥16

MIC breakpoints (µg/ml)

Agent	M100-S19			M100-S20		
	Susc	Int	Res	Susc	Int	Res
Cefuroxime (parenteral)	≤8	16	≥32	≤8	16	≥32
Cefepime	≤8	16	≥32	≤8	16	≥32
Cefotetan	≤16	32	≥64	≤16	32	≥64
Cefoxitin	≤8	16	≥32	≤8	16	≥32

REVIEW

Treatment of infections with ESBL-producing organisms: pharmacokinetic and pharmacodynamic considerations

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Table 1. Clinical outcome in 42 patients with ESBL-producing *Klebsiella* spp. or *E. coli* bacteraemia and treated with cephalosporin monotherapy

Outcome	MIC ≤ 1 mg/L	MIC 2 mg/L	MIC 4 mg/L	MIC 8 mg/L
Success	81%	67%	27%	11%
Failure	19%	33%	73%	89%

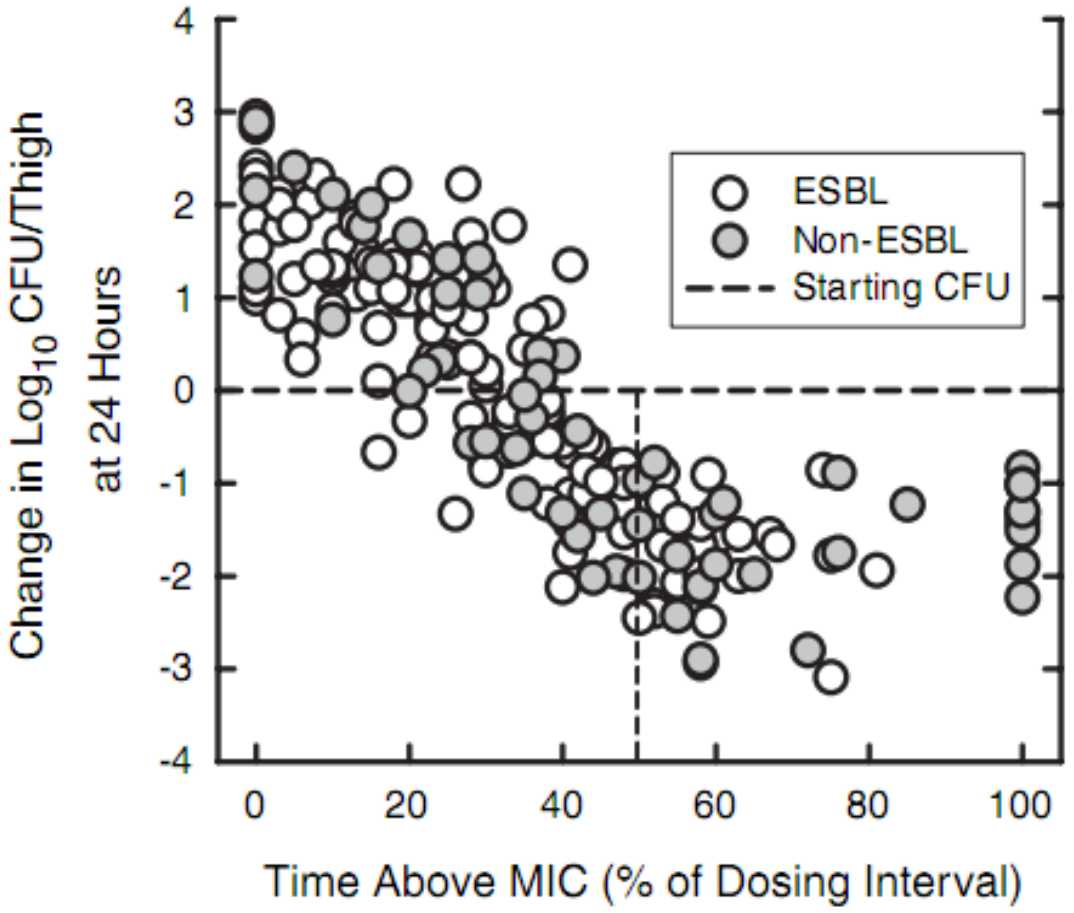
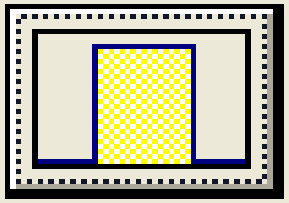


Fig. 3. Relationship between cephalosporin percentage time above MIC and microbiological efficacy against Enterobacteriaciae in a murine thigh infection model. Hollow symbols represent data with ESBL-producing organisms. Solid symbols represents data with non-ESBL-producing organisms. The dashed horizontal line represents the burden of organisms at the start of therapy. The vertical dashed line represent the %T > MIC target associated with a net static effect.

Table 2. Monte Carlo simulation of ceftriaxone: percentage of 10 000 patients attaining indicated pharmacokinetic/pharmacodynamic exposure target

	%*T* > MIC with 2 g every 24 h			
	40%	**50%**	**60%**	**70%**
0.5	100	100	100	100
1	100	100	100	99
2	100	99	93	74
4	87	58	25	6
8	8	1	0	0
16	0	0	0	0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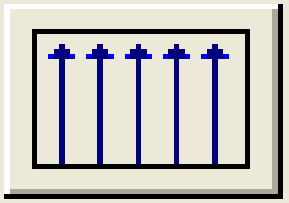
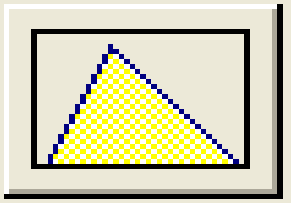
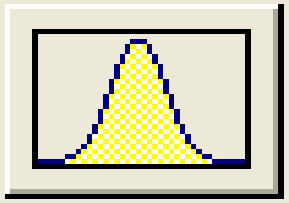

Discrete


Triangular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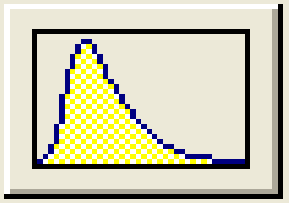
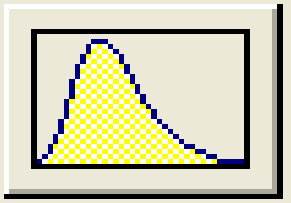
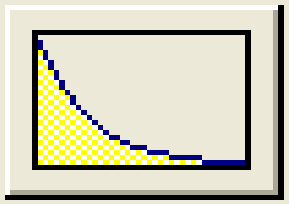
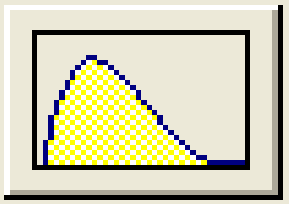
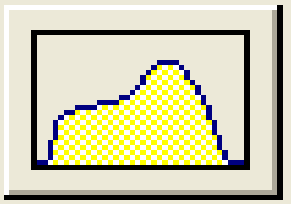
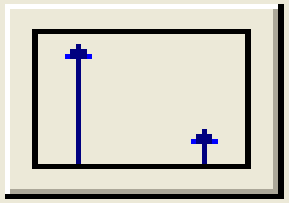

Lognormal

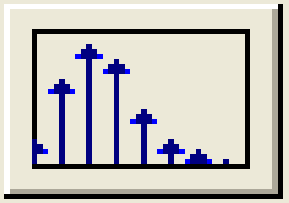

Gamma

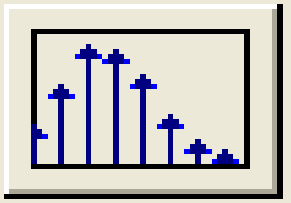

Exponential

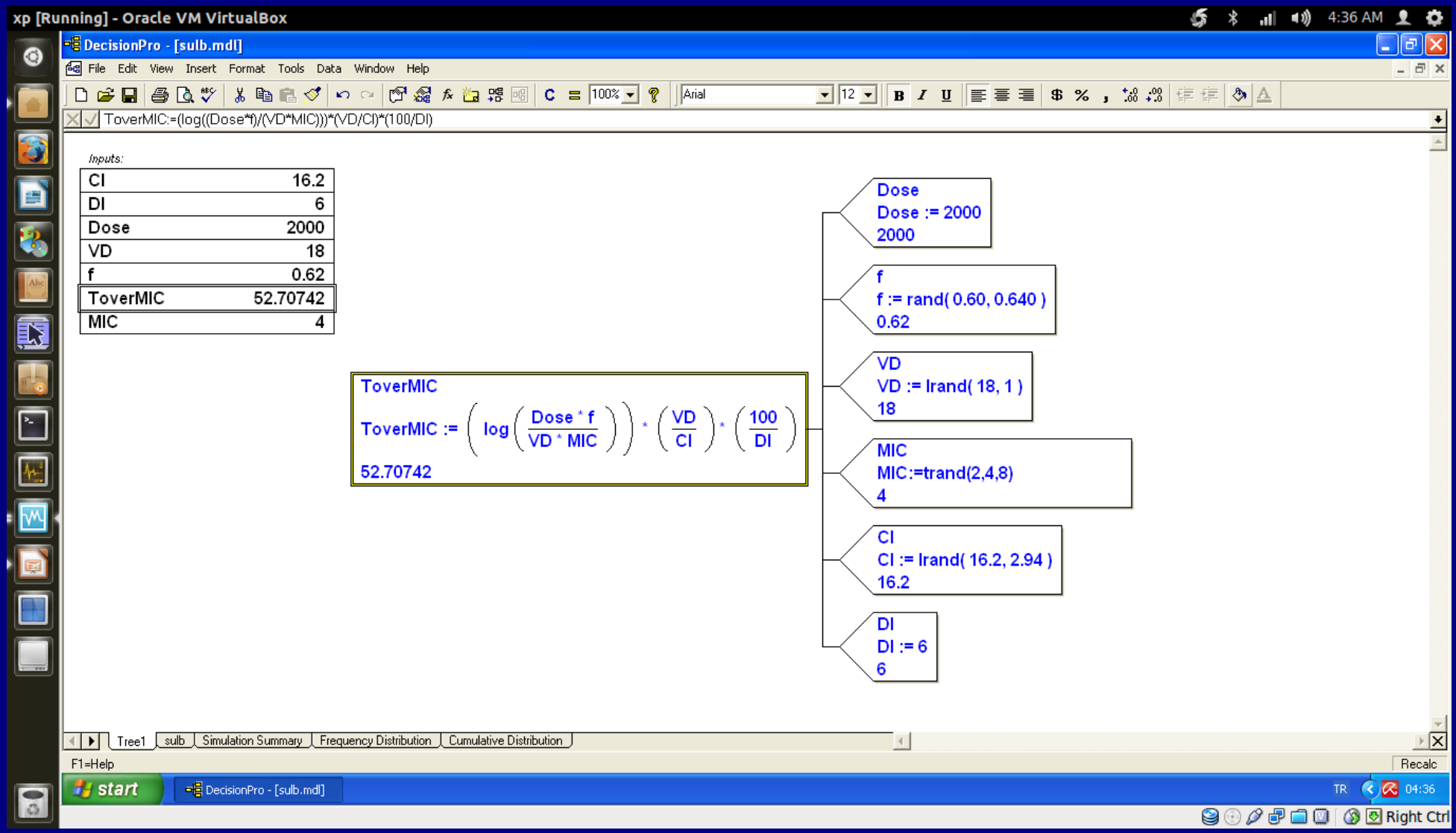

Beta

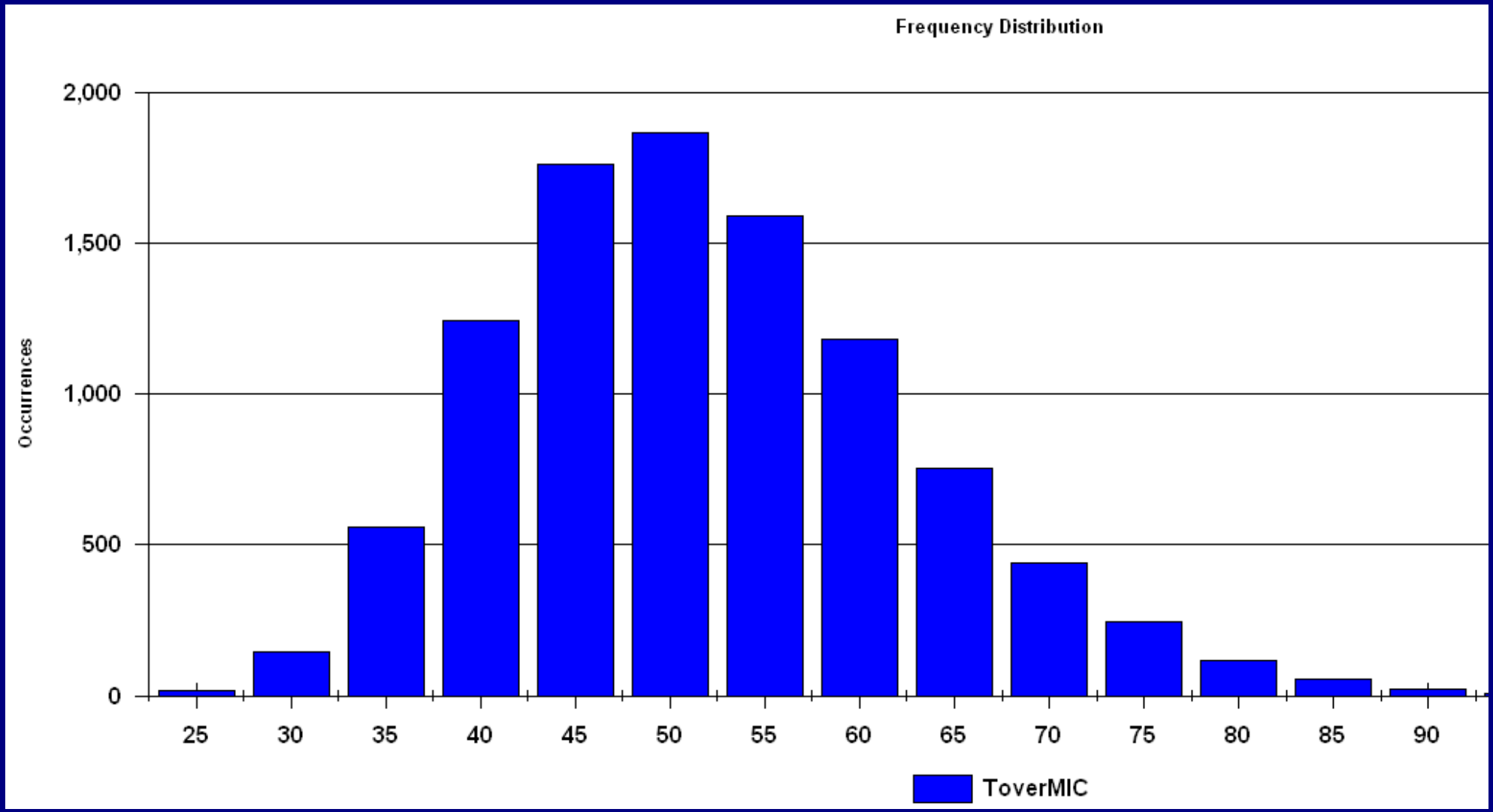

Custom

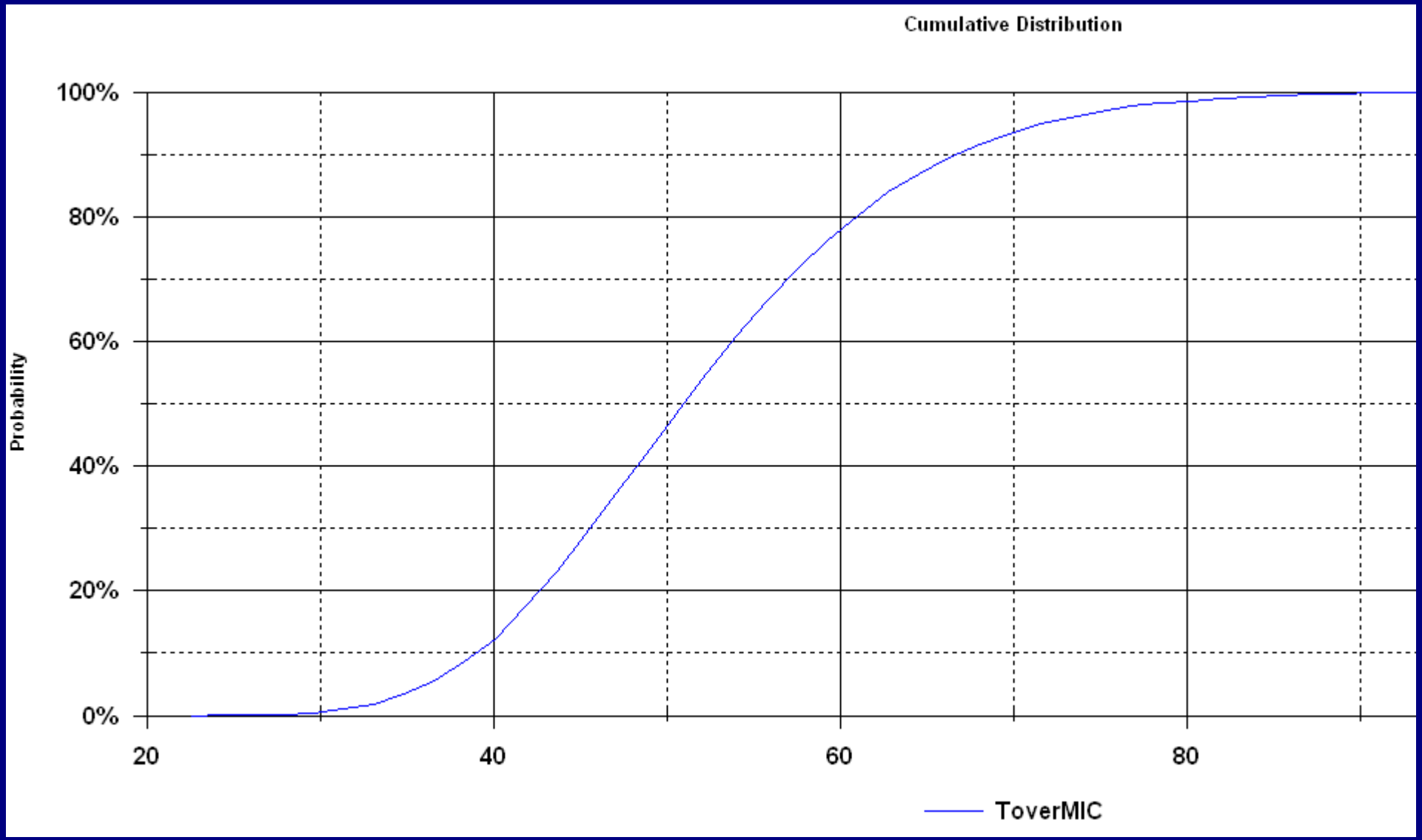

Bernoulli

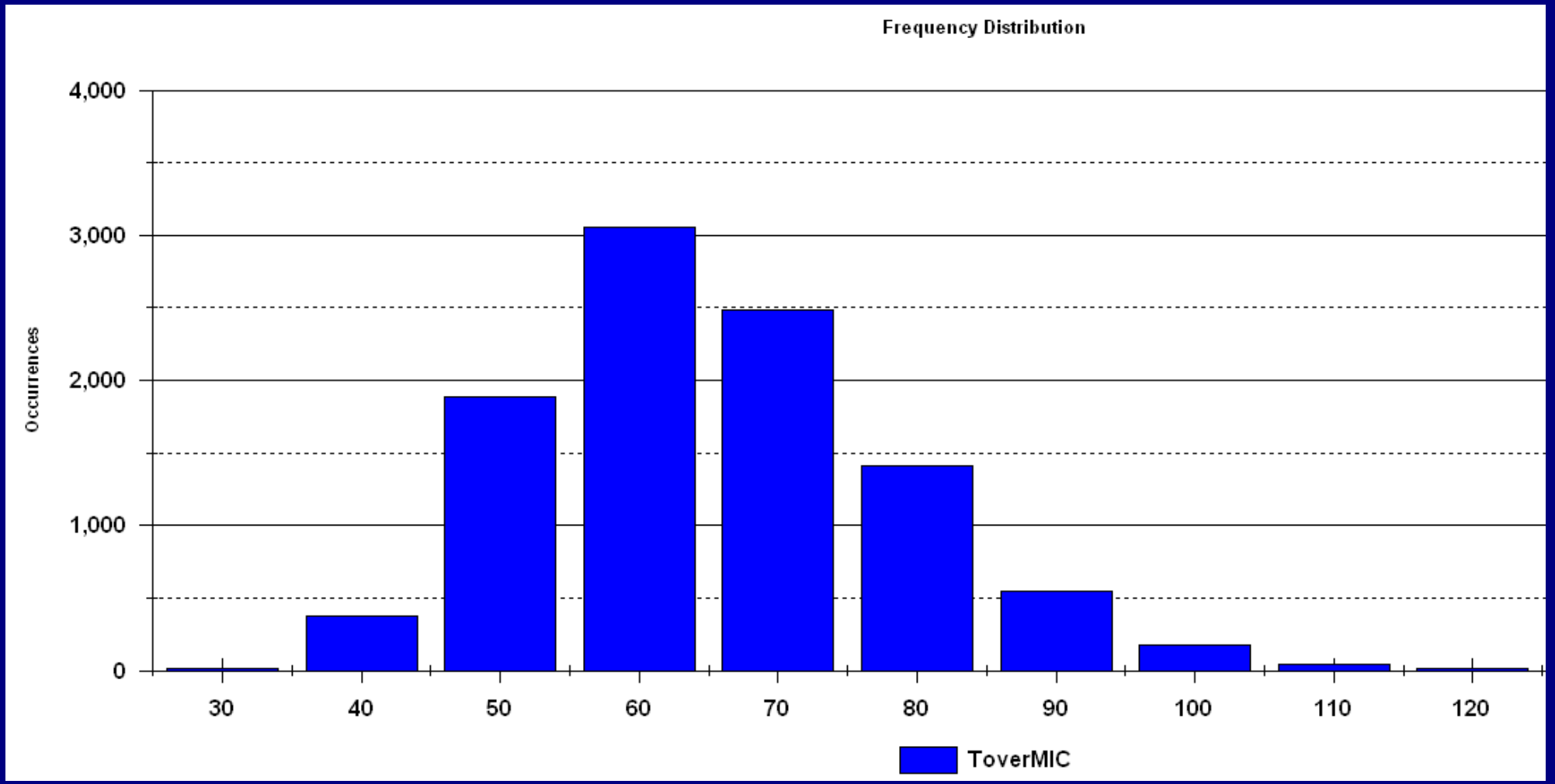

Binomial

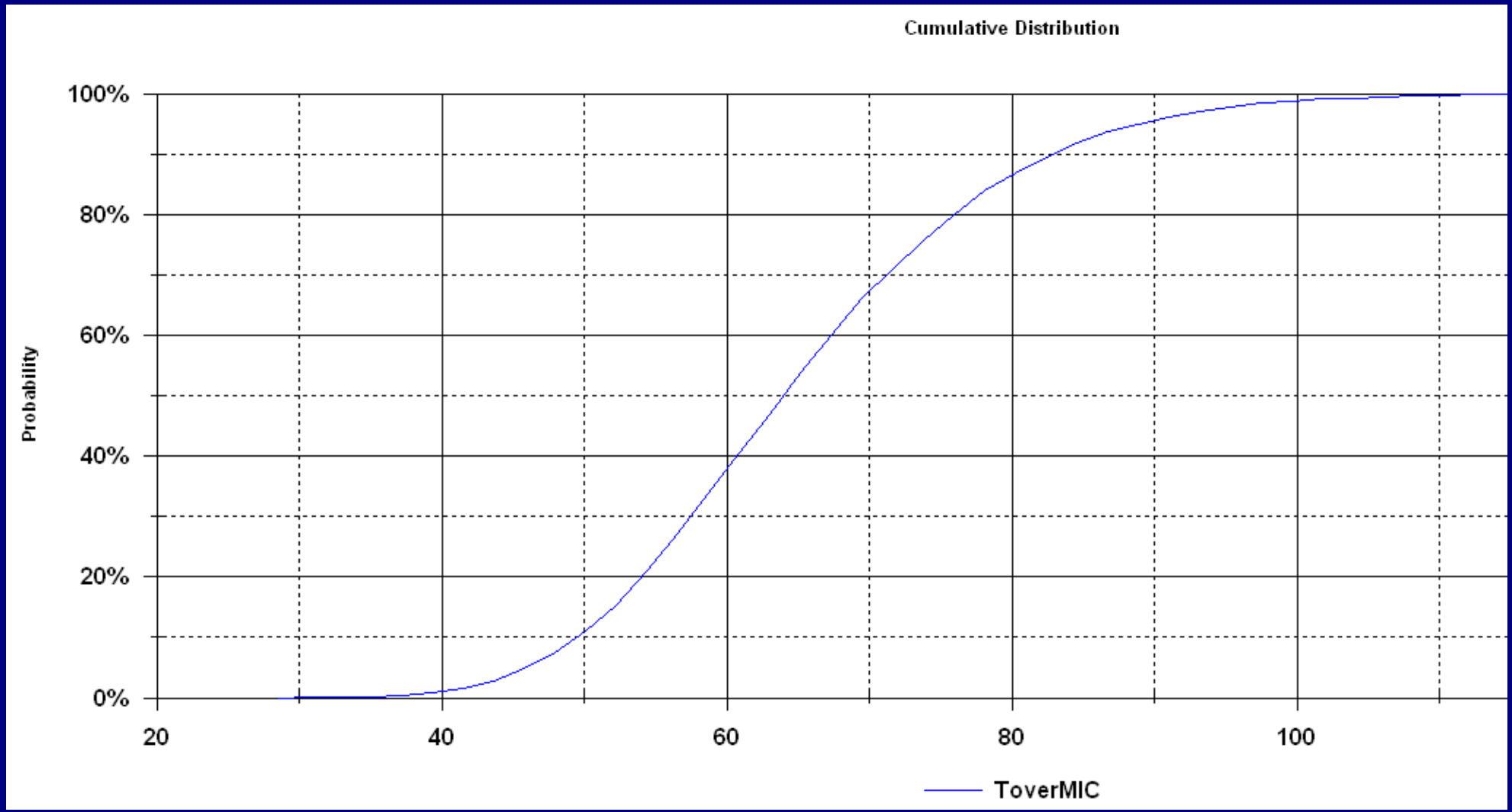

Poisson


xp [Running] - Oracle VM VirtualBox
4:36 AM
DecisionPro - [sulb.mdl]
File Edit View Insert Format Tools Data Window Help
ToverMIC:=(log((Dose*f)/(VD*MIC)))*(VD/CI)*(100/DI)
Inputs:
CI 16.2
DI 6
Dose 2000
VD 18
f 0.62
ToverMIC 52.70742
MIC 4
ToverMIC
ToverMIC := log(Dose * f / VD * MIC) * (VD / CI) * (100 / DI)
52.70742
Dose
Dose := 2000
2000
f
f := rand(0.60, 0.640)
0.62
VD
VD := lrand(18, 1)
18
MIC
MIC:=trand(2,4,8)
4
CI
CI := lrand(16.2, 2.94)
16.2
DI
DI := 6
6
Tree1 sulb Simulation Summary Frequency Distribution Cumulative Distribution
F1=Help
Recalc
start
DecisionPro - [sulb.mdl]
TR 04:36
Right Ctrl


Frequency Distribution
Occurrences
2,000
1,500
1,000
500
0
25
30
35
40
45
50
55
60
65
70
75
80
85
90
ToverMIC


Cumulative Distribution
Probability
100%
80%
60%
40%
20%
0%
20
40
60
80
ToverMIC


Frequency Distribution
Occurrences
4,000
3,000
2,000
1,000
0
30
40
50
60
70
80
90
100
110
120
ToverMIC


Cumulative Distribution
100%
80%
60%
40%
20%
0%
Probability
20
40
60
80
100
ToverMIC