Therapeutic Drug Monitoring (TDM)

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Overview

- Pharmacokinetics (PKs)
- Pharmacogenomics (PGs)
- Purpose of TDM
- Criteria for TDM
- Sampling requirements
- Therapeutic range
- Analytical methods
- Specific drugs

PKs

PHARMACOKINETICS

- Describes what the body does to drugs
- Factors affecting concentration of drug in plasma

- "**ADME**"

- Differs between individuals (inter-individual variation)
- Differs within an individual (intra-individual variation)

PKs

(A) (Adherence)

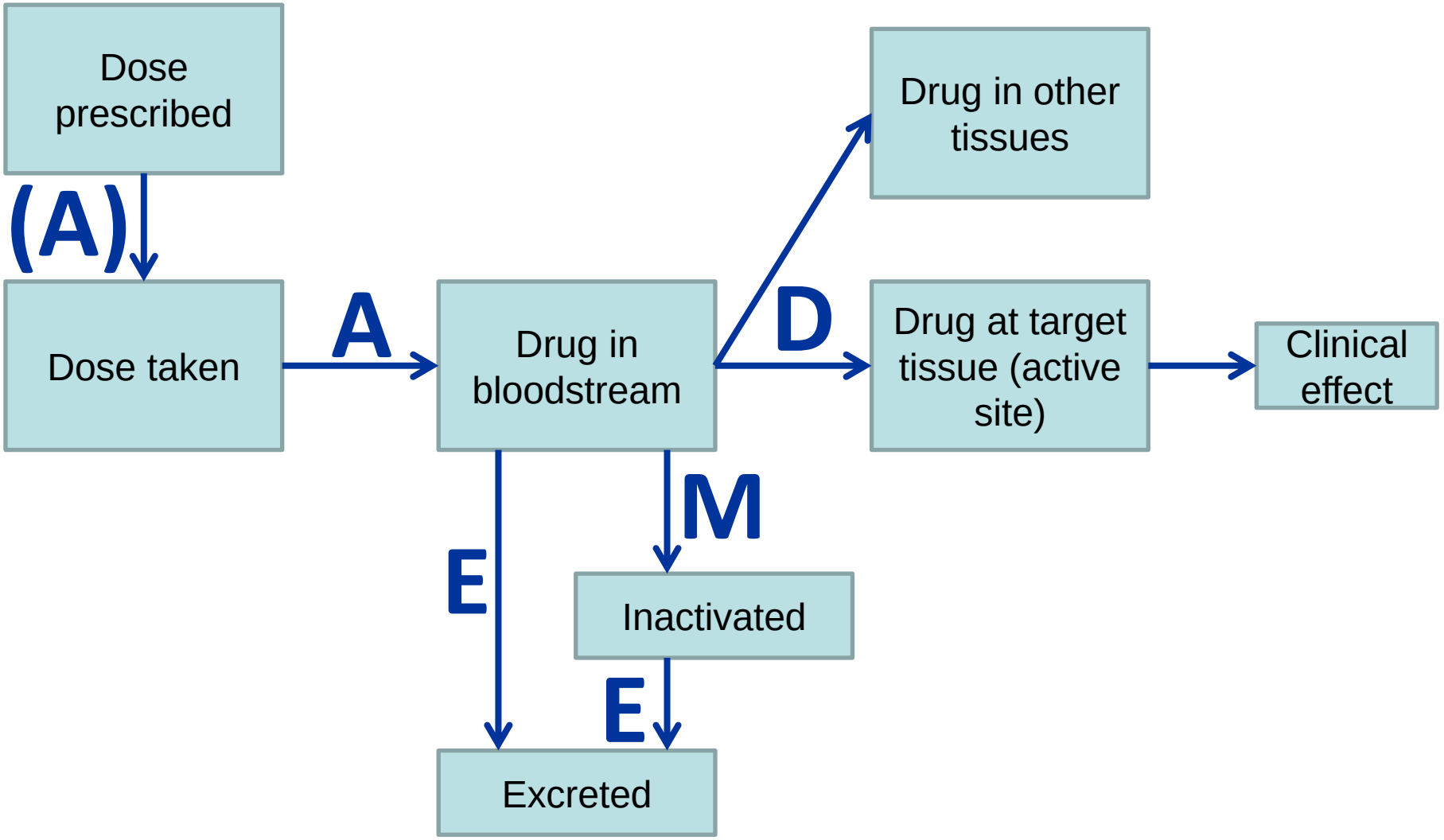
A Absorption

D Distribution

M Metabolism

E Elimination

PKs


Dose prescribed
(A)
Dose taken
A
Drug in bloodstream
D
Drug in other tissues
Drug at target tissue (active site)
Clinical effect
M
Inactivated
E
E
Excreted

(A)

ADHERENCE

- aka “compliance”
- Whether the patient actually takes the drug they have been prescribed, or not
- Issues with chronic therapy

A

ABSORPTION

- Amount of drug taken that actually reaches the bloodstream
    - **iv** = 100%
    - **oral** = variable

- Depends on:
    - Drug formulation
    - Co-administered food / drugs
    - GI tract integrity / function
    - Genetic variability
    - First-pass metabolism

D

DISTRIBUTION

- Once in the bloodstream, drugs are transported around the body to the various tissues
- Drug with either prefer to stay in the bloodstream or to enter the body tissues
- Depends on:
  - Relative solubility in fat or water
  - Binding to plasma proteins
  - Binding to tissue lipids
- ↑ distribution:
  - Fat soluble
  - ↓ Plasma protein binding
  - ↑ Tissue lipid binding

M

METABOLISM

- Process by which the body alters the chemical structure of a compound

- Function:
  - Make drug more water-soluble
  - Enhance excretion

- Location:
  - Mainly in the liver (enzymes)
  - (Other tissues)

- N.B. Metabolism ≠ Inactiviation
- Some drug metabolites are active

E

ELIMINATION

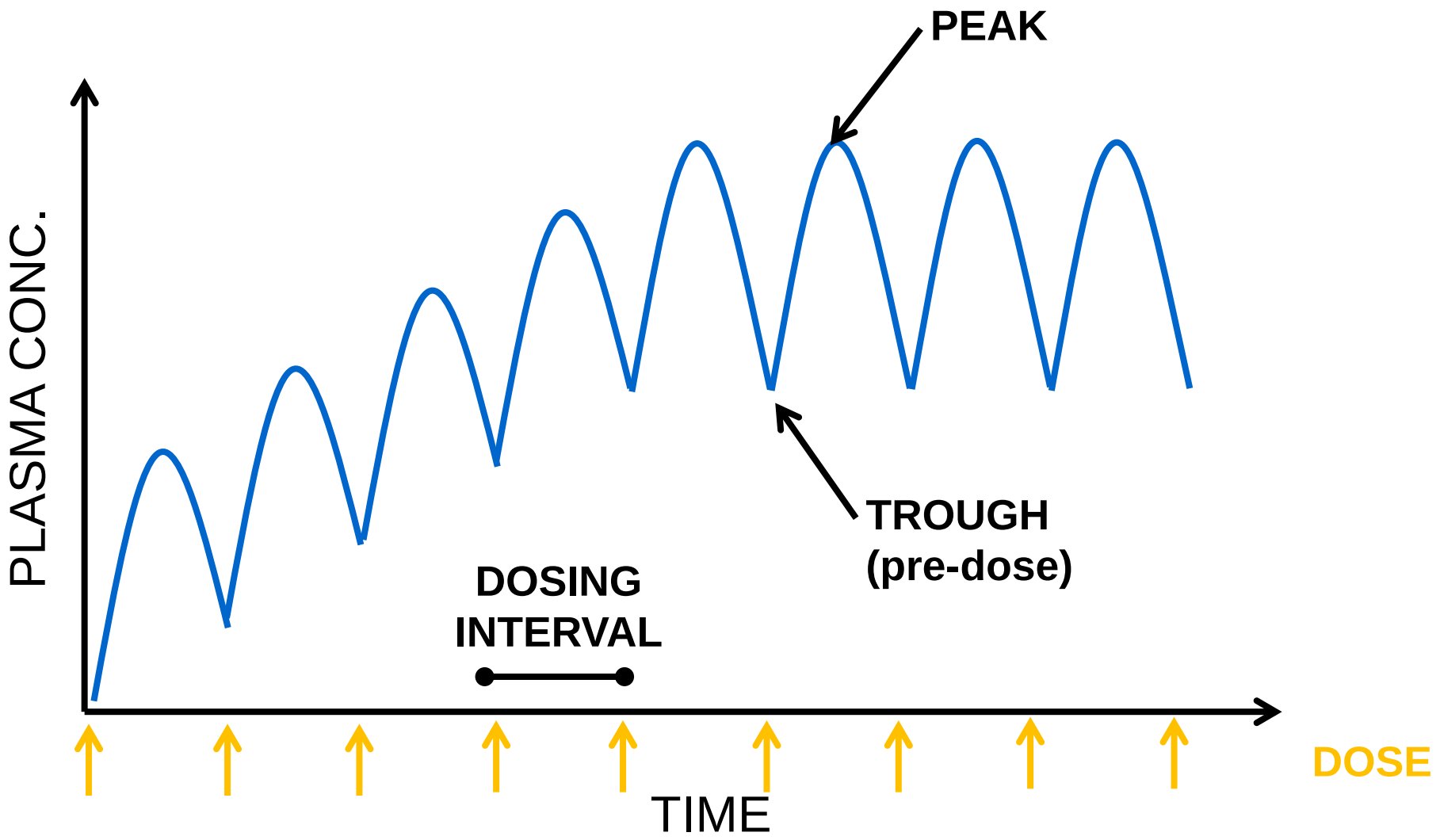
- Removal of drugs from the body

- Routes:
  - Urine
  - Faeces

  - Sweat
  - Breath
  - Breast milk
  - Hair
  - Nails
  - Placental transfer

- Kidney function very important
- Reduced kidney function = reduced elimination

Plasma drug levels



Plasma drug levels

STEADY STATE:

- Point of equilibrium
- Rate of administration **=** Rate of elimination

HALF-LIFE ($t_{1/2}$)

- Time taken to reduce plasma concentration to one-half of its initial value
- $t_{1/2}$ = **dosing interval**
  (drugs usually administered once every $t_{1/2}$)
- Takes 5-7 x $t_{1/2}$ to reach steady-state

PGs

PHARMACOGENOMICS

- The role of genetics in drug response
- Describes how genetic variation alters PKs
  - ADME
- Predict how well a patient will respond to a drug regime based on their genetics
- **“Personalised medicine”**

PGs

FAST METABOLISERS

- Metabolise drugs quickly
- May clear drugs before they have had time to work
- May require higher doses

SLOW METABOLISERS

- Metabolise drugs slowly
- Drug stays in body for longer = ↑ Efficacy
- But potential for build-up of drug > MTC
- Risk of toxicity
- May require lower doses

PGs

EXAMPLE - TPMT

- …

Azathioprine → 6-MP → 6-TIMP → 6-TGN

6-MMP ✗

6-MMP ✗

Purpose of TDM

ROBUST TDM PROGRAMME WILL ALLOW:

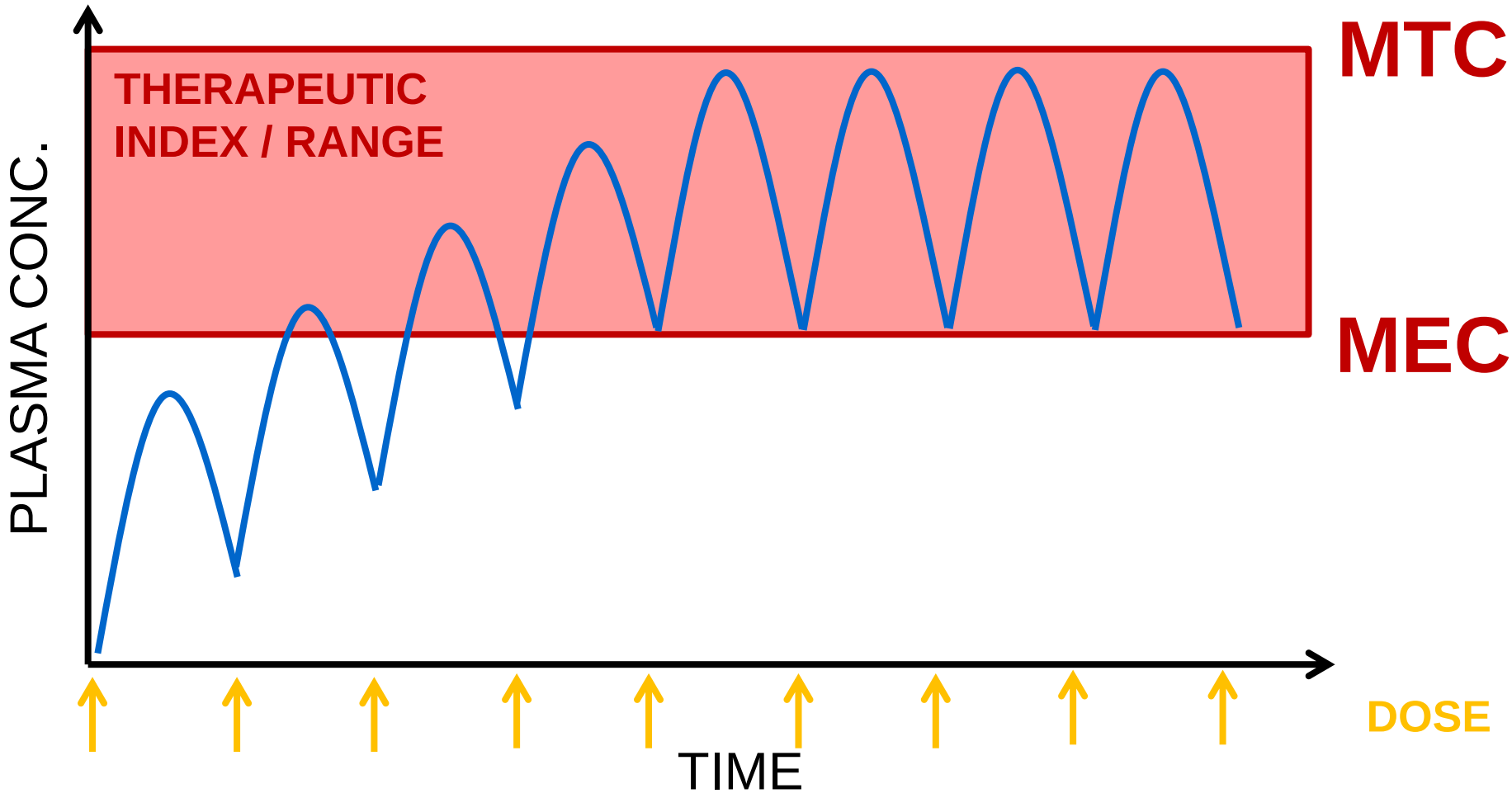
- Better patient management
- Improved patient quality of life
- Support compliance of medication
- Minimize toxicity

Indications

CRITERIA FOR TDM:

1. Narrow therapeutic index (therapeutic range)
2. Long-term therapy
3. Correlation between serum concentration and clinical response
4. Variable pharmacokinetics
   - Intra-individual
   - Inter-individual
5. Absence of suitable biomarker associated with therapeutic outcome
6. Co-administered with potentially interacting drugs

Therapeutic range



Therapeutic range

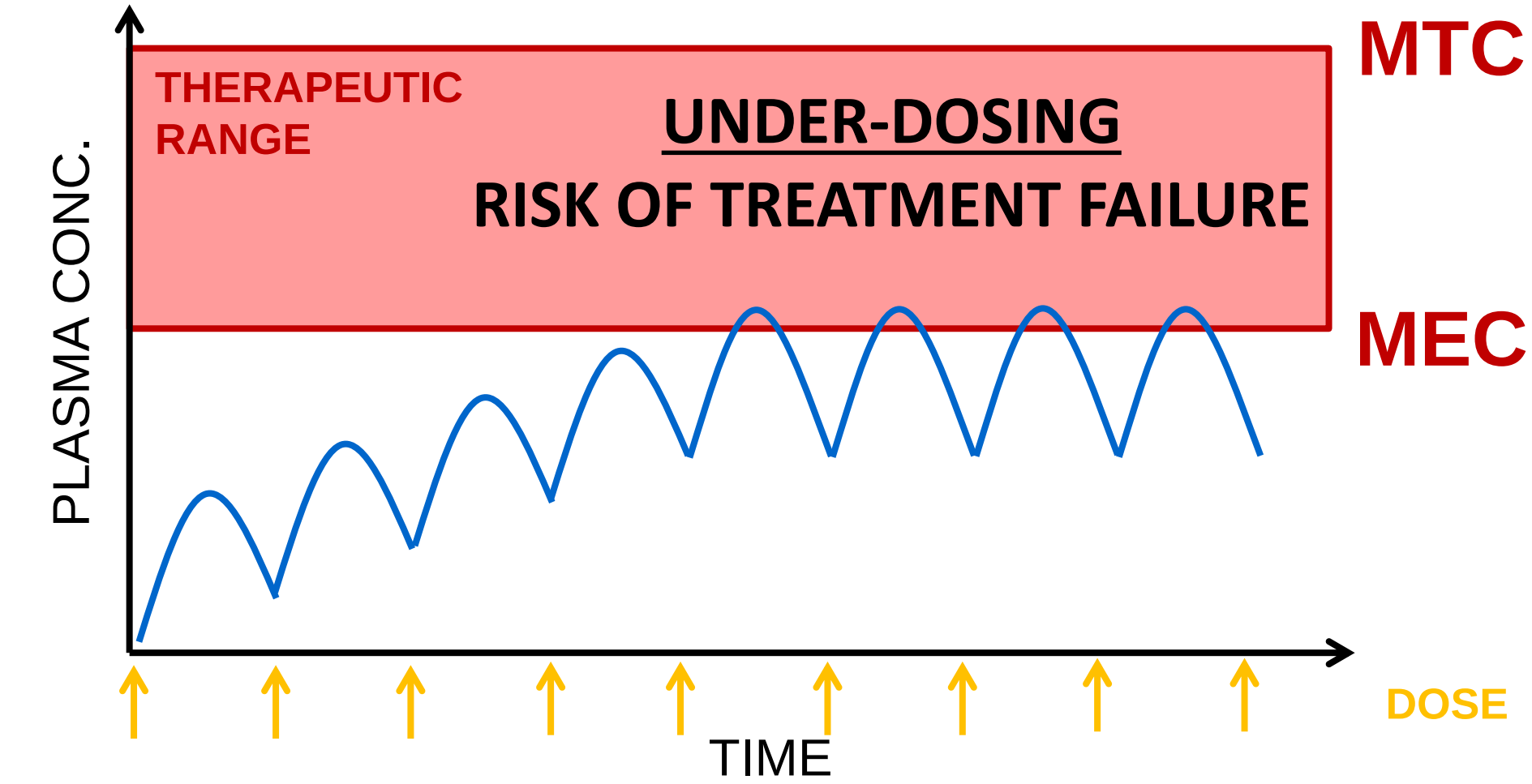
Represents the interval between:

- **MEC** – minimum effective concentration
- **MTC** – maximum therapeutic concentration
  – minimum toxic concentration

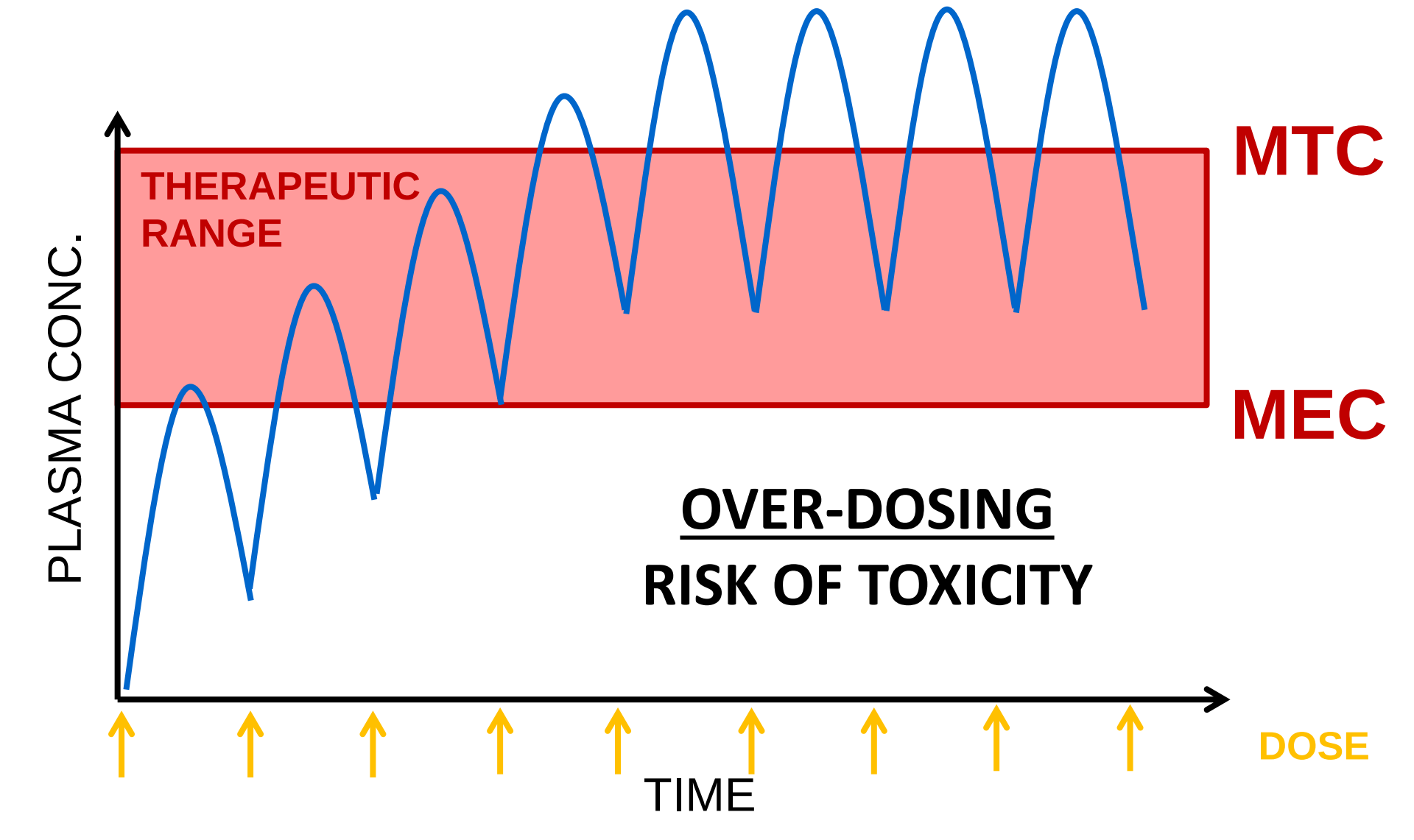
In optimal dosing:

- Trough blood concentration should not fall below the MEC
- Peak blood concentration should not exceed the MTC

Therapeutic range



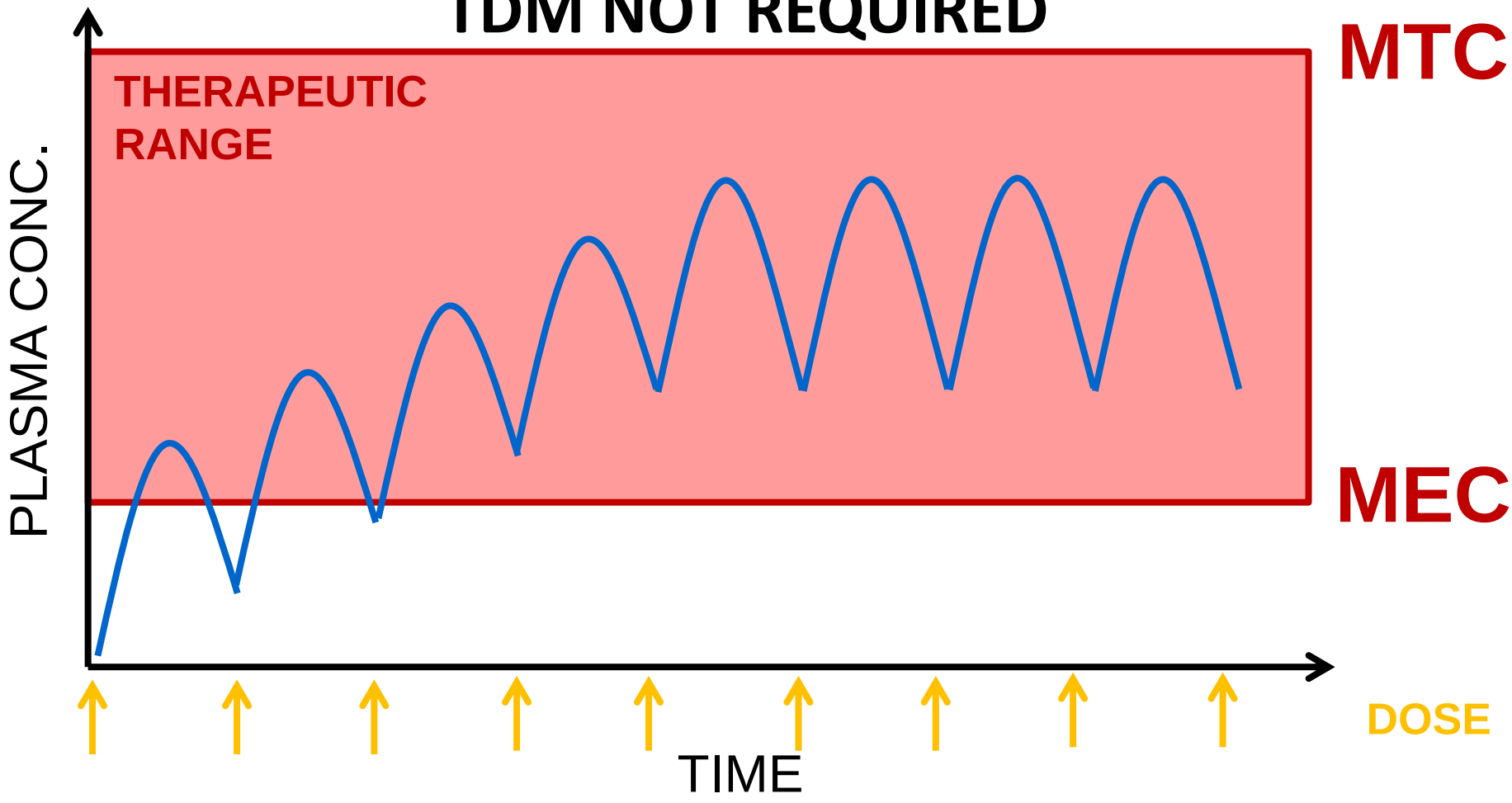
Therapeutic range



Therapeutic range

WIDE THERAPEUTIC RANGE

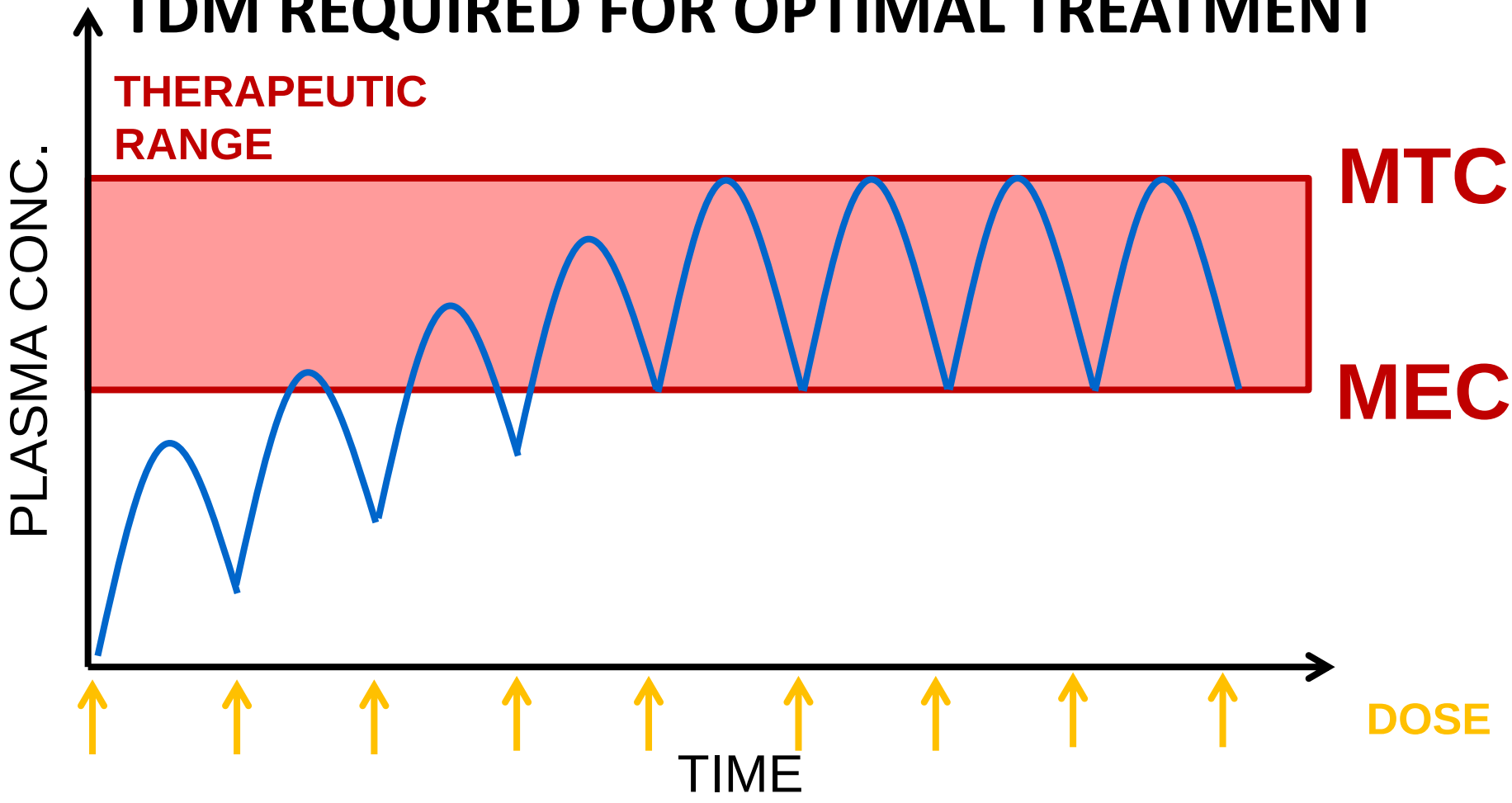
TDM NOT REQUIRED



Therapeutic range

NARROW THERAPEUTIC RANGE

TDM REQUIRED FOR OPTIMAL TREATMENT



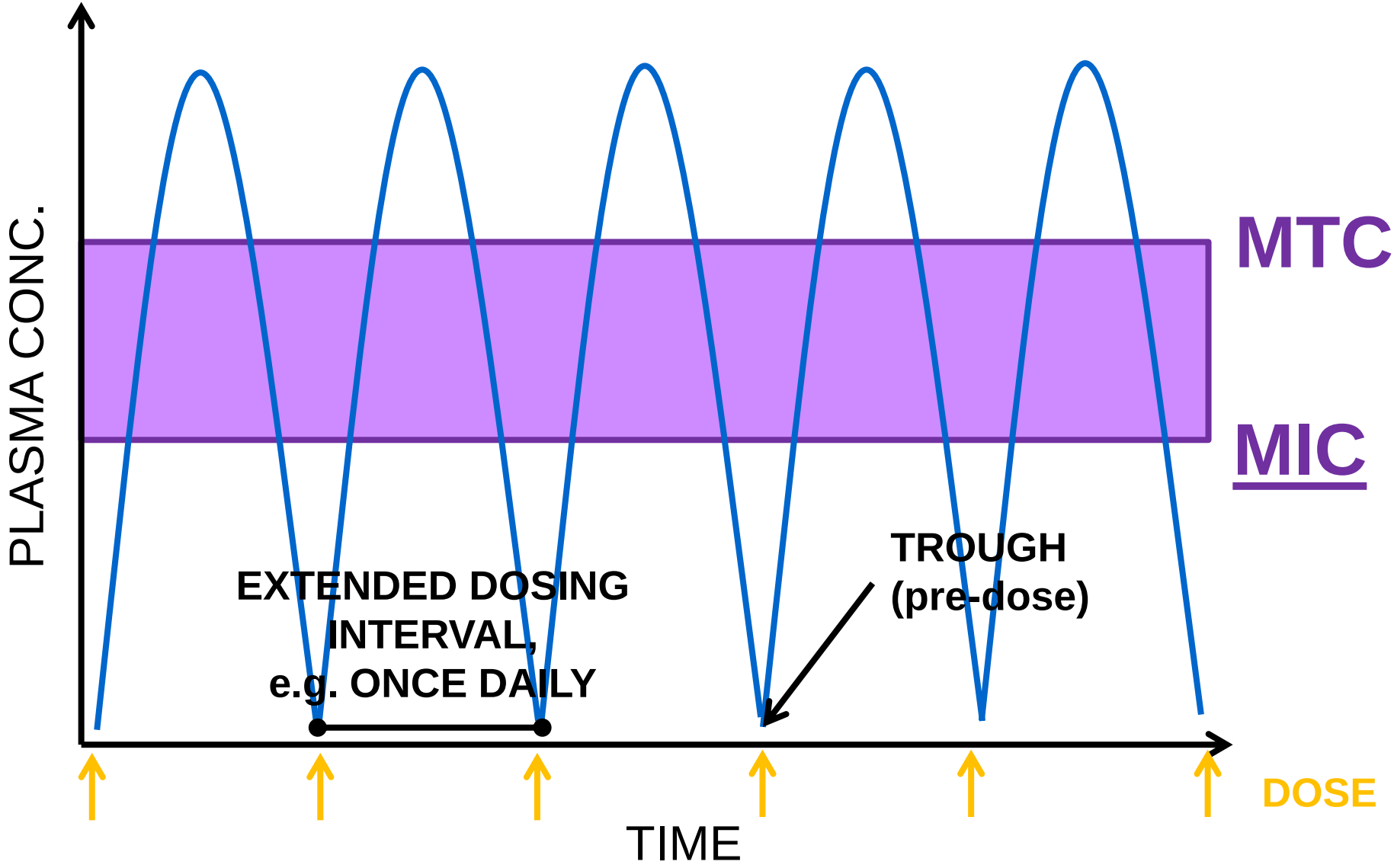
Antibiotics

Different dosing regimes:

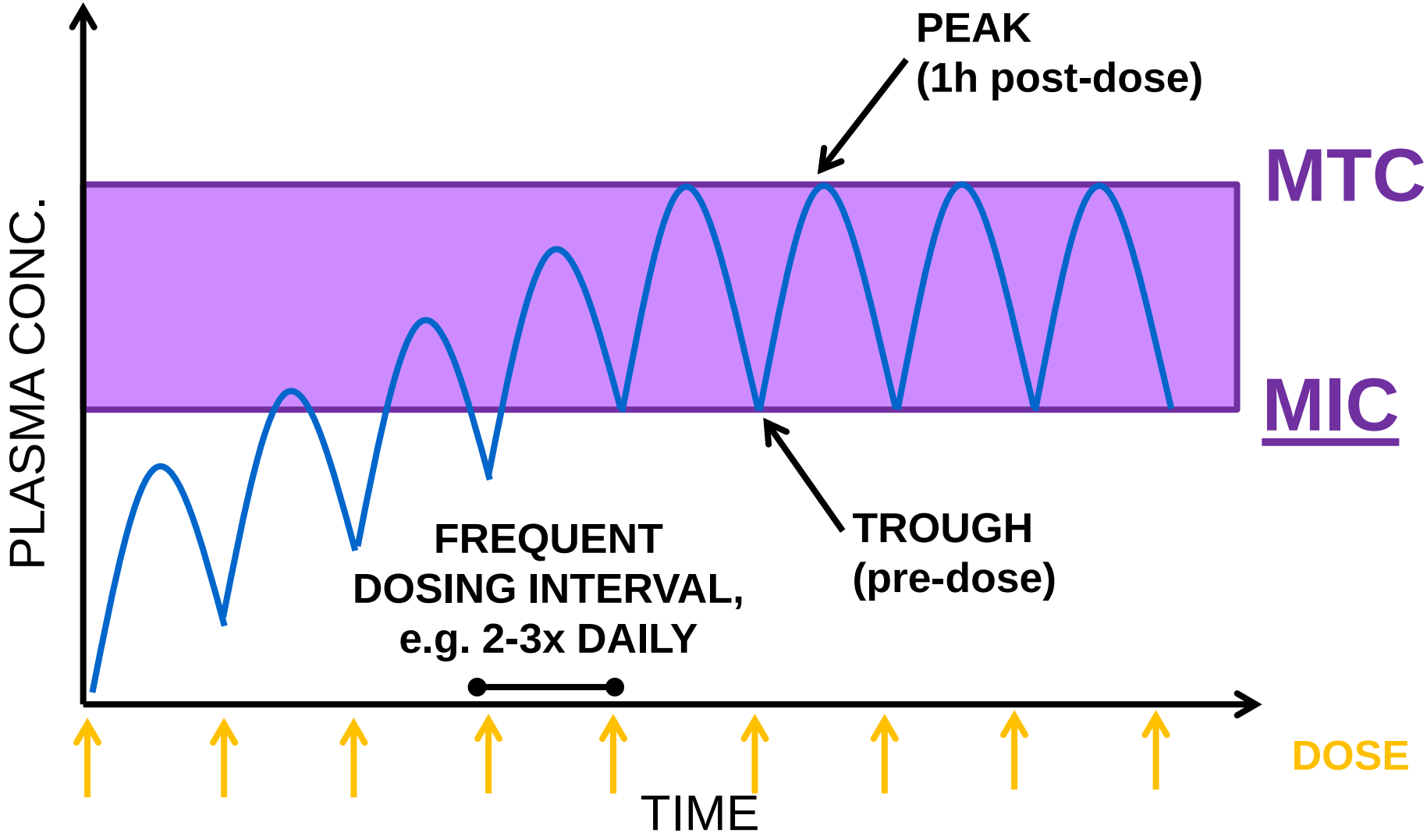
- **Extended** – e.g. once daily
- **Frequent** – e.g. 2-3x daily

- **MIC** – minimum inhibitory concentration

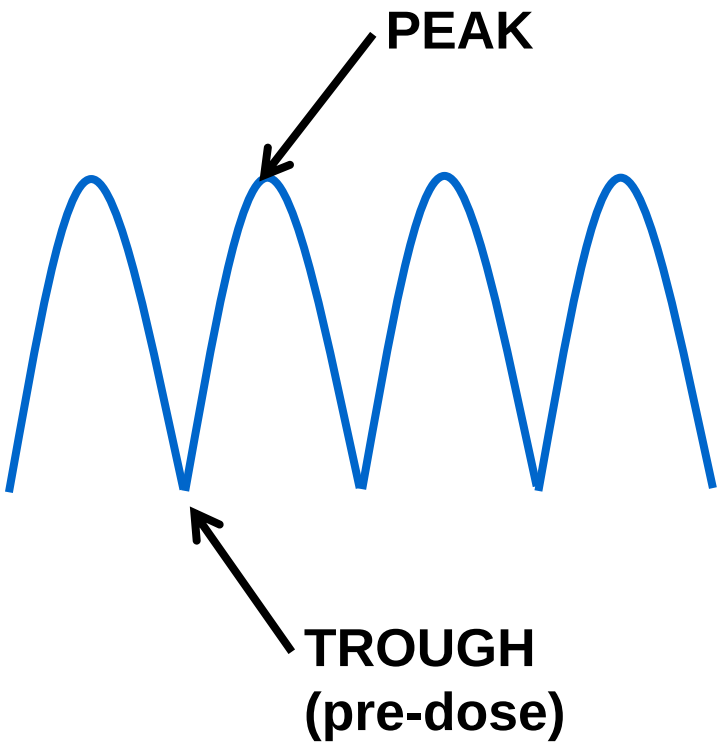
Antibiotics



Antibiotics



Sample timing



PEAK

- Rarely used
- Only for certain drugs in specific circumstances

TROUGH

- Recommended sampling time for most drugs
- Sample collected immediately before next dose
- Least intra- and inter-individual variability
- “Reference ranges” apply to trough measurements

Sample timing

EXAMPLE:

- …

Sample types

PLASMA / SERUM:

- EDTA plasma
- Plain serum
- NO GEL TUBES
- Lithium - NOT LITHIUMHEPARIN PLASMA!!!

WHOLE BLOOD:

- e.g. For drugs found in RBCs, e.g. ciclosporin
- EDTA

BLOODSPOT:

- Home-sampling

Analytical Methods

METHODS FOR TDM

- Spectrophotometry / colorimetry
- Element analysis:
  - ISE
  - AAS
  - ICP-MS
- Immunoassay:
  - EMIT
  - FPIA
  - CEDIA
- Chromatography:
  - HPLC (-UV / -DAD)
  - LC-MS/MS / LC-MS QToF
  - GC-MS

Immunoassay

PROS

- Readily automated
- Rapid results
- ↓ TAT, ↑ Throughput
- Use existing routine chemistry analysers

CONS

- Limited to repertoire provided by manufacturers
- Not available for all (esp. new) drugs
- ↑ Interference (↓ Specificity)

Chromatography

PROS

- ↑ Sensitivity
- ↑ Specificity
- Simultaneous analysis of multiple compounds
- Can work-up in-house methods

CONS

- Require specialist equipment (£££)
- Require technical expertise
- ↑ TAT, ↓ Throughput

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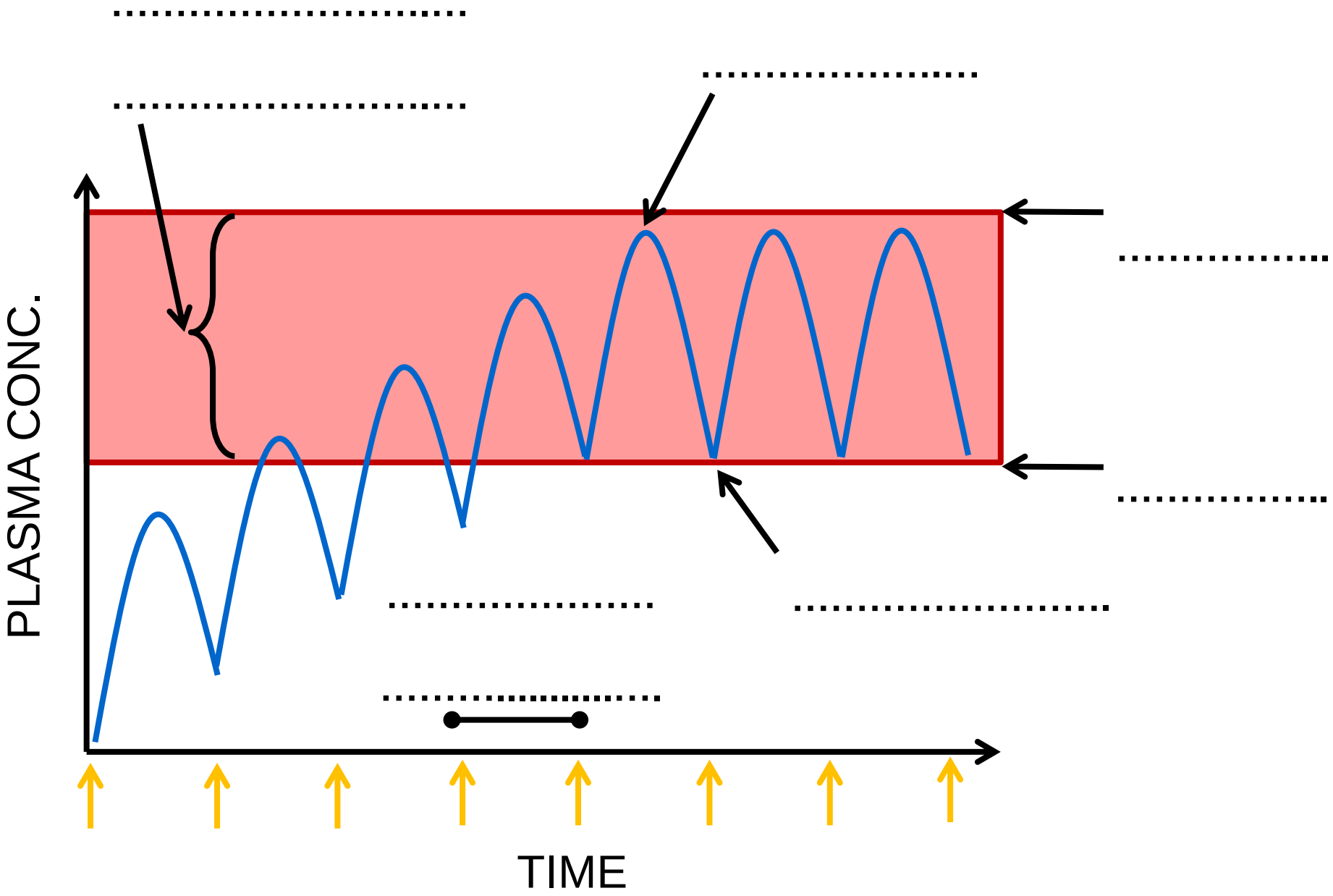
thanks for listening

any questions??


PLASMA CONC.
TIME