

# CALC FROM STRUCTURE



$$E = \frac{1}{r_{ij}} \cdot \frac{q_i \cdot q_j}{\epsilon}$$

COULOMB

HBOND

VDW

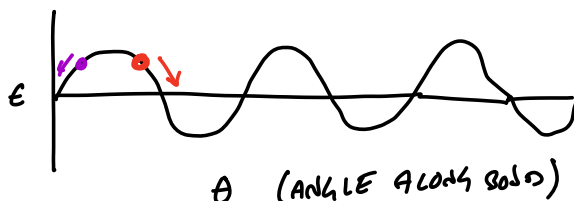
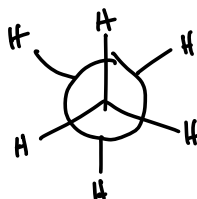
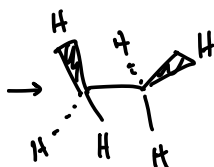
...

①

How do you SAMPLE  
PROTEIN/LIGAND  
MOVEMENT?

②  
pKa VALUES AS SENSORS  
TO LEARN EXPERIMENTALLY  
ABOUT INTERACTIONS.

①



## MOLECULAR DYNAMICS CALCULATION:

$$\frac{dU}{d\theta} = \text{FORCE}$$

IF WE KNOW:

- POSITIONS
- VELOCITIES

} ALL ATOMS

IF WE CALCULATE  
- FORCES

CAN PREDICT TIME EVOLVED  
OF SYSTEM

IN MD SIMULATION: ITERATIVELY CALCULATE FORCE, UPDATE VELOCITY  
UPDATE POSITION, REPEAT.

MAKE MOLECULAR MOVIES.  $\rightarrow$  1 ns / 1 hr

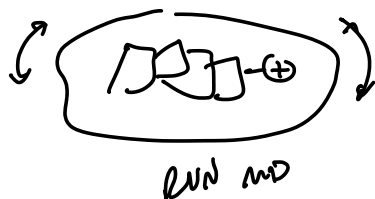
How DOES LIGAND SIT IN POCKET?

$10^{-9}$  s

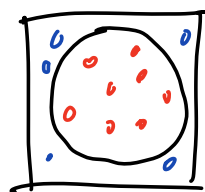
IF YOU WANT  $10^{-3}$  TIMESCALE

1 MILLION HOURS REAL TIME

USEFUL FOR SHORT TIME, SMALL  
SCALE.



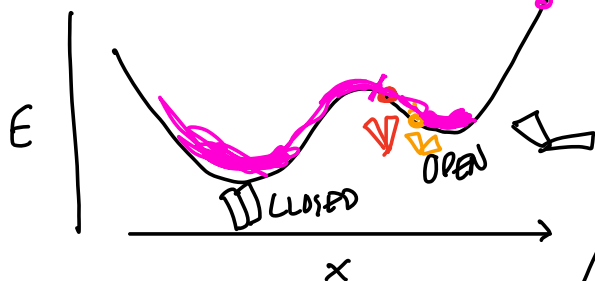
# METROPOLIS - CRITERION MONTE CARLO (MCMC)



CIRCLE AREA

CIRCLE  
IN SQUARE

→ WHAT IS AREA OF CIRCLE?



REPEAT A LOT

ALLOW UPHILL MOVES  
w/ PROBABILITY  
WEIGHTED BY ENERGY.

EXPLORE SPACE WEIGHTED BY PROBABILITY.

① CHOOSE RANDOM START

② CALCULATE ENERGY OF STATE

③ MAKE RANDOM MOVE

④ CALCULATE ENERGY OF NEW STATE.

⑤ IF NEW ENERGY LESS THAN OLD ENERGY, KEEP NEW STATE.

⑥ OTHERWISE:  
IF  $e^{-E/RT} > \text{RANDOM NUMBER}$ ,  
KEEP.



HOW DO YOU KNOW YOU  
SAMPLED ENOUGH?

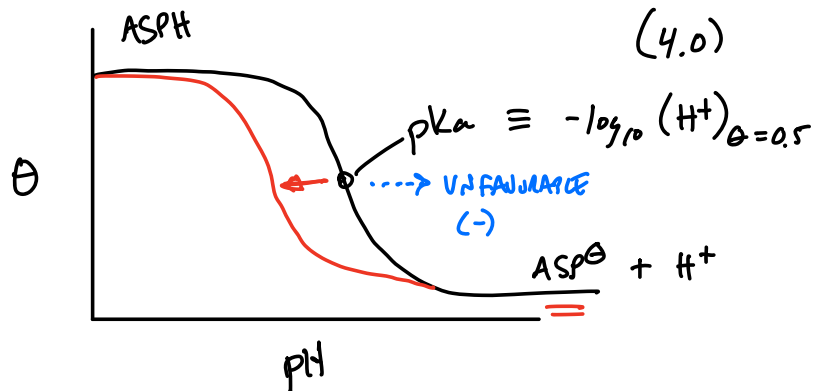
DUMB ANSWER: DO CALL SEVERAL  
TIMES FROM DIFFERENT STARTING  
PLACES.

→ PARALLELIZES VERY WELL. ←

HOW DO WE KNOW WE ARE RIGHT?

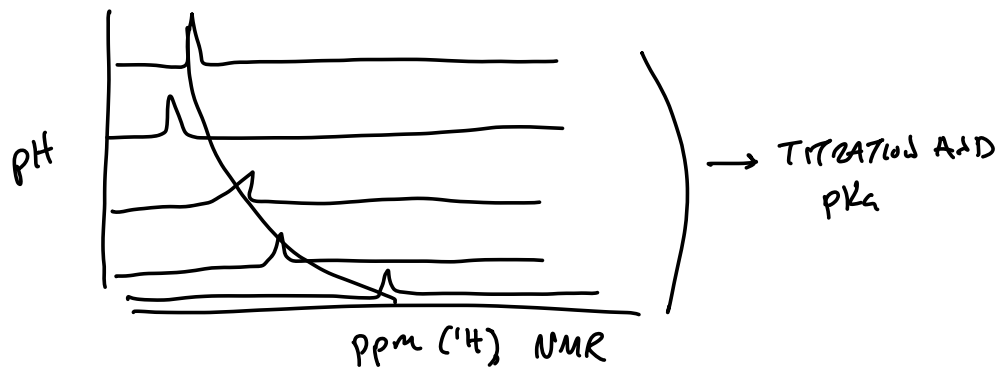
$K_D$  VALUES → CAN WE CALCULATE HOW TIGHTLY A LIGAND  
BINDS?

$pK_a$  VALUES OF IONIZABLE GROUPS ARE GREAT TOOL.

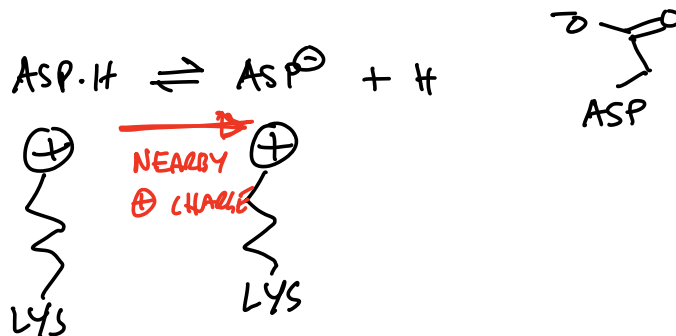


REASONS USEFUL:

- ① LOTS OF IONIZABLE RESIDUES → LOTS OF 'SENSORS'
- ② CAN MEASURE  $pK_a$  BY NMR.  $ASP^-$  AND  $ASPH$  HAVE DIFFERENT CHEMICAL SHIFTS.



- ③ IONIZABLE SIDELAINS ARE CHARGED AND SENSITIVE TO ELECTROSTATIC.



6.0      4.0

↑      ↑

- ④ IF WE MEASURE  $\Delta pK_a$  (WHERE  $\Delta$  IS OBSERVED - REFERENCE) WE LEARN ABOUT ELECTROSTATIC ENVIRONMENT.
- ⑤  $\Delta pK_a$  IS DIRECTLY PROPORTIONAL TO  $\Delta G$