Causality: marginal effects, conditional effects and mechanisms

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Organization of the talk

1. General questions around causality
2. The stochastic system approach to causality
3. Randomized trials and observational studies
4. Illustrations from HIV infection and AIDS

A classification of causal questions

- Prospective questions: “What will be the difference in the outcome for subject *i* between the two actions: giving treatment 0 or giving treatment 1 to subject *i* ?”
- Retrospective questions: “Subject *i* has experienced event *A*; what is the cause of this event”
- Different modalities of prospective and retrospective questions: individual or population level, multiple effects, multiple causes
- Counterfactuals questions are stimulating but not scientifically interesting.

Theories of causality

- Different philosophical theories
- Different mathematical/statistical formulations

Statistical formulations

- Counterfactual approach: development of the potential outcome theory: Neyman, Rubin, Robins...
- Physical laws; dynamic approach: Granger, Aalen, Arjas, Didelez, Commenges...

Counterfactuals

Example: Y_i: headache at t_1; X_i aspirin at $t_0 < t_1$ for subject i.

1. Counterfactual event: Observed $X_i = 0$; $X_i = 1$ is a counterfactual event
2. Counterfactual question: "What would have been Y_i if the counterfactual event $X_i = 1$ had occurred ?"

Potential outcomes

Potential outcomes are defined as variables associated to each potential event, whether counterfactual or not; $Y(1)$ is the potential outcome for $X = 1$, $Y(0)$ is the potential outcome for $X = 0$; so if $X = 0$ has been observed, $Y(0)$ is observed but $Y(1)$ is counterfactual.

Definition of the causal effect via potential outcomes

The causal effect for subject i is:

$$Y_i(1) - Y_i(0).$$

Since only one of the potential outcomes is observed, the causal effect is not observed. Rubin (J Educ Psychol, 1974) showed that it could be estimated under the SUTVA assumptions.

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The stochastic system approach to causality

- Form an abstract system at a certain level
- Physical laws determine the dynamic of the system, except for manipulable factors
- In Perfect systems for Y, the dynamics of Y computed from physical laws is the true dynamics.

There is an axiom of “separability of the universe”; we must find an abstract system which looks like the real system. Perturbations from outside are included in the stochasticity of the dynamics.

Example: the solar system

- We assume we know the physical law at the level of planets (Newton or Einstein)
- Applying the physical law to a good system should give a good description of the movement of the Earth

Examples of systems

- Earth and Mars: applying the gravitation law to this system does not give dynamics consistent with observations
- Earth, Mars and Sun: the gravitation law gives a much better result
- Earth, Mars, Venus, Jupiter...even better result
- Discovery of Neptune (Leverrier, 1846)

The solar system: manipulable and non-manipulable factors

- Here the causal theory applies to non-manipulable factors.
- Distinction between manipulable and non-manipulable factors is not clear cut: factors can be only partially manipulable, factors which are not manipulable at a certain time can become so by development of new technology.
- The same theory applies to the control of the trajectories of a spacecraft; here there are manipulable factors.

Rosetta and Philae

Application to epidemiology

- Here we do not know the physical law !
- We have to learn both law and system...
- But this was true for physics on the long term...

The stochastic process representation

- Statistical causal models have represented factors by random variables: DAGS
- But time is essential to causality, not just a dressing...
- Stochastic processes are fitted to represent phenomena evolving in time

- There are stochastic processes for events: counting processes
- and for continuous markers: diffusion processes

- We need a model for the law of the system
- We also need a model for the observations (we generally do not observe in continuous time and there is a measurement error)

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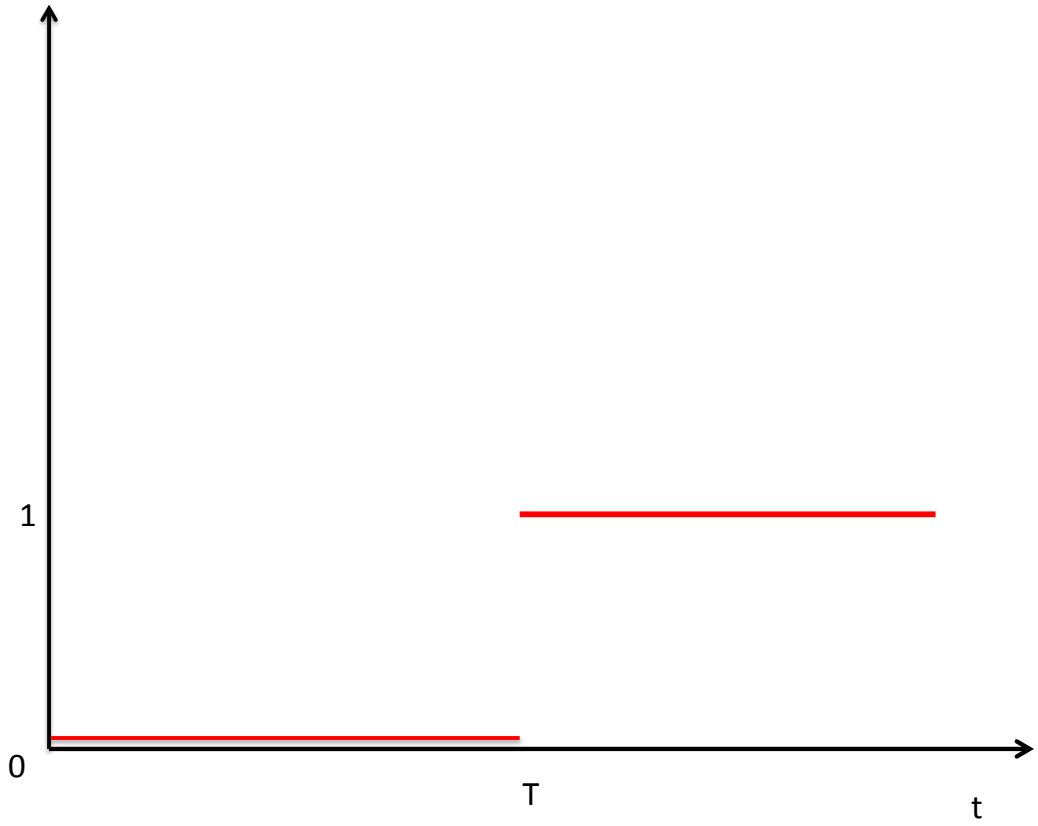
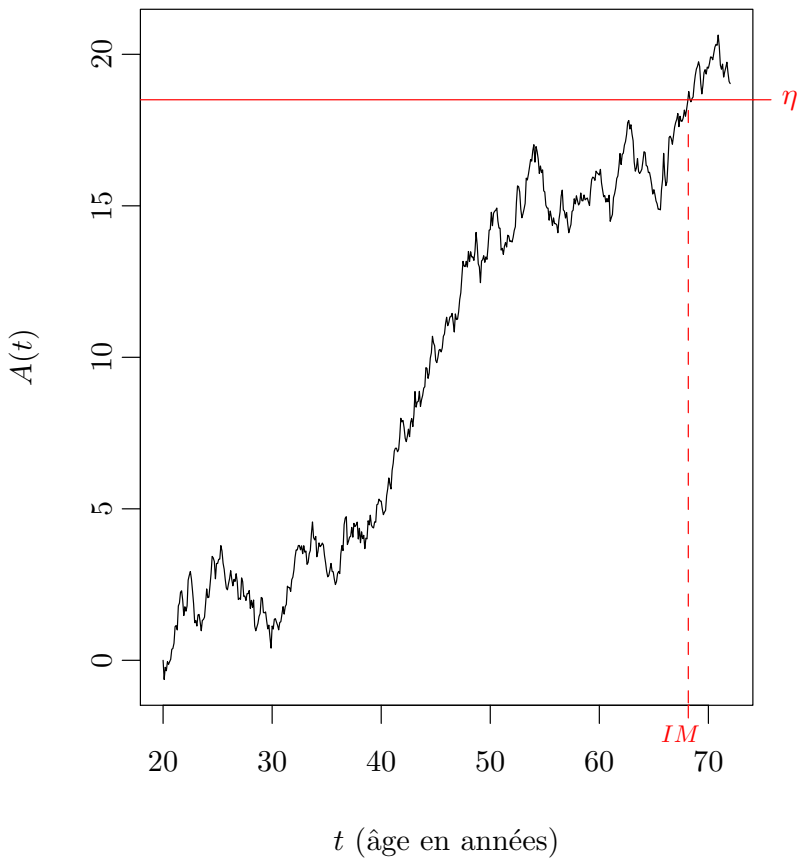
Counting process



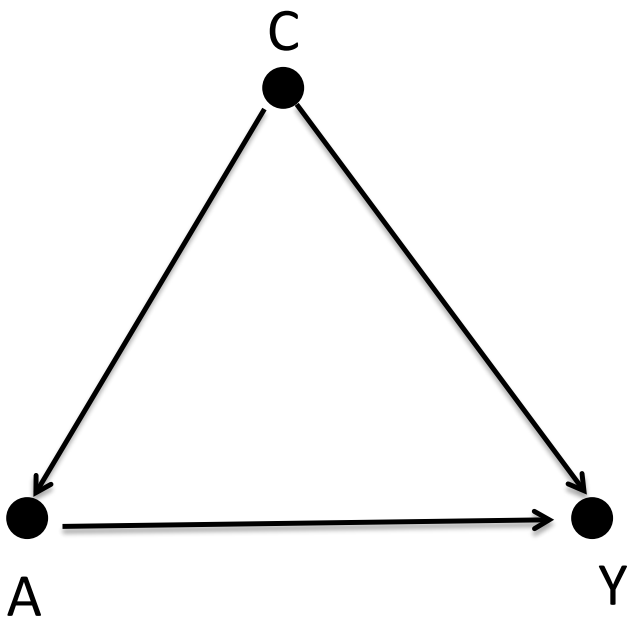
Atheromatous process



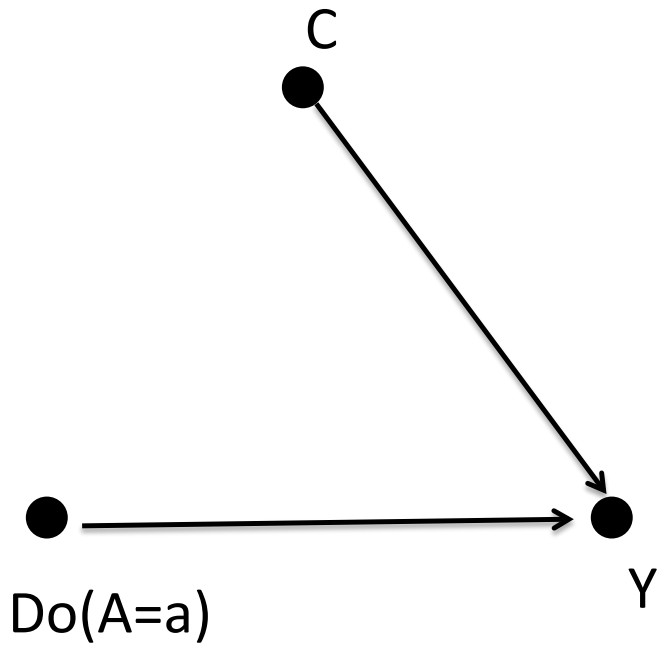
Definition of influence between stochastic processes

- A real system is represented by a multivariate stochastic process: $\boldsymbol{X} = (X_1, X_2, \ldots, X_K)$ (counting processes and diffusion processes)
- A mathematical definition of local independence (WCLI)
- If X_k is not WCLI of X_j then $X_j \longrightarrow_{\boldsymbol{X}} X_k$
- A graph of influences can be drawn; not acyclic

Influence graph for treatment with a confounding factor



a)



b)

Biological mechanism and statistical modeling

- Biological mechanisms are described: precise mechanisms allow to make causal conclusions
- Statistical models can give a quantitative dimension
- Sometimes causal relationships are established before biological mechanisms are clearly described (tobacco and lung cancer)
- Sometimes biological mechanisms allow quantitative models to be developed (HIV infection)
- Epidemiological studies discovered AIDS and suggested it was infectious; biologists discovered the HIV, stat models could be developed.

Influence graph for HIV infection

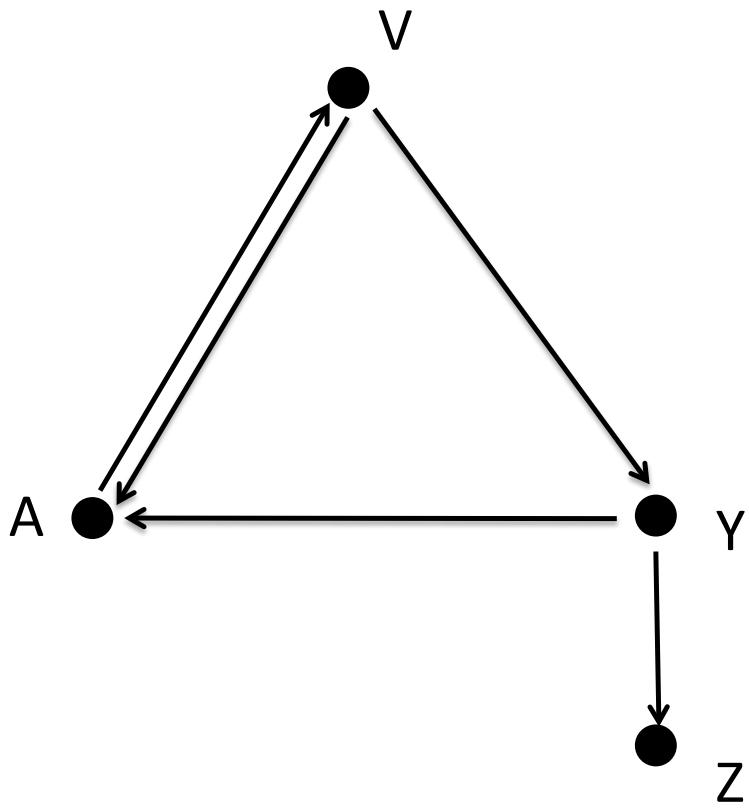
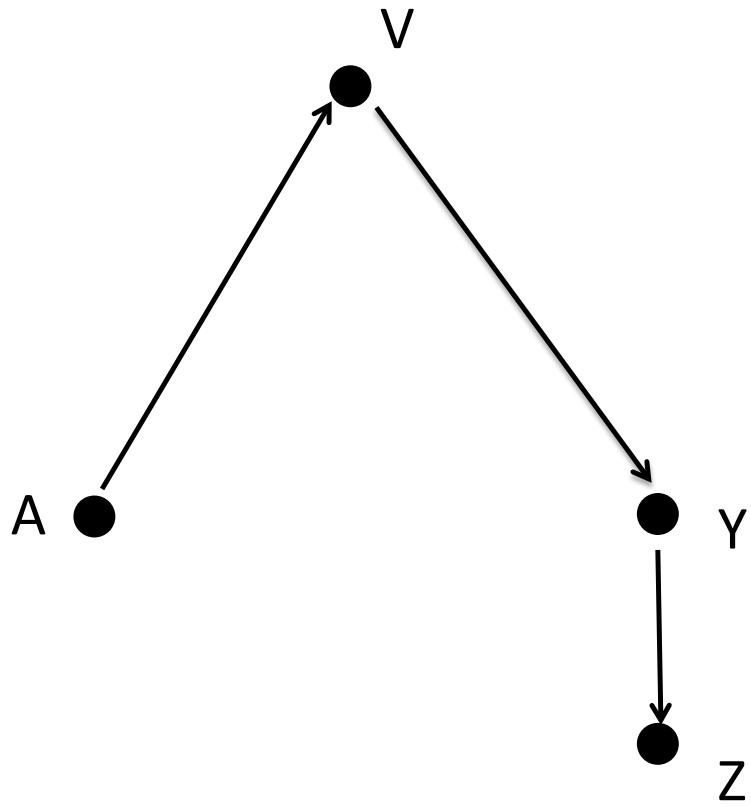
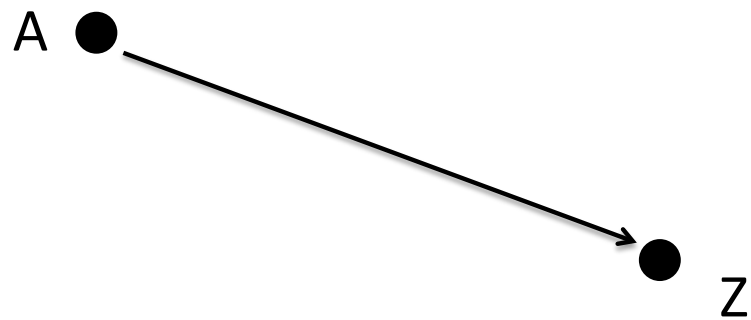


Figure: A: treatment; V: viral load; Y: total T-cells; Z: disease

Influence graph for HIV infection: randomized



Influence graph for HIV infection: collapsed



Limitations of randomized studies

- Randomization is a wonderful tool for assessing marginal causal effect of a treatment
- But there are many limitations

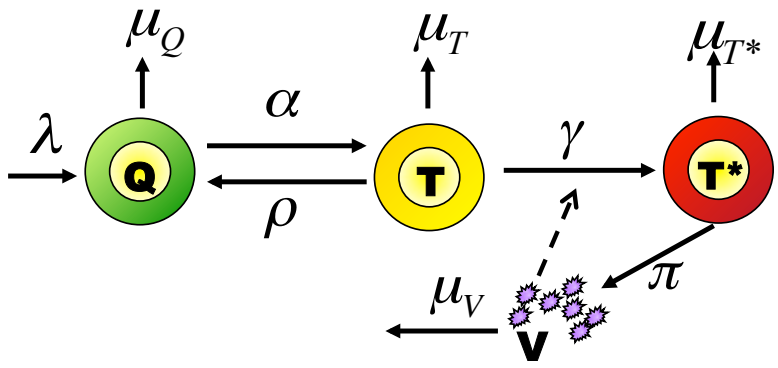
Limitations

- We must first select the treatments to be tested (small number, cost)
- Causal issues are not restricted to treatments
- short term follow-up
- selected population
- non-compliance

Learning from observation studies and apply to experimental situations

- We can learn the physical part of the system dynamics from observational studies
- Then apply to new probability laws representing interventions: where the factor of interest may be randomized or fixed to a certain value, or be partly manipulated

Modeling the interaction between HIV and T-cells: graph



Modeling the interaction between HIV and T-cells: Equations

$$\begin{cases} \frac{\mathrm{d}Q_t}{\mathrm{d}t} &= \lambda + \rho T_t - \alpha Q_t - \mu_Q Q_t, \\ \frac{\mathrm{d}T_t}{\mathrm{d}t} &= \alpha Q_t - \gamma T_t V_t - \rho T_t - \mu_T T_t, \\ \frac{\mathrm{d}T^*{}_t}{\mathrm{d}t} &= \gamma T_t V_t - \mu_{T^*} T^*{}_t, \\ \frac{\mathrm{d}V_t}{\mathrm{d}t} &= \pi T^*{}_t - \mu_V V_t. \end{cases}$$

We must add

- A model for the variability of the parameters between individuals
- Random effects: $\lambda^i, \alpha^i, \mu^i_{T^*}$
- Explanatory variables: a model for $\gamma^i(t)$, as a function of the dose of treatment at time t

Influence graph for the HIV model

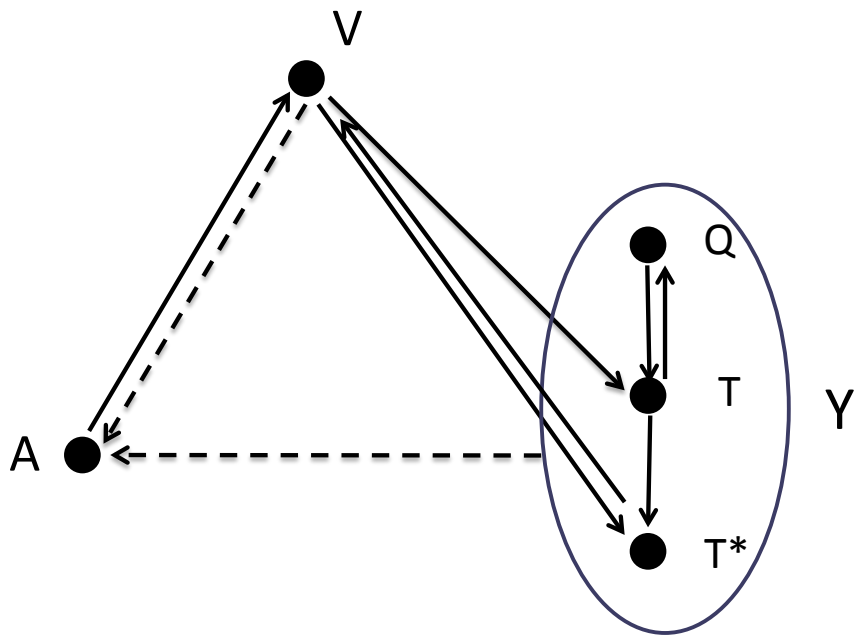


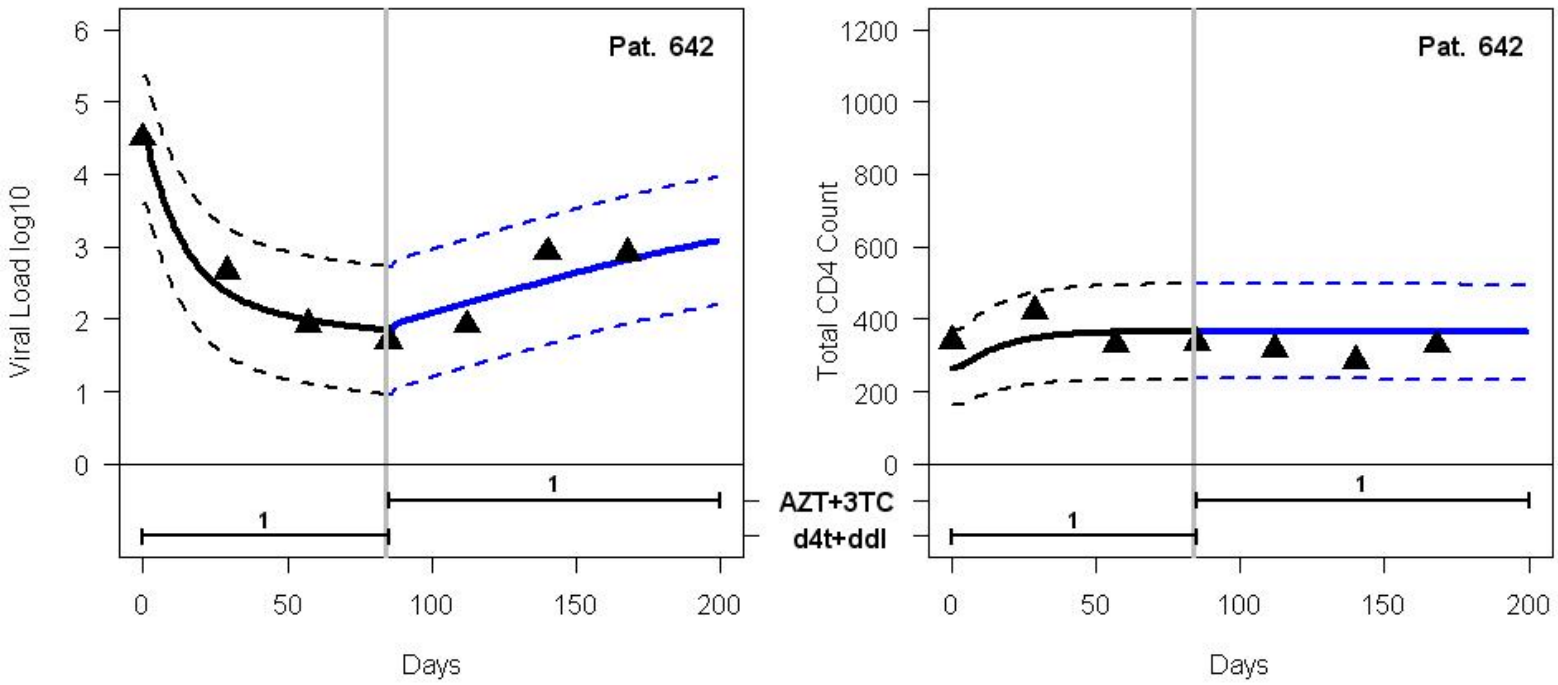
Figure: A: antiretroviral treatment; V: viral load; Q: quiescent T-cells; T: activated T-cells; T*: infected T-cells, Y: total T-cells

Modeling the interaction between HIV and T-cells: Observations and inference

We must add

- A model for the observations: we observe viral load and total CD4-T-cell counts at discrete times
- Estimation of the parameters can be done by maximum likelihood (difficult !)
- We can estimate the random effects and predict trajectories for particular patients

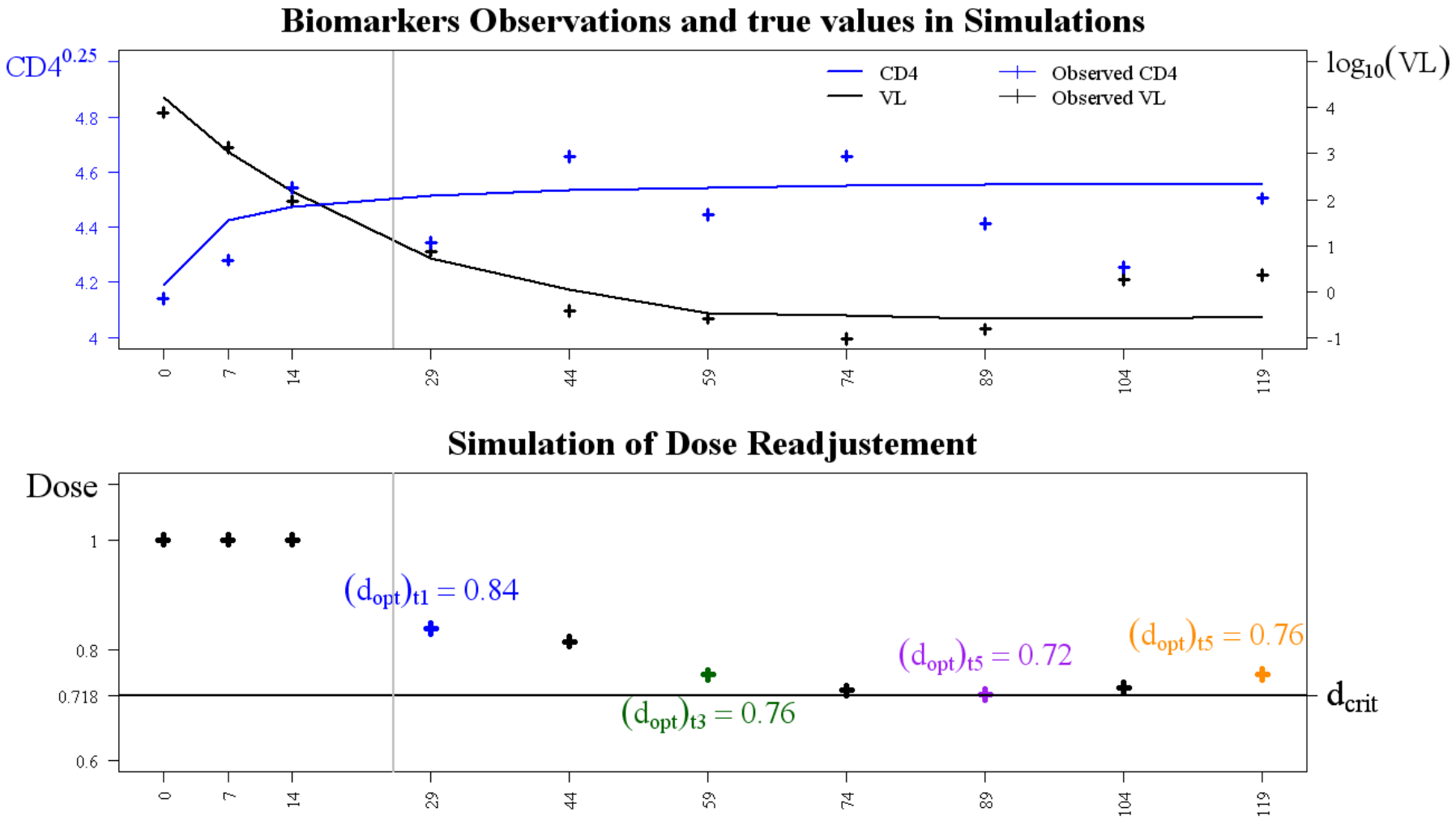
Prediction with the model



Optimal dose

- There exists an optimal dose: the minimum dose which is such that $R_0 < 1$ (reproductive number).
- Given the information at time t we find the dose such as the probability of $R_0 < 1$ is large.
- This can be found by a MCMC algorithm

Adapting the dose



Effect of IL7 on T-cell populations

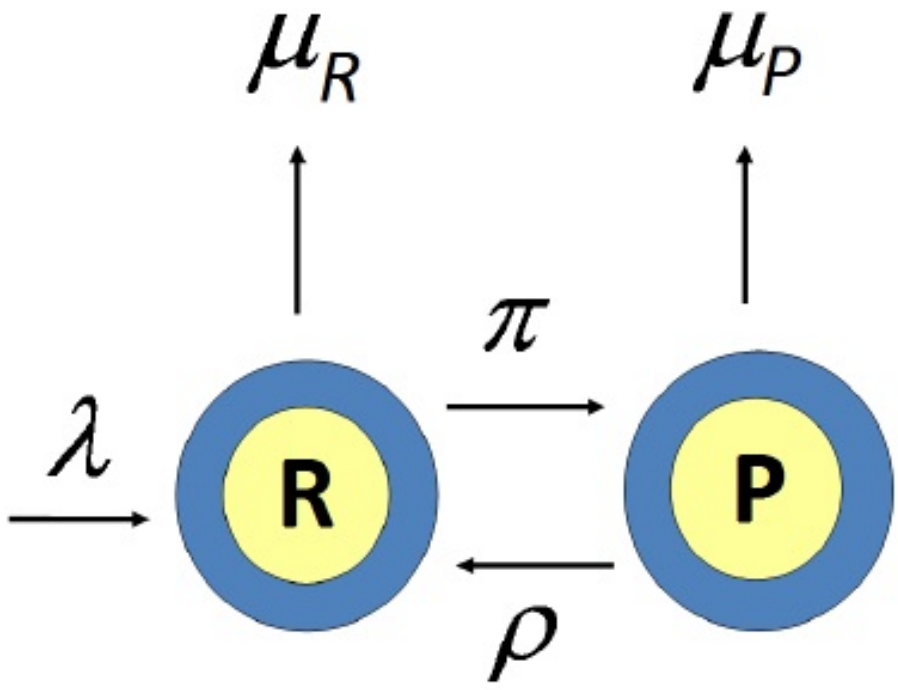


Figure: P : proliferative CD4, R : resting CD4

Effect of IL7 on T-cell populations

$$\begin{cases} \dfrac{dR}{dt} = & \lambda - \pi R + 2\rho P - \mu_R R, \\ \dfrac{dP}{dt} = & \pi R - \rho P - \mu_P P, \end{cases}$$

- A model for the variability of the parameters between individuals
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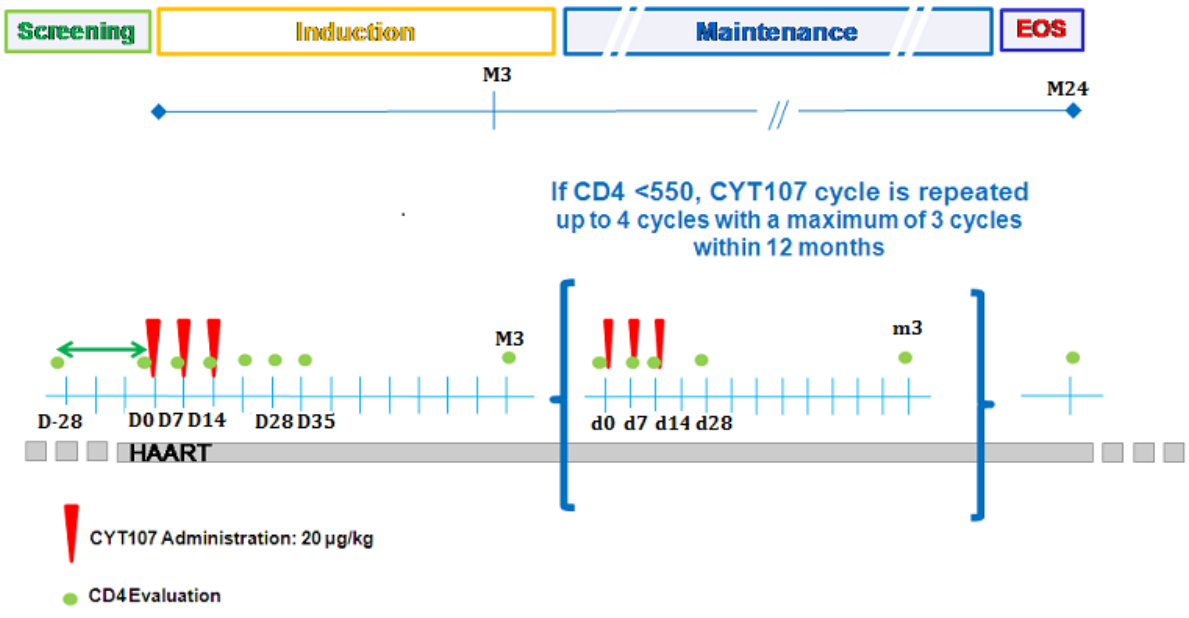
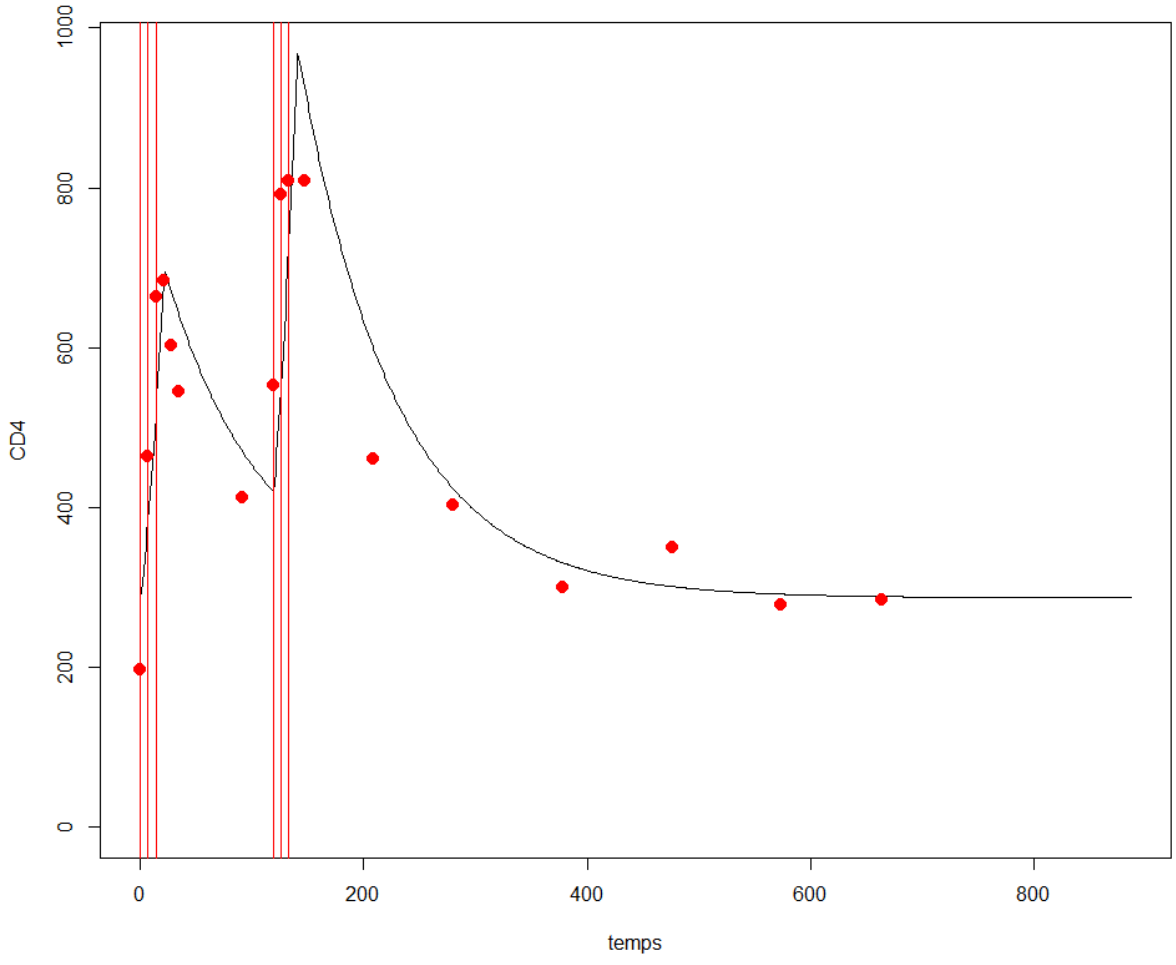
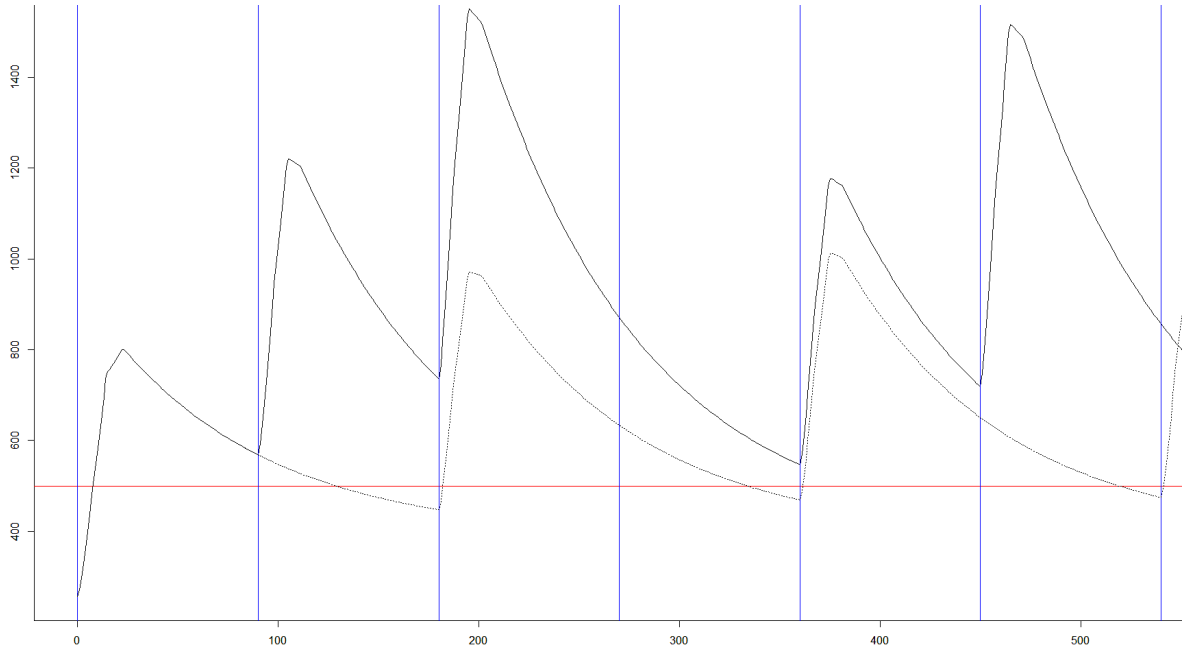
Protocol of INSPIRE studies



Fit of the model



Adapting the protocol of injections



Conclusion: general

- Randomized studies can assess the marginal causal effect of a treatment
- Randomized clinical trials have many limitations
- There is a need to understand mechanisms (biologists also use randomized studies)
- Mechanistic models can be qualitative or quantitative
- The “stochastic system approach to causality” may be a good approach encompassing randomized studies and mechanistic models

Conclusion: quantitative mechanistic models

- Quantitative mechanistic models may allow individualization of therapeutic protocols
- There are limitations to these models: assumptions of the models, numerical problems, insufficient data,...they may be useful in some cases and they must be developed in connection with biological and clinical findings.

References on causal stochastic systems

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