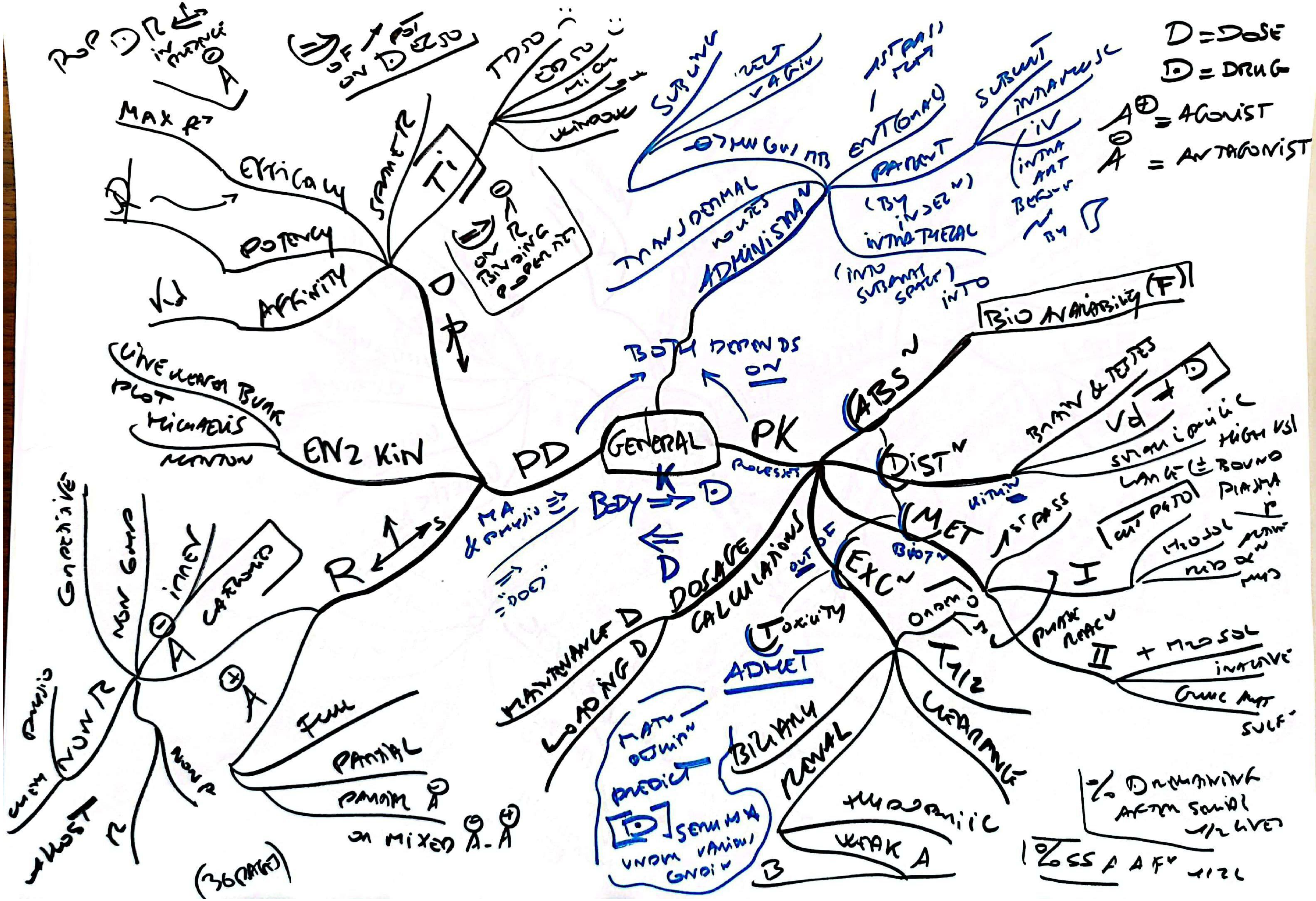
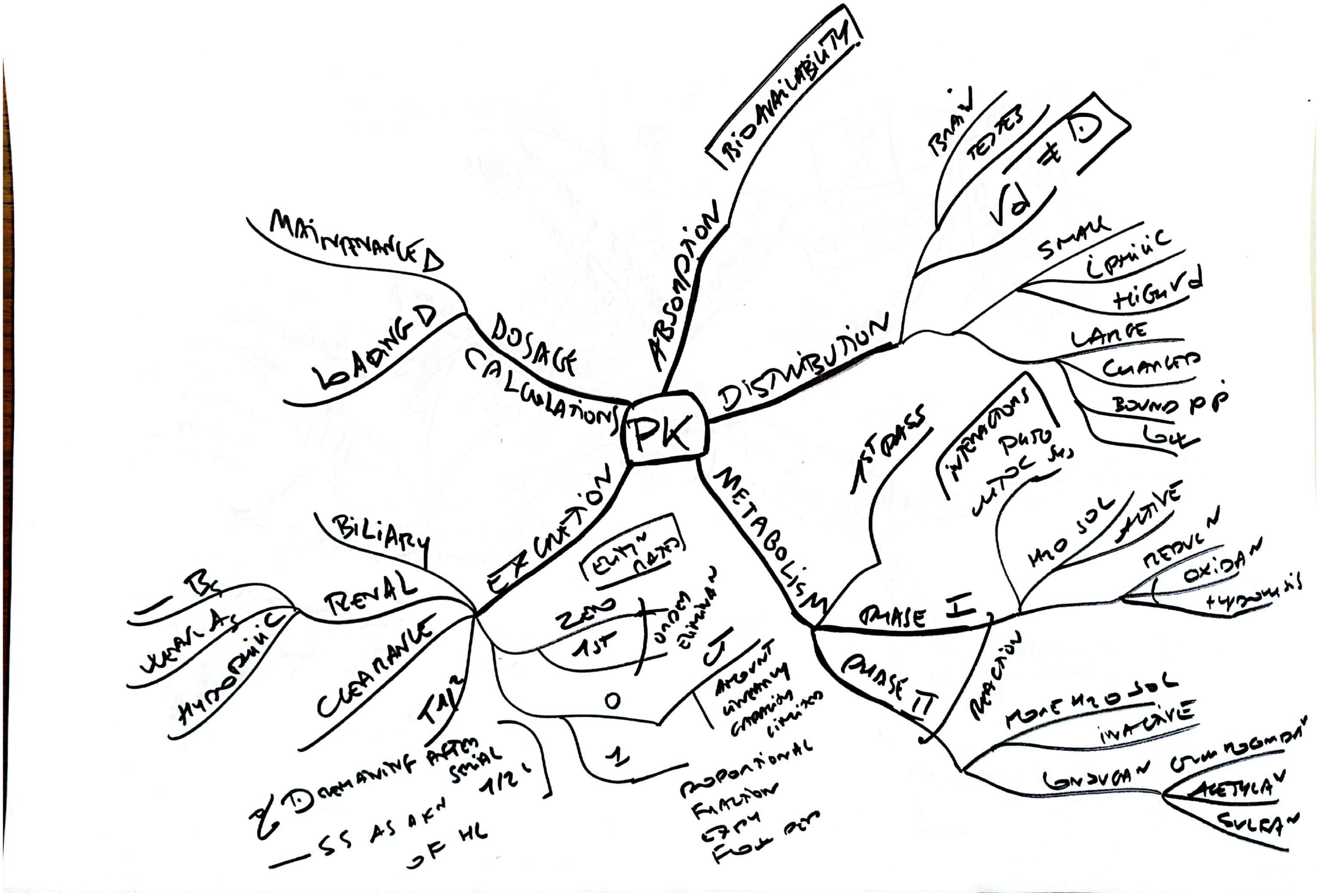
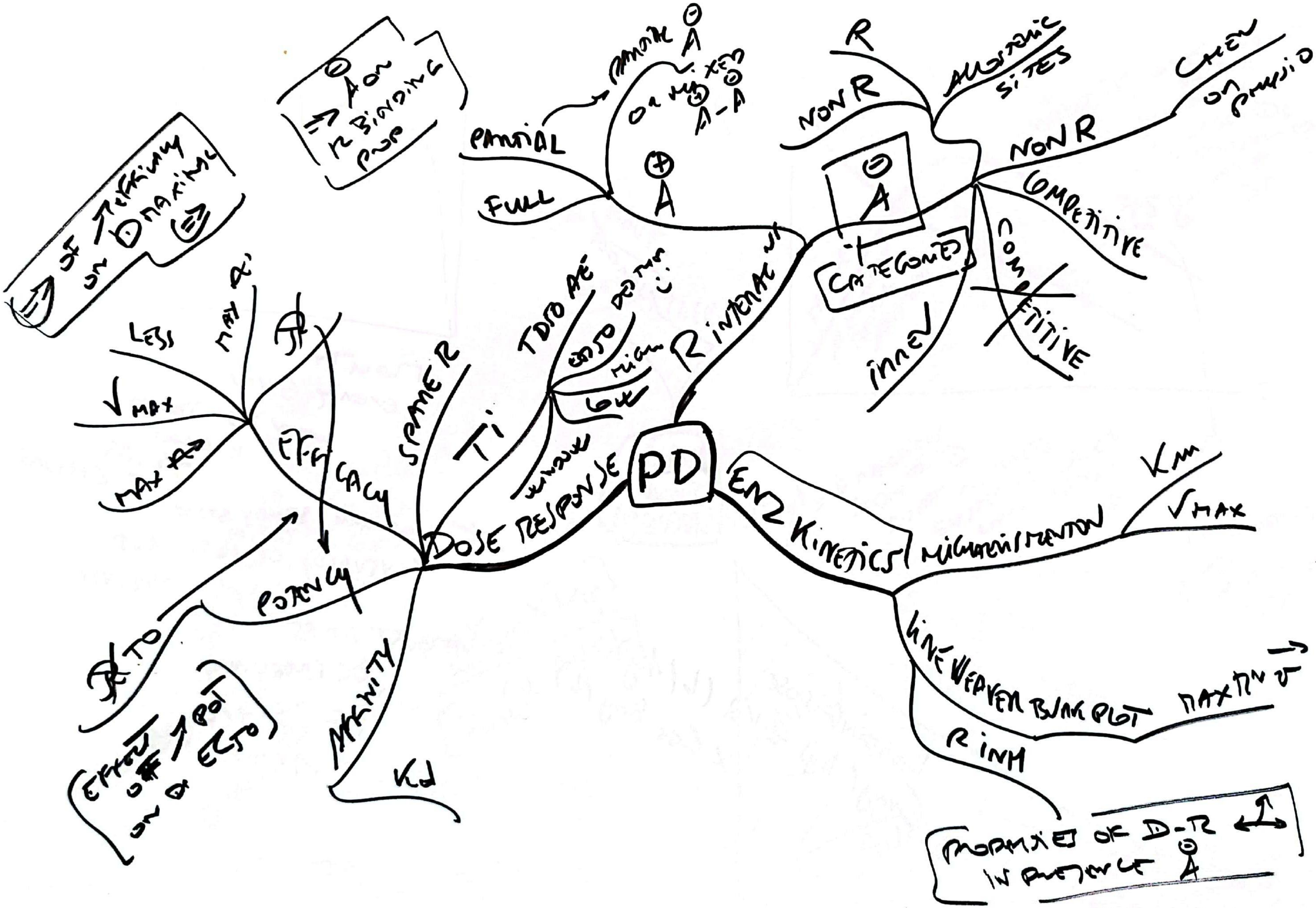
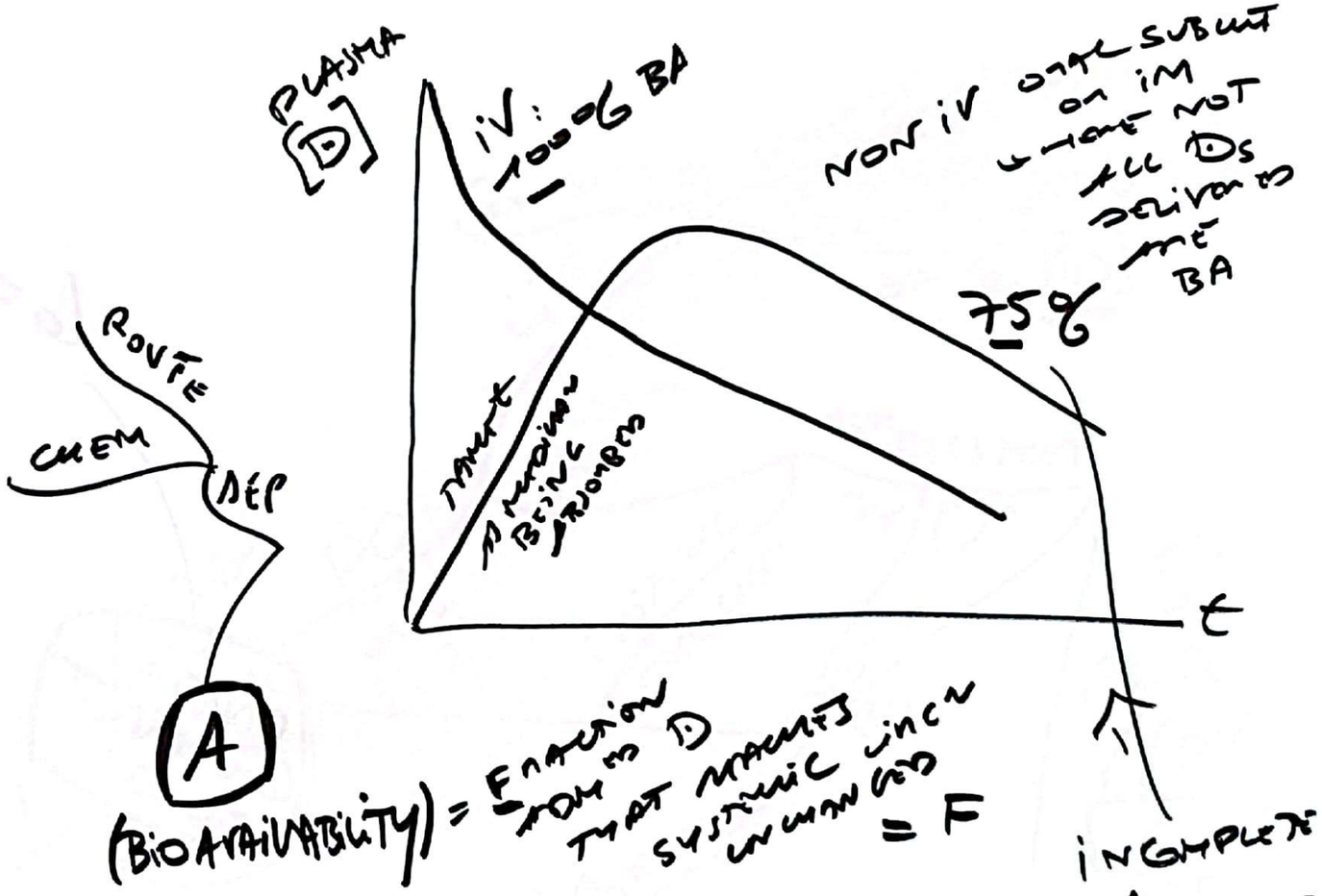


D = DOSE
D = DRUG
A⊕ = AGONIST
A⊖ = ANTAGONIST
PD
GENERAL
PK
K
BODY ⇒ D
⇐ D
BOTH DEPENDS ON
ROUTES ADMINISTRAN
TRANSDERMAL
SUBLING
RECT
VAGIN
1ST PASS
ENTERAL
PARENT
(BY INJECT'N)
SUBCUT
INTRAMUSC
IV
INTRATHECAL
BIO AVAILABILITY (F)
ABS'N
DIST'N
MET
EXC'N
$T_{1/2}$
BRAIN & TESTES
Vd ↑ D
HIGH VD
PLASMA
1ST PASS
I
II + H2O SOL
INACTIVE
SULF-
BILIARY
RENAL
CLEARANCE
THERAPEUTIC
WEAK A
B
% D REMAINING AFTER SEVERAL 1/2 LIVES
TOXICITY
ADMET
PREDICT
DOSAGE CALCULATIONS
MAINTENANCE D
LOADING D
R
ENZ KIN
LINEWEAVER BURK PLOT
MICHAELIS MENTEN
D-R
EFFICACY
POTENCY
AFFINITY
MAX R
SPARE R
Ti
TD50
ED50
WINDOW
POP D R
COMPETITIVE
NON COMP
IRREV
⊖A
⊕A
FULL
PARTIAL
OR MIXED A-A
NON R
ALLOST R
(36 PAGES)





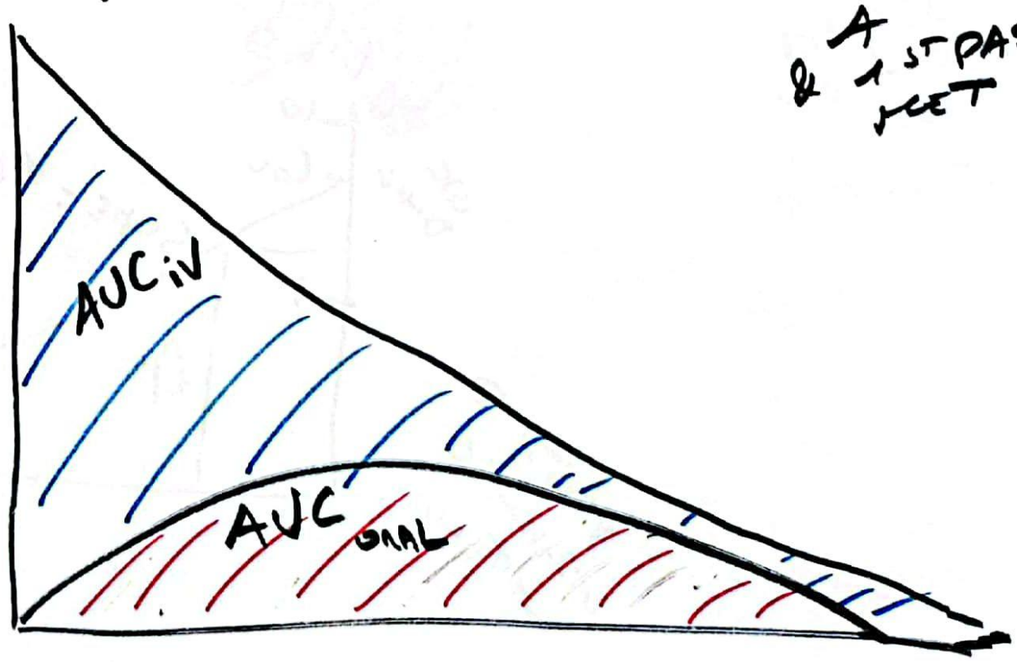
PD
DOSE RESPONSE
EFFICACY
LESS
Vmax
POTENCY
AFFINITY
Kd
SPARE R
Ti
R INTERACT
CATEGORIES
PARTIAL
FULL
NON R
R
ALLOSTERIC SITES
COMPETITIVE
INNER
ENZ KINETICS
Km
Vmax
LINE WEAVER BURK PLOT
R INH

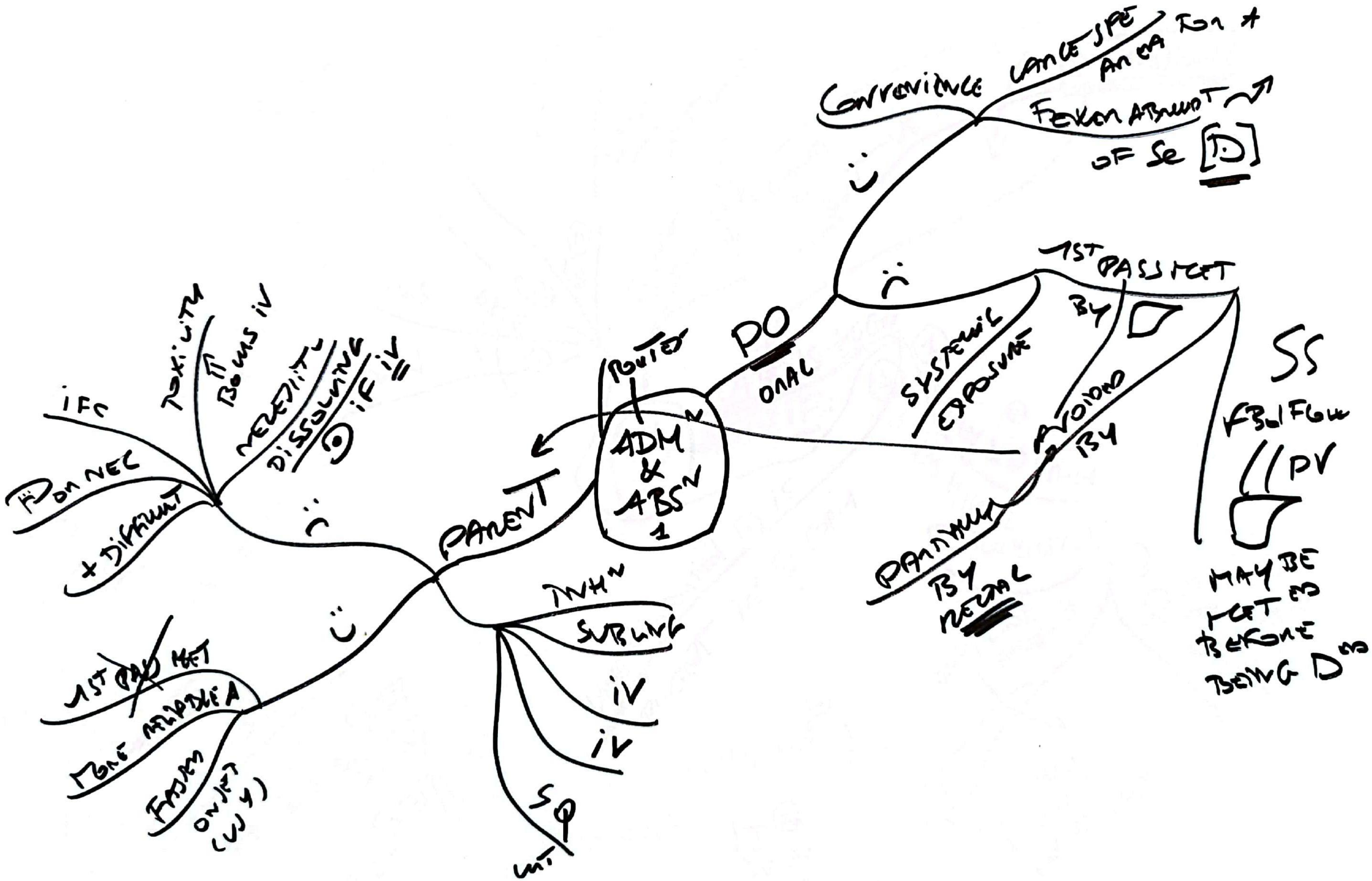


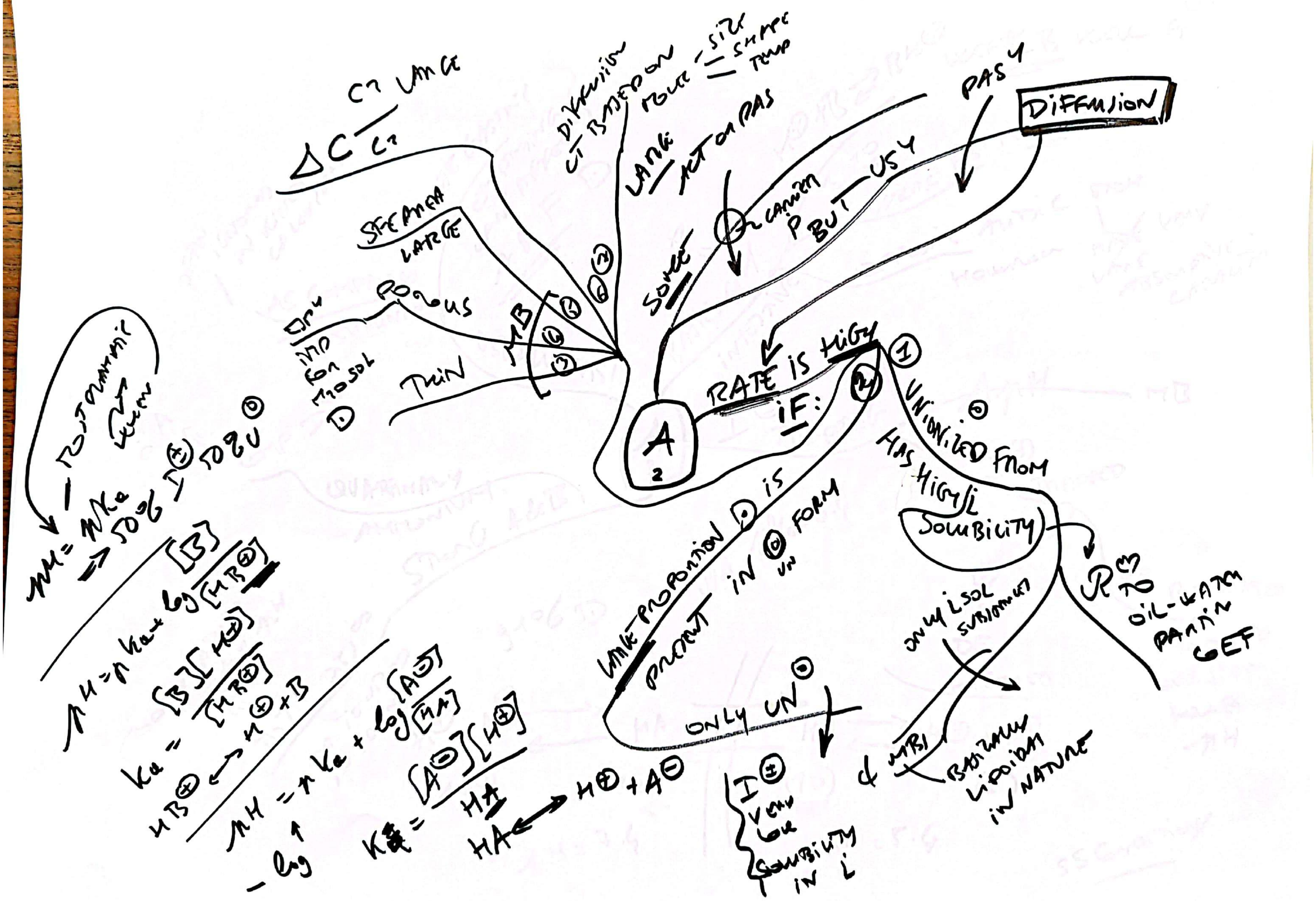
(AREA UNDER CURVE

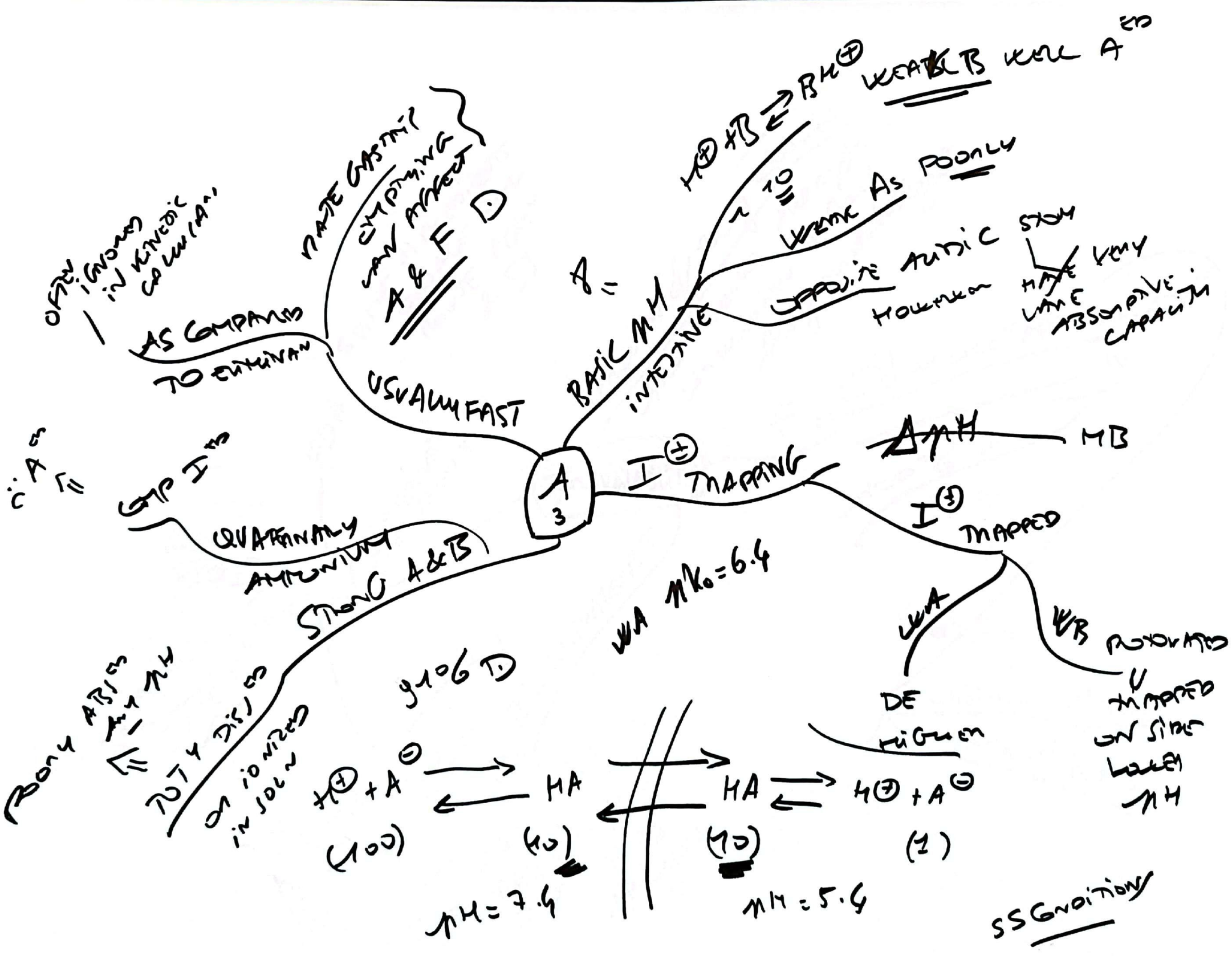
CAN BE CALCULATED

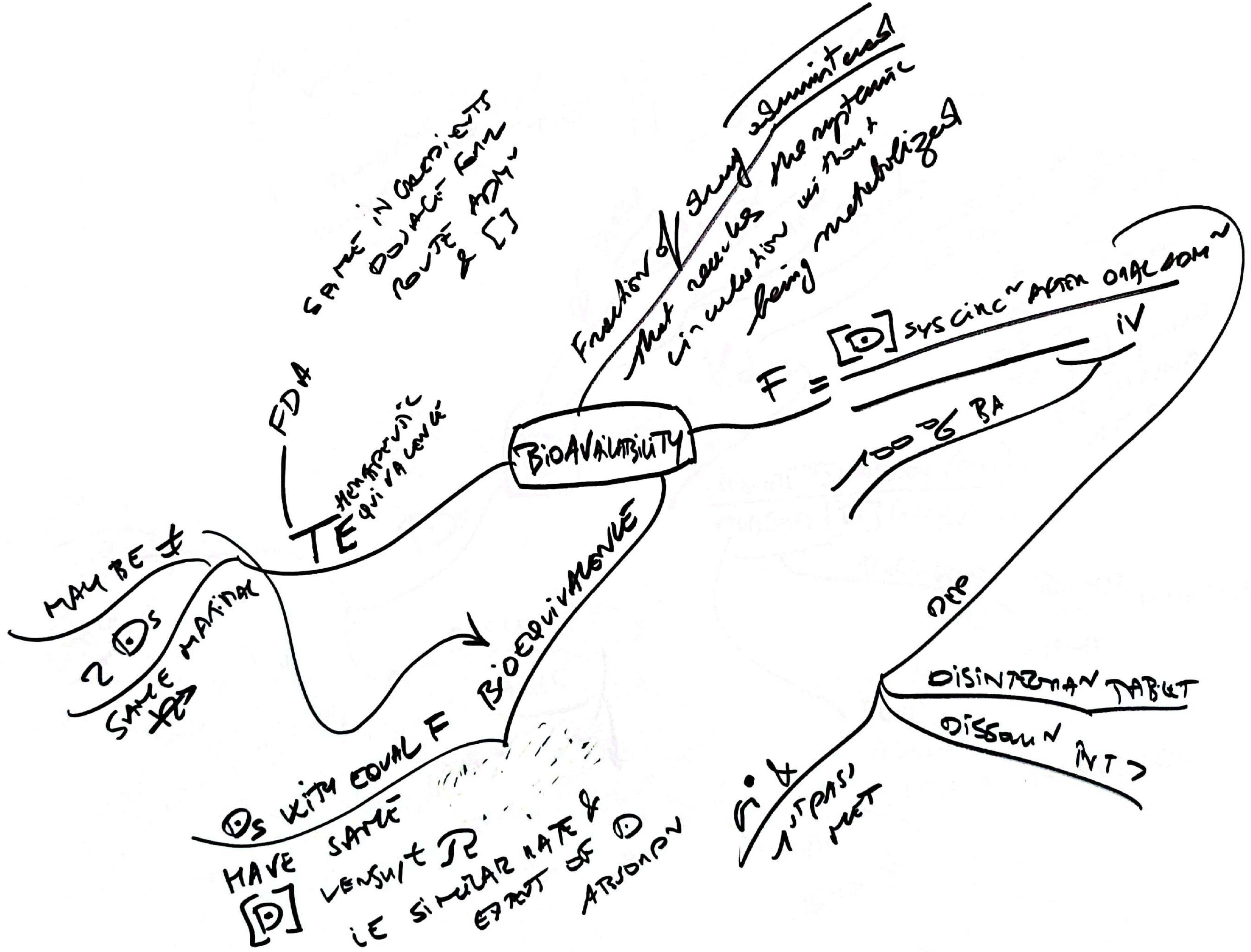
$$F = \frac{[AUC_{oral} \times D_{iv}]}{[D_{oral} \times AUC_{iv}]}$$






DIFFUSION
RATE IS HIGH
IF:
A
UNIONIZED FROM
HAS HIGH L SOLUBILITY
OIL-WATER
LARGE PROPORTION
IS
PRESENT IN
FORM
ONLY UN
IN NATURE
THIN
POROUS
LARGE
ΔC
LARGE
SOLUBILITY
pH = pKa + log [A-]/[HA]
pH = pKa + log [B]/[HB+]
HA ⇌ H+ + A-
HB+ ⇌ H+ + B



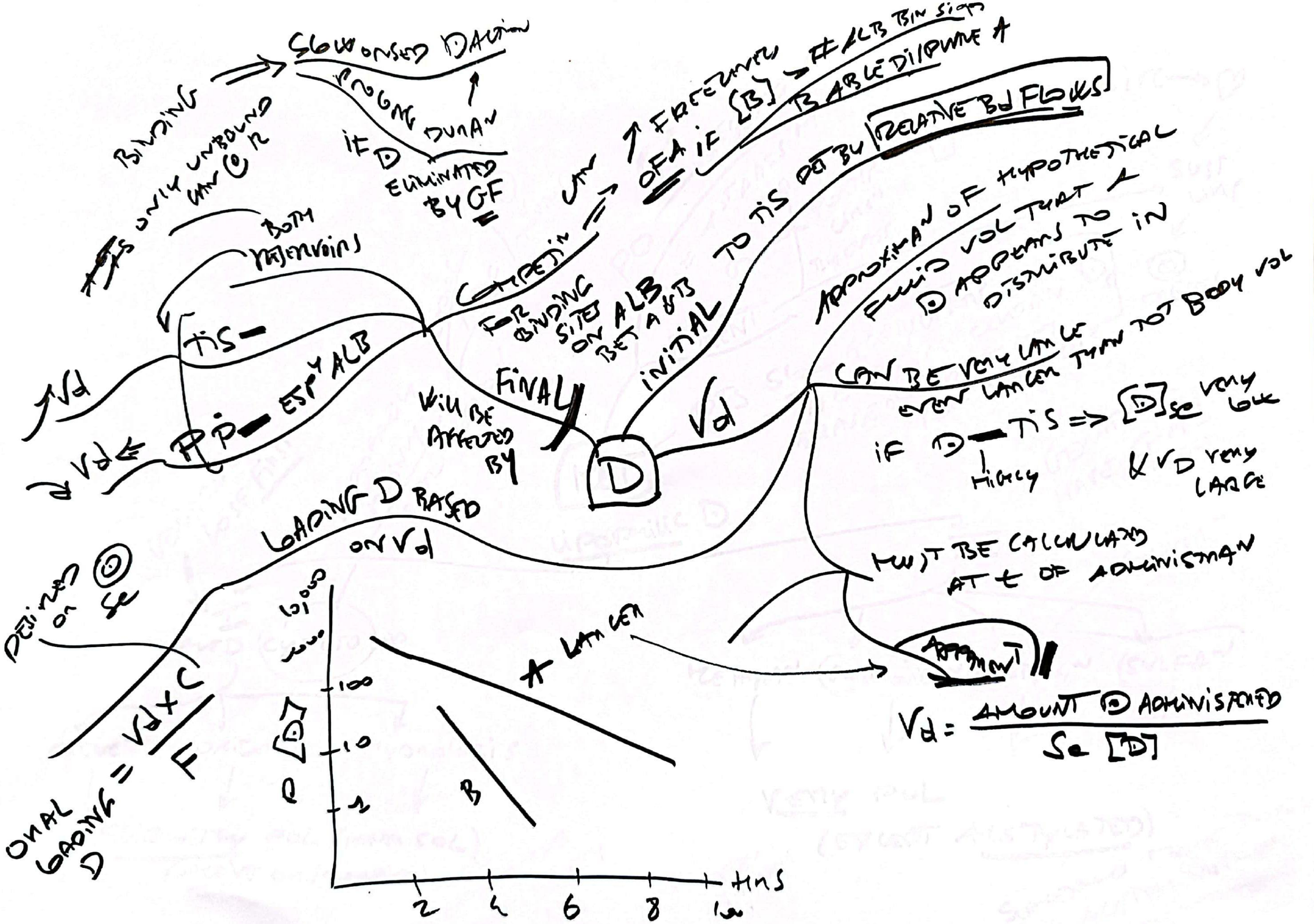

BIOAVAILABILITY
Fraction of drug administered that reaches the systemic circulation without being metabolized
F = [D] sys circ^n after oral adm^n / iv
100% BA
FDA
TE
Therapeutic equivalence
same ingredients dosage form route adm^n & [ ]
May be ≠
2 Ds same material
BIOEQUIVALENCE
Ds with equal F
have same [D]
ie similar rate & extent of D absorption
Dep
Disintegration tablet
Dissolu^n in GI
GI &
1st pass met

V_d

- THEORICAL V OCCUPIED BY THE TOT AMOUNT OF D IN BODY RELATIVE TO ITS P [ ]
- APPARENT V_d OF P $\dot{P}$-D CAN BE ALTERED BY [ ] & [ ] DISEASE ($\downarrow \dot{P}$ BINDING, $V_d \uparrow$)
- Ds MAY DISTRIBUTE IN MORE THAN 1 COMP
- HEMODIALYSIS MOST EFFECTIVE FOR Ds WITH LOW V_d

$$V_d = \frac{\text{AMOUNT D IN BODY}}{[D]P}$$

V_d	COMP	D TYPE
LOW	INTRAVASC	LARGE/CHARGED MOLEC; $\dot{P}\dot{P}$ BOUND
MEDIUM	ECF	SMALL HYDROPHILIC
HIGH	TOT D INF FAT	—— LIPOPHILIC, ESP IF BOUND TO TIS $\dot{P}$



PO → SYSTEMIC

= 1ST PASS M

Gi → PORTAL CIRCN BYPASS → HEPR → IVC → ♡

SYST CIRC → ORGANS

PATIENT

PTS SLOW ACETYLATORS → AE FROM CERTAIN D'S BECAUSE OF → PARENT MOL (EG ISONIAZID)

MET

LIPOPHILIC D

GERIATRIC HAVE G-AS

GERIATRIC LOSE FIRST

SYSTEMIC MAINLY ENTER / LEAVE / D & TOXINS

H

PRED CYP450 DEP

REDUC^N OXIDAN HYDROLYSIS

SLIGHTLY POL (WEAK SOL) (ACTIVE OR INACTIVE)

ADDS OR UNMASKS POLAR MOIETY IN D

II

GLUCUR^N

METHYLAN GLUCURONIDAN ACETYLAN SULFAN

VERY POL (EXCEPT ACETYLATED)

OFTEN INACTIVE

SOMETIMES MORE TOXIC ACETAMINOPHEN

CYP450

⊕

CHRONIC ALCOHOLICS → ALC USE •

STEAL
- PHEN
- PHEN
- NEVER
- REFUSE
- GRISEO
- CARB

&

- ST JOHN'S WORT
- PHENYTOIN •
- PHENOBARBITAL (BARB) •
- NEVIRAPINE
- RIFAMPICIN •
- GRISEOFULVIN
- CARBAMAZEPINE
- CIGARETTE SMOKE
- OMEPRAZOLE
- DOXORUBICIN
- NEFAZODONE
- VALPROIC ACID
- ZILEUTON

S

- ALWAYS (A) ANTIEPIL
- THINK (T) THEOPHYLLINE
- WHEN (W) WARFARIN
- OUTDOORS (O) OCPs

⊖

AAA ↑ ALC ABUSE
- R RITONAVIR •
- A AMIODARONE
- C CIMETIDINE •
- K KETOCONAZOLE •
- S SULFONAMIDES

IN ISONIAZID (INH)

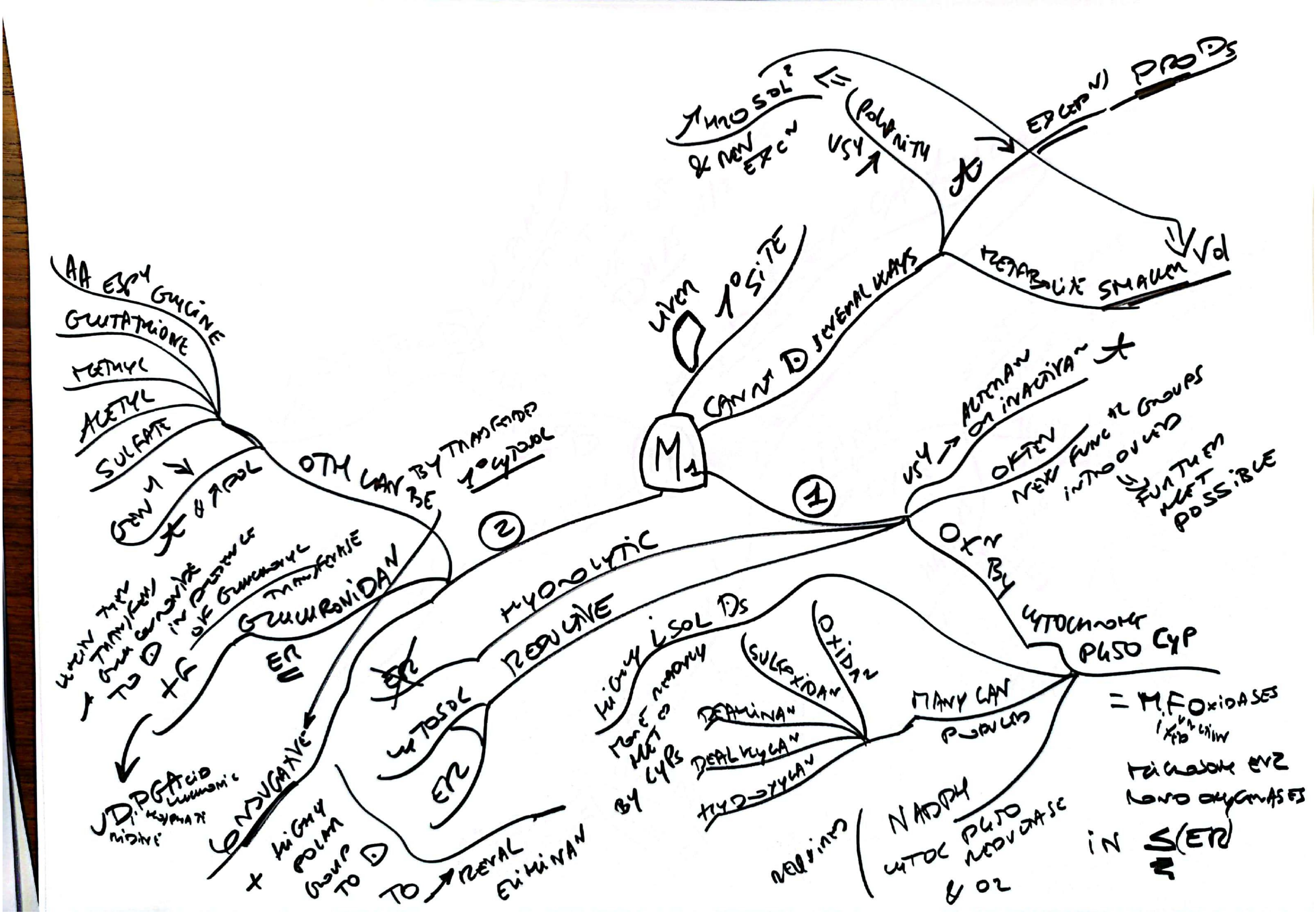
G GRAPEFRUIT •

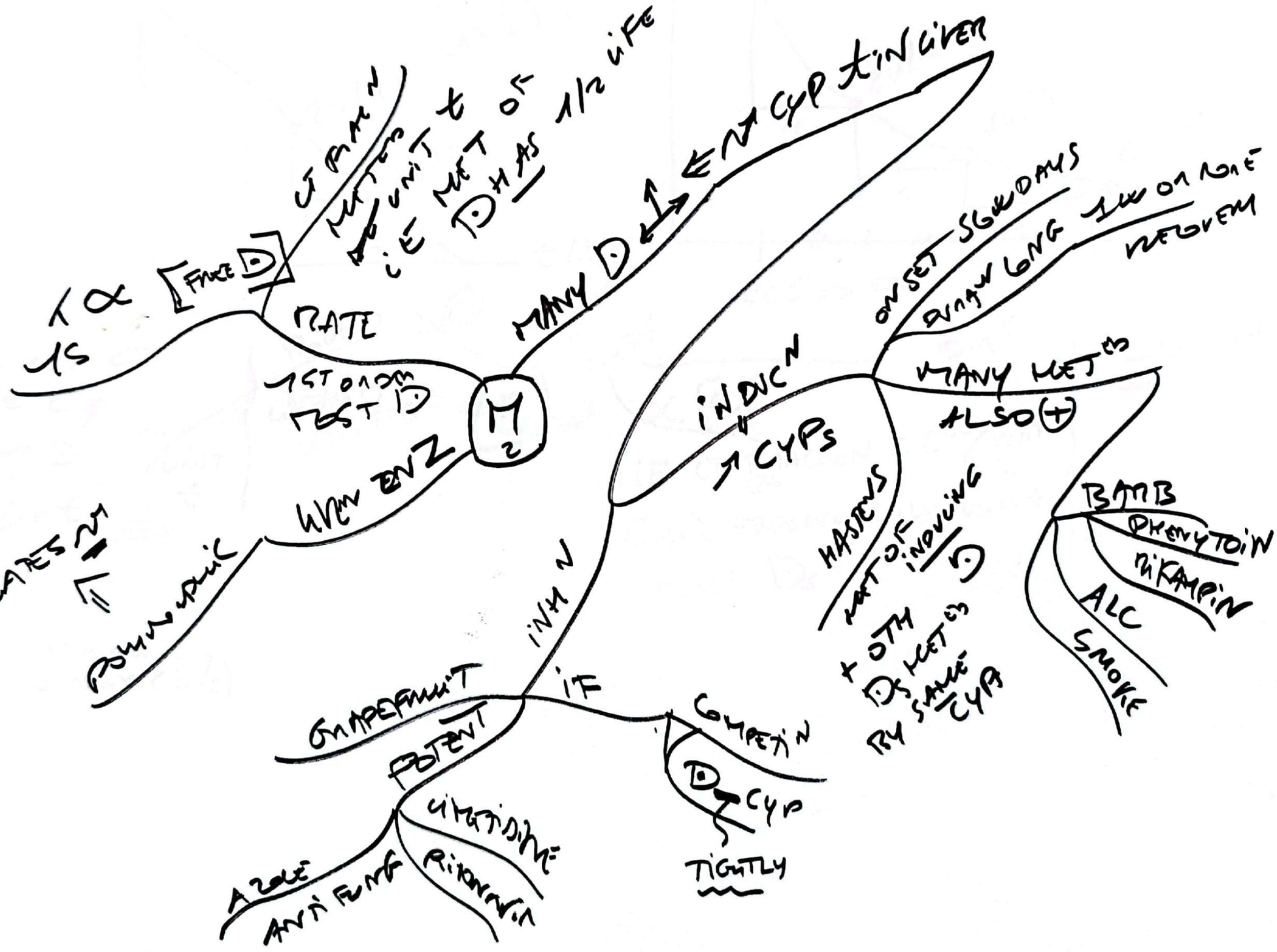
GQ QUINIDINE

MACROLIDES (AZITHROMYCIN)

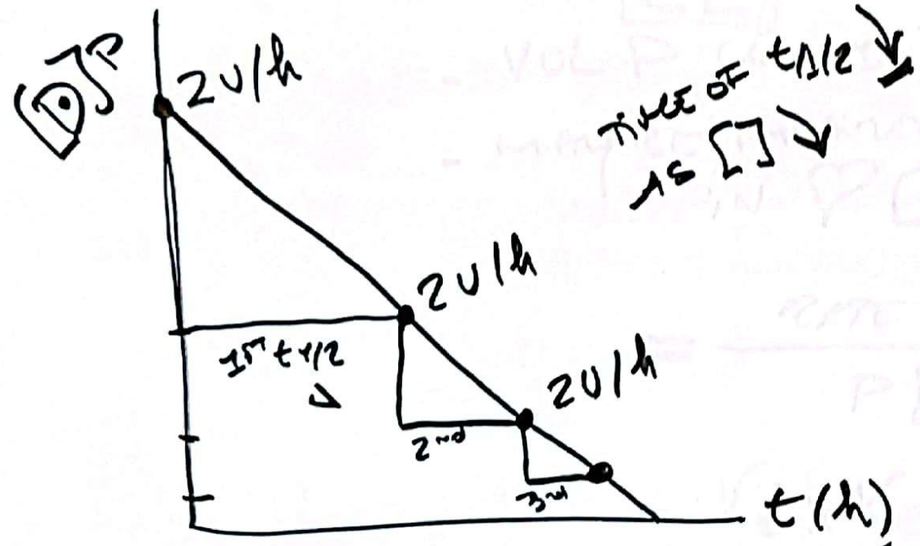
MACRAME

- FLUOXETINE
- VERAPAMIL
- DISULFIRAM
- METRONIDAZOLE
- CIPROFLOXIN
- GEMFIBROZIL

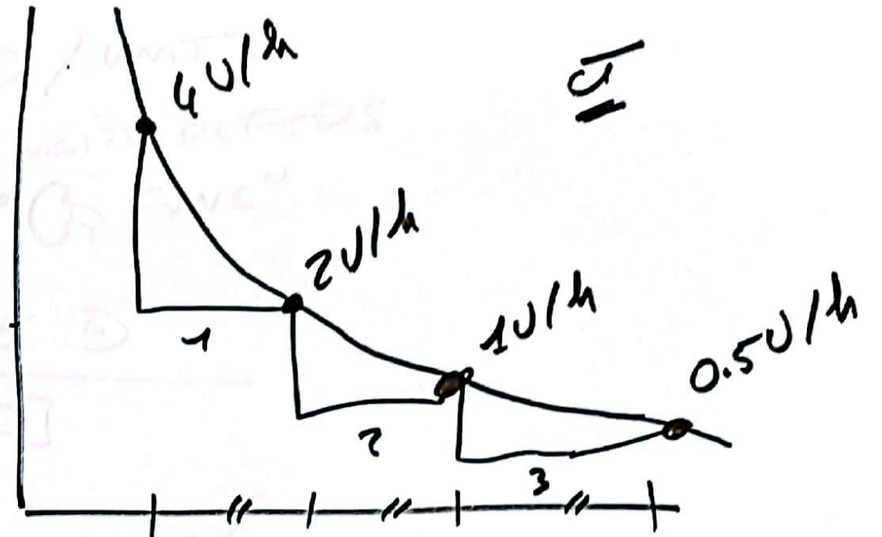




ELIMINATION RATE (= SLOPE)



TIME OF $t_{1/2}$ ↓ IS [ ] ↓



- RATE OF ELIM'N IS CT REGARDLESS OF C_p (IE, CT AMOUNT D ELIM'D / UNIT t)
- C_p ↓ CONTINUOUSLY WITH t
- EX PHENYTOIN, ETHANOL, ASPIRIN (AT HIGH OR TOXIC [ ]s)

ROUND, CAPACITY-LIMITED

E

1ST FIRST

∝ [D]

(IE CT FRACTION D ELIM'D / UNIT t)

- C_p ↓ EXPONENTIALLY WITH t
- MOST Ds

ORDER, FLOW-DEP

CL

- VOL P CLEARED D / UNIT T
- MAY BE IMPAIRED WITH DEFECTS IN ♥ 🫁 🫘 FUNC^N

$$= \frac{\text{RATE E D}}{P[D]}$$

$$= V_d \times K_e \rightarrow \in T$$

$t_{1/2}$

REQUIRED TO ↓ AMOUNT D IN BODY BY 1/2 DURING E

SS = DYN ⇌ VERIFIED $[D] = CT$ RATE E = RATE ADM^N

1ST ORDER D INFUSED AT CT RATE

TAKE 4-5 HALF LIVES TO REACH SS

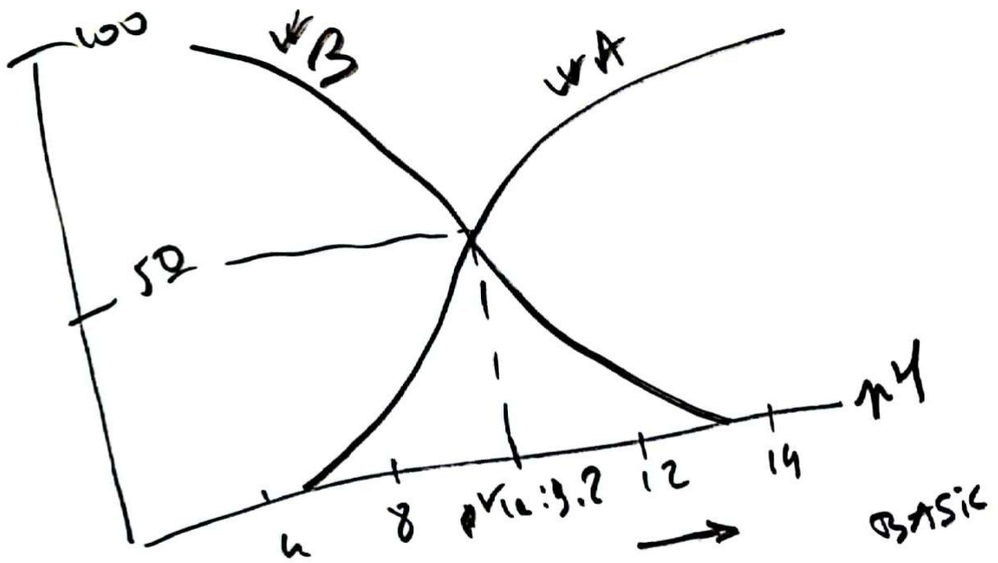
3.3 ——— ~ 90% ~

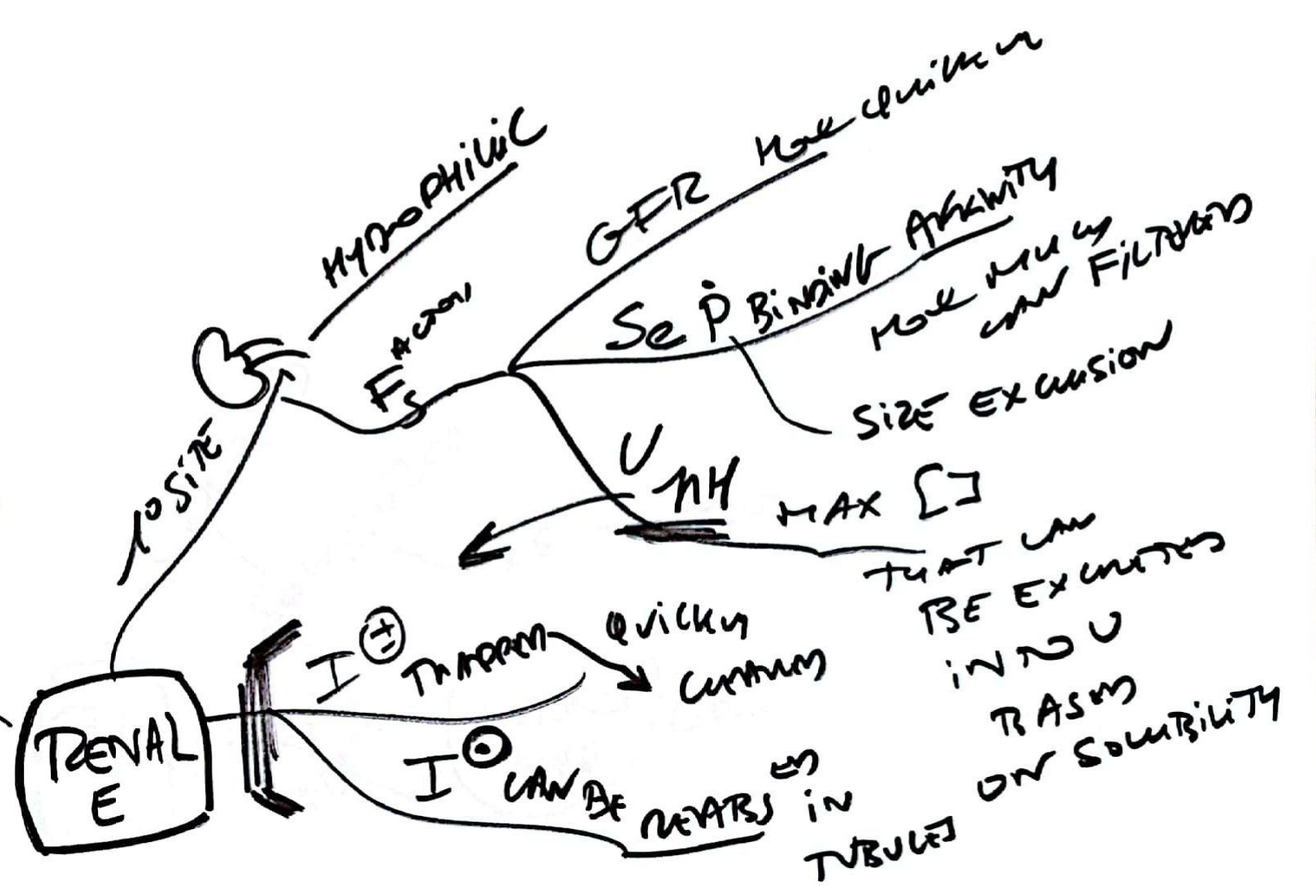
$$t_{1/2} = \frac{0.7 \times V_d}{CL}$$

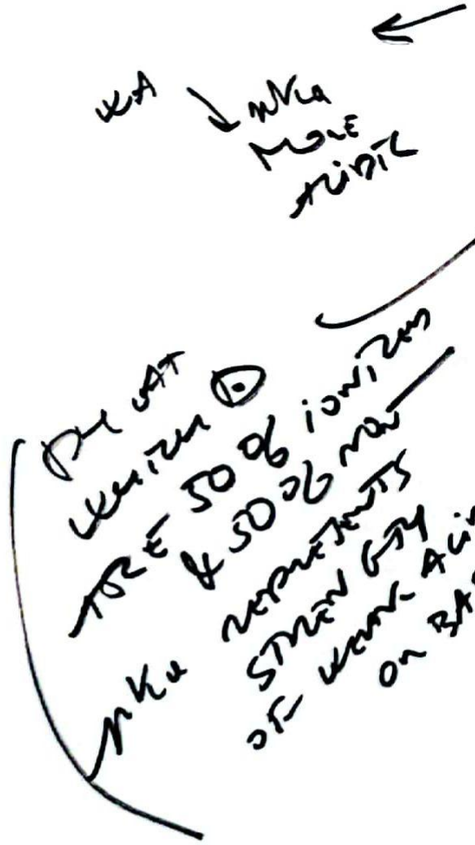
% SS AS A FUNC^N OF $t_{1/2}$ LIVE

# $t_{1/2}$ LIVES	1	2	3	3.3	4
[ ] %	50	75	87.5	90	93.75

# HALF LIVES	1	2	3	4
% REMAINING	50%	25%	12.5 %	6.25%







WEAK A

- PHENOBARBITAL METHOTREXATE ASPIRIN (SALICYLATES)
- TRAPPED IN BASIC ENV^{T}
- TT OVERDOSE WITH SODIUM BICARBONATE TO ALKALINIZE U

$RCOOH \rightleftharpoons RCOO^{\ominus} + H^{\oplus}$

(ISOL) (TRAPPED)

B

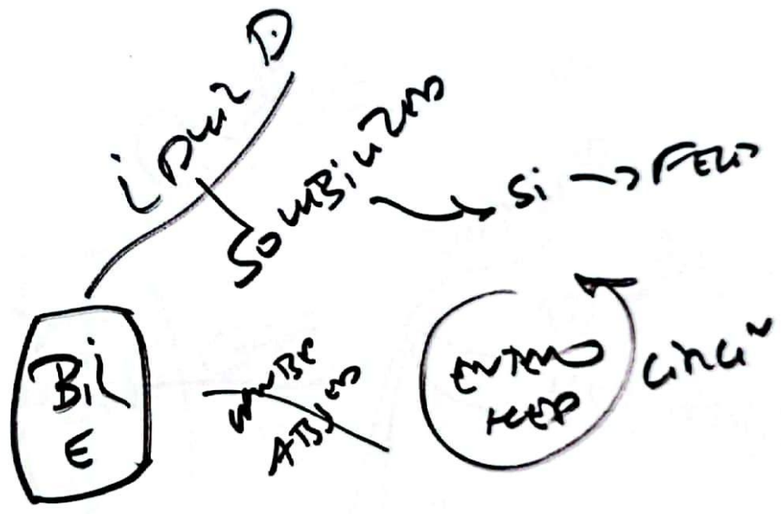
TCAs, AMPHET

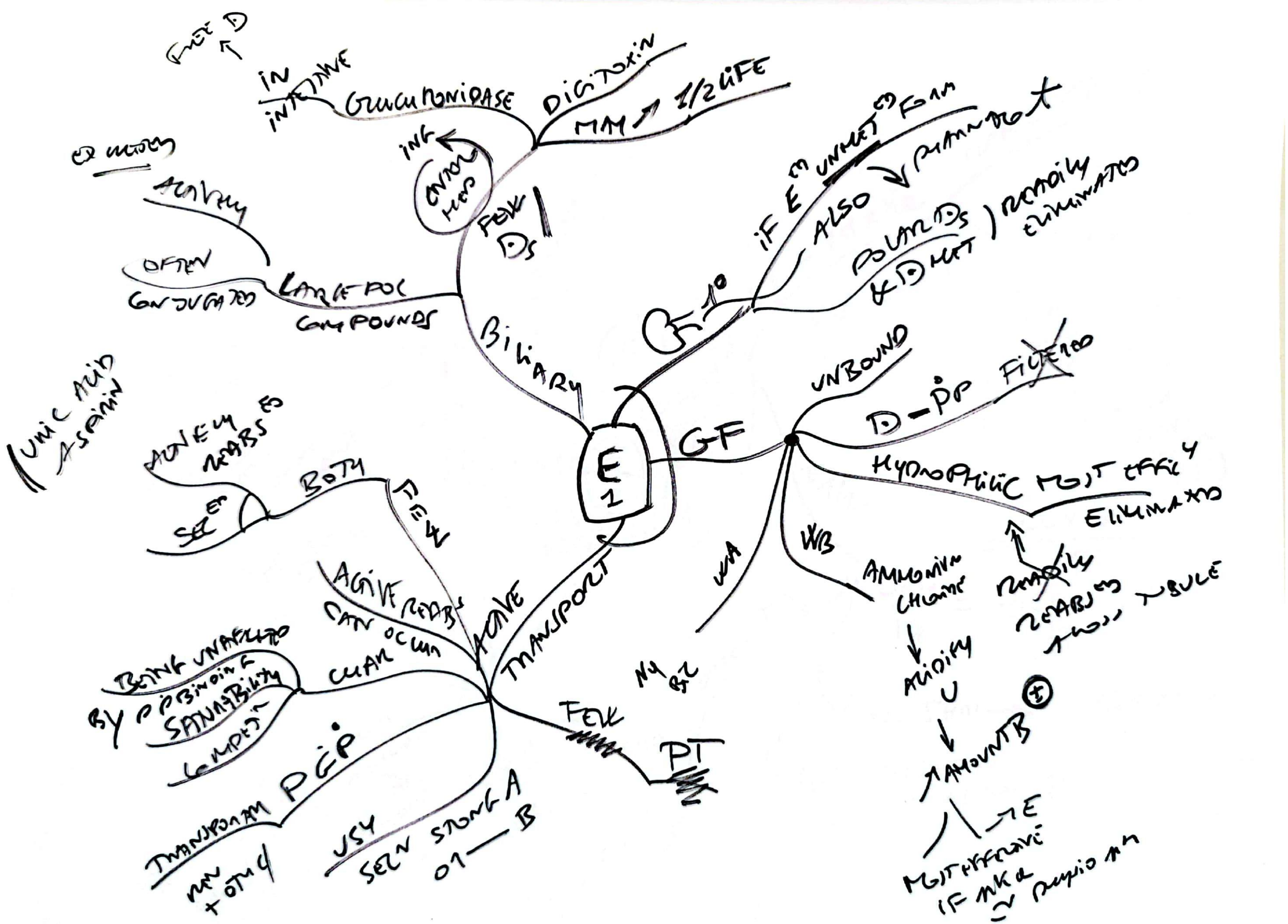
$RNH_3^{\oplus} \rightleftharpoons RNH_2 + H^{\oplus}$

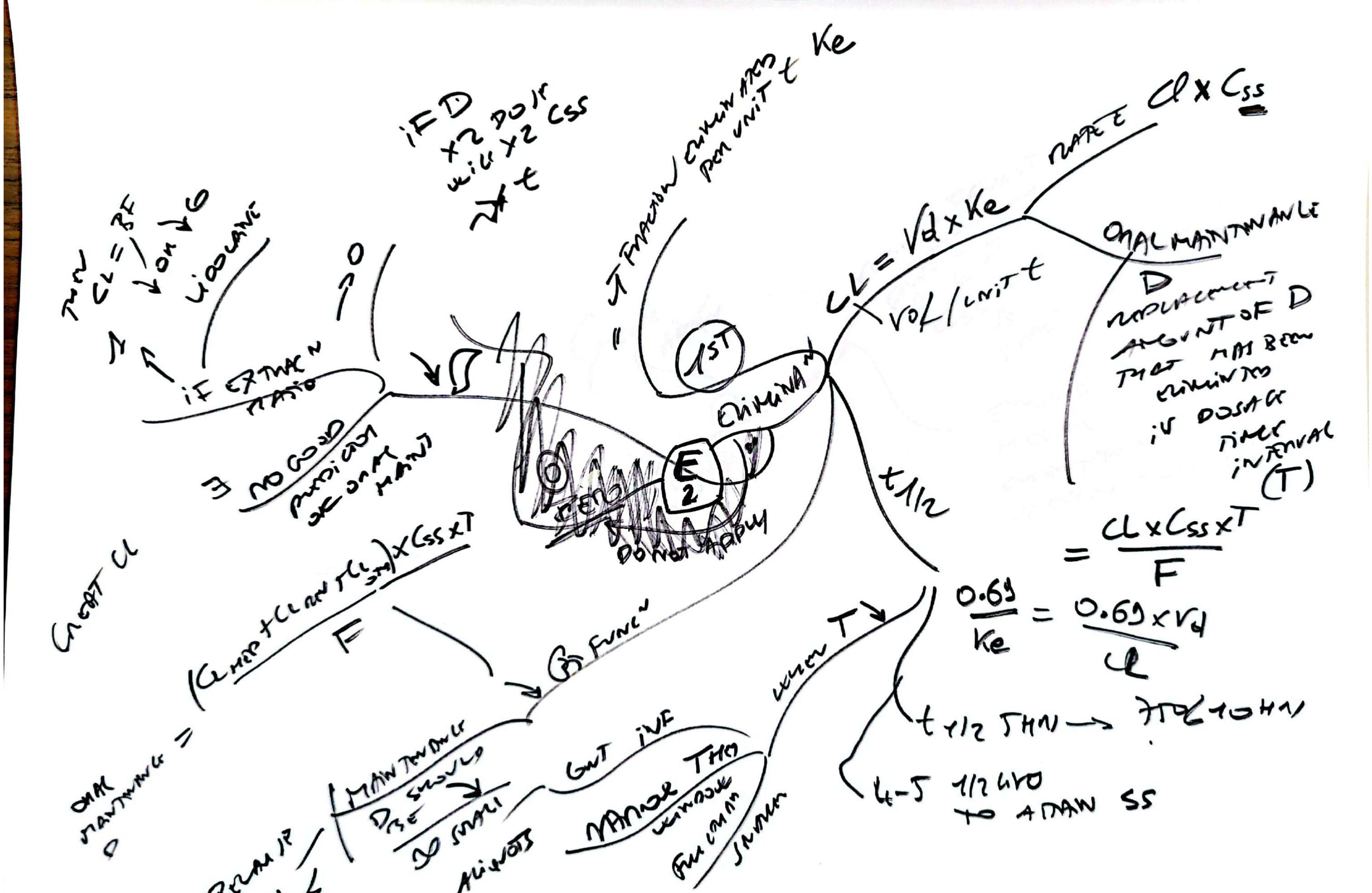
TOX^{Y} IS INITIALLY TT'ED WITH Na CHAN BLOCKING TO OVERCOME ACTIVITY OF TCAs

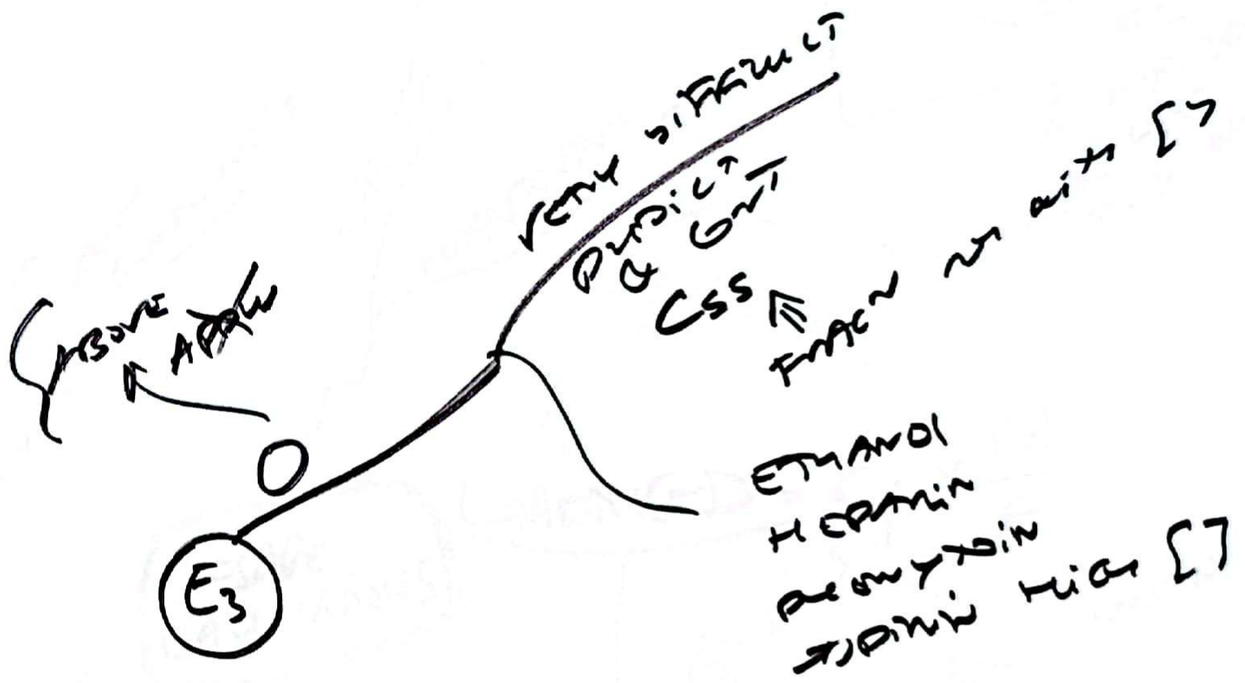
TT'S ♡ TOXICITY BUT ODDS NOT $\frac{Q}{=}$ D E

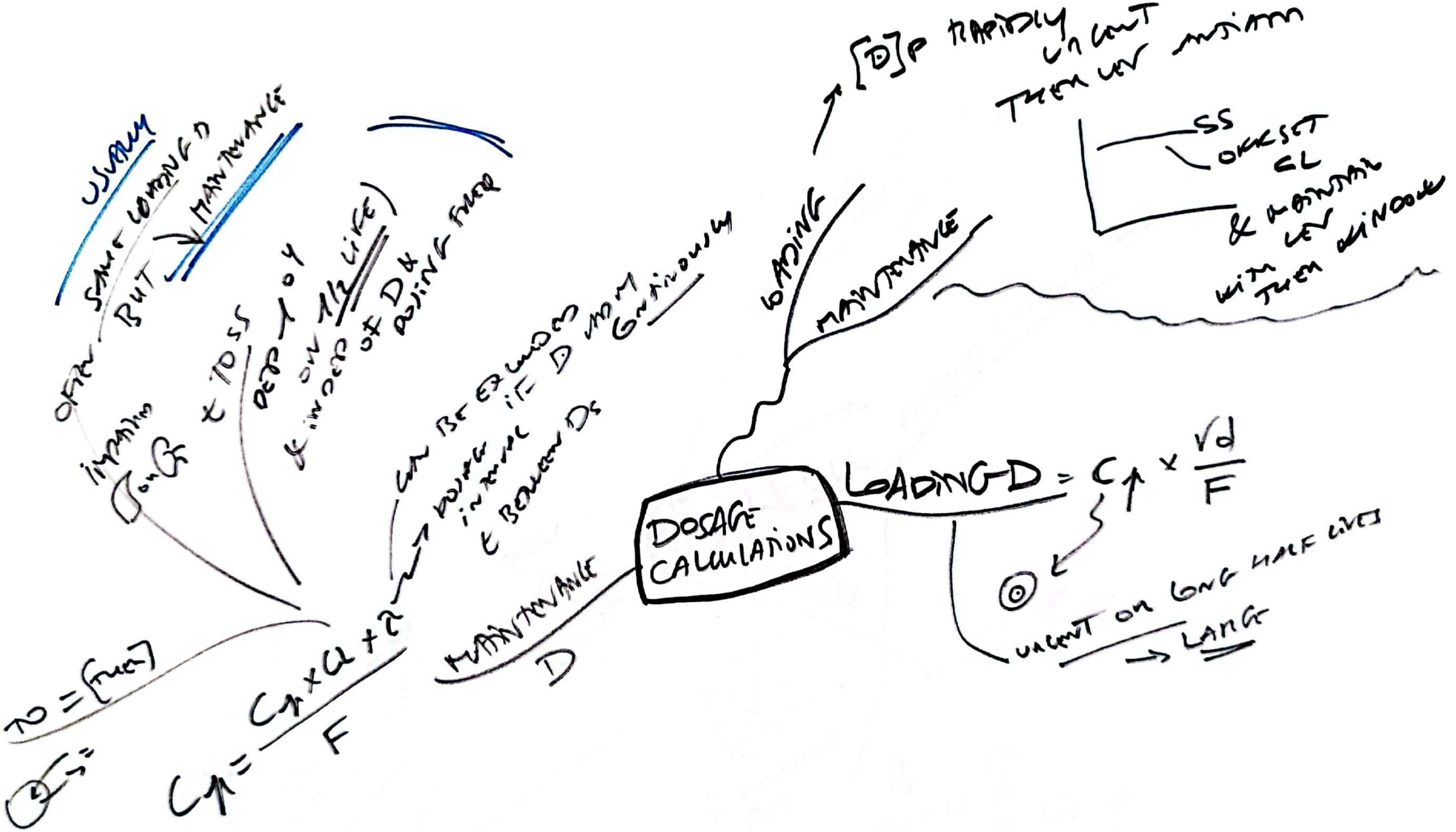
TT' AMMONIUM CHLORIDE CAN ↑ CL

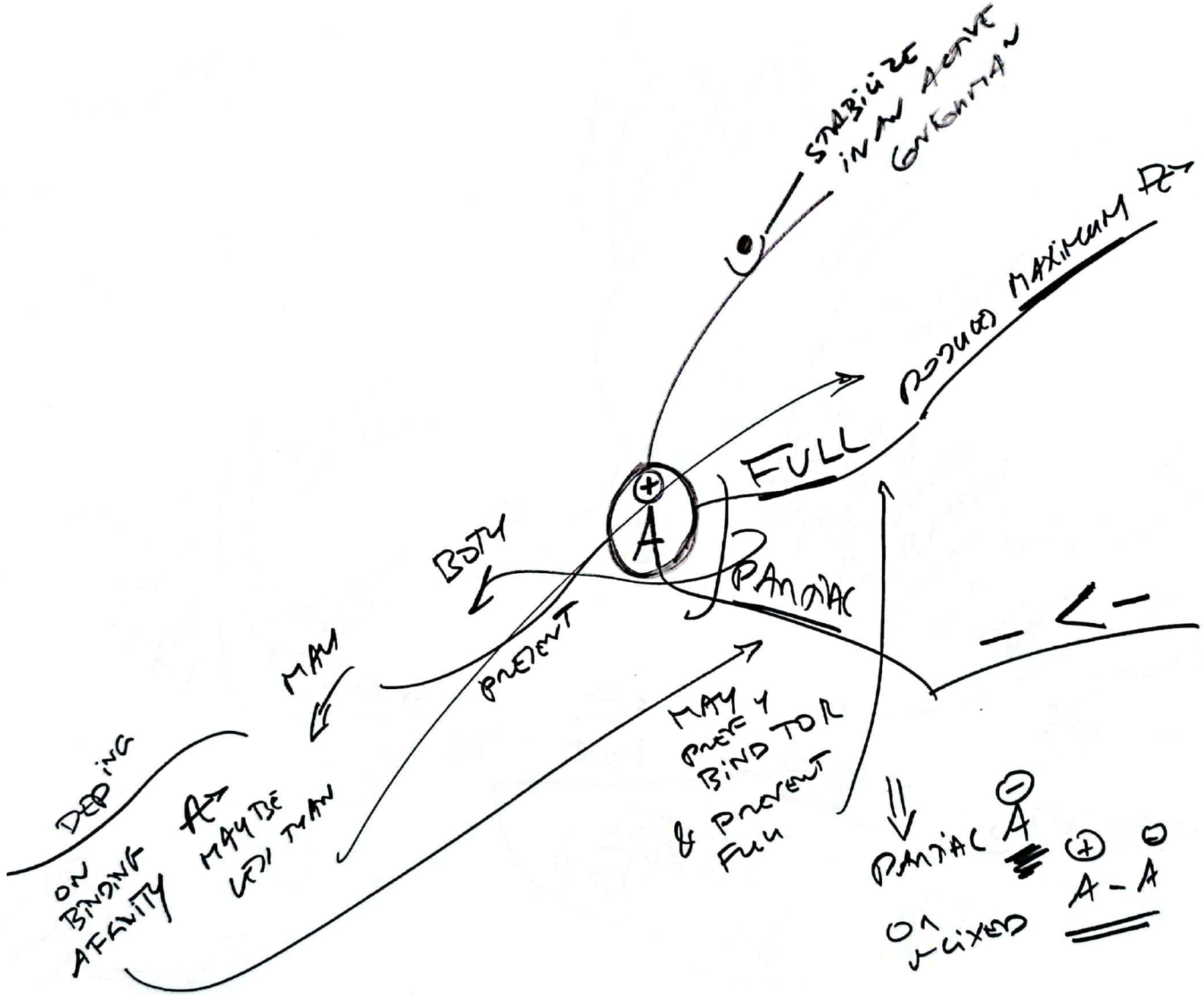









DOSAGE CALCULATIONS
LOADING
MAINTENANCE
[D]p RAPIDLY
URGENT
SS
OFFSET
CL
& MONITOR
WITH LEV
THEN WINDOW
LOADING D = Cp x Vd / F
URGENT OR LONG HALF LIVES
→ LARGE
MAINTENANCE D
Cp = Cp x CL x τ / F
τ = [freq]
USUALLY
OFTEN SAME LOADING
BUT → MAINTENANCE
τ TO SS
DEP ON 1/2 LIFE
& INDEP OF D & DOSING FREQ
CAN BE EXCLUDED IF D GIVEN CONTINUOUSLY
DOSING INTERVAL


STABILIZE IN AN ACTIVE CONFORMATION
FULL
PARTIAL
BUT
PREVENT
MAY
DEPING ON BINDING AFFINITY
MAY BE LESS THAN
MAY PREF Y BIND TO R & PREVENT FULL
PARTIAL
A - A
MIXED

- NALOXONE A
  - OPIOID OVERDOSE
  - BUPRENORPHINE
    - DAMAGE OPIOID R A
    - ADDICTION
      - DEPENDENCE
      - ANALGESIA

↑ ORAL METHADONE IN OPIOID ADDICTION

NB

INVOLVES IN R

CANNOT BE OVERCOME BY FLOODING

ANTAGO CANNOT BE OVERCOME

ACTIVE SITE

ALLOSTERIC BINDING

REV

GMP

CAN BE OVERCOME BY FLOODING

PROTAMINE HEPARIN

ATROPINE

ENZYME KINETICS

MICHAELIS MENTEN KINETICS

1/α AFFINITY OF ENZ FOR SUBSTRATE

α [E] ENZ

TEST HYPERBOLIC

SIGMOID USY INDICATE COOPERATIVE (Hb)

V EQUIL

SATN'N

VMAX

1/2 VMAX

[S]

KM

⇒ OF ENZ INHIBITION

COMPINH ⇐

UNCOMP INHIBITOR

LINEWEAVER-BURK PLOT

- THE CLOSER TO O ON Y AXIS, THE HIGHER VMAX
- $\frac{\text{———}}{\text{———}} X \frac{\text{—}}{K_M}$
- HIGHER KM LOWER AFFINITY

1/V

UNINHIBITED

SLOPE $\frac{K_M}{V_{MAX}}$

1/VMAX

$-\frac{1}{K_M}$

1/[S]

- COMPETITIVE INH ONS CROSS EACH OTHER WHEREAS NON COMP DO NOT
- KOMPETITIVE INHIBITORS INCREASE KM

UNCOMP

COMP

	CMP ⇆	COMP ✗	CMP ✗
RESEMBLE S	YES	YES	NO
OVERCOME BY ↑ [S]	YES	NO	NO
BIND ACTIVE SITE	YES	YES	NO
EFFECT ON V_{MAX}	=	↘	↘
K_M	↗	=	=
PD	↘ POTENCY	↘ EFFICACY	↘ EFFICACY

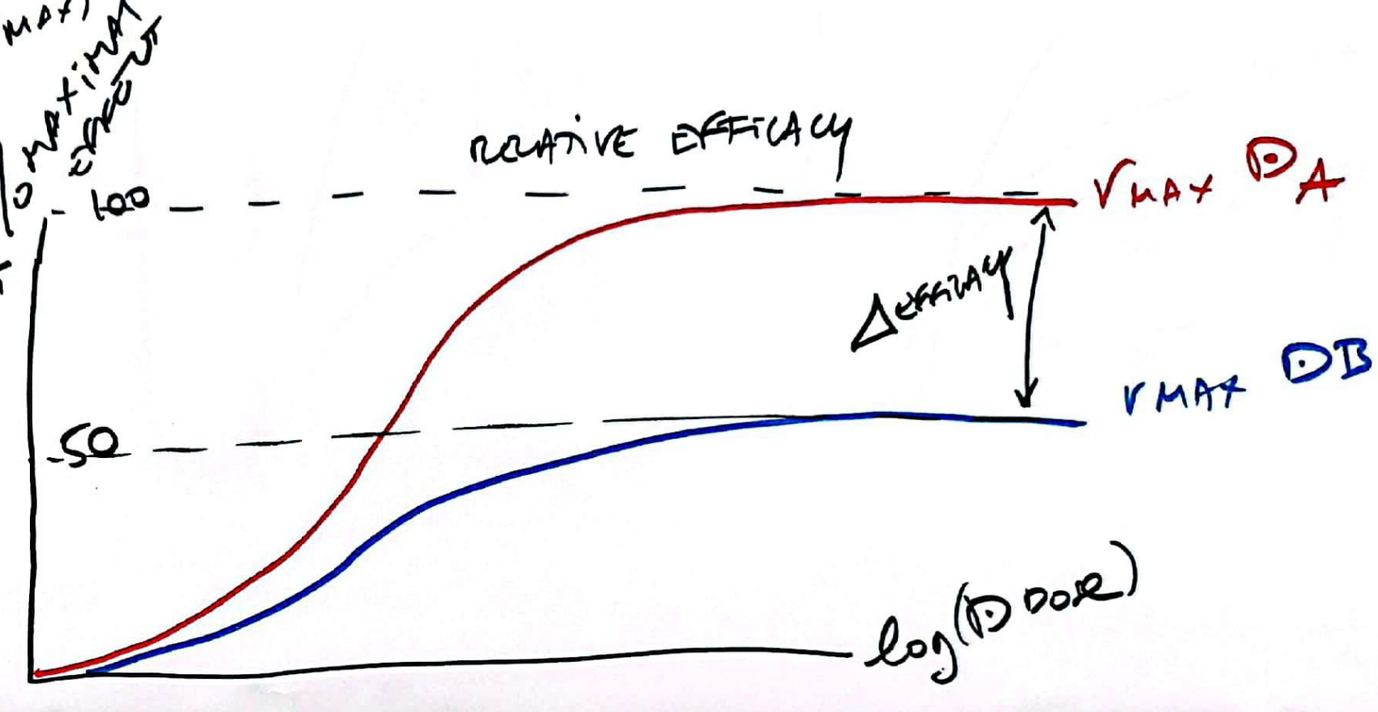
AFFINITY

- MEAS OF HOW TIGHTLY D-R
- 1/K_d ASSOCIATION

EFFICACY

- MAXIMAL (⇒ ↑ D) CAN PRODUCE
- REP BY y-VALUE (VMAX)
- ↑ y VAL = ↑ VMAX = ↑ EFF
- EFFICACIOUS Ds CAN HAVE HIGH OR LOW POT
- PARTIAL AGO HAVE LESS EFF THAN FULL

VMAX



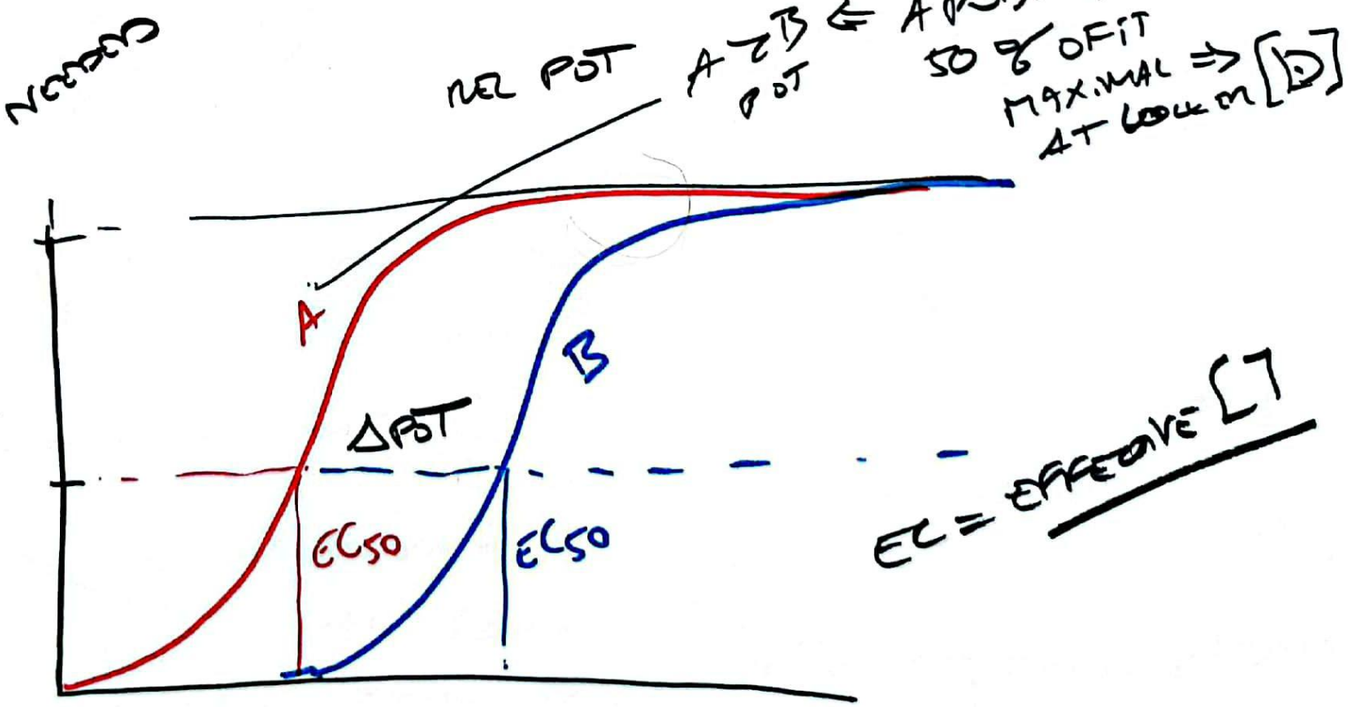
POTENCY

- AMOUNT D NEEDED FOR A GIVEN ⇒
- REPRESENTED BY THE x-VALUE (EC_{50})

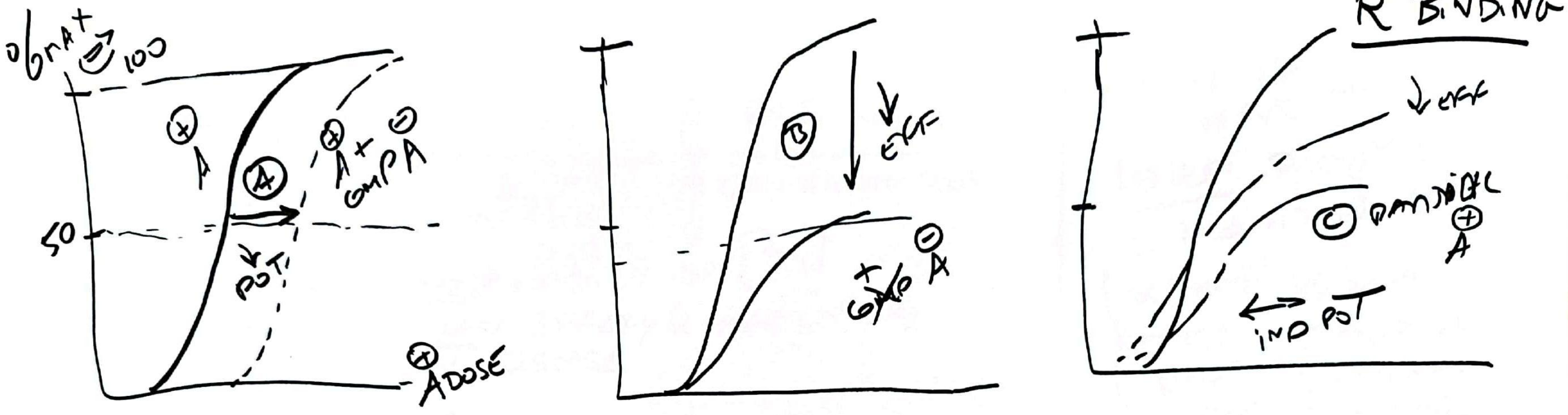
MEASURED

LEFT SHIFTING = ↓ EC_{50} = ↑ POT = ↓ D NEEDED

- UNRELATED TO POT Ds CAN HAVE ~~HIGH~~ HIGH OR LOW EFF



R BINDING



⊕ A WITH	POT	EFF	REMARKS	EX
Ⓐ COMP ⊖ A	↓	=	CAN BE OVERCOME BY ↑ [⊕ A]	DIAZEPAM ⊕ A + FLUMAZENIL COMP ⊖ A ON $GABA_A$ R
Ⓑ ~~COMP~~ ⊖ A	=	↓	CANNOT BE —	NE ⊕ A + PHENOXYBENZAMINE ~~COMP~~ ⊖ A ON α
Ⓒ PARTIAL ⊕ A (ALONE)	IND	↓	ACTS AT SAME SITE AS FULL ⊕ A	MORPHINE (FULL ⊕ A) VS BUPRENORPHINE (PARTIAL ⊕ A) AT MR

SPARE R

Fewer spare nAch R
EYE LID MM
MYAS GRAVIS
⇒ ↓ # nAch R
INITIALLY EYELID DROP

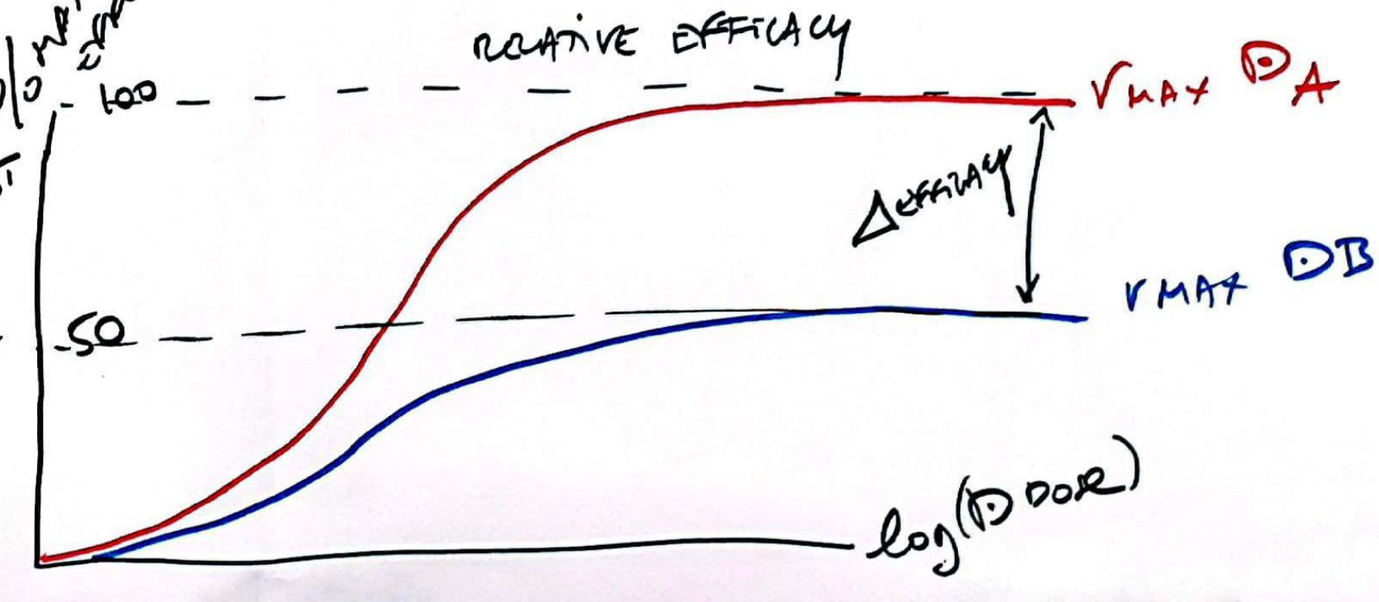
- Not all R have to be occupied for max R→
- In presence, max R→ occurs at conc ⊕ A dose that are for R saturation
- Less than 50% R needs to be bound to achieve 1/2 max R→ such as POT < KD

AFFINITY

- MEASURE OF HOW TIGHTLY D BINDS TO R
- 1/Kd is Kd

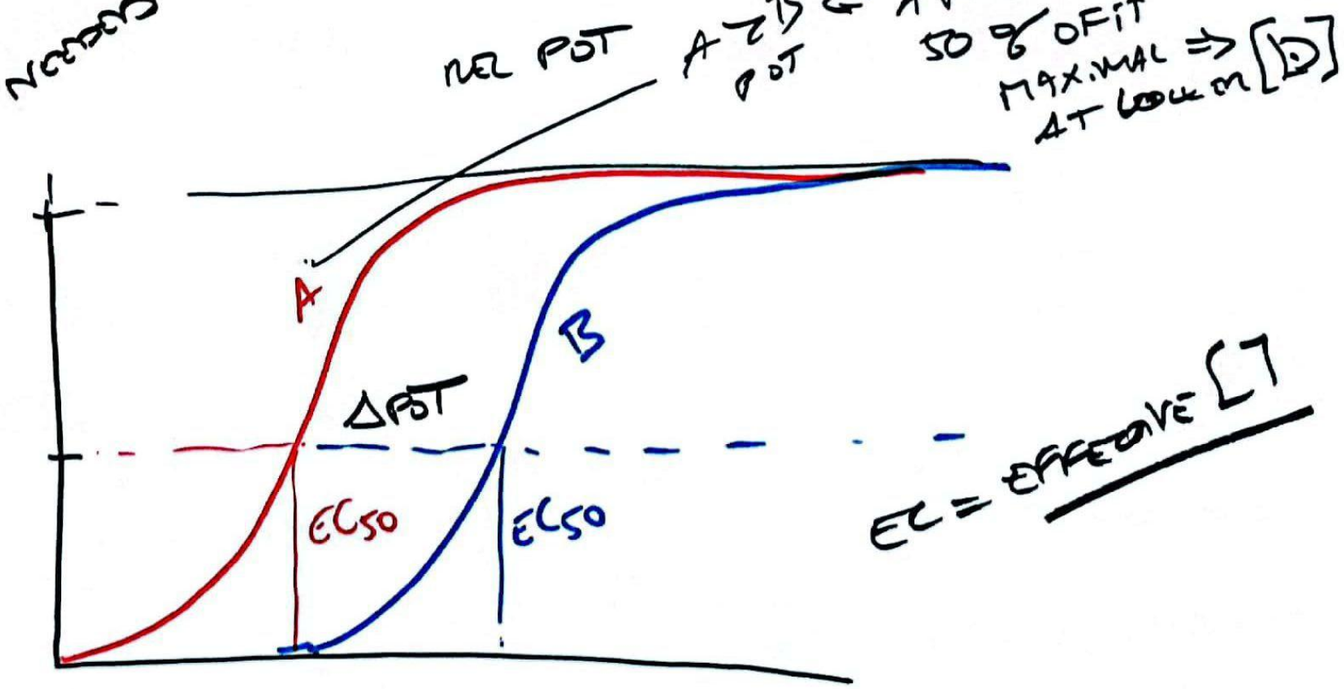
EFFICACY

- MAXIMAL (⇒) AMT D CAN PRODUCE
- REP BY y-VALUE (VMAX)
- ↑ y val = ↑ VMAX = ↑ EFF
- EFFICACIOUS Ds CAN HAVE HIGH OR LOW POT
- PARTIAL AGO HAVE LESS EFF THAN FULL



POTENCY

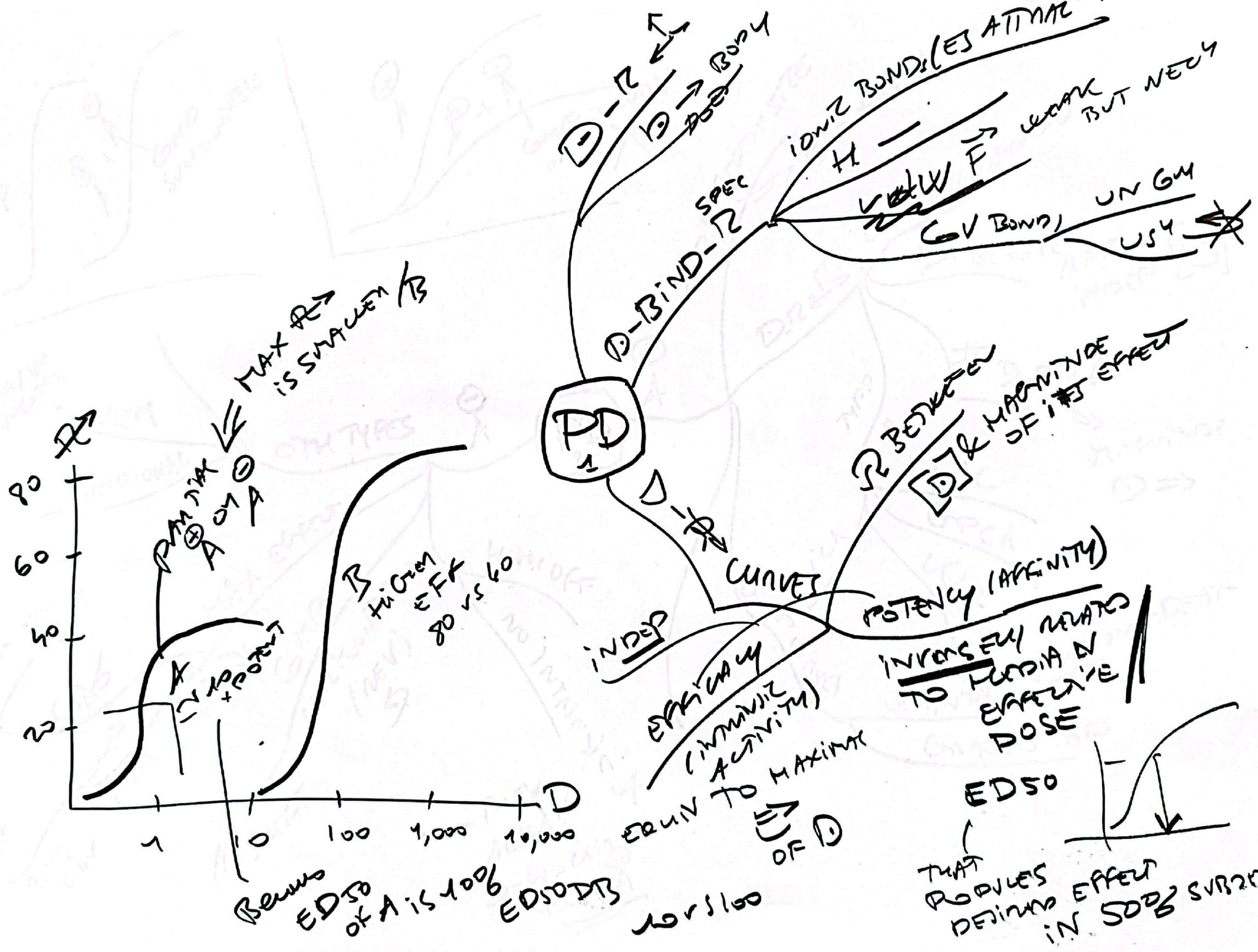
- AMOUNT D NEEDED FOR A GIVEN ⇒
- REPRESENTED BY THE x-VALUE (EC50)
- LEFT SHIFTING = ↓EC50 = ↑POT = ↓D NEEDED
- UNRELATED TO EFF Ds CAN HAVE HIGH OR LOW EC50

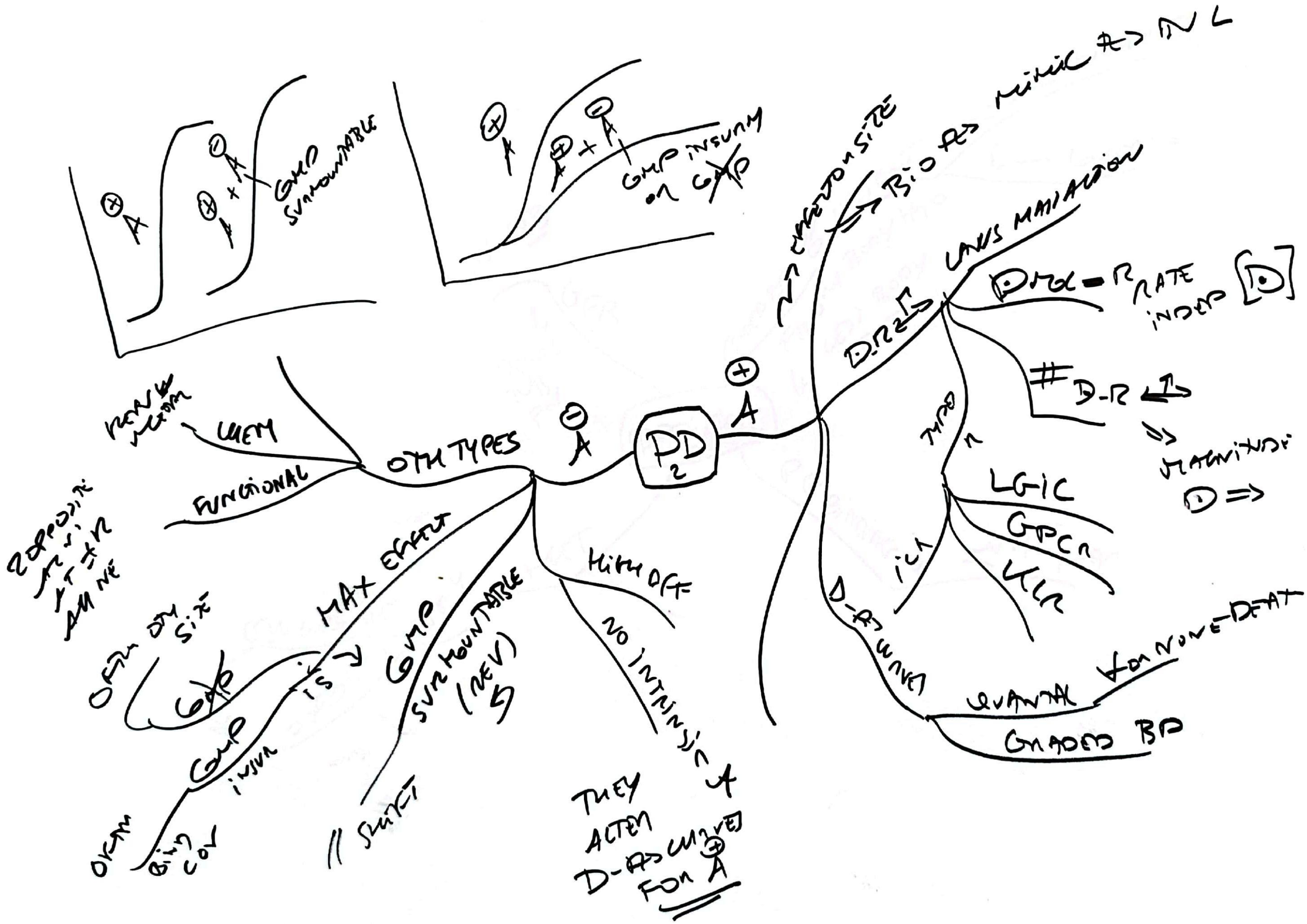


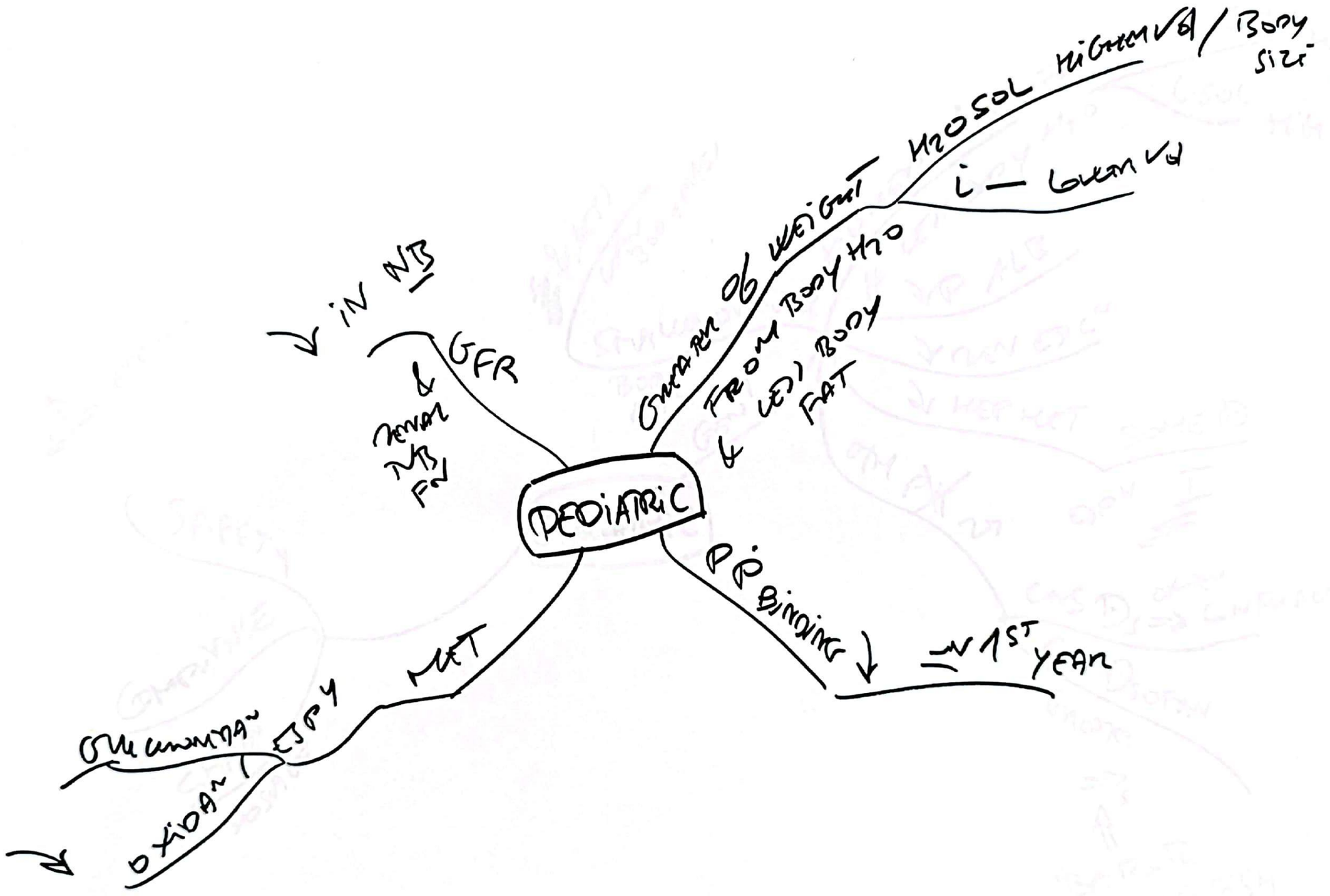
EC = EFFECTIVE [ ]

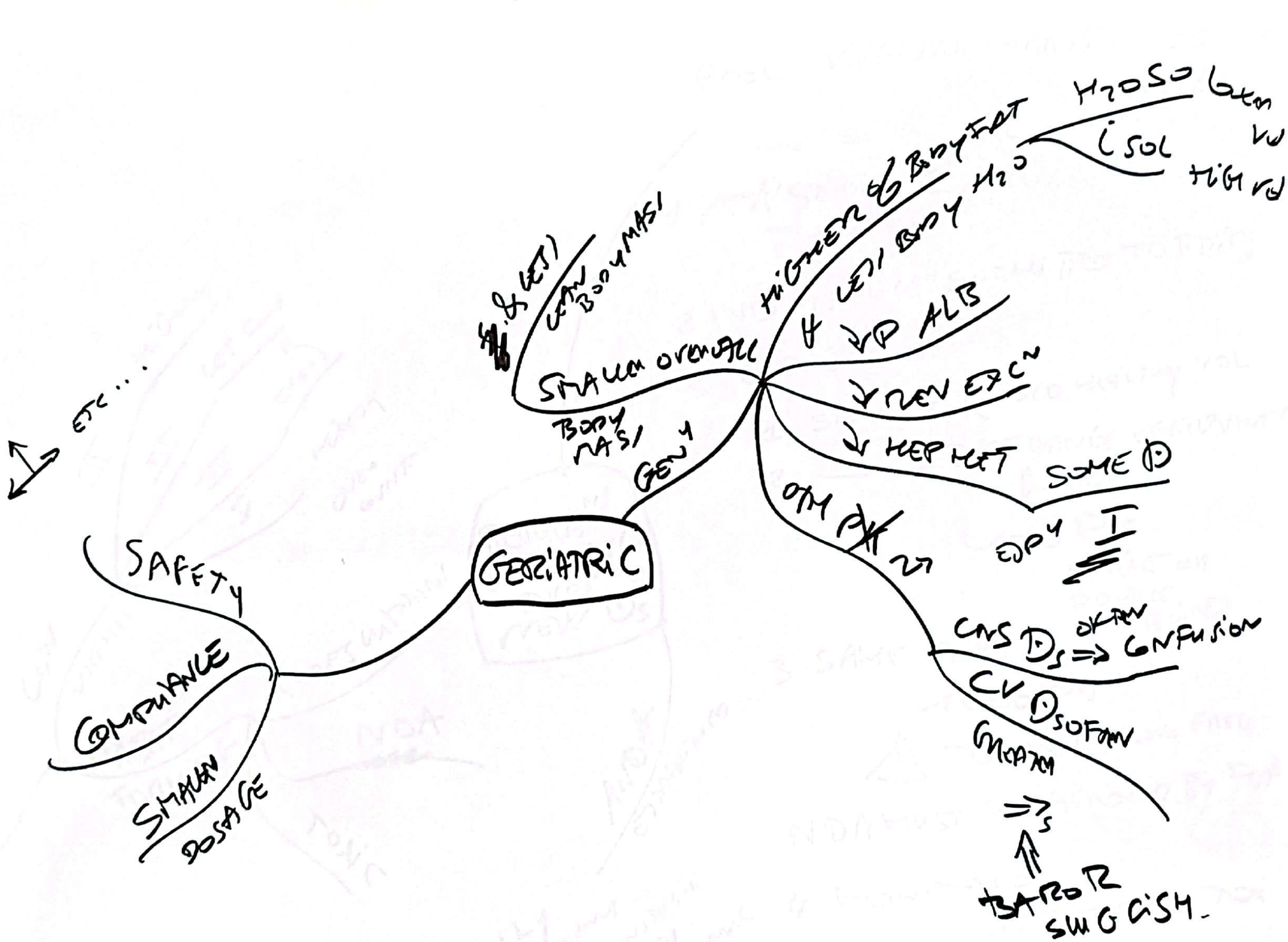
D ⇒ MODIFICATIONS

TERM	DEFINITION	EXAMPLE
ADDITIVE	⇒ A & B TOGETHER IS = SUM INDIVIDUALS ⇒ s	ASPIRIN & ACETAMINOPHEN "2+2=4"
PERMISSIVE	PRESENCE A IS REQUIRED FOR FULL EFFECT OF B	CRITICAL ON CAT R⇒ ECS
SYNERGISIC	EFFECT OF A & B TOG IS GREATER THAN SUM —	CLOPIDOGREL WITH ASPIRIN "2+2>4"
POTENTIATION	≃ BUT B WITH NO THEM ACN → THEM ACN OF A	CARBIDOPA ONLY TO PREVENT PERIPH CONVERSION OF LEVODOPA "2+0>2"
ANTAGONIST	EFFECT A&B TOGETHER IS LESS THAN SUM —	ETHANOL ANTIDOTE FOR METHANOL TOX "2+2<4"
TACHYPHYLAXIE	↗↘ IN R⇒ TO D AFTER INITIAL/REPEATED ADMN	REPEAT USE OF NITRATES OXYGEN THERAPY → THEM R⇒ (WITH REBOUND CONGESTION)









PROC KEFAUVER-HARRIS AMENDMENT 1963

1 PRECLINICAL STUDIES → TOX
→ 1 SPECIES

2 IND APPLICAN SUBMITTED TO FDA

3 CLIN
1 STUDIES K 10 HEALTHY VOL
2 —— DOSE RANGE EFFECTIVENESS & TOX
100 PTS
SINGLE OR DOUBLE BLIND

3 SAME PARAM
1000 PTS
⚠ TOX WITH LOW FREQ

NDA MUST BE APPROVED BY FDA
MONITORED
DETECT RARE TOX

ANDA ESTABLISHES
ONLY NECESSARY TO DEMONSTRATE BIOEQUIV FOR A GENERIC FORM OF AN APPROVED D

REGULATIONS GOVERNING DVPT NEW DS

PRESUMPTIVE

NDA

TOXIC

HABIT FORMING

CI

CONTRA USE

CLIN USEFUL

CLIN

I
II
III
IV
V
MINOR OVER COUNTER