Two ~neglected principles in systems pharmacology

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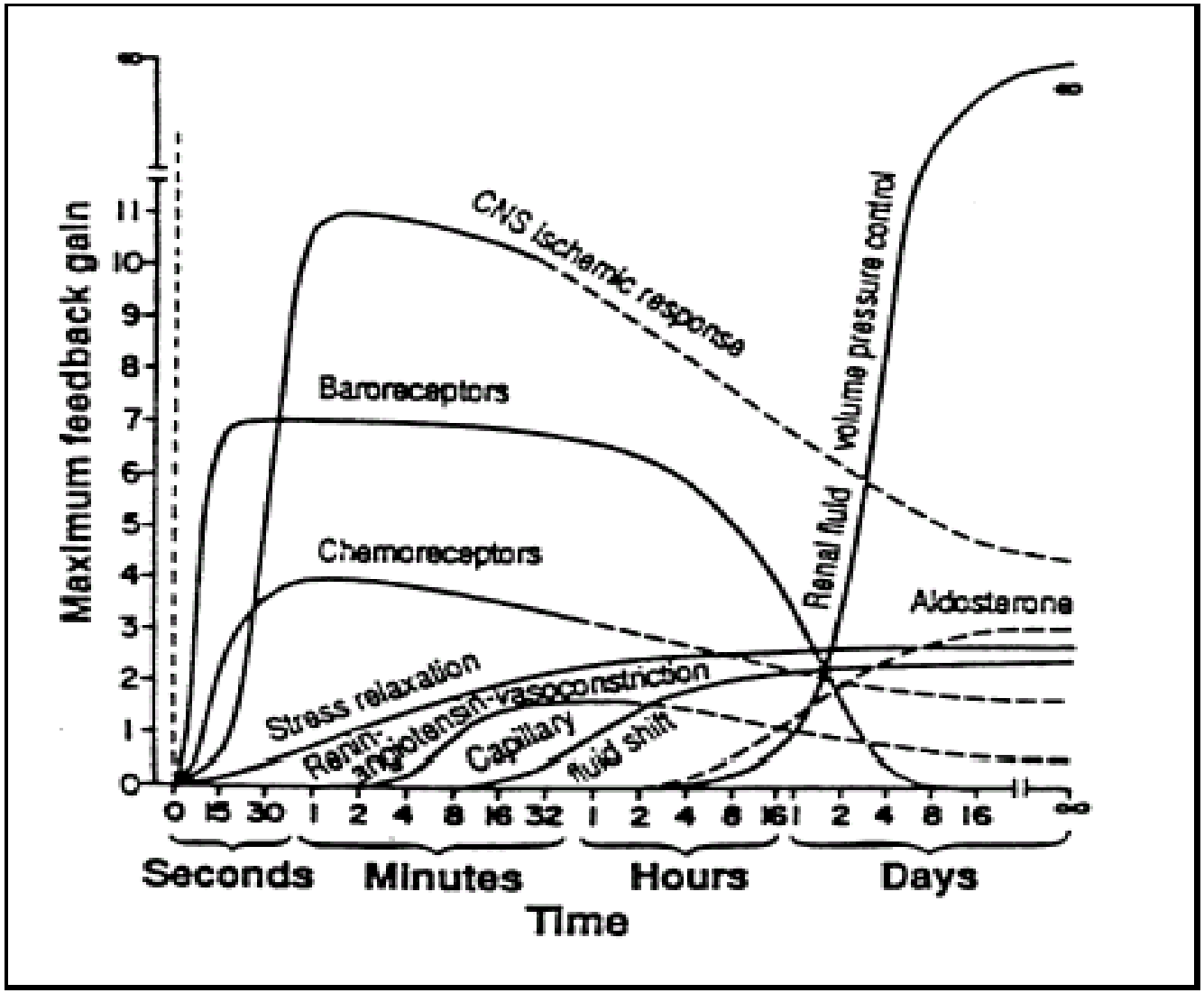
What are the two neglected principles?

- One is that drug actions are modulated more or less continually by physiological counter-regulatory, i.e., homeostatic, responses to the drug's primary (pharmacological) actions.
- Second, counter-regulatory strengths of physiological control systems wax and wane at different rates with the passage of time.
- Upshot: what we call PD is the outcome of a constantly shifting arm-wrestling match between the drug's primary actions and the body's changing counteractions.

Thus,

- Drug actions trigger physiological counter-regulatory actions – a natural consequence of the pervasiveness of multiple homeostatic regulatory mechanisms
  - These homeostatic mechanisms operate on different time-scales, with different counter-regulatory strengths (gain, as engineers say)
  - Thus, they tend to oppose primary pharmacological actions, but they act on widely differing time-scales with differing counter-regulatory strengths
- Let’s look at how that plays out in blood pressure control, as described by one of the great physiologists, Arthur Guyton…



Guyton AC. Science 252: 1813-16, 1991

Each field of therapeutic intervention has its own array of homeostatic mechanisms entering and leaving center-stage

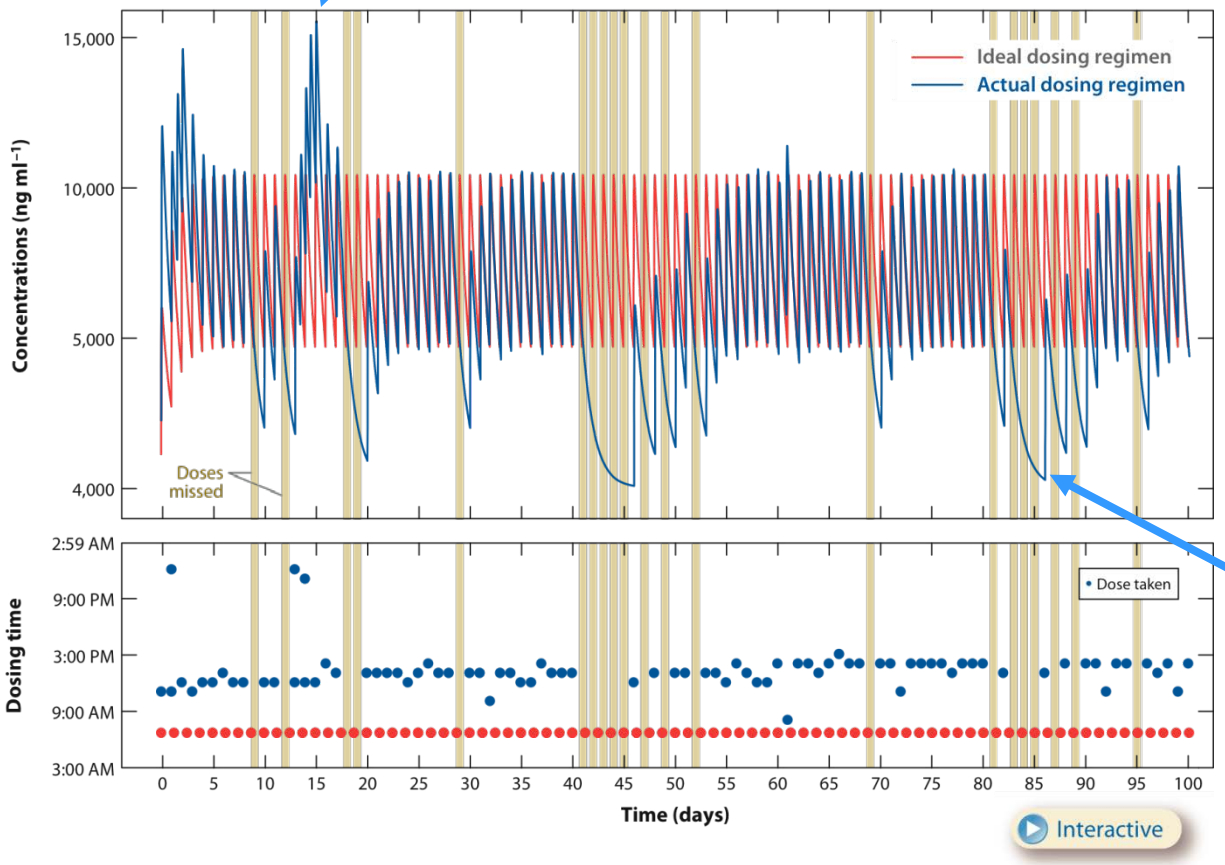
The arm-wrestling metaphor is frequently *perturbed* by patients' periodic lapses in dosing. These lapses irregularly interrupt drug action during long-term treatment of chronic disease.

What's new?

- We now have extensive data on the prevailing wide variations in drug exposure during long-term pharmaceutical treatment of major chronic diseases.
- Electronic methods for capturing drug dosing history data were pioneered in the 1980's, but their clinical applications started with narrow time-windows and small numbers of patients, and expanded very slowly.
- Now, with multi-month data on thousands of ambulatory patients' dosing histories in a number of therapeutic situations, we have a clear picture of the wide variability of drug exposure patterns in long-term treatment of major chronic diseases.

Patients vary the dosing intervals and keep the dose constant

Occasional toxicity

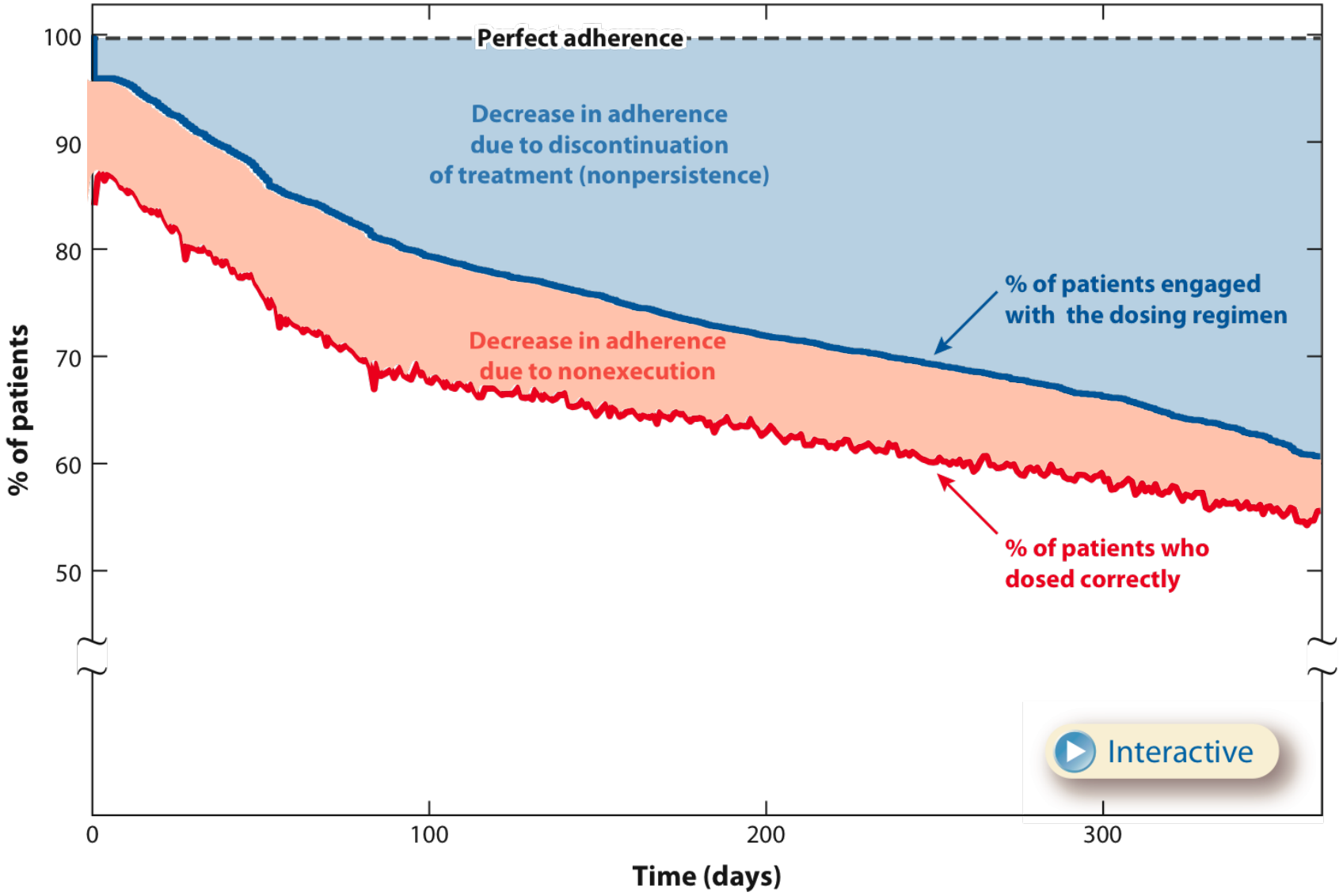


Periodic loss of effectiveness & emergence of drug resistance (HIV)

Blaschke, Osterberg, Vrijens, Urquhart, Ann Rev Pharmacol & Toxicol, in press 2012

Changing adherence during year one: the longitudinal view

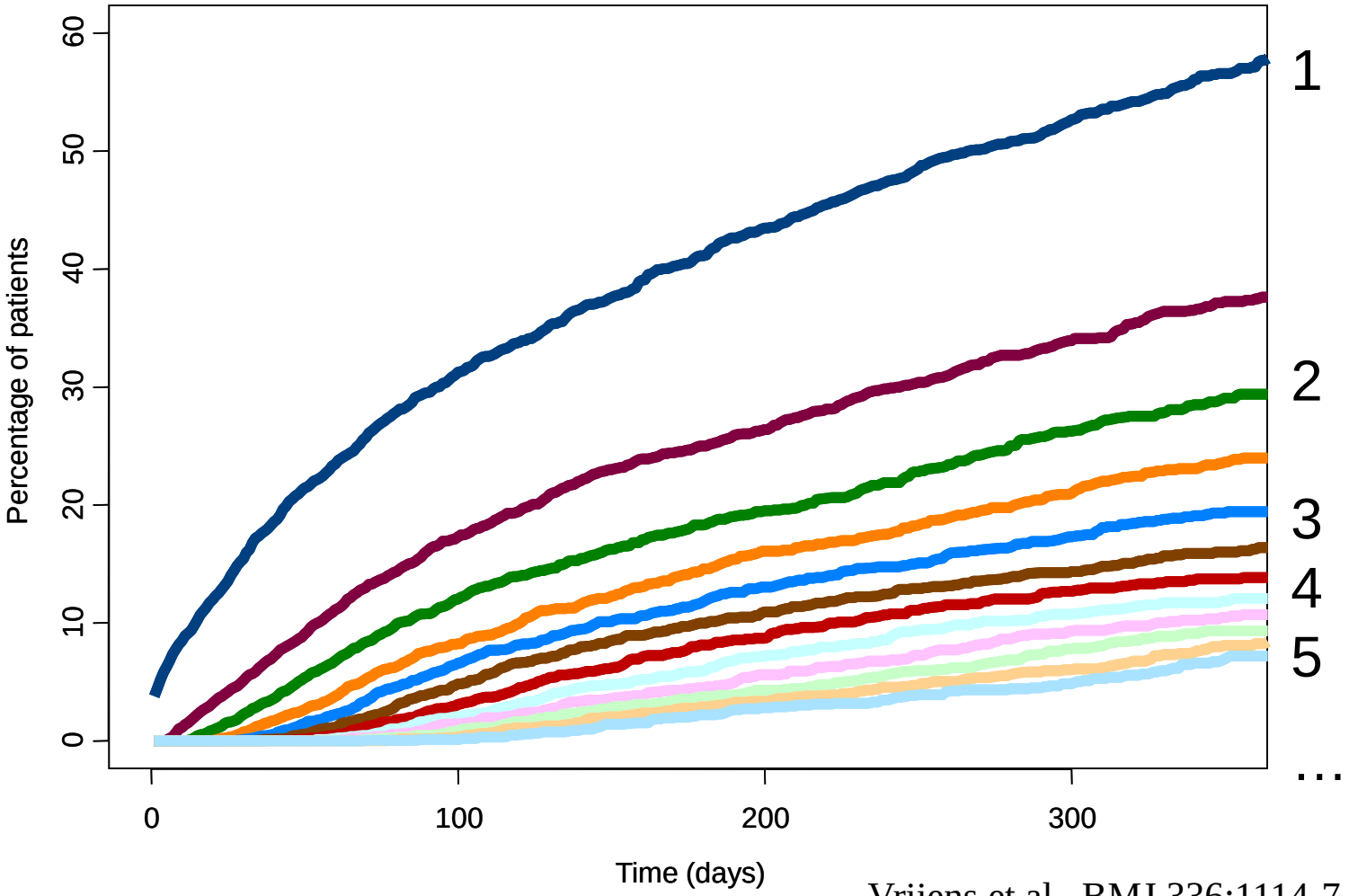
16,907 participants from 95 clinical studies



Blaschke, Osterberg, Vrijens, Urquhart, Ann Rev Pharmacol Toxicol in press 2012

Cumulative probability of experiencing drug holidays (≥3 days)

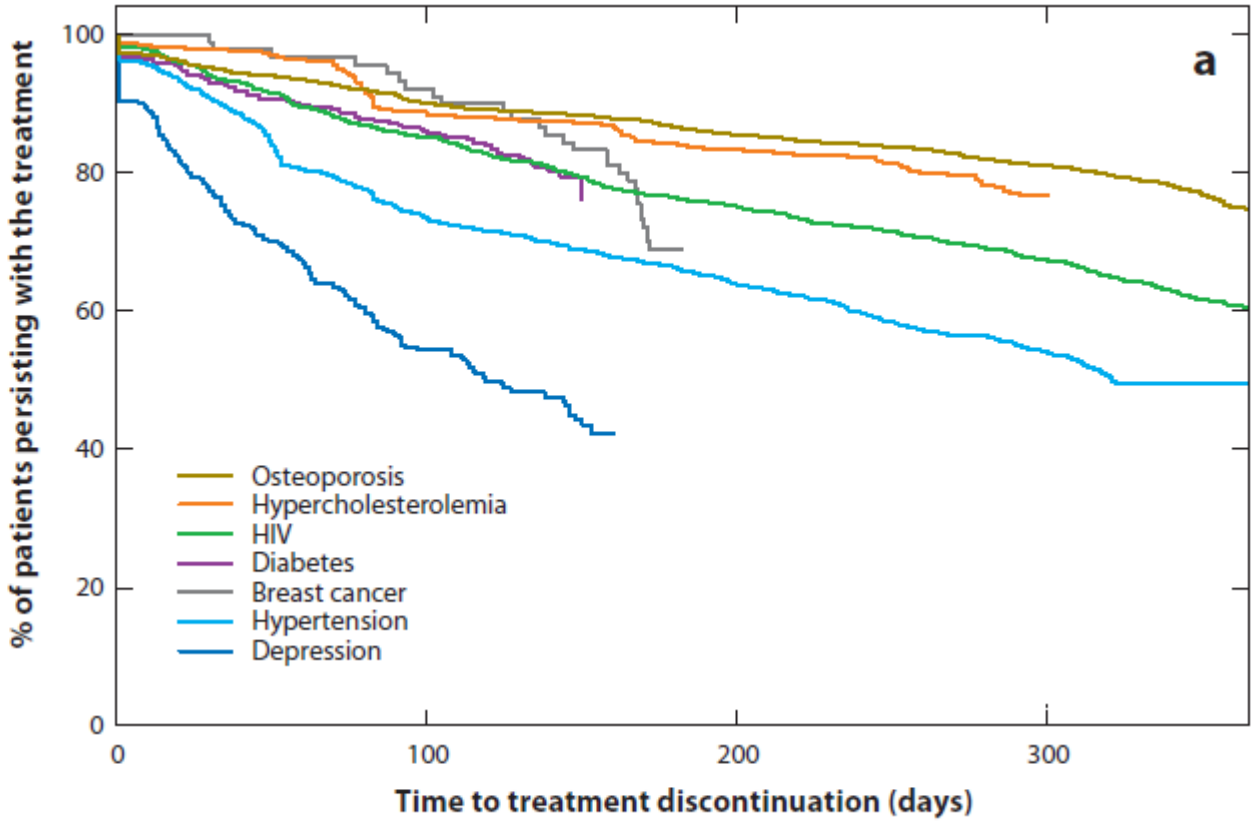
n = 4783



Vrijens et al., BMJ 336;1114-7, 2008

Persistence: time to treatment discontinuation

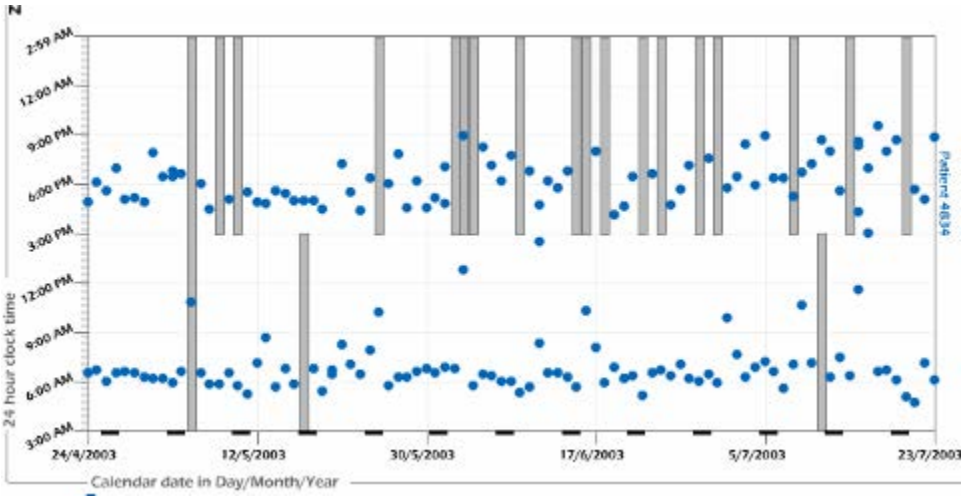
~40% of patients will have discontinued dosing during the first 12 month of treatment

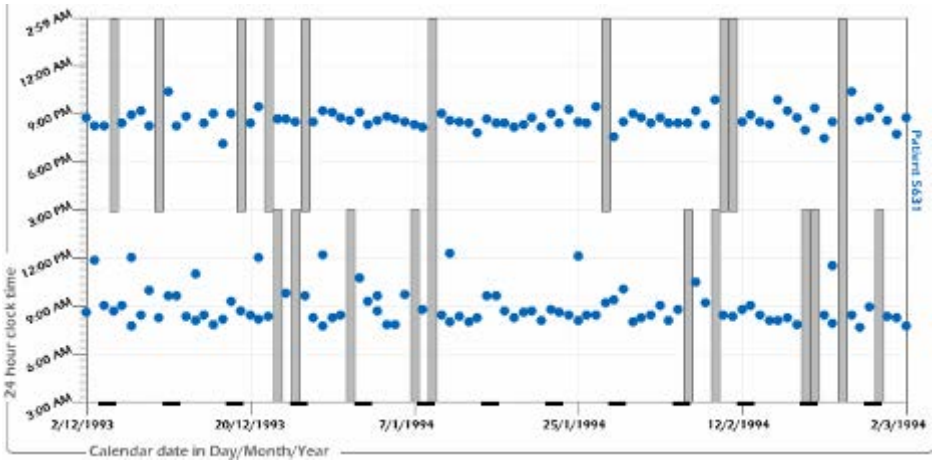


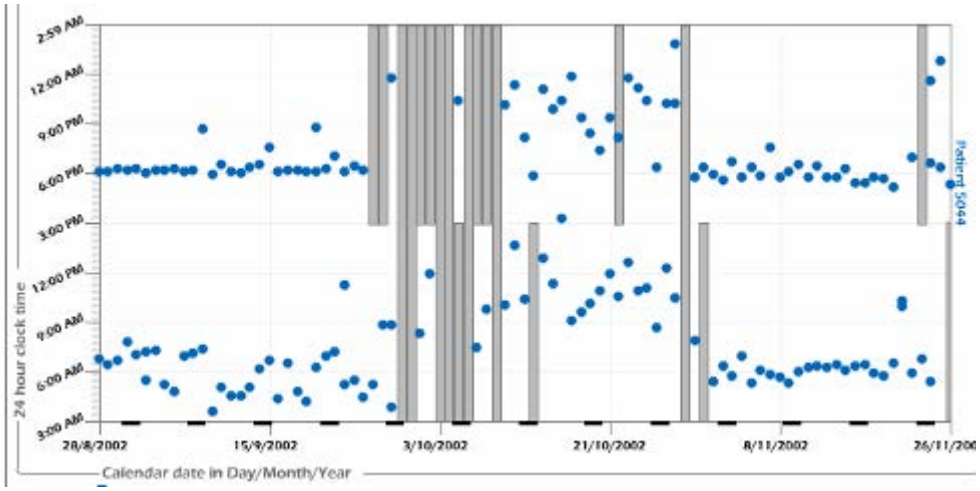
Blaschke, Osterberg, Vrijens, Urquhart, Ann Rev Pharmacol Toxicol, in press 2012

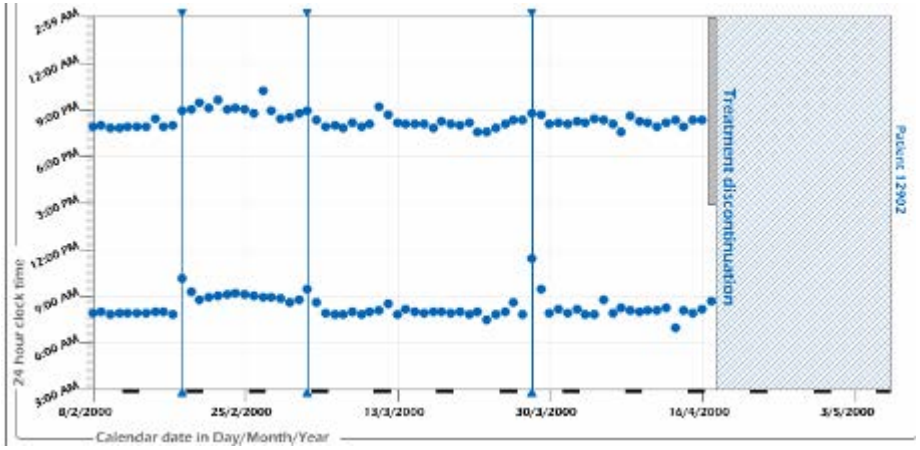
Pre-electronic methods cannot differentiate these patterns

Each patient took 75% of prescribed doses during the 3-month period









Model-based projections

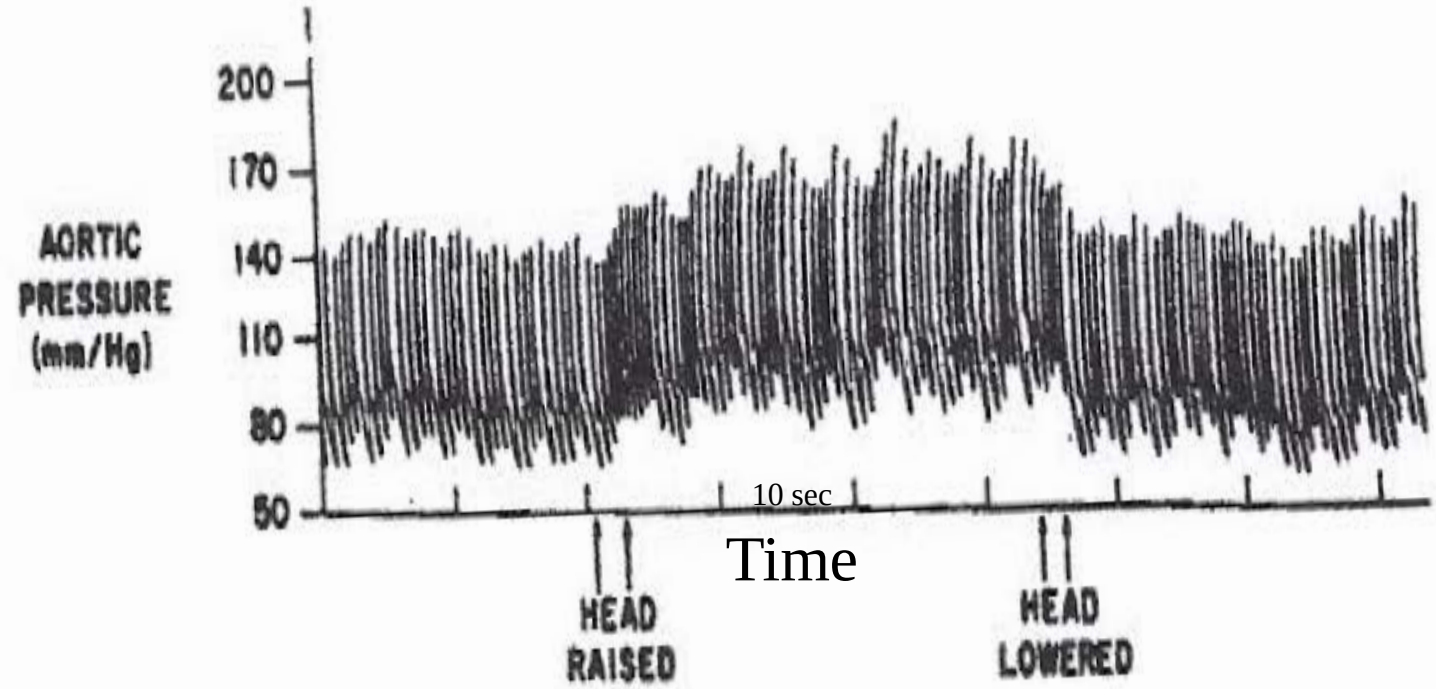
1. PK projections of continuous time course of drug concentration in plasma, from electronically compiled dosing times
    a. accuracy verifiable by direct, single-point chemical assays.
    b. PK models are essentially linear, with only soft nonlinearities, thus superposition usually obtains, or can be approximated
2. what about PD projections of continuous actions of test drugs, from the continuous time course of concentration of the drug in question, in plasma?
    a. here we encounter substantive problems in M&S:
        superposition is unreliable and probably sometimes very misleading
    b. We have to rely on data-based PD models that incorporate salient nonlinearities.

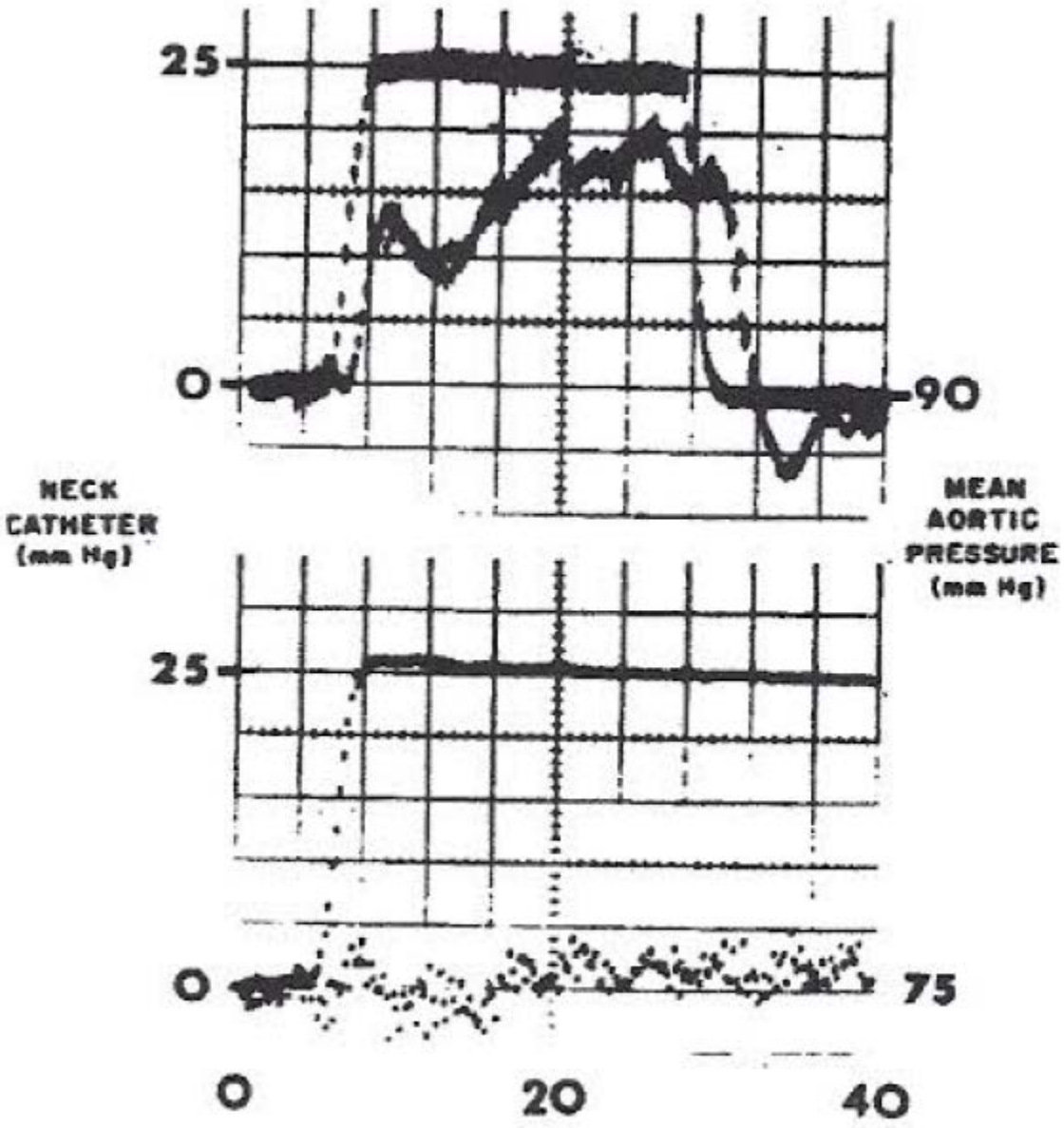
What is the paradigm?

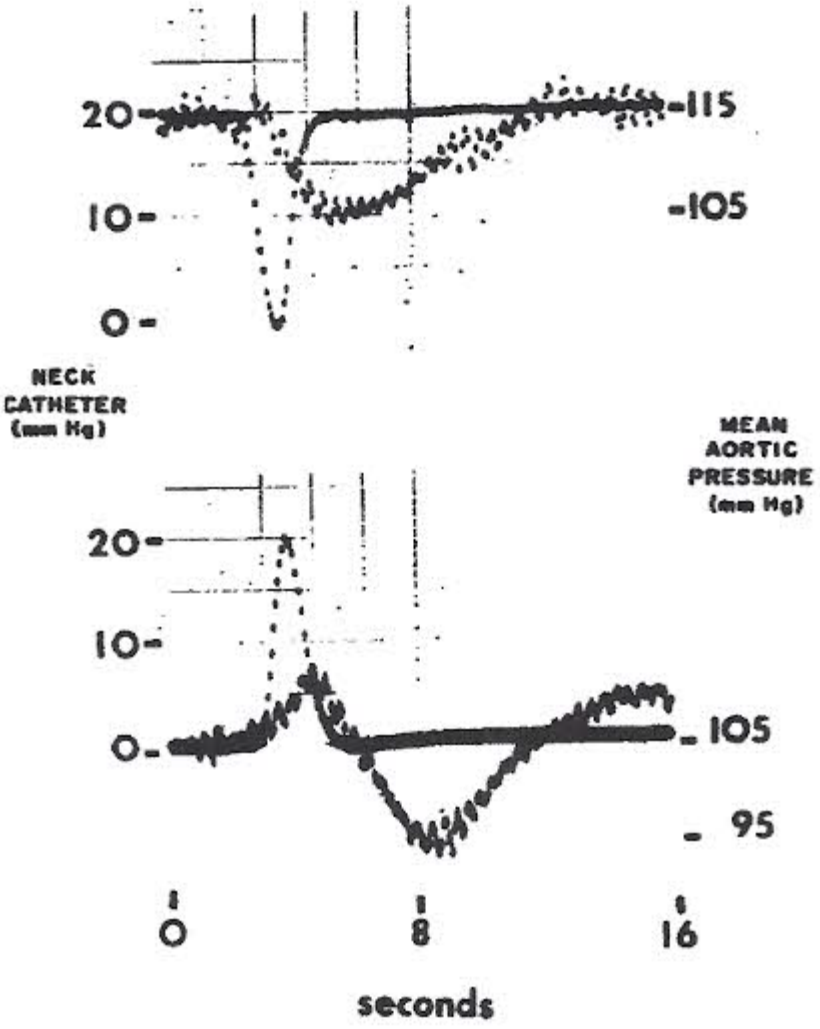
- PD is the ongoing net result of the arm-wrestle between widely varying primary drug actions and the counter-regulatory actions of pervasive, nonlinear, self-regulatory physiological systems
  - superposition is frequently inapplicable
  - a key challenge is to identify circumstances that can trigger unexpected actions of drugs.
  - some of these unexpected actions are beneficial, others are adverse
  - dynamic asymmetries of ‘on’ & ‘off’ responses
  - many show unidirectional rate sensitivity (UDRS)
    - a very ‘hard’ nonlinearity, not linearized by small perturbations, but rather made ‘worse’

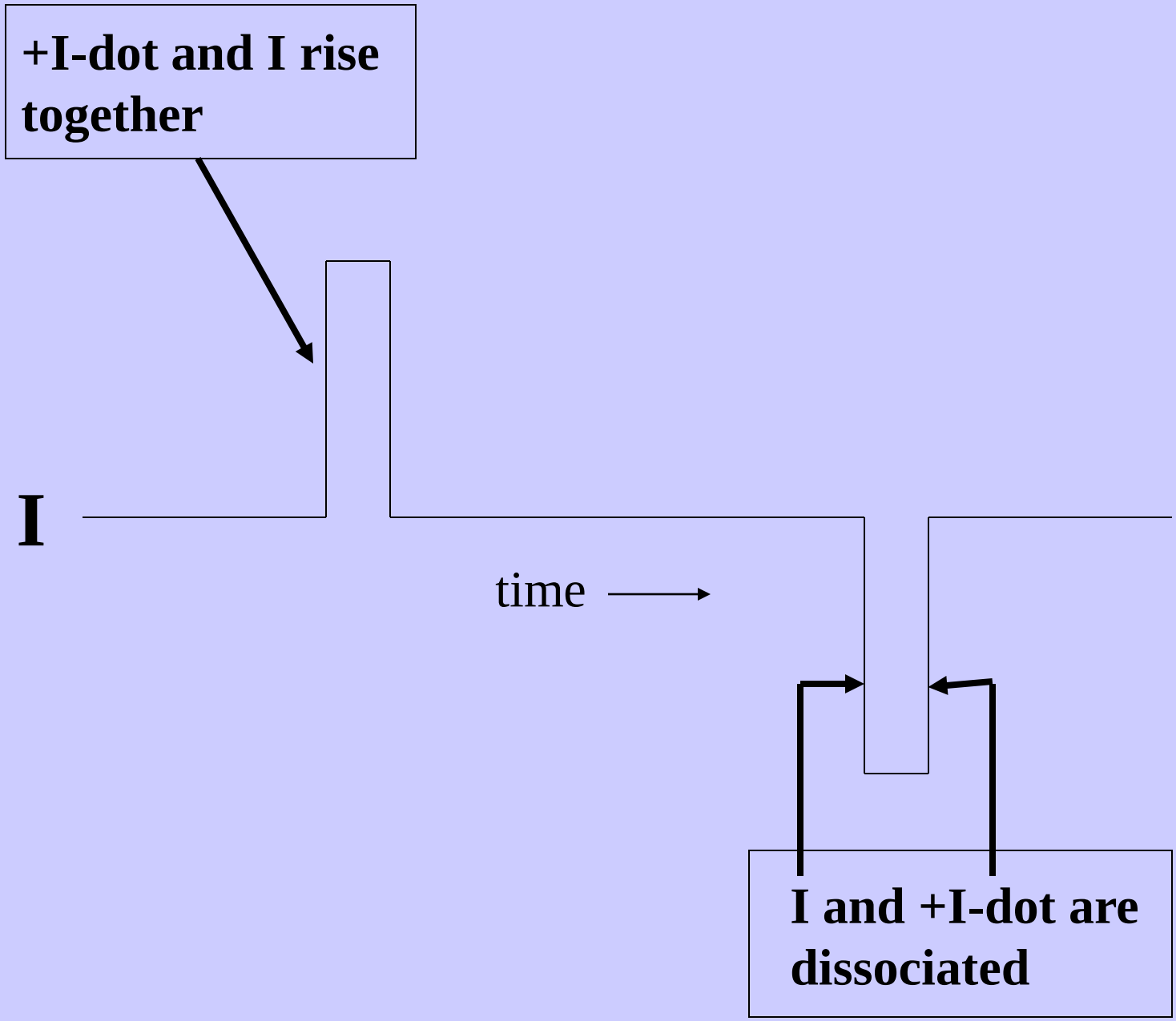
A look at the baroreceptor reflexes during their peak effectiveness

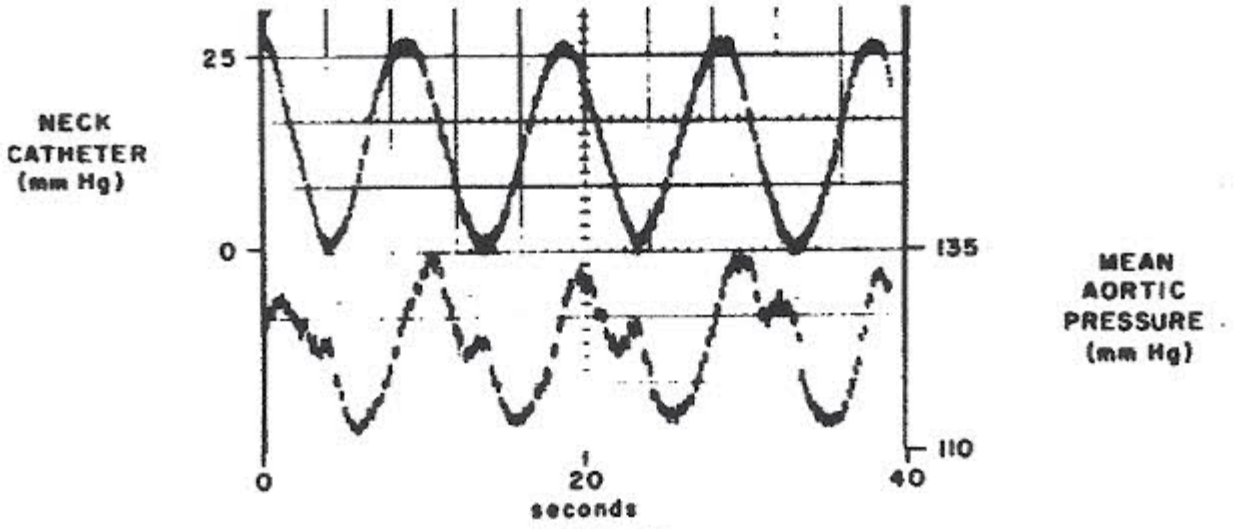
- Their dynamics can be observed in conscious, unrestrained dogs
- Vertical head motion subtracts (on head raising) about 30 mm Hg hydrostatic pressure at the carotid sinus
- Lowering the head, from full-up to full-down, adds (on head lowering) about 30 mm Hg hydrostatic pressure at the carotid sinus.

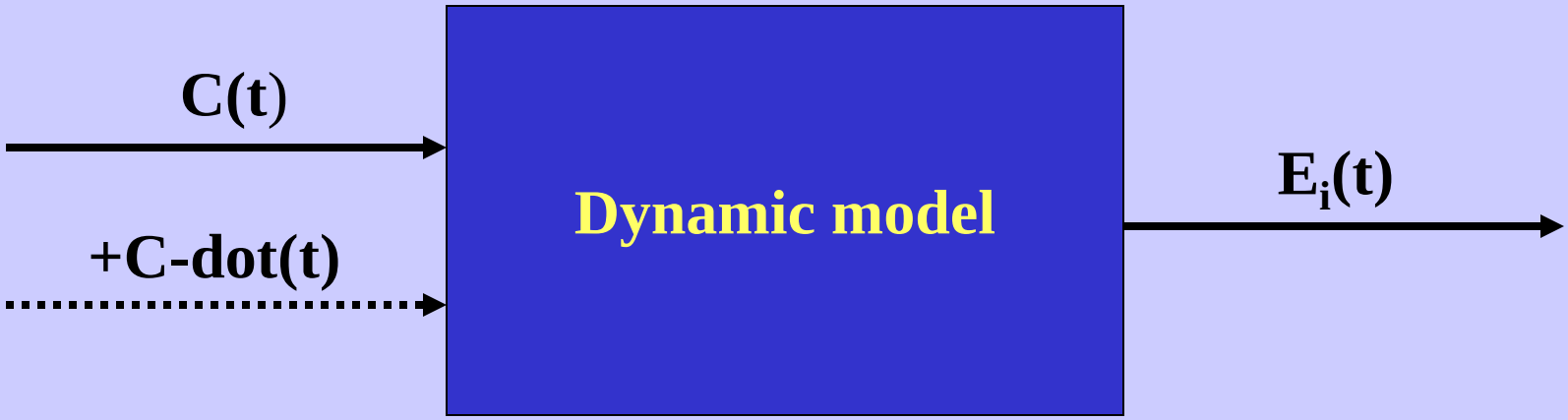

AORTIC
PRESSURE
(mm/Hg)
200
170
140
110
80
50
10 sec
Time
HEAD
RAISED
HEAD
LOWERED


25
0
90
NECK CATHETER (mm Hg)
MEAN AORTIC PRESSURE (mm Hg)
25
0
75
0
20
40
seconds


20
10
0
115
105
NECK CATHETER (mm Hg)
MEAN AORTIC PRESSURE (mm Hg)
20
10
0
105
95
0
8
16
seconds


+I-dot and I rise together
I
time
I and +I-dot are dissociated

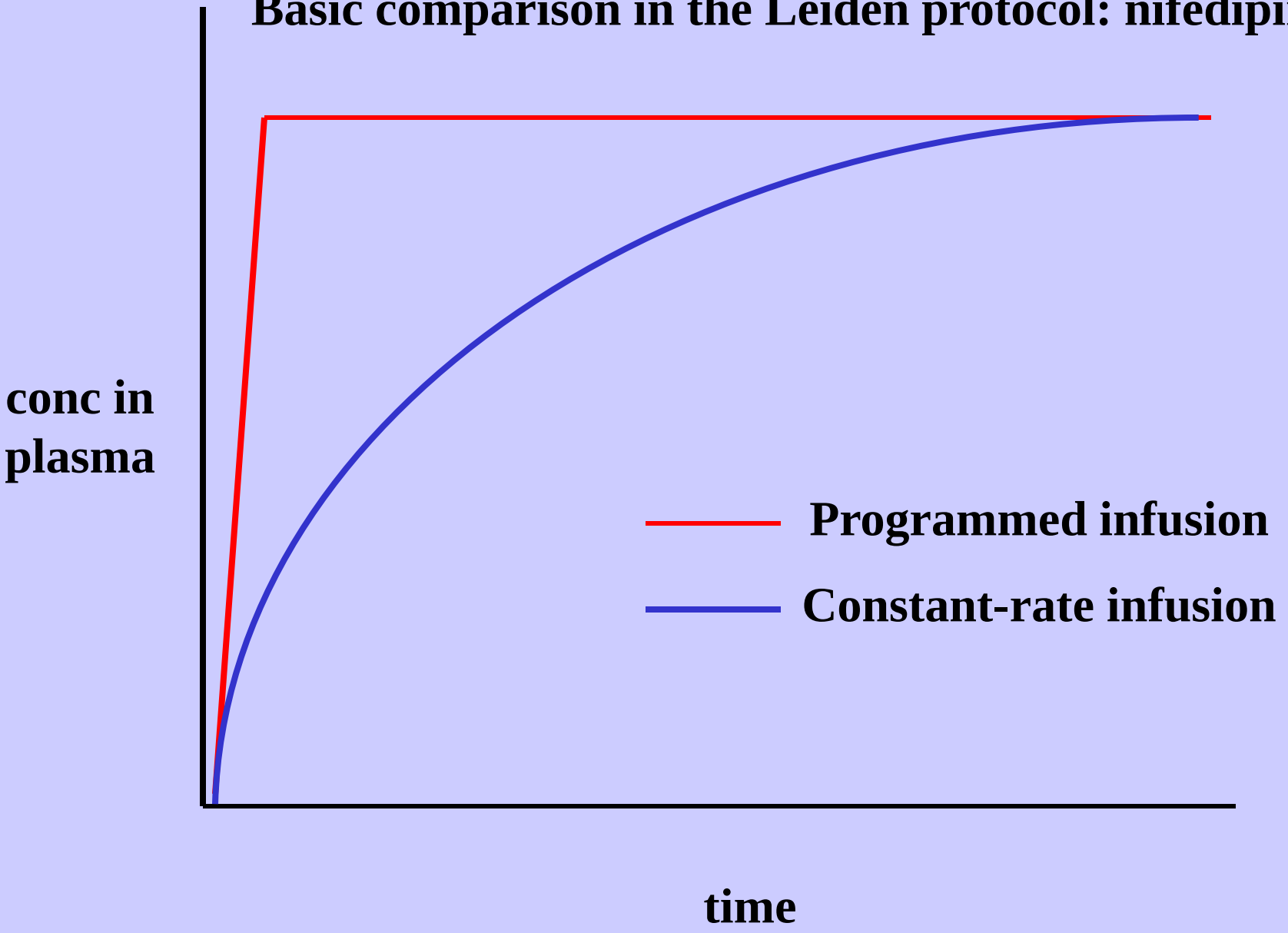

NECK
CATHETER
(mm Hg)
25
0
135
110
MEAN
AORTIC
PRESSURE
(mm Hg)
0
20
40
seconds



Goal: reliable simulation of the drug's dose- and time-dependent effects

C = concentration of drug
+C-dot = rate of increase of C
E = drug effect(s)
t = time
i = enumerator of the E's

Basic comparison in the Leiden protocol: nifedipine



Obstacle: the inherent nonlinearity of PD

- Superposition misleads
  - Inability to generalize from response to one input pattern to responses to other patterns
  - How many/which temporal patterns need to be studied adequately to constrain dynamic models?
- ‘Hard’ nonlinearities
  - paradoxical or out-of-character responses
  - some are exaggerated when changes are small
- Paucity of data on persistence of therapeutic actions after dosing stops: ‘off ’ responses

PD is not an easy topic

- There's a clear need for more information, especially in light of the large amount of dosing history data now available
- The academic approach follows…

The ‘minimal cassette’ of input patterns for exposing salient PD nonlinearities

A. In the 1st days of drug exposure:

- Dose-response
- Sudden on
- Sudden off
- Gradual on
- Gradual off
- High vs low rates of increase of drug concentration in plasma

B. After 90-150 days of exposure:

- Dose-response repeated and contrasted with A. If surprising, repeat other patterns
- If the drug has a first-dose effect, determine how long exposure can be interrupted without the need to re-titrate.

A practical approach is to seek recurring clinical correlates of particular dosing patterns, looking for …

* Temporal sequence
* Plausibility
* Therapeutic relevance

with adequate measurability of key clinical events.

COMMENTS, QUESTIONS, SLIDES, SOME REFERENCES

KEY WEBSITE: www.iadherence.org

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Useful Reading

- Experimental strategies
  - Lamberti JJ Jr, Urquhart J, Siewers RD. Observations on the regulation of arterial blood pressure in unanesthetized dogs. Circulation Research 23: 415-428, 1968. appendix on modeling
  - Urquhart J. Physiological actions of adrenocorticotropic hormone, in, Handbook of Physiology, Endocrinology. Washington, D.C.: Amer Physiol Soc, 1974, Sect. 7, vol. IV, chap. 27, pp. 133-57.
  - Kleinbloesem CH, et al. Rate of increase in the plasma concentration of nifedipine as a major determinant of its hemodynamic effects in humans. Clin Pharmacol Ther 41: 26-30, 1987.
  - Urquhart J. History-informed perspectives on the modeling and simulation of therapeutic drug actions. In: Simulation for designing clinical trials. Eds: Ko HC, Duffull S. Marcel Dekker, 2002, 245-69.
  - Blaschke T, Osterberg L, Vrijens B, Urquhart J. Adherence to medication… Ann Rev Pharmacol Toxicol, 2012 (in press)
- modeling UDRS in physiology
  - Urquhart J, Li CC. Dynamic testing and modeling of adrenocortical secretory function. Ann NY Acad Sci 156(2): 756-78, 1969.
    - This entire volume is devoted to UDRS in many physiological systems