100
1908 - 2008
UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

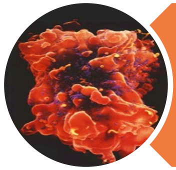
28 July 2017
36th Chinese Control Conference
Dalian, China

The Common Myths about Control Systems Modelling

Prof. Xiaohua Xia 夏小华

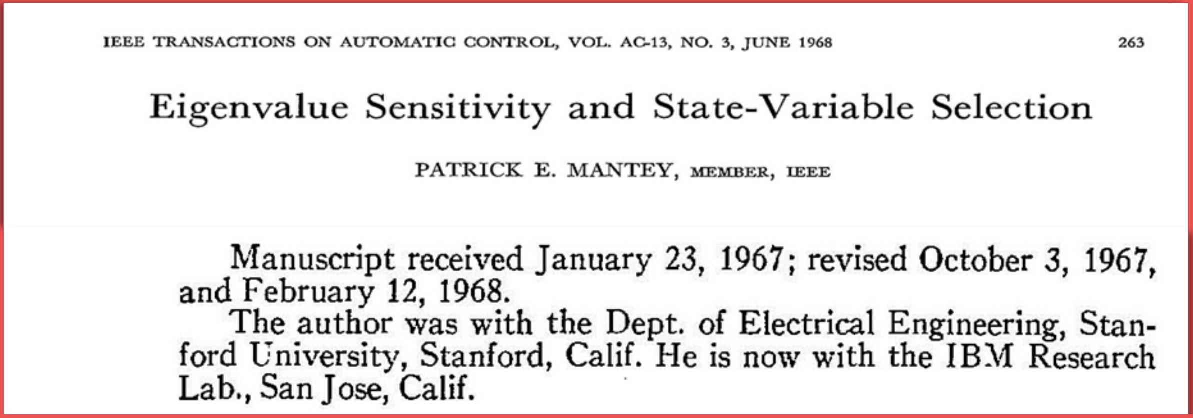
Projects/stories in South Africa

Heavy haul trains



HIV/AIDS

Energy efficiency



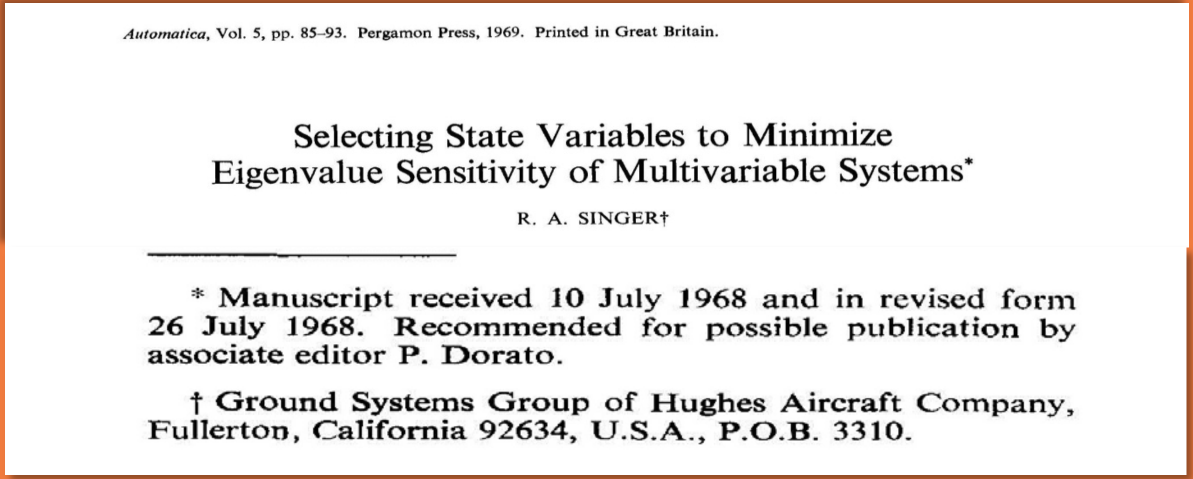
IEEE TRANSACTIONS ON AUTOMATIC CONTROL, VOL. AC-13, NO. 3, JUNE 1968 263

Eigenvalue Sensitivity and State-Variable Selection

PATRICK E. MANTEY, MEMBER, IEEE

Manuscript received January 23, 1967; revised October 3, 1967, and February 12, 1968.

The author was with the Dept. of Electrical Engineering, Stanford University, Stanford, Calif. He is now with the IBM Research Lab., San Jose, Calif.



Automatica, Vol. 5, pp. 85–93. Pergamon Press, 1969. Printed in Great Britain.

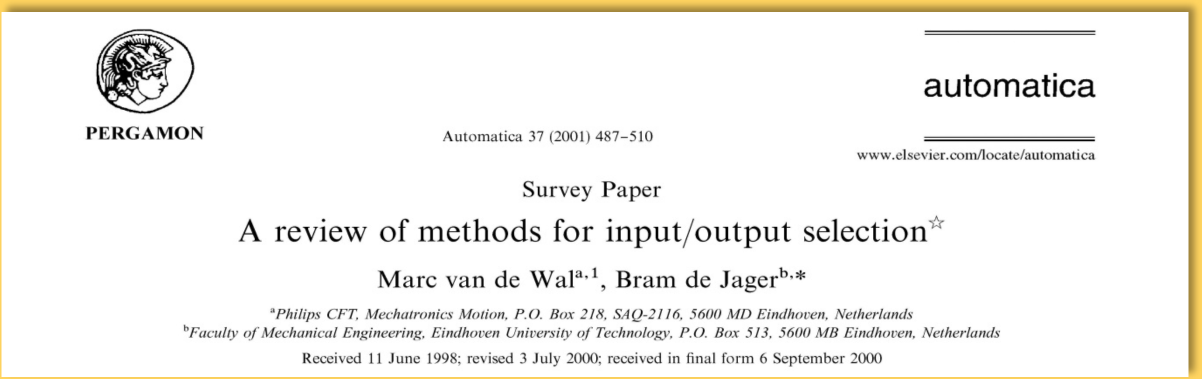
Selecting State Variables to Minimize Eigenvalue Sensitivity of Multivariable Systems*

R. A. SINGER†

---

* Manuscript received 10 July 1968 and in revised form 26 July 1968. Recommended for possible publication by associate editor P. Dorato.

† Ground Systems Group of Hughes Aircraft Company, Fullerton, California 92634, U.S.A., P.O.B. 3310.



PERGAMON

Automatica 37 (2001) 487–510

automatica

www.elsevier.com/locate/automatica

Survey Paper

A review of methods for input/output selection☆

Marc van de Wal[a,1], Bram de Jager[b,*]

[a] Philips CFT, Mechatronics Motion, P.O. Box 218, SAQ-2116, 5600 MD Eindhoven, Netherlands
[b] Faculty of Mechanical Engineering, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, Netherlands

Received 11 June 1998; revised 3 July 2000; received in final form 6 September 2000

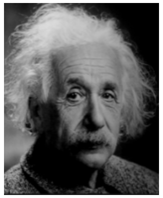
Great minds on modeling

Our acceptance of models should thus be guided by ‘usefulness’ rather than ‘truth.’

- Lennart Ljung

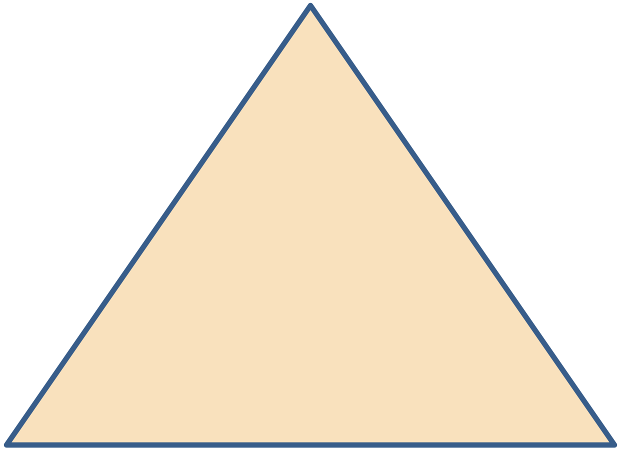
1. Get the physics right
2. After that, it is all mathematics.

- Rudolf E Kalman



Make things as simple as possible, but not simpler.

- Albert Einstein



True 真

Useful 益

Simple 朴

All models are wrong, some are useful.

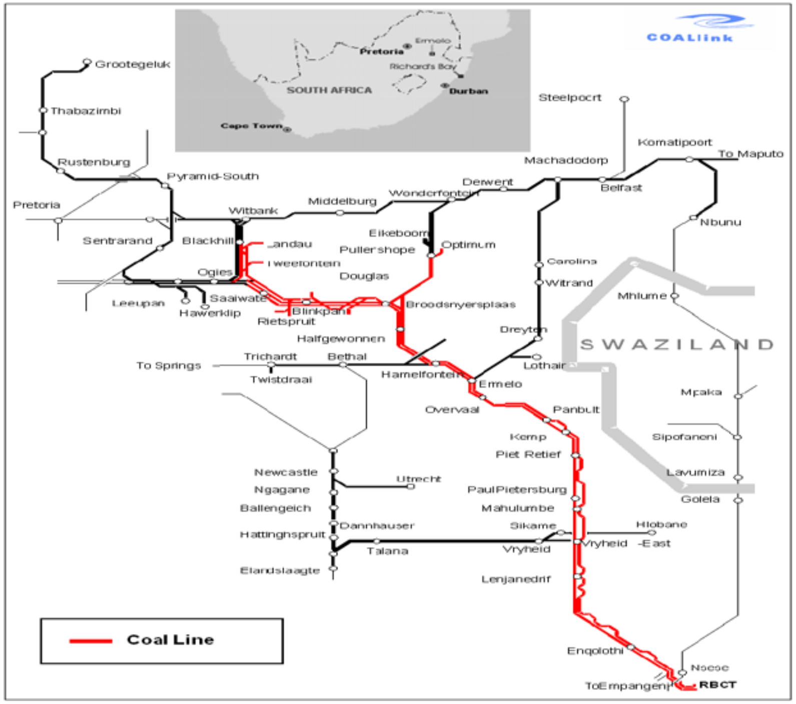
- George E P Box

Outline

1. Heavy haul trains modelling – the myth about state selection
2. HIV modelling – the myth about output selection
3. Building energy maintenance modelling – the myth about input selection
4. Take home messages

1. Heavy haul trains modelling – the myth about state selection


POLOKWANE
MOKOPANE
NELSPRUIT
PRETORIA
RUSTENBURG
JOHANNESBURG
POTCHEFSTROOM
VRYBURG
KLERKSDORP
KROONSTAD
BETHLEHEM
NEWCASTLE
NAKOP
UPINGTON
KEIMOES
KAKAMAS
GROBLERSHOOP
KIMBERLEY
ALEXANDER BAY
POFADDER
STEINKOPF
BLOEMFONTEIN
LADYSMITH
ESTCOURT
RICHARDS BAY
EMPANGENI
PIETERMARIZBURG
DURBAN
SPRINGBOK
KOKSTAD
GARIES
QUEENSTOWN
CLANWILLIAM
BEAUFORT WEST
GRAAFF-REINET
CRADOCK
CITRUSDAL
VREDENBURG
SALDANHA
MALMESBURY
WORCESTER
SWELLENDAM
OUDTSHOORN
GEORGE
GRAHAMSTOWN
EAST LONDON
PORT ALFRED
CAPE TOWN
PAARL
MOSSEL BAY
PORT ELIZABETH


COALlink
Pretoria
Ermelo
Richard's Bay
SOUTH AFRICA
Durban
Cape Town
Grootegeluk
Thabazimbi
Rustenburg
Pyramid-South
Pretoria
Sentrarand
Steelpoort
Komatipoort
To Maputo
Machadodorp
Belfast
Derwent
Wonderfontein
Middelburg
Witbank
Blackhill
Landau
Tweefontein
Eikeboom
Pullershope
Optimum
Douglas
Ogies
Saaiwater
Leeupan
Hawerklip
Blinkpan
Rietspruit
Broodsnyersplaas
Carolina
Witrand
Nbunu
Mhlume
Halfgewonnen
Dreyton
SWAZILAND
Trichardt
Bethal
To Springs
Twistdraai
Hamelfontein
Ermelo
Lothair
Overvaal
Panbult
Mpaka
Kemp
Piet Retief
Sipofaneni
Lavumiza
Golela
Newcastle
Ngagane
Ballengeich
Utrecht
PaulPietersburg
Mahulumbe
Dannhauser
Sikame
Hlobane
Hattinghspruit
Talana
Vryheid
Vryheid -East
Elandslaagte
Lenjanedrif
Enqolothi
Nsese
ToEmpangeni
RBCT
Coal Line

Project definition

Problems

- Speed
- Energy
- In-train force

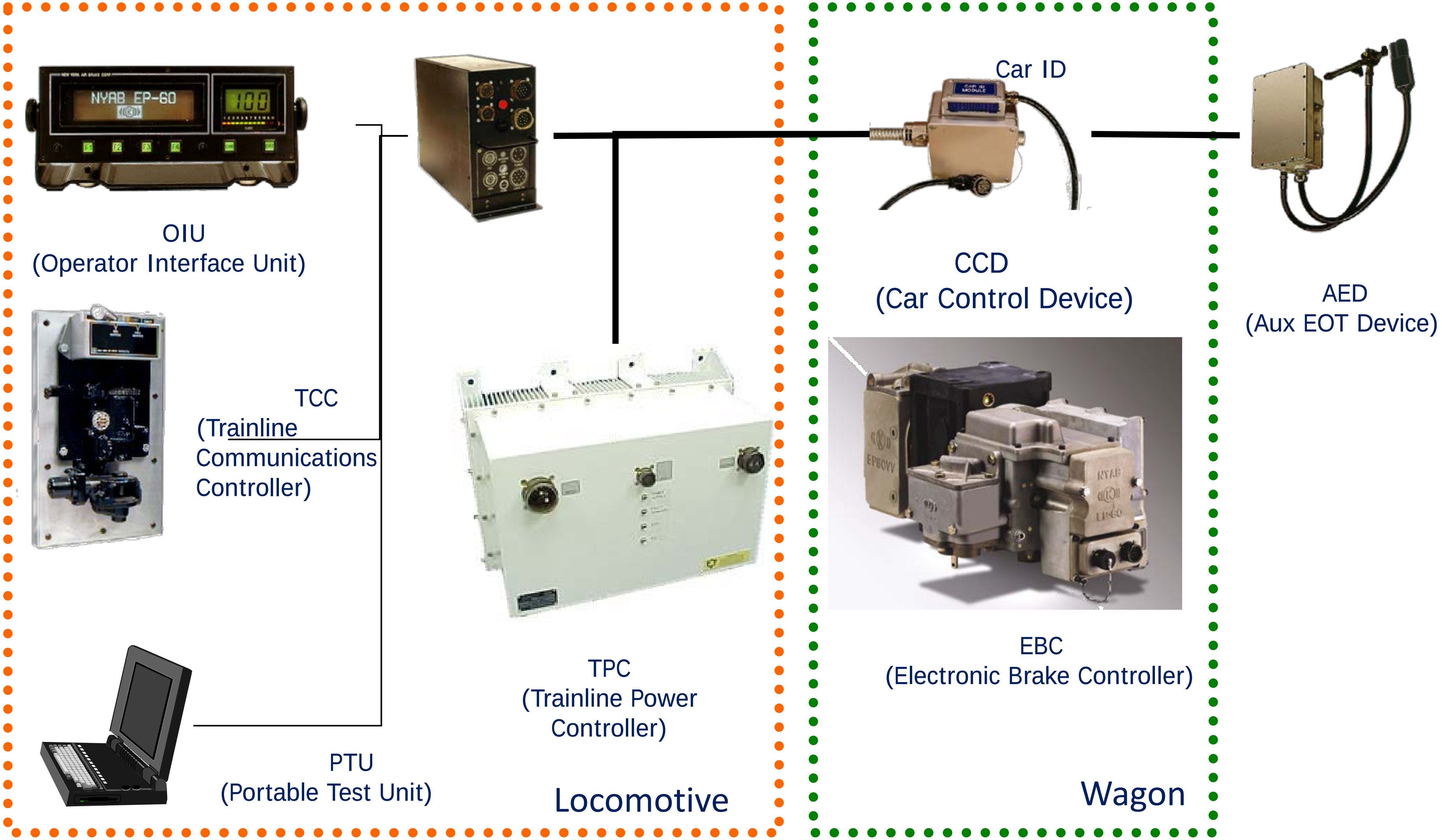
Objective of project

- The development of an applied software system for the control and handling of long trains (800 wagons, 10km long)

Industry partners

- Spoornet
- Knorr-Bremse/New York Air Brake

EPC: EP-60 System Components



OIU
(Operator Interface Unit)

TCC
(Trainline Communications Controller)

PTU
(Portable Test Unit)

TPC
(Trainline Power Controller)

Locomotive

Car ID

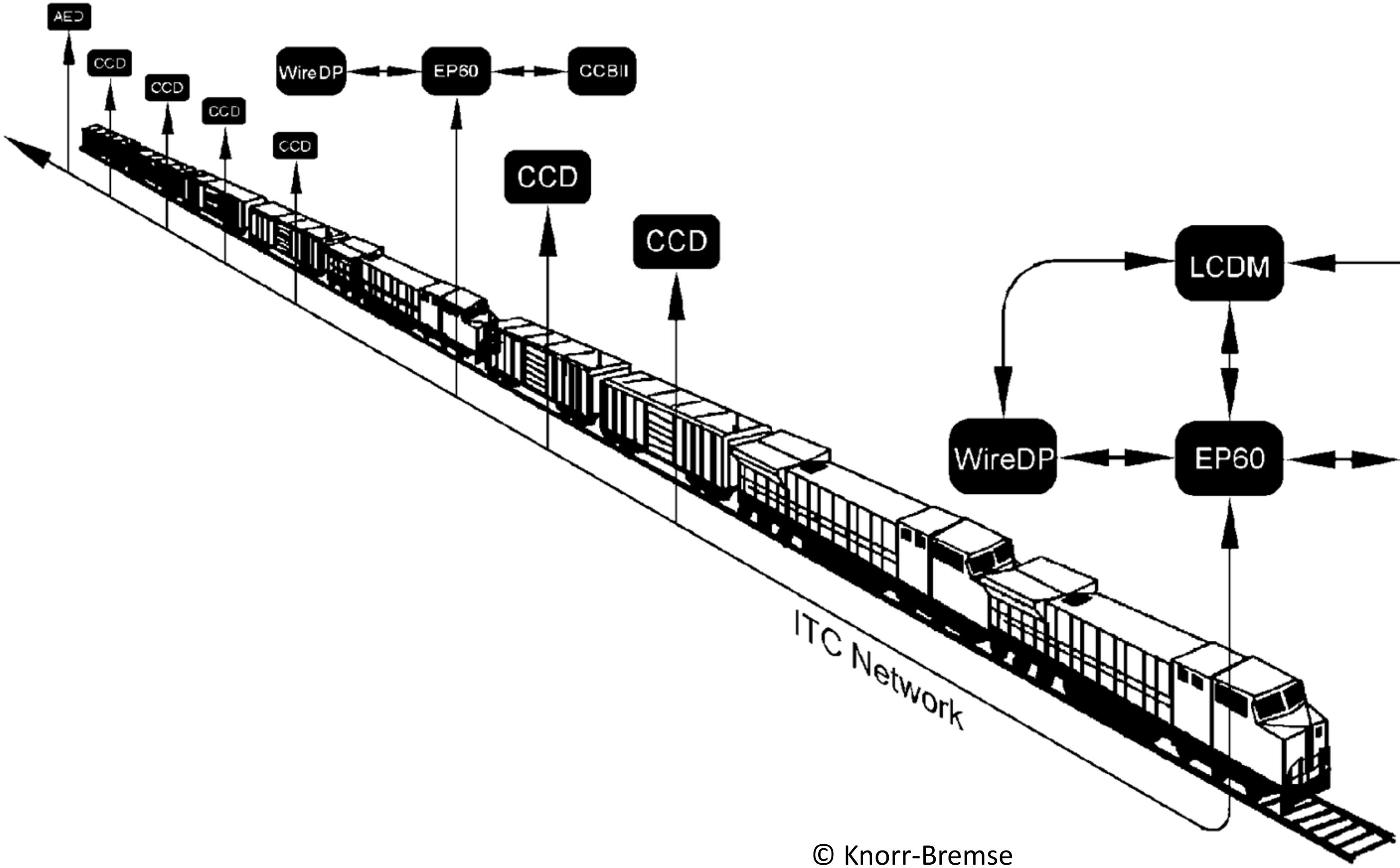
CCD
(Car Control Device)

EBC
(Electronic Brake Controller)

Wagon

AED
(Aux EOT Device)

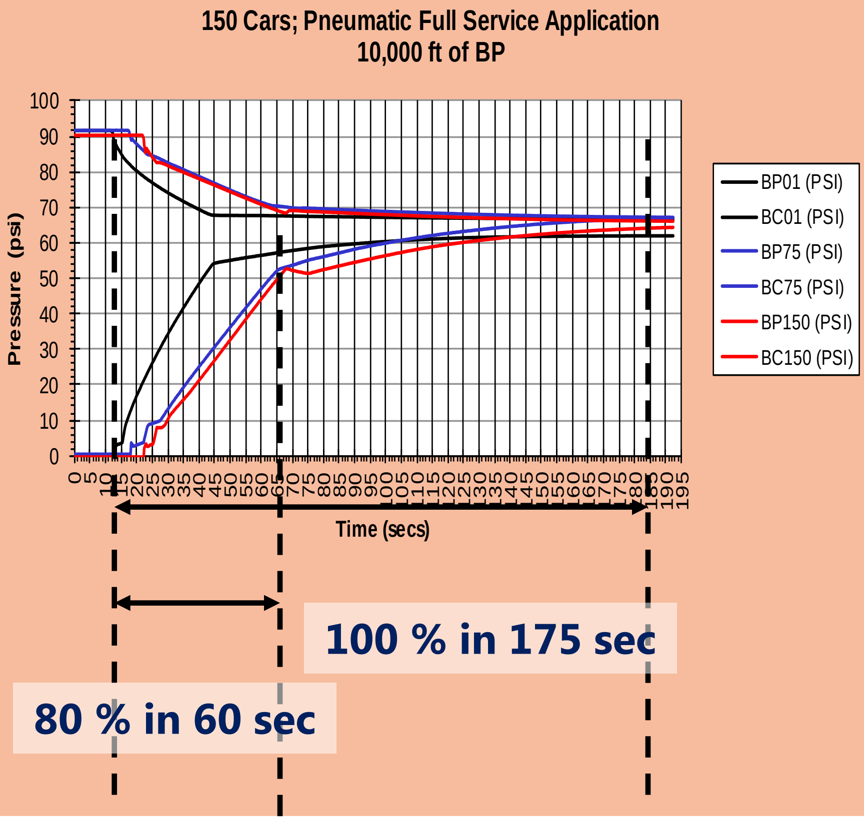
Independent distributed power (iDP)



© Knorr-Bremse

Pneumatic control vs ECP

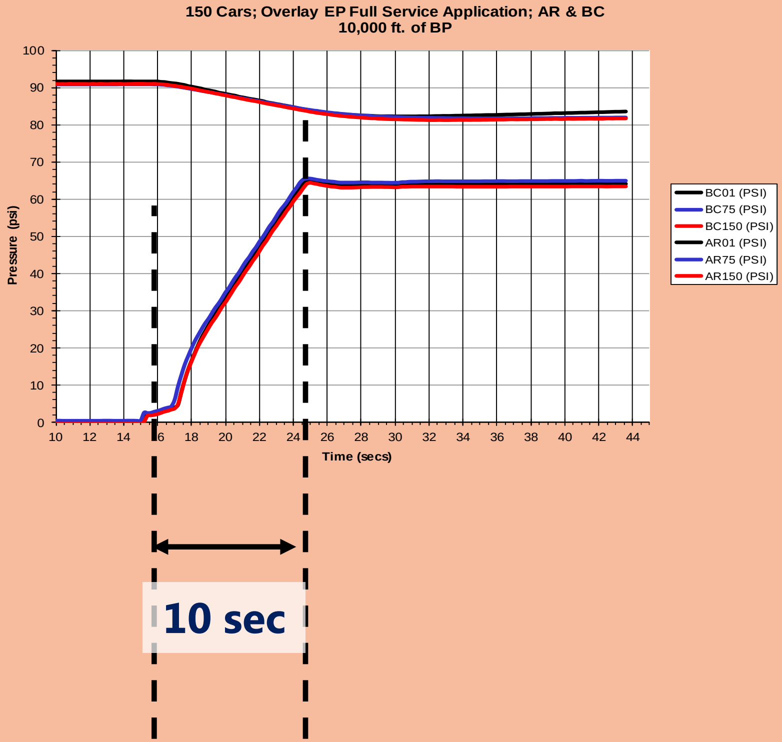
Pneumatic control



100 % in 175 sec

80 % in 60 sec

ECP

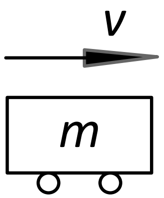


10 sec

Model choice

Mass-point model

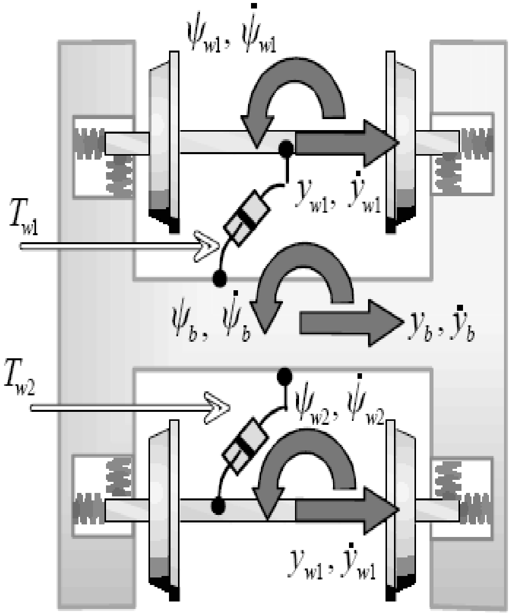
- ❑ Internal dynamics is ignored
- ❑ iDP control cannot be considered
- ❑ In-train forces is not investigated and thus the safe running can not be guaranteed



Model choice

Suspension model

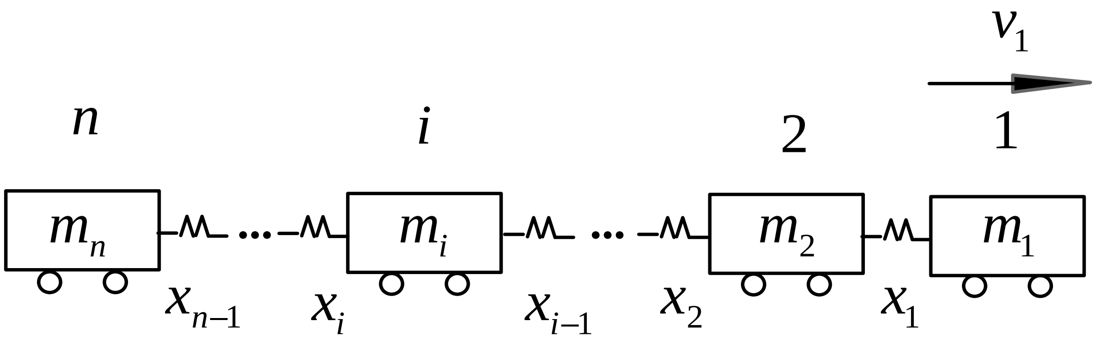
$$m_w\ddot{y}_{w1} + \left(C_{py} + \frac{2f_{22}}{V_s}\right)\dot{y}_{w1} + K_{py}y_{w1} - 2f_{22}\psi_{w1}$$
$$-C_{py}\dot{y}_b - K_{py}y_b - C_{py}L_b\dot{\psi}_b - K_{py}L_b\psi_b = 0,$$
$$I_w\ddot{\psi}_{w1} + \frac{2f_{11}\lambda e}{r_0}y_{w1} + \left(\frac{2f_{11}e^2}{V_s} + C_{p\psi}\right)\dot{\psi}_{w1}$$
$$+K_{p\psi}\psi_{w1} - C_{p\psi}\dot{\psi}_b - K_{\psi b}\psi_b = T_{w1},$$
$$m_w\dot{y}_{w2} + \left(C_{py} + \frac{2f_{22}}{V_s}\right)\dot{y}_{w2} + K_{py}y_{w2} - 2f_{22}\psi_{w2}$$
$$-C_{py}\dot{y}_b - K_{py}y_b + C_{py}L_b\dot{\psi}_b + K_{py}L_b\psi_b = 0,$$
$$I_w\ddot{\psi}_{w2} + \frac{2f_{11}\lambda e}{r_0}y_{w2} + \left(\frac{2f_{11}e^2}{V_s} + C_{p\psi}\right)\dot{\psi}_{w2}$$
$$+K_{p\psi}\psi_{w2} - C_{p\psi}\dot{\psi}_b - K_{p\psi}\psi_b = T_{w2},$$
$$m_b\ddot{y}_b - C_{py}\dot{y}_{w1} - K_{py}y_{w1} - C_{py}\dot{y}_{w2} - K_{py}y_{w2}$$
$$+2C_{py}\dot{y}_b + 2K_{py}y_b = 0,$$
$$I_b\ddot{\psi}_b - C_{py}L_b\dot{y}_{w1} - K_{py}L_by_{w1} - C_{p\psi}\dot{\psi}_{w1}$$
$$-K_{p\psi}\psi_{w1} + C_{py}L_b\ddot{y}_{w2} + K_{py}L_by_{w2} = 0$$



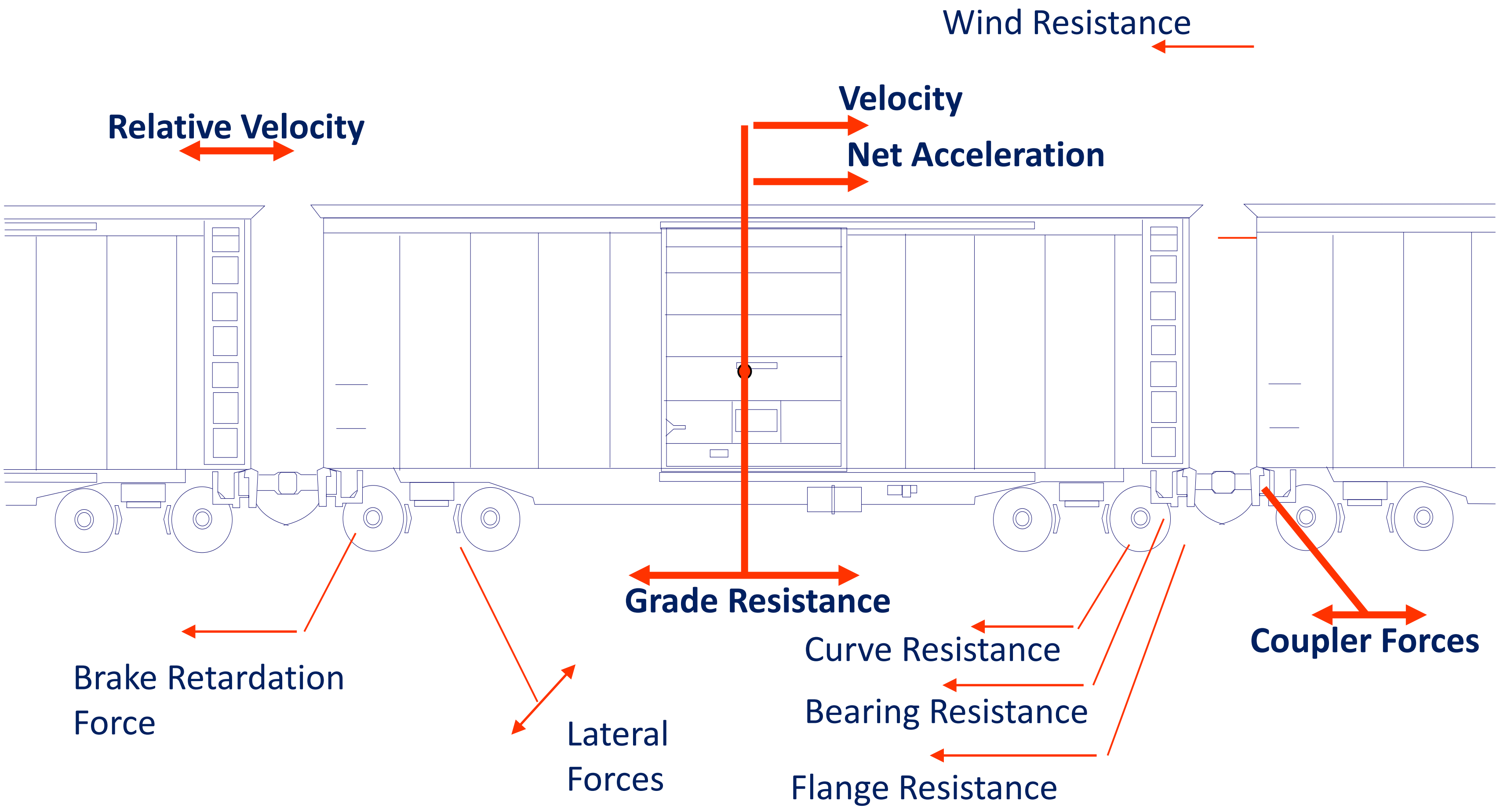
Model choice

Cascade-mass-point model

- ☐ More accurate
- ☐ Internal dynamics
- ☐ In-train force
- ☐ Full ECP/iDP



Longitudinal force model



Longitudinal dynamics model

in-train force

Control input

velocity

in-train force

mass

$$m_i\dot{v}_i = u_i + f_{in_{i-1}} - f_{in_i} - f_{\alpha_i}, i = 1, \cdots, n,$$

$$\dot{x}_i = v_i - v_{i+1}, \qquad i = 1, \cdots, n-1,$$

coupler relative displacement

gravity force

$$f_{a_i} = f_{aero_i} + f_{g_i} + f_{c_i}$$

aerodynamic force

curvature force

Equations of motion

$$m_1\ddot{x}_1 = u_1 - k_1(x_1 - x_2) - d_1(\dot{x}_1 - \dot{x}_2) - \underbrace{(c_0 + c_v\dot{x}_1)m_1}_{R^r}$$

$$- \underbrace{c_a\dot{x}_1^2\left(\sum_{i=1}^{n} m_i\right)}_{R_a} - 9.98\sin\theta_1\, m_1 - 0.004D_1m_1,$$

$$m_i\ddot{x}_i = u_i - k_i(x_i - x_{i+1}) - k_{i-1}(x_i - x_{i-1})$$

$$+d_{i-1}(\dot{x}_{i-1} - \dot{x}_i) - d_i(\dot{x}_i - \dot{x}_{i+1})$$

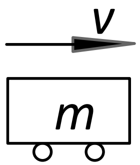
$$-(c_0 + c_v\dot{x}_i)m_i - 9.98\sin\theta_i\, m_i - 0.004D_im_i, i$$

$$= 2, \cdots, n-1,$$

$$m_n\ddot{x}_n = u_n - k_{n-1}(x_n - x_{n-1}) - d_{n-1}(\dot{x}_n - \dot{x}_{n-1})$$

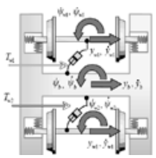
$$-(c_0 + c_v\dot{x}_n)m_n - 9.98\sin\theta_n\, m_n - 0.004D_nm_n$$

State variable dimensions



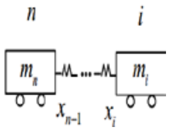
Mass-point model

- 2



Suspension model

- 12n (9600)



Cascade mass-point model

- n/2 (400)

Model validation

Trial on the 11th, 18th and 24th November 2003

- on the 11th: 4 locomotives—200 wagons—2 locomotives,
- on the 18th: 4 locomotives—100 wagons—2 locomotives—100 wagons,
- on the 24th: 6 locomotives—200 wagons.

GPS data

- Longitude and Latitude
- Track heights

GIS data

- Grade and curvature
- Other track characteristics

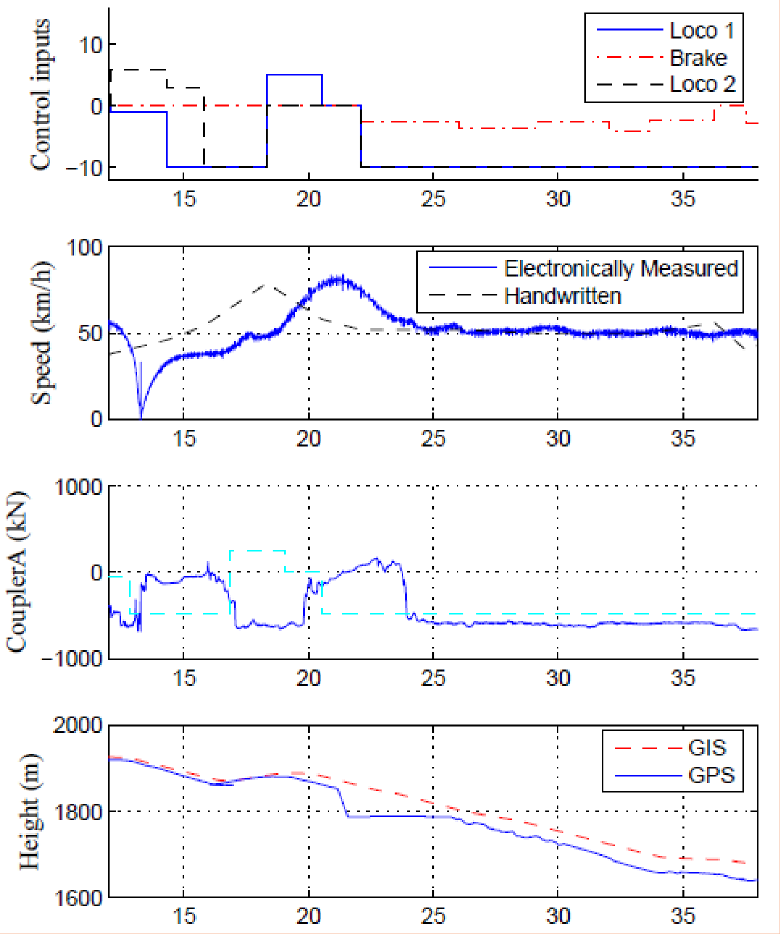
Validation: Trial run

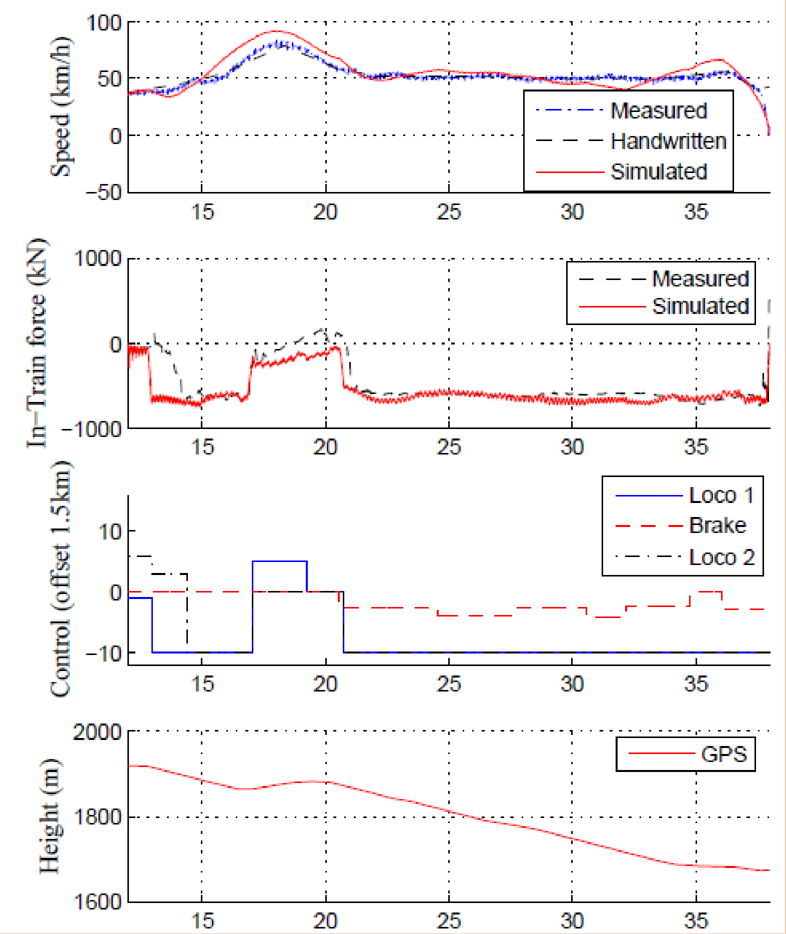
Handwritten data:

- Current velocity
- Locomotive notch level
- Percentage brake applied

Electronically recorded data:

- Current velocity
- In-train force
- Brake pipe pressure


Control inputs
Loco 1
Brake
Loco 2
Speed (km/h)
Electronically Measured
Handwritten
CouplerA (kN)
Height (m)
GIS
GPS
10
0
−10
100
50
0
1000
0
−1000
2000
1800
1600
15
20
25
30
35


Speed (km/h)
Measured
Handwritten
Simulated
In−Train force (kN)
Measured
Simulated
Control (offset 1.5km)
Loco 1
Brake
Loco 2
Height (m)
GPS
100
50
0
−50
1000
0
−1000
10
0
−10
2000
1800
1600
15
20
25
30
35

What about Energy !

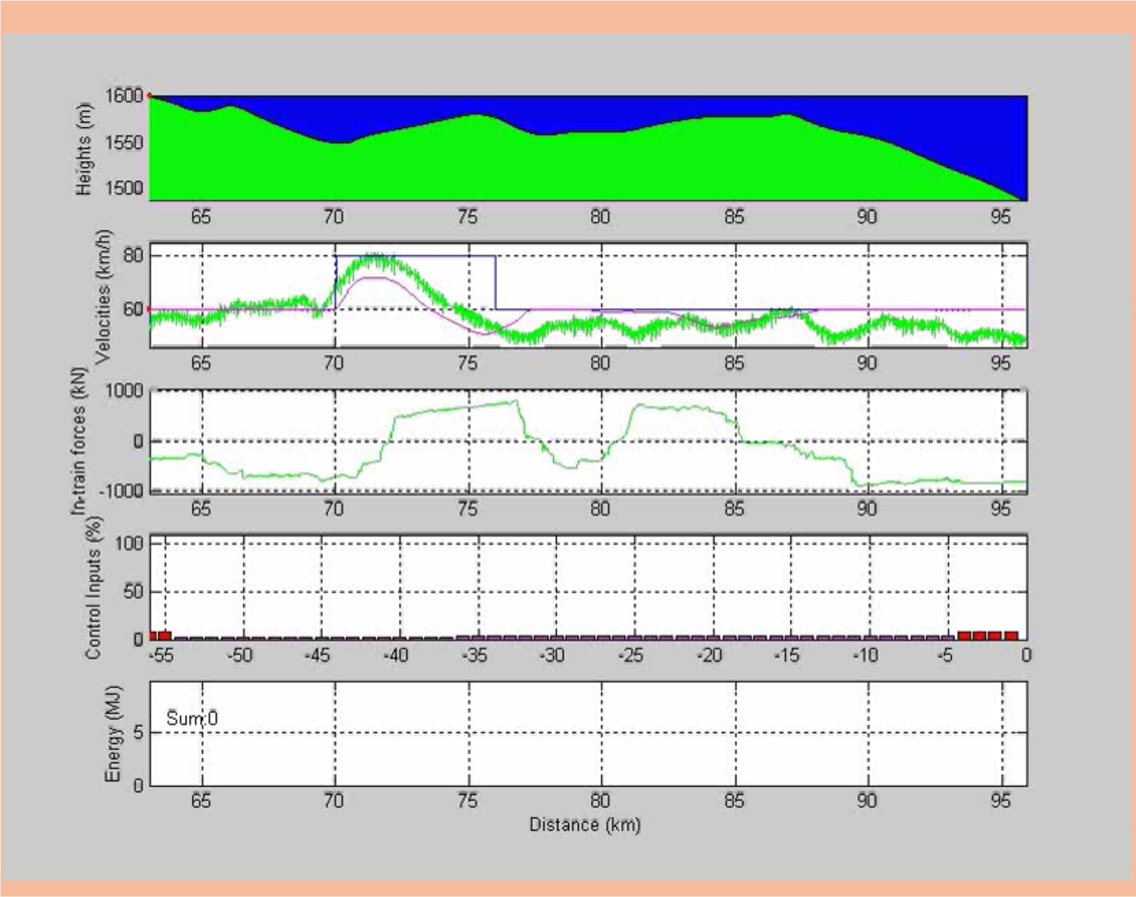
$$E = \sum_{i=1}^{n} \int u_i R_i u_i = \sum_{loco} \int u_i R_i u_i + \sum_{wagon} \int u_i R_i u_i$$

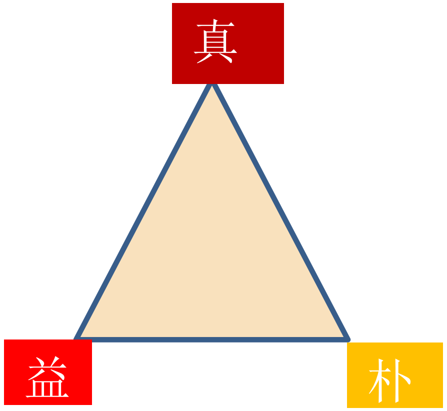
$$= Loco\ \&\ Wagon\ Energy\ Consumption - Wagon\ Regenerative\ Energy$$

Control

- Open loop scheduling
- Linearisation
- LQR
- Speed regulator
- Observers
- Fault tolerant

Driver GUI





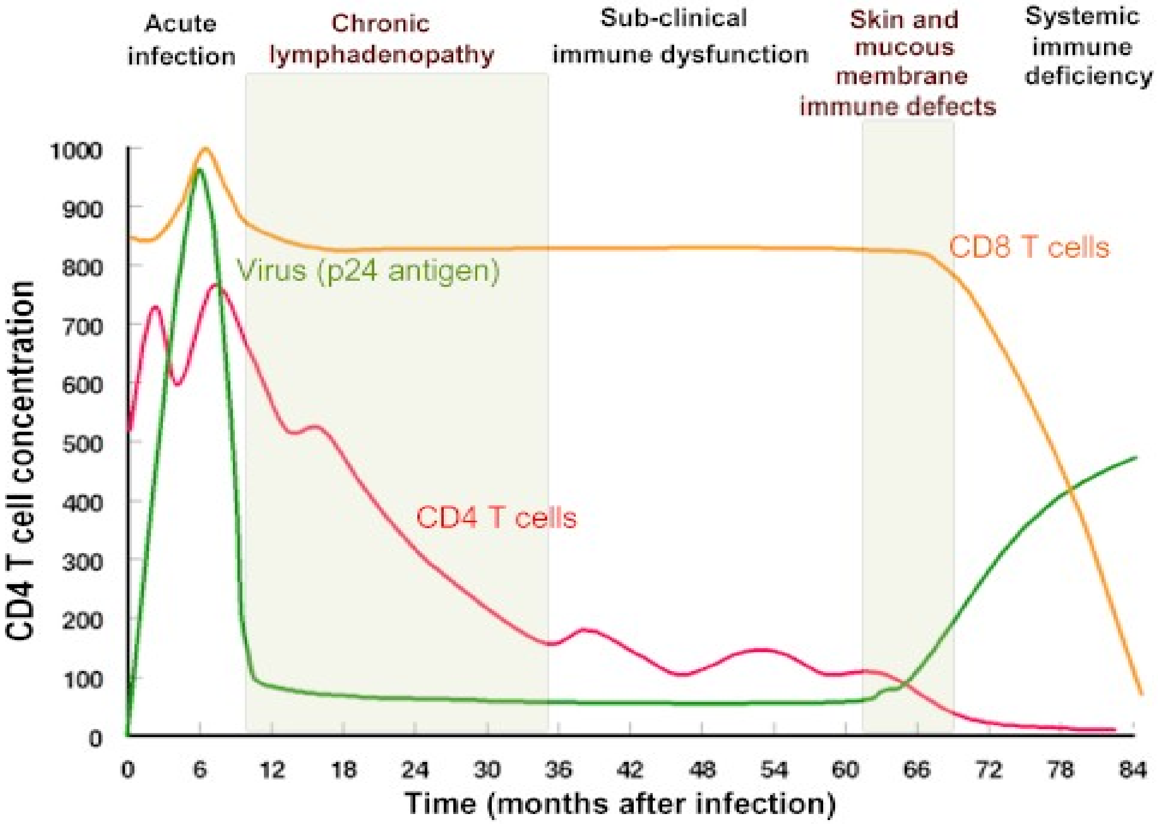
真

益

朴

2. HIV modelling – the myth about output selection

Progression



HIVNET28: Vaccine Readiness

Patients: 51 patients (10 Zimbabwean, 6 Malawian, 16 Zambian and 19 South African): 42 female, median age 28.

Objective: set-point estimation

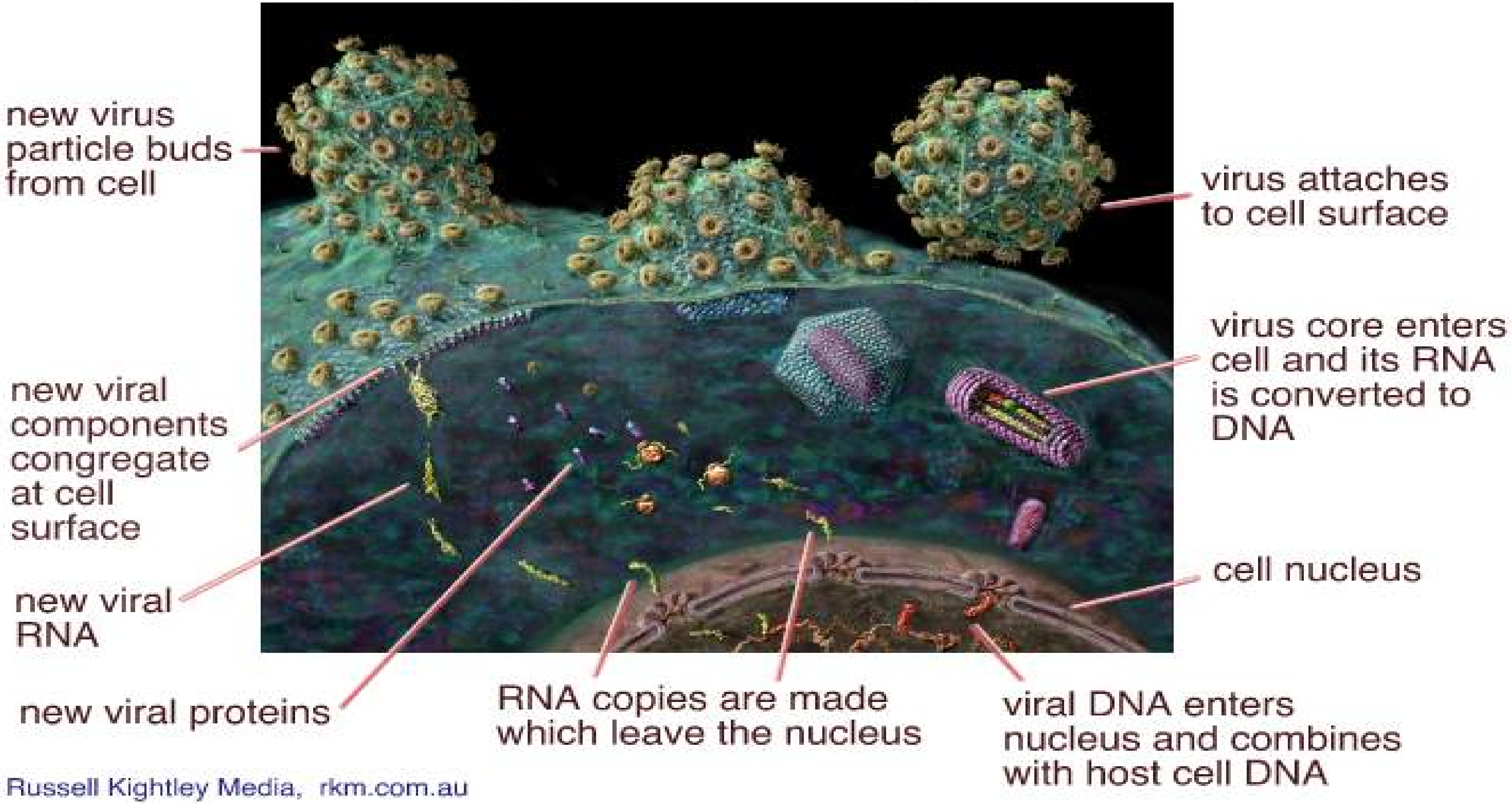
"IT SEEMED TO ME THAT WE COULD NOT BLAME EVERYTHING ON A SINGLE VIRUS."

FORMER SOUTH AFRICAN PRESIDENT THABO MBEKI

- average 8.9 months from seroconversion to first viral load measurement
- follow-up measurements at 2, 4, 7 and 9 months
- blood samples for plasma RNA levels, lymphocyte subset analysis and DNA isolation
- 34 with (5+4) measurements (viral load and CD4+)
- 10 with (4+4, 4+3) measurements
- 7 useless

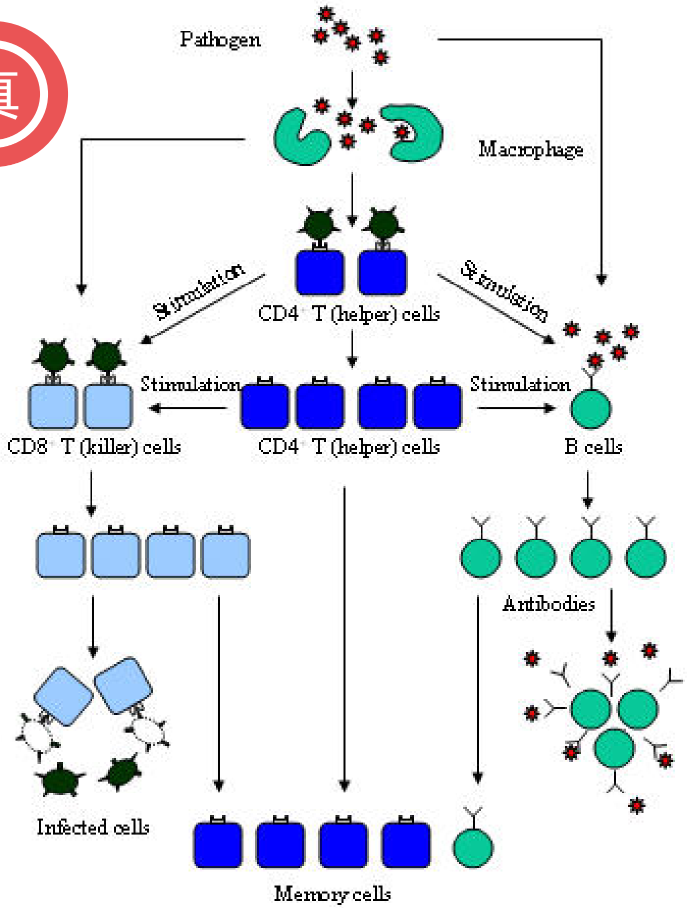
Models 3D: biological backup and model

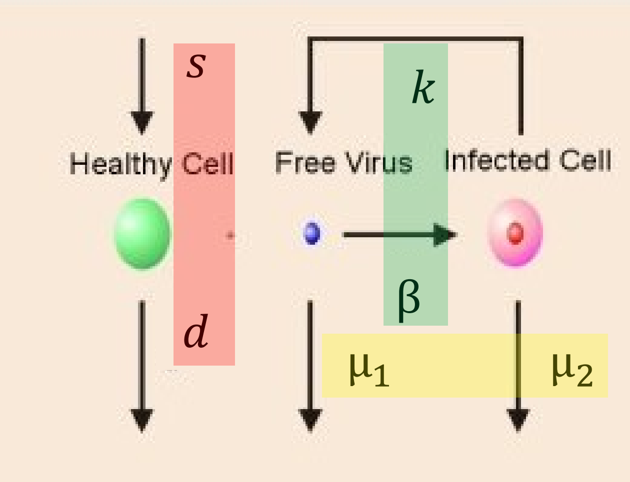
simplified HIV life-cycle



Russell Kightley Media, rkm.com.au

Models 3D: biological backup and model





$$\frac{dT}{dt} = s - dT - \beta T v,$$
$$\frac{dT^*}{dt} = \beta T v - \mu_1 T^*,$$
$$\frac{dv}{dt} = kT^* - \mu_2 v.$$

6 parameters

- immune
- virus
- drug
  - -- β RTI
  - -- k PI

Models 3D: reality reflection

True

Two operating points

$$P_1 = \left(\frac{s}{d}, 0{,}0\right);$$

$$P_2 = \left(\frac{\mu_1\mu_2}{\beta k}, \frac{s}{\mu_1} - \frac{d\mu_2}{\beta k}, \frac{ks}{\mu_1\mu_2} - \frac{d}{\beta}\right);$$

$$R = \frac{\beta s k}{d\mu_1\mu_2}.$$

If $R < 1$, P_1 is stable

Infection not spreading, vaccination

If $R > 1$, P_1 is unstable, P_2 is stable

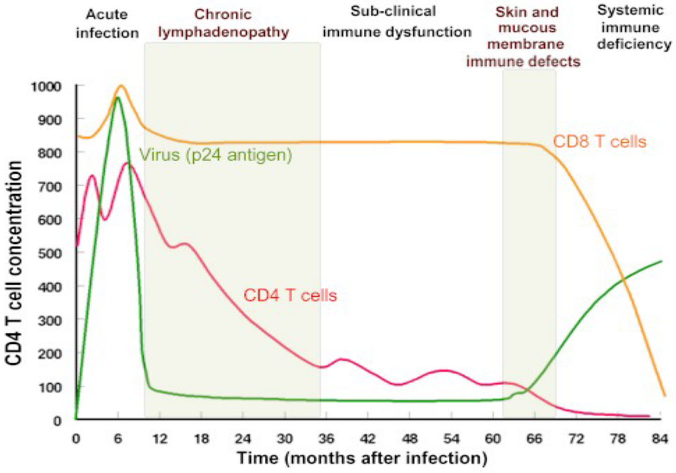
Infection spreading

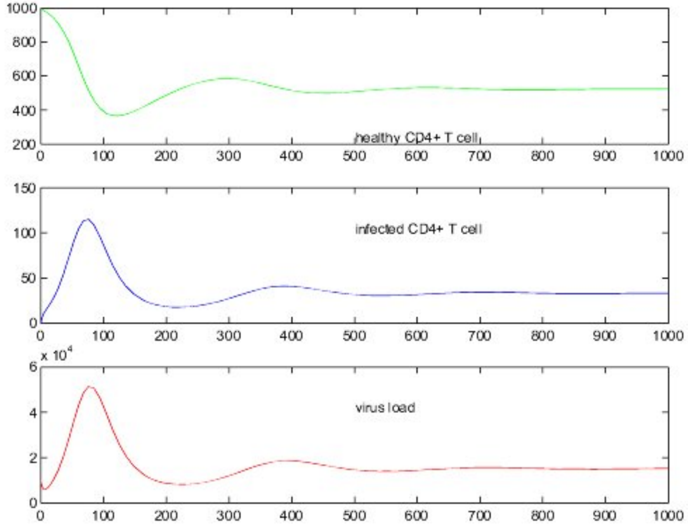
Models 3D: the model is good (I)

Useful

- It simulates the stage from infection to clinic latency
- Set-point calculation is robust

$$v^* = \frac{ks}{\mu_1\mu_2} - \frac{d}{\beta}$$



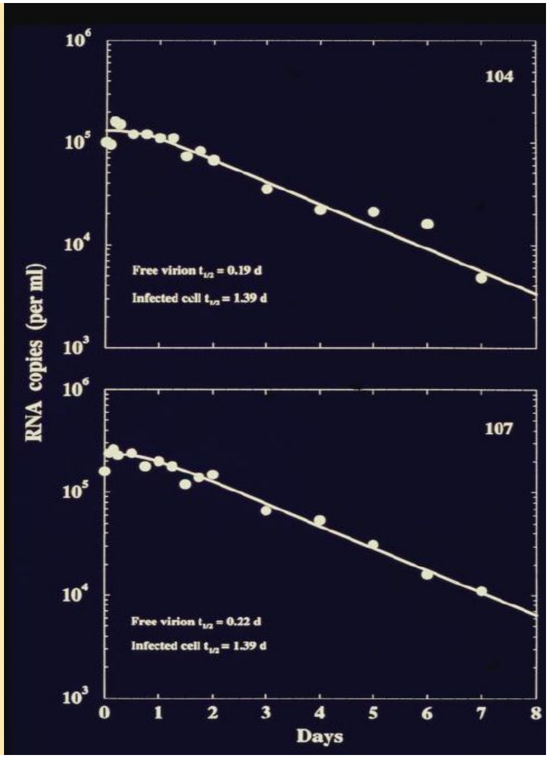


Models 3D: the model is good (II)

Useful

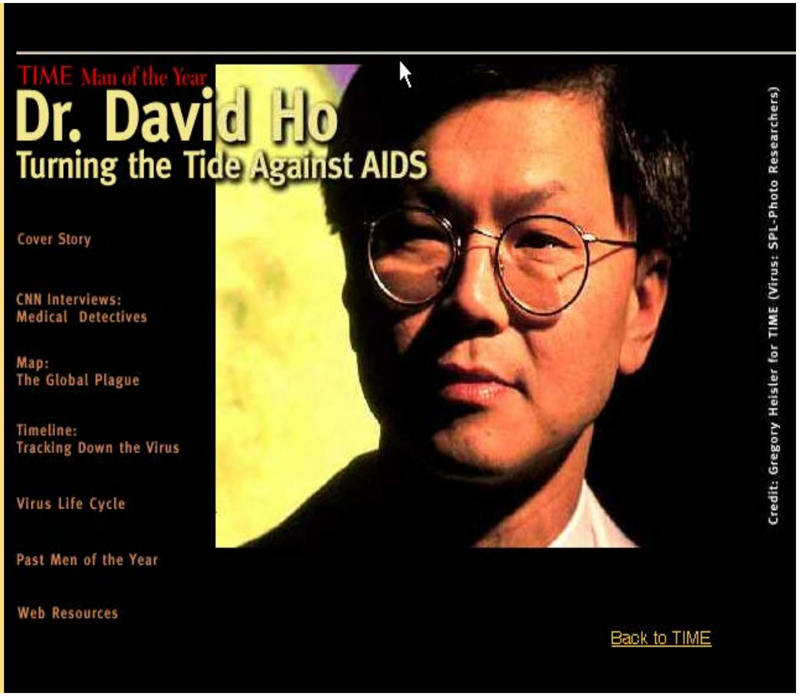
- it simulates drug response

$$\frac{dT}{dt} = s - dT - \beta T v,$$
$$\frac{dT^*}{dt} = \beta T v - \mu_1 T^*,$$
$$\frac{dv}{dt} = kT^* - \mu_2 v.$$



The legendary

- Two Nature papers (Ho et al 95, Wei et al 95)
  - half life of virus = 6 hours ($\mu_2 = 3$), half life of infected cells = 1 day ($\mu_1 = 0.45$): rapid dynamics vs slow disease
- Citation over 500 within the year of publication
- Ho was elected the Man of the Year 1996, Time Magazine



Models 3D: the model is simple

Simple

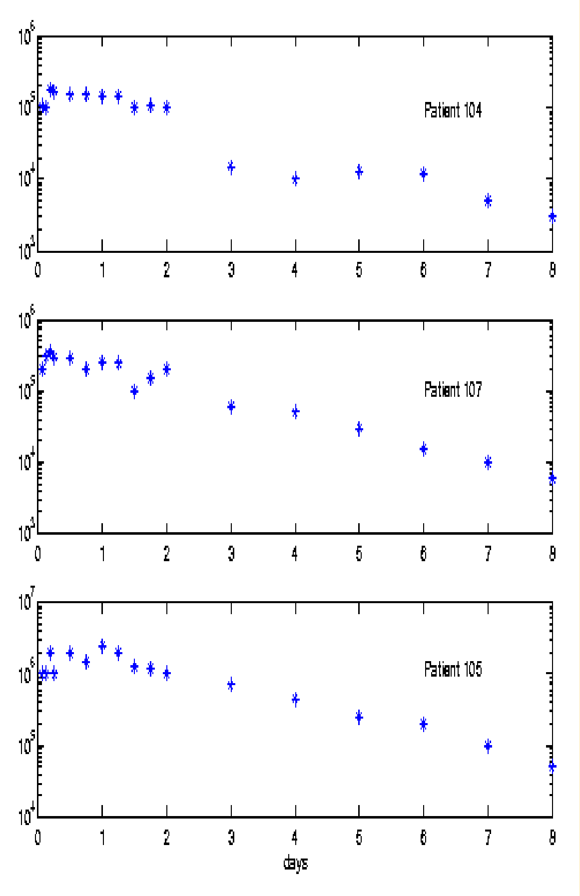
Other models are more complex

Other Models: biological/immunological reasoning

- Burden theory
  - Explanation of CD4 depletion
- long-lived cell (4D)
  - Actively infected cells
  - Latently infected cells
- Multi-compartment theory: additional cellular reservoirs of virus (6D)
  - Follicular dendritic cells
  - Macrophage

Problems with current monitoring

- Measure anything
  - CD8+
  - actively infected CD4+
  - latently infected CD4+
- Measure anytime
  - in asymptomatic stage
- Measure many times
  - hundreds over 10 years
  - 16 in 8 days by Ho



Call for nonlinear identifiability theory

linear identifiability (well-known)

Tunali & Tarn (1987): first paper on nonlinear identifiability - geometrical identifiability: one-one property of the i/o map w.r.t parameter

Diop (1991), Ljung & Glad (1994) and Glad (1997): algebraic and algorithmic — algebraic identifiability

Effects of initial conditions on identifiability noted in all papers, still under then current investigation in Denis-Vidal, Joly-Blanchard & Noiret (2001) and Saccomani, Audoly & Leontina (2003).

Nonlinear identifiability - concepts

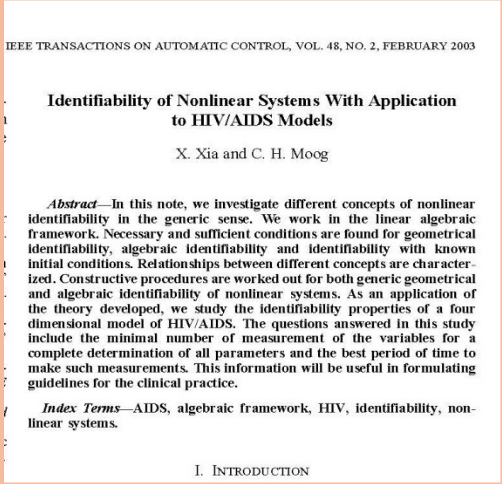
Consider a nonlinear system,

$$\Sigma_\theta\colon \begin{cases} \dot{x} = f(x,\theta,u), x(0,\theta) = x_0 \\ y = h(x,\theta,u), \end{cases}$$

where $x \in R^n, u \in R^m$ and $y \in R^p$ are the state, input and output variables of the system. Assume that

$$\operatorname{rank} \partial h(x,\theta,u)/\partial x = p.$$

θ is the parameter to be identified.



IEEE TRANSACTIONS ON AUTOMATIC CONTROL, VOL. 48, NO. 2, FEBRUARY 2003

Identifiability of Nonlinear Systems With Application to HIV/AIDS Models

X. Xia and C. H. Moog

***Abstract*—In this note, we investigate different concepts of nonlinear identifiability in the generic sense. We work in the linear algebraic framework. Necessary and sufficient conditions are found for geometrical identifiability, algebraic identifiability and identifiability with known initial conditions. Relationships between different concepts are characterized. Constructive procedures are worked out for both generic geometrical and algebraic identifiability of nonlinear systems. As an application of the theory developed, we study the identifiability properties of a four dimensional model of HIV/AIDS. The questions answered in this study include the minimal number of measurement of the variables for a complete determination of all parameters and the best period of time to make such measurements. This information will be useful in formulating guidelines for the clinical practice.**

***Index Terms*—AIDS, algebraic framework, HIV, identifiability, nonlinear systems.**

I. INTRODUCTION

Definition 1 The system Σ_θ is said to be x_0-identifiable at θ through an admissible input u (on $[0,T]$) if there exists an open set $\mathcal{P}^0 \subset \mathcal{P}$ containing θ such that for any two θ_1, $\theta_2 \in \mathcal{P}^0$, $\theta_1 \neq \theta_2$, the solutions $x(t,\theta_1,x_0,u)$ and $x(t,\theta_2,x_0,u)$ exist on $[0,\epsilon]$, $0 < \epsilon \leq T$, and their corresponding outputs satisfy, on $t \in [0,\epsilon]$, $y(t,\theta_1,x_0,u) \neq y(t,\theta_2,x_0,u)$.

Definition 2 The system Σ_θ is said to be structurally/geometrically identifiable if …

Definition 3 The system Σ_θ is said to be algebraically identifiable if …

Definition 4 The system Σ_θ is said to be identifiable with known initial conditions if …

Nonlinear identifiability - algebraic framework

Let $\mathcal{K}$ be the field consisting of meromorphic functions of x, θ, u and finite derivatives of u, and define

$$E = \mathrm{span}_{\mathcal{K}}\{\mathrm{d}\mathcal{K}\},$$

The vectors in E are called one-forms.

The differentiation of a function $\phi(x, \theta, u, \ldots, u^{(k)})$ along the dynamics of the system is defined as

$$\dot{\phi} = \frac{\partial \phi}{\partial x} f(x, \theta, u) + \sum_{i=0}^{k} \frac{\partial \phi}{\partial u^{(i)}} u^{(i+1)},$$

and this operation can be extended to differential one-forms $\omega = \kappa_x \mathrm{d}x + \kappa_\theta \mathrm{d}\theta + \sum \eta_i \mathrm{d}u^{(i)} \in E$ as the following:

$$\dot{\omega} = \dot{\kappa}_x \mathrm{d}x + \dot{\kappa}_\theta \mathrm{d}\theta + \sum \dot{\eta}_i \mathrm{d}u^{(i)} + \kappa_x \, \mathrm{d}f(x, \theta, u) + \sum \eta_i \mathrm{d}u^{(i+1)}.$$

Denote $\mathcal{Y} = \bigcup_{k=0}^{\infty} \mathrm{span}\{\mathrm{d}y, \mathrm{d}\dot{y}, \ldots, \mathrm{d}y^{(k)}\}, \mathcal{X} = \mathrm{span}\{\mathrm{d}x\},$

$$\mathcal{U} = \bigcup_{k=0}^{\infty} \mathrm{span}\{\mathrm{d}u, \mathrm{d}\dot{u}, \ldots, \mathrm{d}u^{(k)}\}, \Theta = \mathrm{span}\{\mathrm{d}\theta\}$$

Nonlinear identifiability - results

Theorem 1 The system is algebraically identifiable if and only if

$$\Theta \subset (\mathcal{Y} + \mathcal{U}).$$

Theorem 2 The following statements are equivalent

(1) The system Σ_θ is structurally identifiable;

(2)

$$\Theta \subset \mathcal{X} + \mathcal{Y} + \mathcal{U},$$

(3)

$$\dim \frac{\mathcal{Y}+\mathcal{X}+\mathcal{U}}{\mathcal{X}+\mathcal{U}} = q.$$

(4) The system Σ_θ is identifiable with known initial conditions.

Theorem 3 (1) If

$$\mathcal{X} \cap (\mathcal{Y} + \Theta + \mathcal{U}) = \mathcal{X} \cap (\mathcal{Y} + \mathcal{U}) \qquad \text{(A)}$$

then the system is algebraically identifiable if and only if it is structurally identifiable.

(2) If the system is algebraically identifiable, then (A) holds.

Nonlinear identifiability - algorithm 1

$$\mathrm{d}y = \xi_1 \mathrm{d}x \ + \gamma_1 \mathrm{d}\theta (\operatorname{mod} \mathcal{U})$$

$$\vdots$$

$$\mathrm{d}y^{(n-1)} = \xi_n \mathrm{d}x \ + \gamma_n \mathrm{d}\theta \ (\operatorname{mod} \mathcal{U})$$

One can also compute $\mathrm{d}y^{(n)}$ as

$$\mathrm{d}y^{(n)} = \xi_{n+1} \mathrm{d}x \ + \gamma'_{n+1} \mathrm{d}\theta \ (\operatorname{mod} \mathcal{U}), \qquad \text{(B)}$$

Due to observability, the matrix $[\xi_1^T, \dots, \xi_n^T]^T$ is invertible, therefore $\mathrm{d}x$ can be written as a linear combination of $\mathrm{d}y, \dots, \mathrm{d}y^{(n-1)}$ and $\mathrm{d}\theta \ (\operatorname{mod} \mathcal{U})$. Substitution of $\mathrm{d}x$ in (B) yields the following expression of $\mathrm{d}y^{(n)}$: $\mathrm{d}y^{(n)} = \sum_{i=1}^{n} \eta_i \mathrm{d}y^{(i-1)} + \gamma_{n+1} \ \mathrm{d}\theta \ (\operatorname{mod} \mathcal{U})$

More generally, one computes

$$\mathrm{d}y^{(n+1)} = \sum_{i=1}^{n} \eta_{1i} \mathrm{d}y^{(i-1)} + \gamma_{n+2} \ \mathrm{d}\theta \ (\operatorname{mod} \mathcal{U})$$

$$\vdots$$

$$\mathrm{d}y^{(k^*)} = \sum_{i=1}^{n} \eta_{k^*-n,i} \mathrm{d}y^{(i-1)} + \gamma_{k^*+1} \ \mathrm{d}\theta \ (\operatorname{mod} \mathcal{U})$$

Nonlinear identifiability - algorithm 2

The system is geometrically identifiable if and only if there is a $k^* \geq q$ such that the matrix

$$\Gamma_g = \begin{bmatrix} \gamma_1 \\ \vdots \\ \gamma_k \end{bmatrix}$$

is of rank q.

The system is *algebraically identifiable* if and only if there is an $l^* \geq n + q$ such that the matrix

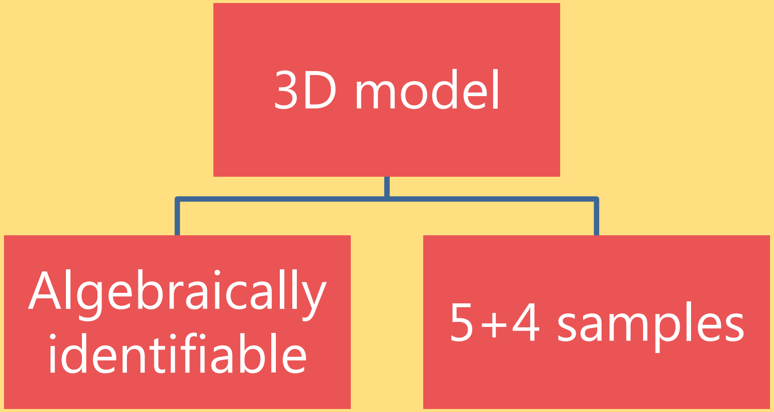
$$\Gamma_a = \begin{bmatrix} \gamma_{n+1} \\ \vdots \\ \gamma_{l^*} \end{bmatrix}$$

is of rank q.

Extension to: time-delay systems (Automatica02, TAC06)
left Ore ring – non-commutative
modules over the left Ore ring

3D model identifiability

Virus load
T cell counts



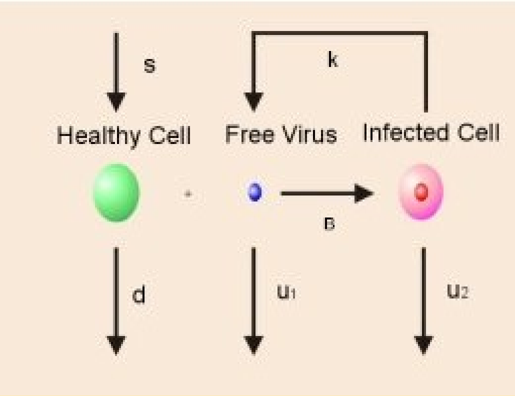
3D model

Algebraically identifiable

5+4 samples

4D & 6D models? !

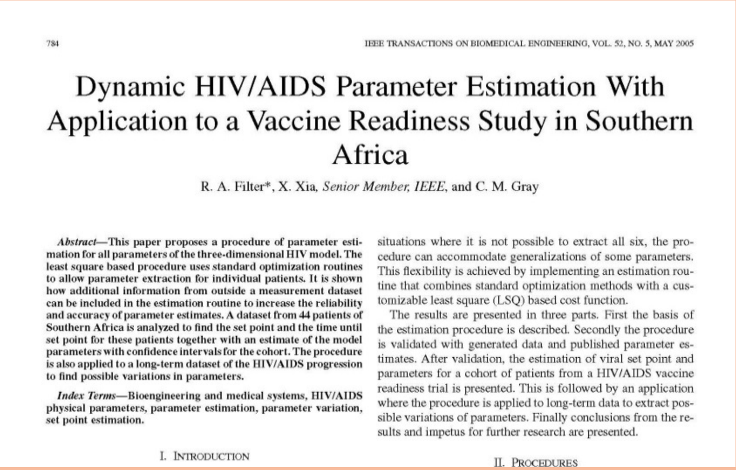
Results



Set-point estimation

Results

- Mean estimates of parameter $=(7.48,0.00085,1.4\times10^{-6},1.56,0,80,2834)^T$
- Estimated set-point = 4.08 $\log_{10}$ (12143 RNA copies/ml), time to set-point = 16.57 months
- (No difference with the European and US studies)



Dynamic HIV/AIDS Parameter Estimation With Application to a Vaccine Readiness Study in Southern Africa

R. A. Filter*, X. Xia, *Senior Member, IEEE*, and C. M. Gray

***Abstract*—This paper proposes a procedure of parameter estimation for all parameters of the three-dimensional HIV model. The least square based procedure uses standard optimization routines to allow parameter extraction for individual patients. It is shown how additional information from outside a measurement dataset can be included in the estimation routine to increase the reliability and accuracy of parameter estimates. A dataset from 44 patients of Southern Africa is analyzed to find the set point and the time until set point for these patients together with an estimate of the model parameters with confidence intervals for the cohort. The procedure is also applied to a long-term dataset of the HIV/AIDS progression to find possible variations in parameters.**

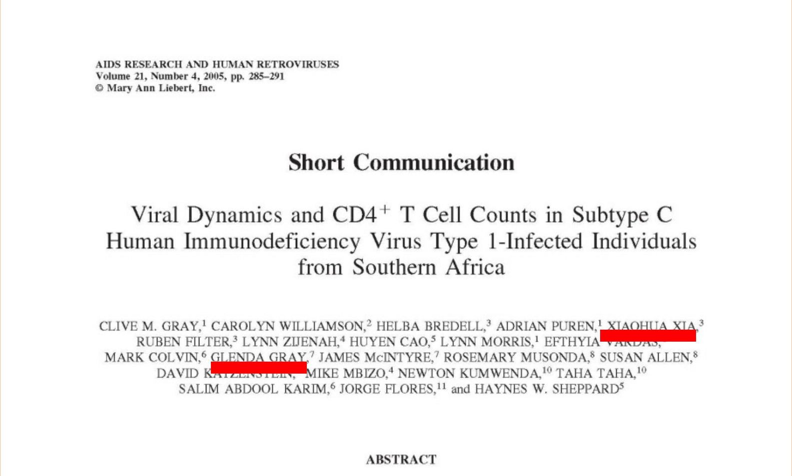
***Index Terms*—Bioengineering and medical systems, HIV/AIDS physical parameters, parameter estimation, parameter variation, set point estimation.**

I. INTRODUCTION

situations where it is not possible to extract all six, the procedure can accommodate generalizations of some parameters. This flexibility is achieved by implementing an estimation routine that combines standard optimization methods with a customizable least square (LSQ) based cost function.

The results are presented in three parts. First the basis of the estimation procedure is described. Secondly the procedure is validated with generated data and published parameter estimates. After validation, the estimation of viral set point and parameters for a cohort of patients from a HIV/AIDS vaccine readiness trial is presented. This is followed by an application where the procedure is applied to long-term data to extract possible variations of parameters. Finally conclusions from the results and impetus for further research are presented.

II. PROCEDURES



AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 21, Number 4, 2005, pp. 285–291
© Mary Ann Liebert, Inc.

Short Communication

Viral Dynamics and CD4$^+$ T Cell Counts in Subtype C Human Immunodeficiency Virus Type 1-Infected Individuals from Southern Africa

CLIVE M. GRAY,[1] CAROLYN WILLIAMSON,[2] HELBA BREDELL,[3] ADRIAN PUREN,[1] XIAOHUA XIA,[3]
RUBEN FILTER,[3] LYNN ZIJENAH,[4] HUYEN CAO,[5] LYNN MORRIS,[1] EFTHYIA VARDAS,
MARK COLVIN,[6] GLENDA GRAY,[7] JAMES McINTYRE,[7] ROSEMARY MUSONDA,[8] SUSAN ALLEN,[8]
DAVID KATZENSTEIN, MIKE MBIZO,[4] NEWTON KUMWENDA,[10] TAHA TAHA,[10]
SALIM ABDOOL KARIM,[6] JORGE FLORES,[11] and HAYNES W. SHEPPARD[5]

ABSTRACT

HIV / Nantes trial

RECHERCHE

Le traitement du sida amélioré grâce à des équations mathématiques

L'Institut de recherche en communications et cybernétique de Nantes met au point une aide au diagnostic pour le traitement du sida. Une étude a commencé en mars sur un échantillon de patients.

En devenant ingénieur, Claude Moog, de l'Institut de recherche en communications et cybernétique de Nantes (IRCCyN), directeur de recherche au CNRS, n'envisageait pas forcément de s'occuper, un jour, du traitement du sida.

Pourtant, un projet démarré en 2002 est en train de se concrétiser par une étude en temps réel, après de longs mois de préparation : « *L'idée a été lancée par un collègue sud-africain.*

Le gouvernement de son pays a lancé un programme de lutte contre le sida qui implique tous les domaines scientifiques.

Pourquoi ne pas mettre l'outil mathématique au service du traitement de la maladie ? ».

Adapter finement le traitement à chaque patient

Le CHU de Nantes et l'université de Prétoria partenaires

Claude Moog et Adama Ouattara ont mis au point leur modèle mathématique en utilisant les données cliniques stockées à Nantes depuis 1986 et concernant douze patients sur une période longue.

Leurs résultats ont été de nature à convaincre les médecins de l'intérêt de la méthode.

Le professeur François Raffi notamment, qui dirige le service infectiologie du CHU de Nantes, a tendu une oreille attentive, car le travail de l'IRCCyN pourrait apporter aux praticiens une aide précieuse. Le CHU est donc devenu partenaire de l'opération, aux côtés de l'université de Prétoria et du CNRS.

Depuis 1996, les multithérapies anti-VIH associant plusieurs médicaments ont considérablement augmenté l'espérance et le confort de vie des personnes atteintes par le virus.

Elles associent essentiellement deux familles de médicaments dont la combinaison accroît de manière spectaculaire l'efficacité du traitement.

Cependant, leur action et leurs effets secondaires varient d'un malade à l'autre, en fonction de multiples paramètres.

Diagnostic en un mois au lieu de six

Jusqu'à présent, les médecins prescrivent un traitement, effectuent des prises de sang régulières chaque mois et sont en mesure de modifier les dosages, le cas échéant en fonction du résultat des analyses et de l'état du patient, au bout d'environ six mois de traitement.

Claude Moog et Adama Ouattara, doctorant, ont imaginé d'identifier ces paramètres à partir des examens biologiques sanguins : « *Les molécules de traitement agissent très rapidement.*

En effectuant trois prises de sang dès la première semaine, nous serions en mesure de donner au médecin des indications sur l'action du traitement et les modifications de prescription ou de dosage qu'il pourrait envisager ».

Un mois suffirait pour calculer les paramètres de l'infection et anticiper son évolution à court terme, afin d'adapter finement le traitement à chaque patient.

Soit un gain de temps considérable, une économie non négligeable car les médicaments sont coûteux et, surtout, une amélioration du confort et de la qualité de vie du malade.

Premiers résultats en septembre

D'ores et déjà une dizaine de volontaires ont été recrutés pour cette expérimentation prévue sur neuf mois, soit jusqu'en septembre. Il ne s'agit pas encore d'appliquer les résultats des calculs, mais dans un premier temps de vérifier s'ils corroborent l'observation clinique.

Si tel est le cas, et selon la réactivité des médecins et administrations concernés, il ne resterait qu'à trouver un partenaire pour rendre l'outil convivial de manière à pouvoir généraliser son usage.

« *Le coût est négligeable, il suffit de faire tourner un ordinateur. Et, même si cette première approche est encore grossière, elle ne peut qu'être meilleure que le néant antérieur !* ».

L'équipe nantaise est en effet seule à proposer cette approche. « *Je suis très optimiste*, affirme Claude Moog, *ça va forcément donner quelque chose* ».

Pascale Wester

Adama Ouattara, doctorant, et Claude Moog, directeur de recherche.

Centre Universitaire Hospitalier de Nantes

IRCCYN

Institut de Recherche en Communication et Cybernétique de Nantes

University of Pretoria

Goal and Protocol

Goal

To predict the efficacy of a therapy

To predict an immunologic or virologic failure….

Towards an early diagnosis…

Protocole

Initiation of a therapy for naiive patients

3 blood tests during the 1st week

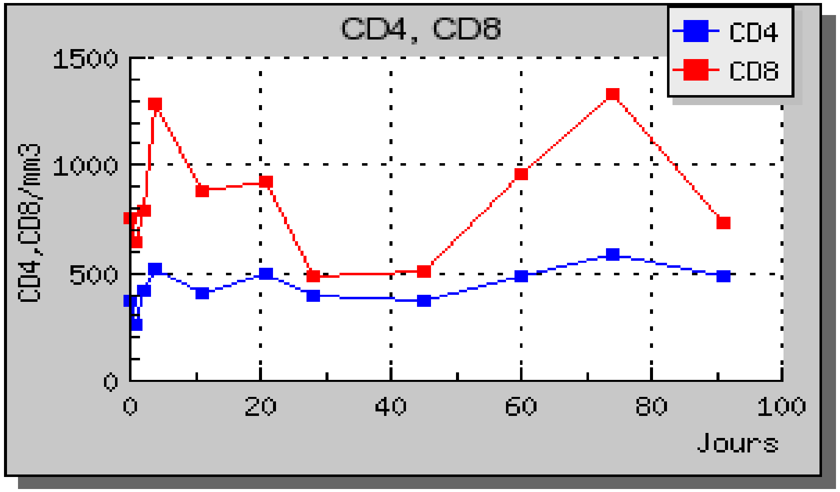
2 blood tests during the 2nd week

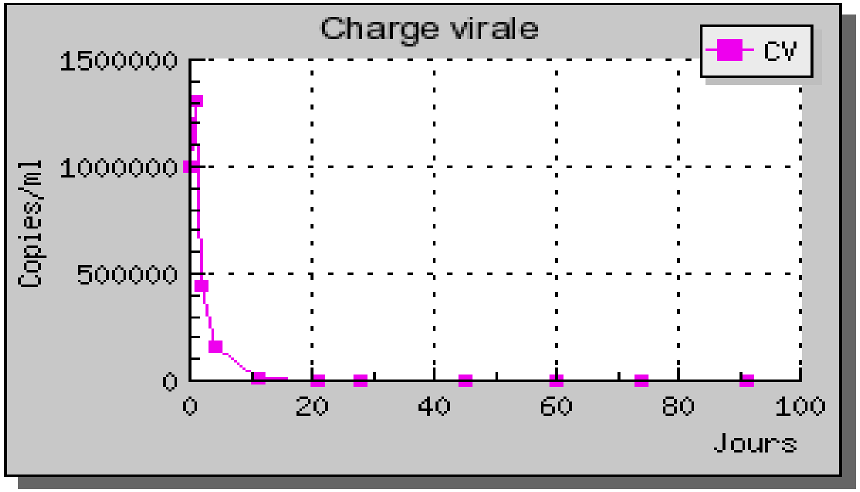
7 blood tests during the 1st month

….

11 blood tests for 3 months……

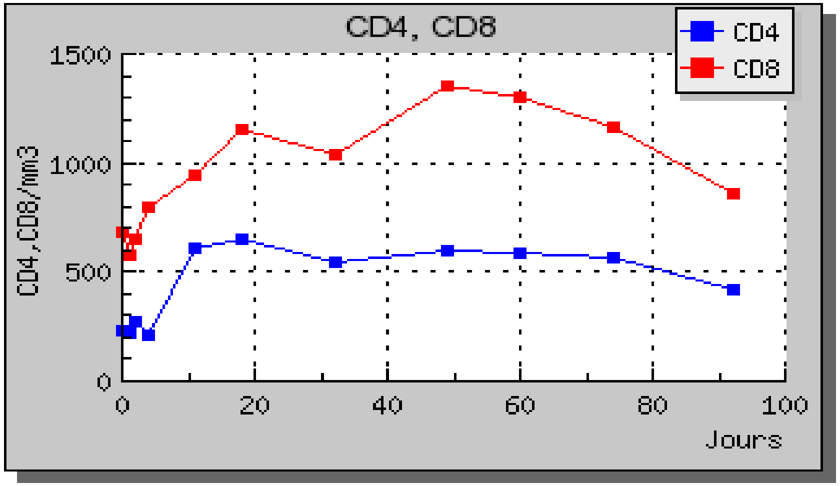
Clinical data – patient 1

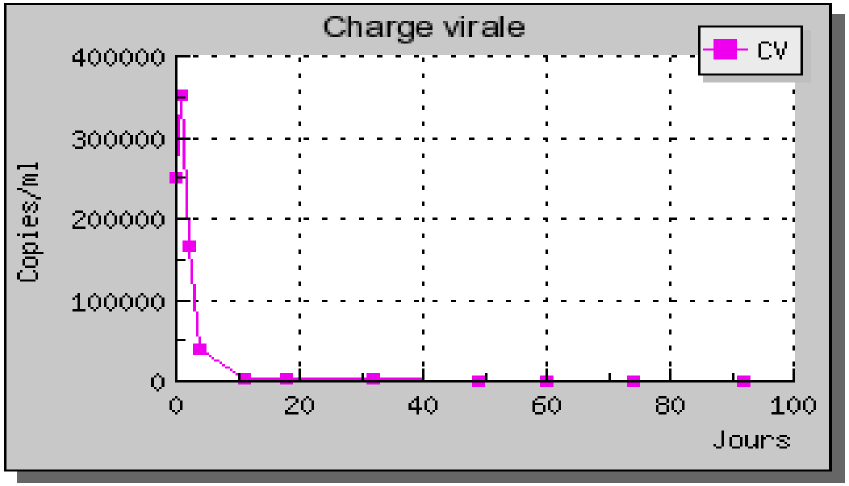




N	Date	t (Jours)	CD4 (CD4/mm^3)	CD8 (CD8/mm^3)	CV (Copies/ml)	log10(CV)
1	14-Mar-2005	0	376	754	999833	6.00
2	15-Mar-2005	1	261	642	1309960	6.12
3	16-Mar-2005	2	422	788	442896	5.65
4	18-Mar-2005	4	524	1291	160130	5.20
5	25-Mar-2005	11	411	876	9684	3.99
6	4-Apr-2005	21	491	925	2956	3.47
7	11-Apr-2005	28	398	486	2297	3.36

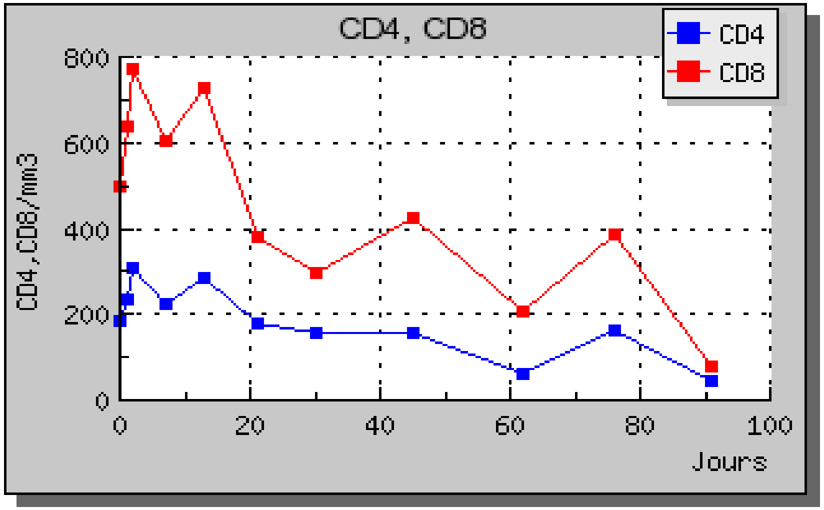
Clinical data – patient 2

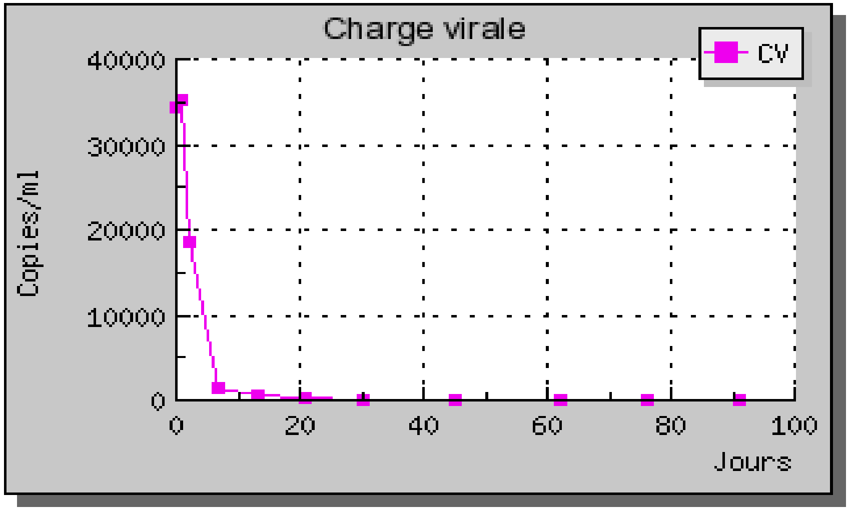




N	Date	t (Jours)	CD4 (CD4/mm^3)	CD8 (CD8/mm^3)	CV (Copies/ml)	log10(CV)
1	14-Mar-2005	0	230	681	252013	5.40
2	15-Mar-2005	1	217	578	351121	5.55
3	16-Mar-2005	2	268	651	165919	5.22
4	18-Mar-2005	4	208	802	39214	4.59
5	25-Mar-2005	11	609	947	2966	3.47
6	1-Apr-2005	18	653	1151	1579	3.20
7	15-Apr-2005	32	547	1037	1534	3.19

Clinical data – patient 3



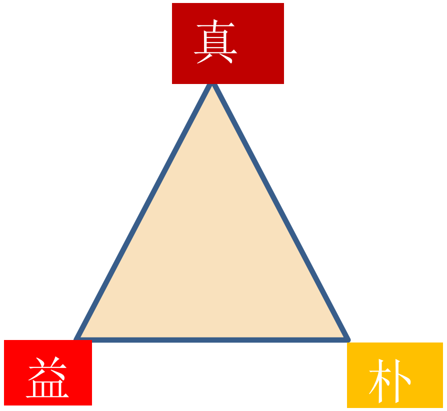


N	Date	t (Jours)	CD4 (CD4/mm^3)	CD8 (CD8/mm^3)	CV (Copies/ml)	log10(CV)
1	22-Mar-2005	0	185	497	34423	4.54
2	23-Mar-2005	1	237	636	35199	4.55
3	24-Mar-2005	2	305	772	18490	4.27
4	29-Mar-2005	7	223	603	1541	3.19
5	4-Apr-2005	13	286	726	494	2.69
6	12-Apr-2005	21	181	379	170	2.23
7	21-Apr-2005	30	154	299	40	1.60

Results

	patient	s	δ	k	μ	s/δ
1	01	**6.93**	**0.011**	0.01	0.03	**630**
2	02	**7.15**	**0.011**	0.03	0.02	**650**
3	03	**0.40**	**0.014**	0.04	0.05	**30**
4	04	**5.16**	**0.014**	0.00	0.03	**390**
5	05	**5.87**	**0.010**	0.05	0.05	**590**
6	06	**6.11**	**0.009**	0.03	0.05	**680**

Immunologic failure



3. Building energy maintenance modelling – the myth about input selection

Control application in large scale lighting project

60 W	14 W	10 W
1000 hour	10 000 hours	60 000 hours
R 10	R 32	R 260

Funding Scheme Examples

United Nations Climate Change
Carbon Mechanisms

CDM: issue carbon emission reduction credits

- Large Scale
- Small Scale

Eskom

Eskom: R 0.45 / kWh (R 0.55 for LED) savings for 3 years

- CFL Mass Rollout
- Performance Contracting
- Standard Offer

SANEDI: R 0.95 / kWh savings for 12 months

- 12 L Energy Efficiency Tax Incentive

Project Incentive Policy

- Project crediting period: 10 years
- PDs invest project implementation and maintenance
- PDs receive their rebate on annual basis
- PDs replace part/all of the failed EE lamps
- Savings reported by a third-party M&V inspection company
- Lamps maintained to ensure survival rate over 50%

Lighting Population Decay

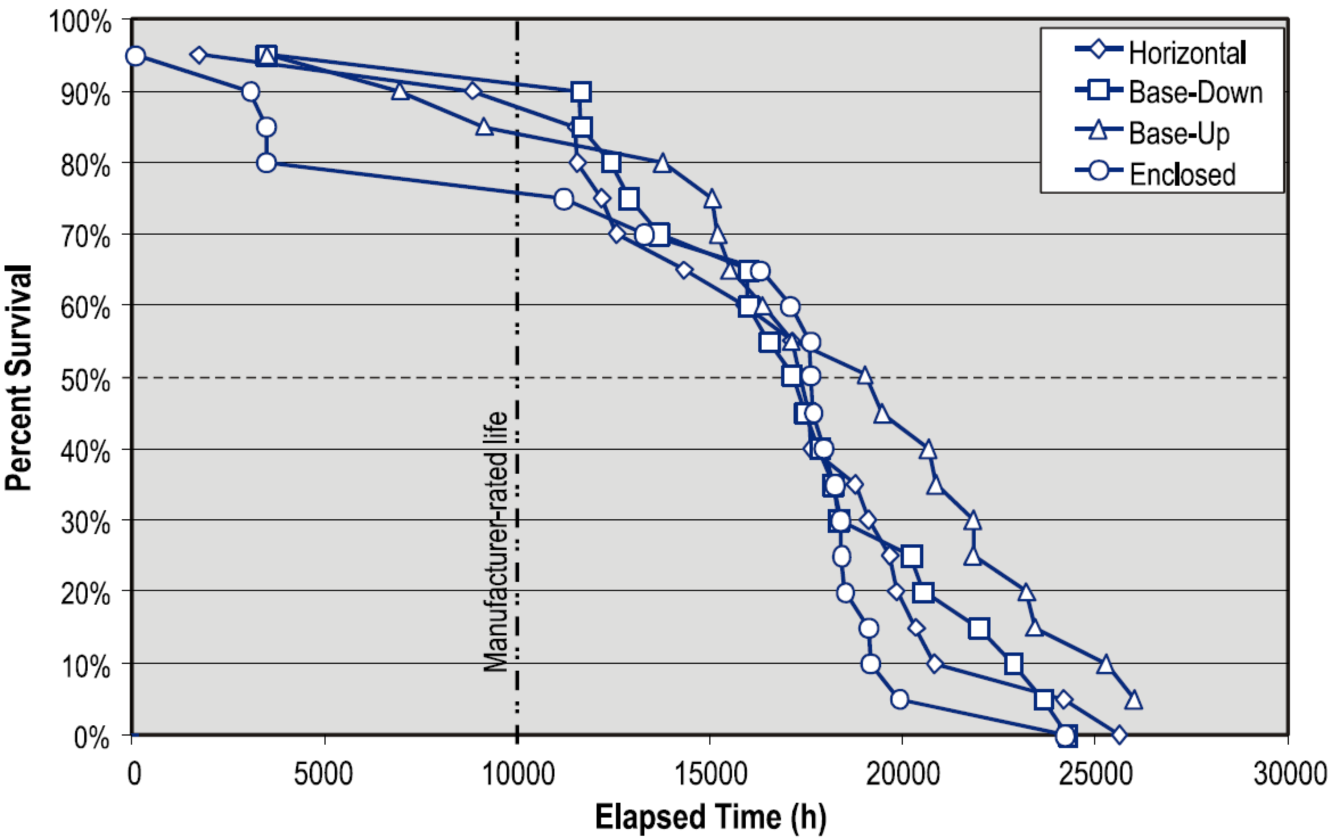
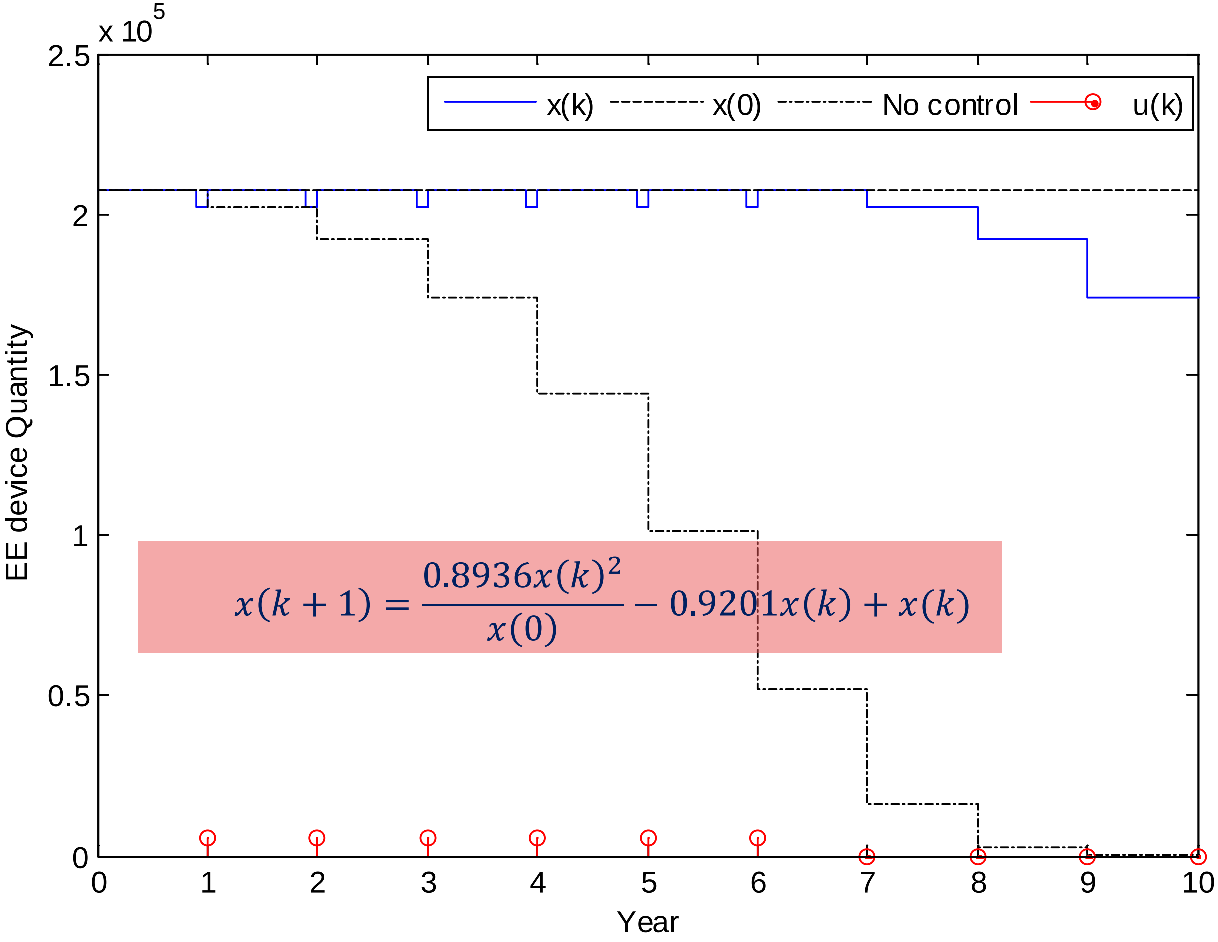


Figure: CFL survival vs. elapse time.

Source: National Lighting Product Information Programme

Optimal Solutions (1)



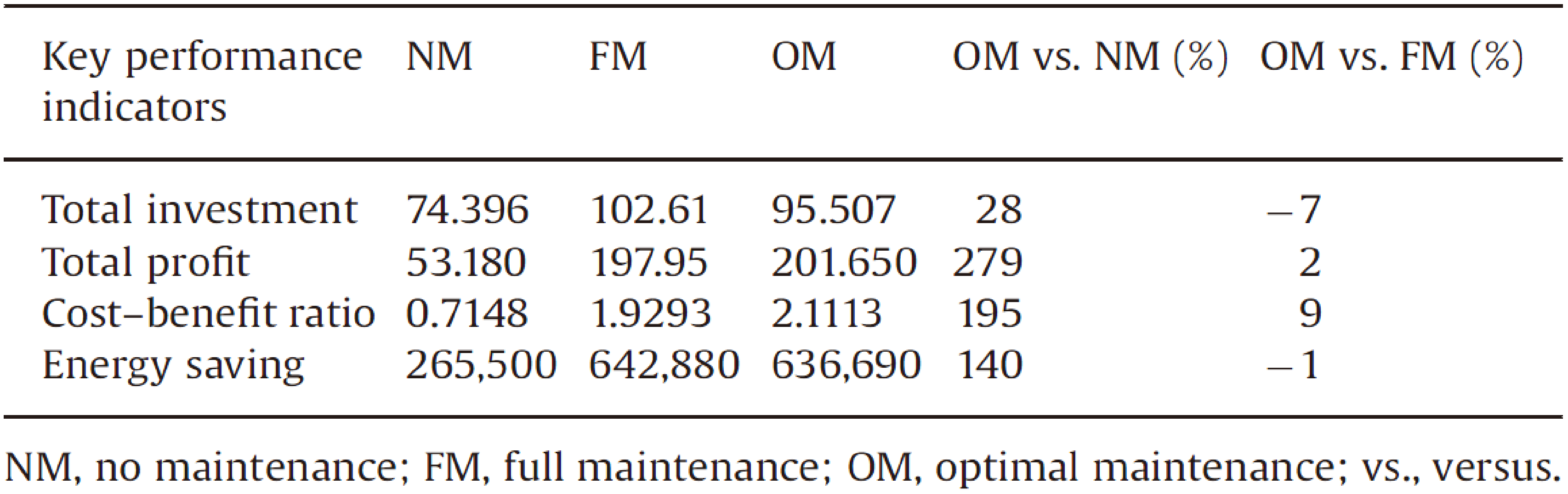
$$x(k+1) = \frac{0.8936x(k)^2}{x(0)} - 0.9201x(k) + x(k)$$

u(k)
5488
5490
5490
5490
5490
5490
0
0
0
0

Figure: Optimal control strategy of LED replacement.

Optimal Solutions (2)

Table: Key performance indicators with maintenance.



Key performance indicators	NM	FM	OM	OM vs. NM (%)	OM vs. FM (%)
Total investment	74.396	102.61	95.507	28	−7
Total profit	53.180	197.95	201.650	279	2
Cost–benefit ratio	0.7148	1.9293	2.1113	195	9
Energy saving	265,500	642,880	636,690	140	−1

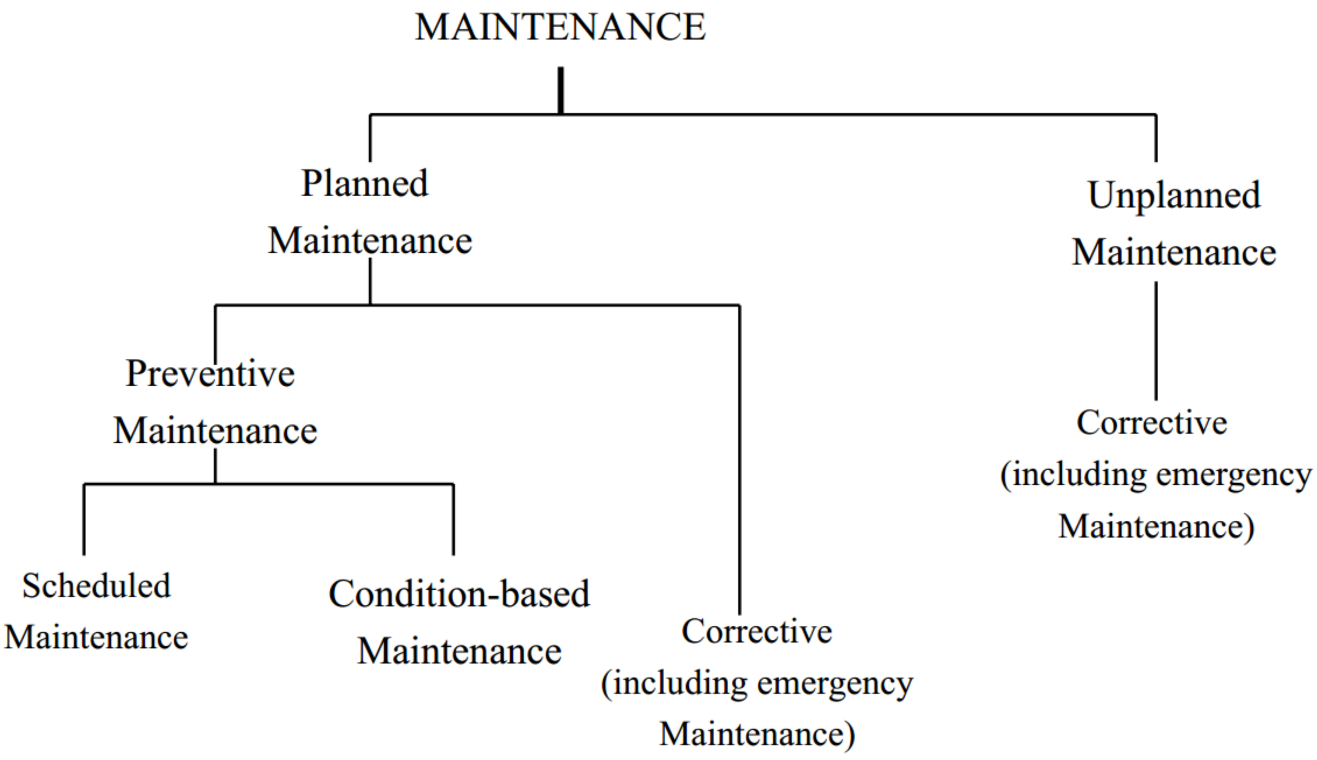
NM, no maintenance; FM, full maintenance; OM, optimal maintenance; vs., versus.

Ref

[1] X. Ye and X. Xia, *in Proceedings of the 19th World Congress of the IFAC*, Cape Town, South Africa, August 24-29, 2014.
[2] X. Ye, X. Xia, L. Zhang, and B. Zhu, ***Control Engineering Practice*** 37(2015): 1–10.

Control System Inputs and Disturbances

- British Standard 3811 classified building maintenance as the followings:



MAINTENANCE

Planned Maintenance

Unplanned Maintenance

Preventive Maintenance

Scheduled Maintenance

Condition-based Maintenance

Corrective (including emergency Maintenance)

Corrective (including emergency Maintenance)

u_p u_0 u_c d_i

Control System Inputs: u_i

Maintenance type

Corrective or preventive maintenance

Maintenance schedule

Periodically: weekly, monthly, annually
Optimised: action on demand *or* event-triggered

Maintenance intensity

How many units to maintain

Control problems in BEE R&M - General Control System Framework

$$\begin{cases} \dot{x}_i = f_i(x,u) + d_i \\ y_j = h_j(x) + \omega_j \end{cases} \qquad \textbf{(1)}$$

$\boldsymbol{i}$: grouping;

$\boldsymbol{f_i}(\cdot)$: control system **dynamics**;

$\boldsymbol{u_i}$: control system **inputs**;

$\boldsymbol{d_i}$: **modelling** errors;

$\boldsymbol{y_j}$: control system **outputs**;

$\boldsymbol{h_j}(\cdot)$: control system output function;

$\boldsymbol{\omega_j}$: **measurement** errors and **sampling** errors.

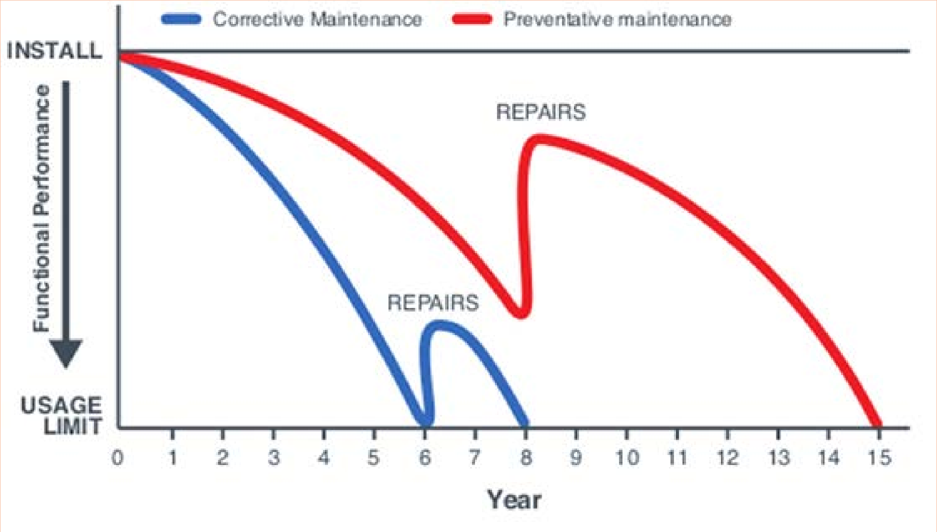
BEE R&M: Failure Inspection and Modelling

Repairable

- Category: building envelopes, HVAC, water heaters
- Life span: long (> 10 years)

Non-repairable

- Category: lights, timers, switches, plug-device
- Life span: short (< 5 years)

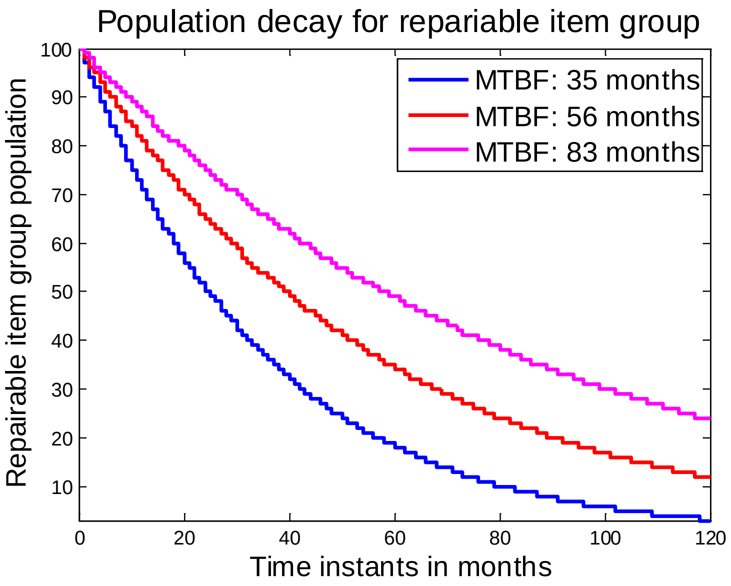


Exponential Model: $\boldsymbol{f_i(x_i, u_i)}$

Reparable failure modelling

$$x_i(k+1) = x_i(k)(1-\xi_i),$$

where $\xi_i = (\theta_i)^{-1}$, θ_i is the mean time between failure (MTBF).



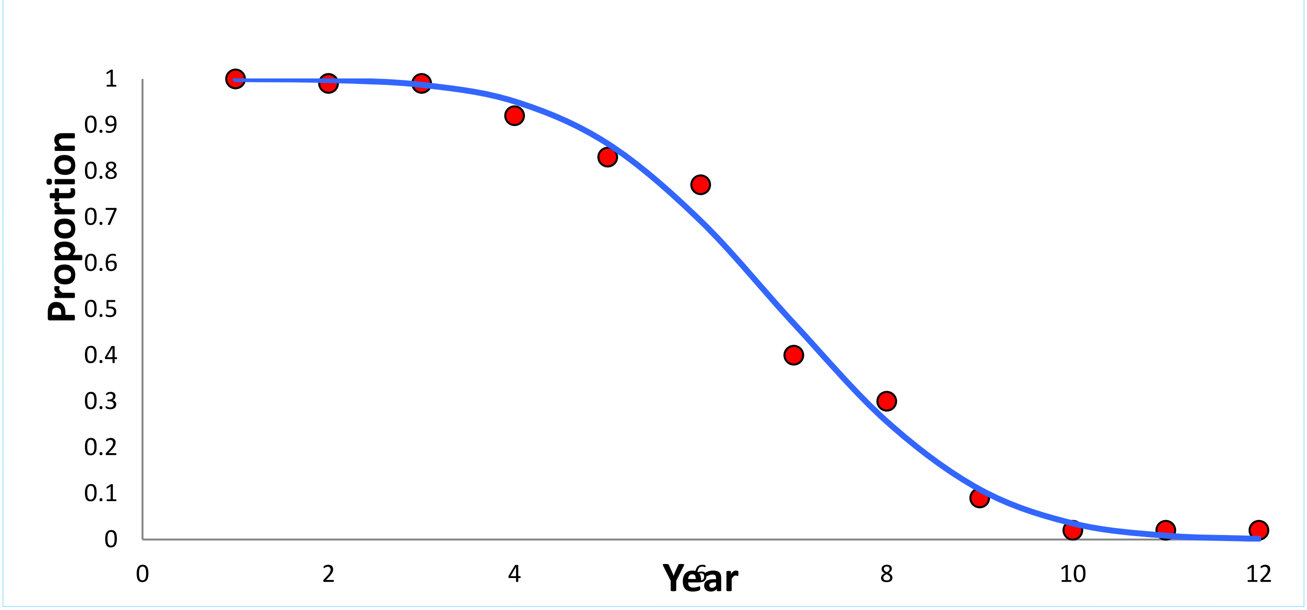
Ref

[1] B. Wang, X. Xia, and J. Zhang. ***Energy and Buildings*** 77 (2014): 227-235.
[2] EM Malatji, J. Zhang, and X. Xia. (2013). ***Energy and Buildings***, 61(2013): 81-87.
[3] Y. Fan and X. Xia, An optimal maintenance plan for building envelope insulation materials after retrofitting, CAC 2015, 28 November 2015.

PELP Study: $\boldsymbol{f_i(x_i, u_i)}$

Non-repairable failure modelling

$$x_i(k+1) = \frac{\tilde{b}_i \tilde{c}_i x_i(k)^2}{x_i(0)} - \tilde{b}_i x_i(k) + x_i(k) + u_i(k).$$



Ref

[1] H. Carstens, X. Xia, and X. Ye, ***Applied Energy*** 126(2014): 256 - 265.

Interactions (2): $\boldsymbol{f_i(x_i, u_i)}$

Example 1

Interaction between lighting and HVAC

$$\begin{cases} \dot{x}_{Lamp} = \hat{f}_1\left(x_{Lamp}\right) + u_{Lamp}, \\ \dot{x}_{HVAC} = \hat{f}_2\left(x_{HVAC}, x_{Lamp}\right) + u_{HVAC}. \end{cases}$$

Example 2

Interactions between retrofit and maintenance

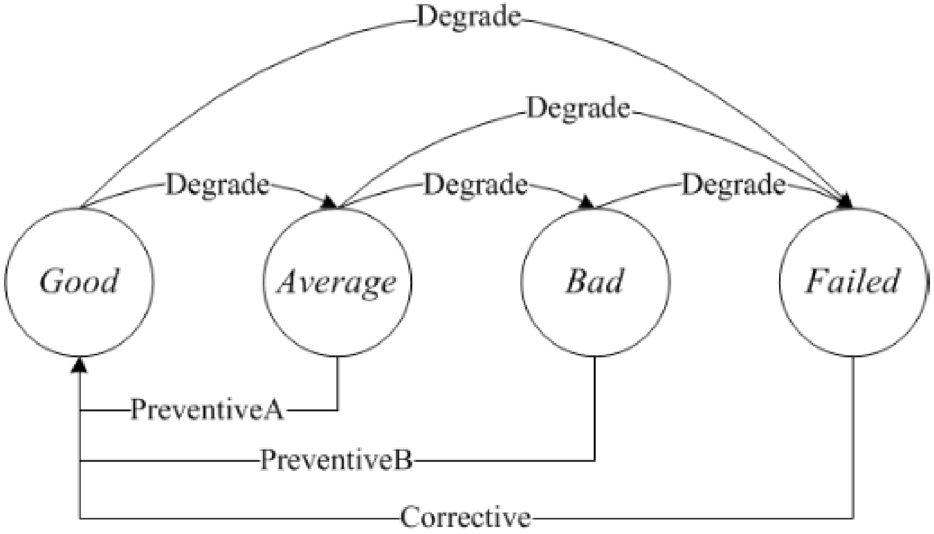
$$\begin{cases} \dot{x}_{Retro} = \tilde{f}_1(x_{Retro}) + u_{Retro}, \\ \dot{x}_{Maint} = \tilde{f}_2(x_{Maint}, x_{Retro}) + u_{Maint}. \end{cases}$$

Ref

[1] B. Wang, N. Wang and X. Xia, Maintenance plan optimization with performance interplay in building energy efficiency retrofitting, CAC2015, 29 November 2015.

[2] Z. Wu, B. Wang and X. Xia, Optimal planning of large-scale building energy efficiency retrofit, ICAE 2016, Beijing.

Multi-State: $f_i(x_i, u_i)$



$$\begin{cases} \Delta x_{l,M_l}(t_k) = -f^l_{M_l,M_l-1}\big(x_{l,M_l}(t_k)\big) - f^l_{M_l,F}\big(x_{l,M_l}(t_k)\big) + \sum_{i=1}^{M_l-1} u^l_i(t_k) + u^l_c(t_k) \\ \Delta x_{l,M_l-1}(t_k) = \ f^l_{M_l,M_l-1}\big(x_{l,M_l}(t_k)\big) - f^l_{M_l-1,M_l-2}\big(x_{l,M_l-1}(t_k)\big) - f^l_{M_l-1,F}\big(x_{l,M_l-1}(t_k)\big) - u^l_{M_l-1}(t_k) \\ \vdots \\ \Delta x_{l,2}(t_k) = \ f^l_{3,2}\big(x_{l,3}\,(t_k)\big) - f^l_{2,1}\big(x_{l,2}(t_k)\big) - f^l_{2,F}\big(x_{l,2}(t_k)\big) - u^l_2(t_k) \\ \Delta x_{l,1}(t_k) = \ f^l_{2,1}\big(x_{l,2}\,(t_k)\big) - f^l_{1,F}\big(x_{l,1}(t_k)\big) - u^l_{1,M_l}(t_k) \end{cases}$$

Ref

B. Wang, Z. Wu, and X. Xia. ***IEEE Transactions on Control Systems Technology***, vol. 25, no. 1, January 2017, pp. 374-381.

Optimal Maintenance Plan (1): u_i

Type

Corrective

Schedule

periodically

Intensity

number of units to be repaired

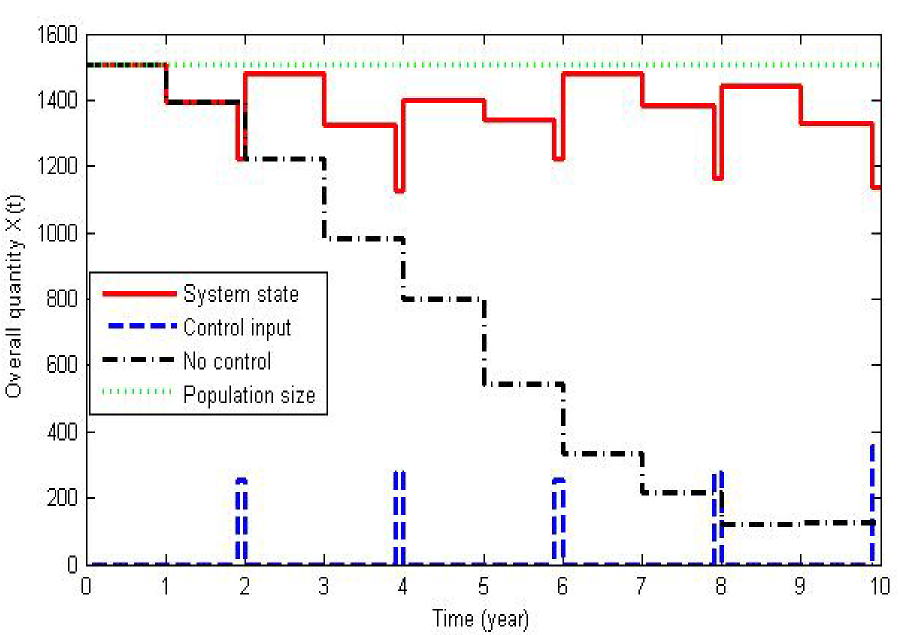


Figure: The optimal control trajectory.

Ref

[1] B. Wang, and X. Xia. *The 19th IFAC World Congress, Cape Town, South Africa,* 2014.
[2] B. Wang and X. Xia. ***Energy and Buildings*** 96 (2015): 299-308.

Optimal Maintenance Plan (1): u_i

Results

Comparing with full maintenance strategy:

- Up to 30.7% of the maintenance cost is reduced,
- only 1.5% of the percentage energy saving is lost.

Optimal Maintenance Plan (2): u_i

Type

CM & PM

Schedule

periodically

Intensity

number of units to be repaired

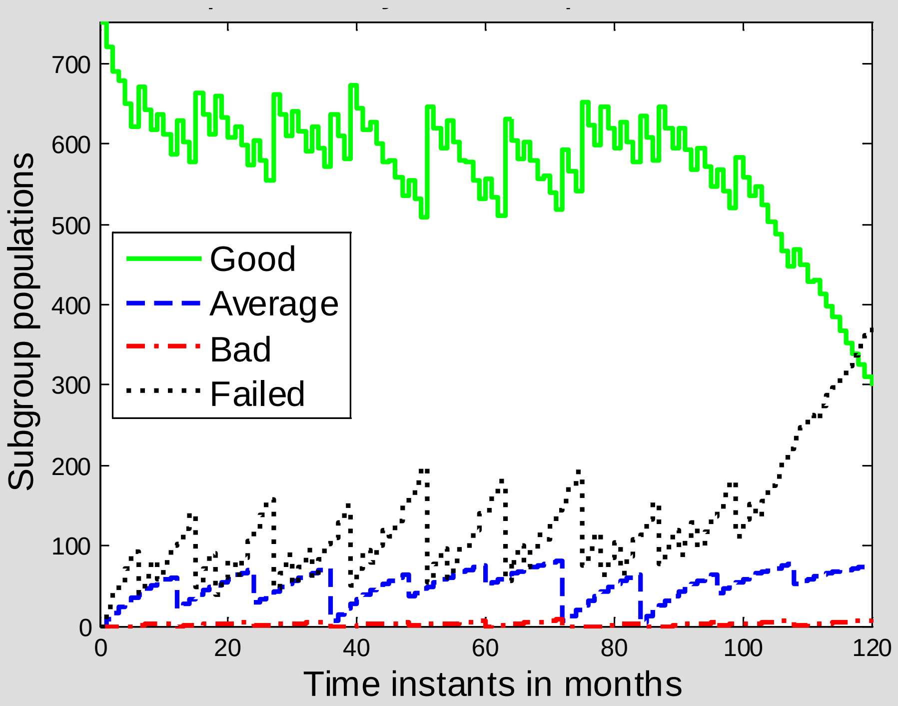


Figure: The optimal control trajectory.

Ref

B. Wang, Z. Wu, and X. Xia. IEEE Transactions on Control Systems Technology, vol. 25, no. 1, January 2017, pp. 374-381.

Optimal Maintenance Plan (3): u_i

Interactions between lighting and HVAC considered

Type

CM & PM

Schedule

periodically

Intensity

number of units to be repaired

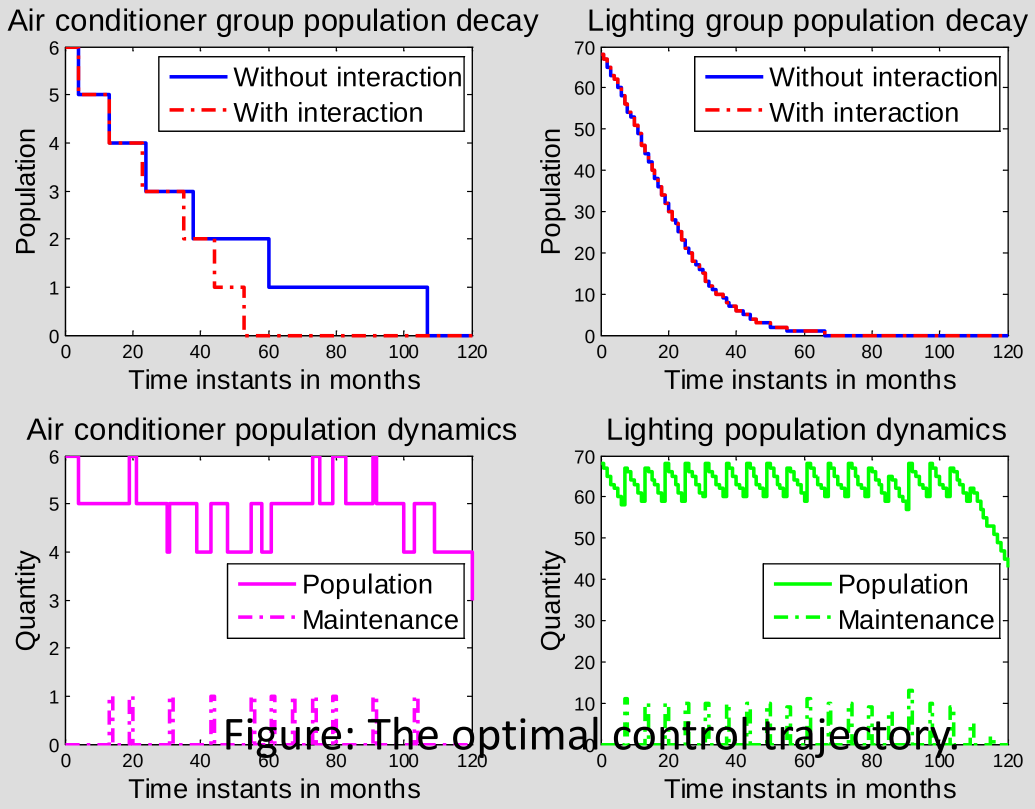


Figure: The optimal control trajectory.

Ref

B. Wang, N. Wang and X. Xia, Maintenance plan optimization with performance interplay in building energy efficiency retrofitting, CAC2015, 29 November 2015.

Optimal Maintenance Plan (4): $\boldsymbol{u_i, Q_i}$

Type

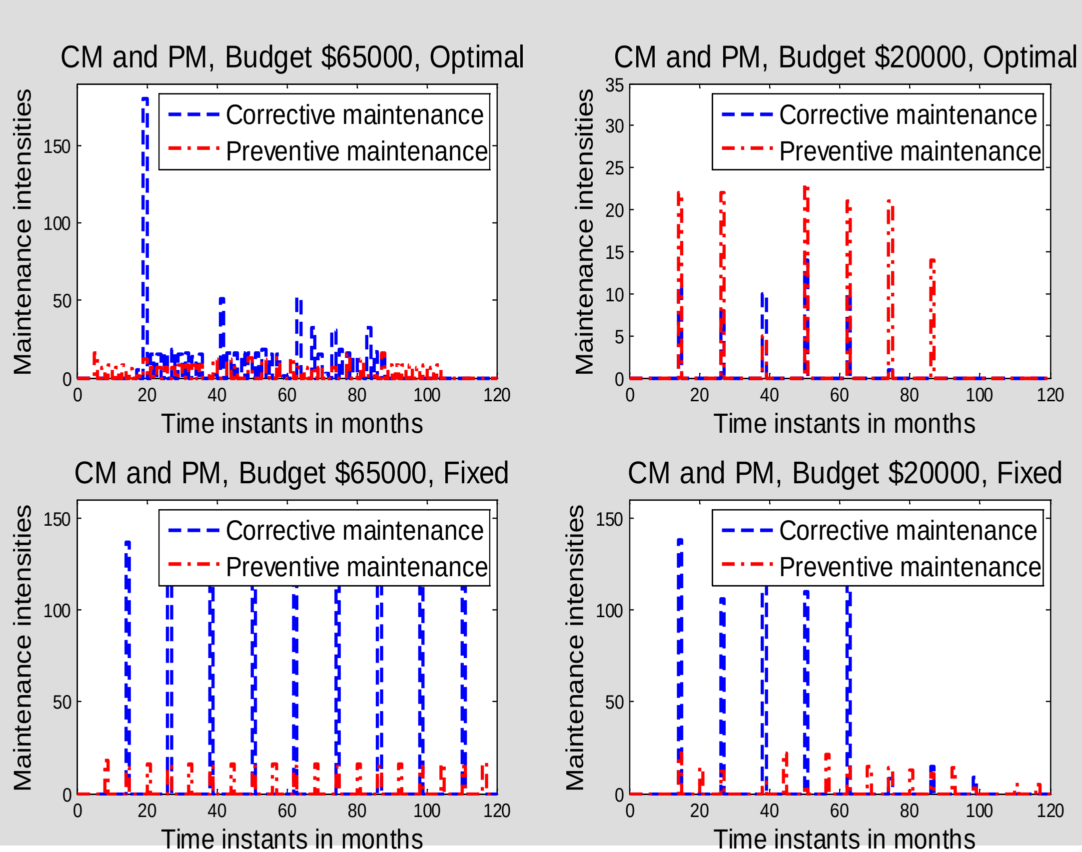
CM & PM

Schedule

Event-triggered

Intensity

number of units to be repaired



Ref

B. Wang, Z. Wu, B. Zhu and X. Xia. Optimal Control of Maintenance Instants and Intensities in Building Energy Efficiency Retrofitting Project. The 54th IEEE Conference on Decision and Control, Osaka, Japan, 2015.

Optimal Maintenance Plan (4): $\boldsymbol{u_i, Q_i}$

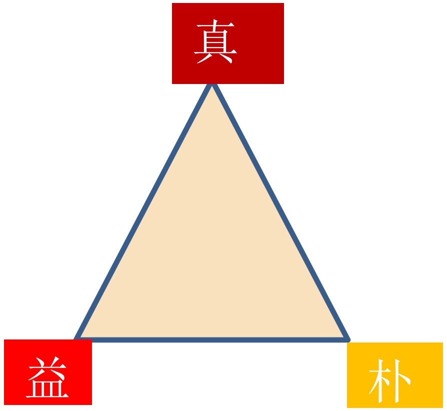
Results

Comparing with fixed-time-schedule:

- Up to 21.7% more energy saving, and
- up to 5.7% improvement on IRR.

Other issues

- Outputs;
- Objective functions;
- Errors, disturbances and uncertainties;
- Algorithms;
- Groups.



4. Take home messages

… 复归于朴 朴散则为器 圣人用之 则为官长 故大制不割 …

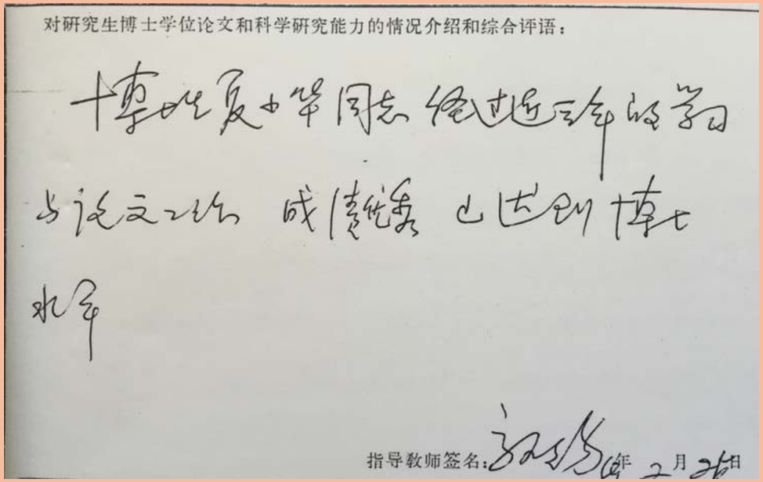
老子《道德经》28

"When Simplicity is broken up, It is made into instruments. Evolved individuals who employ them, Are made into leaders. In this way, the Great System is United."

\- Lao Tzu The Tao Te Ching (Verse 28)

致谢

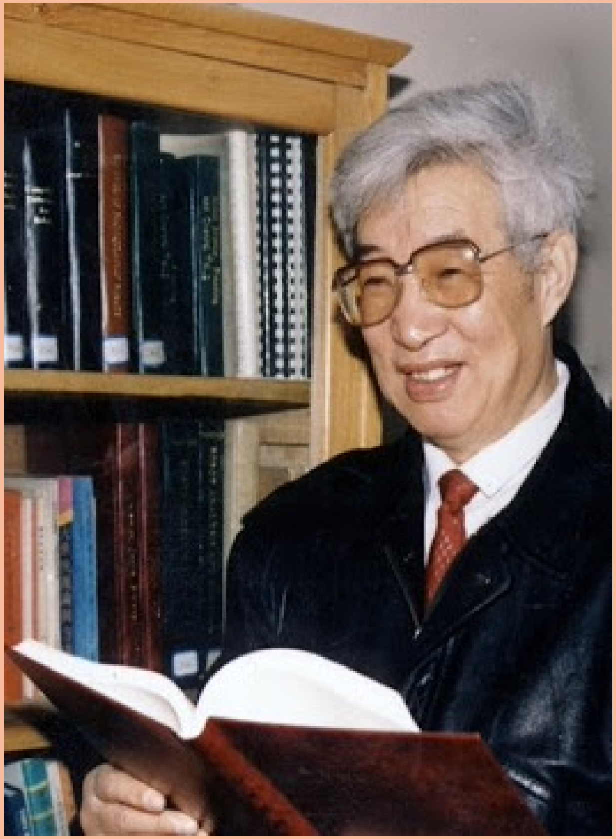
并纪念高为炳教授！



对研究生博士学位论文和科学研究能力的情况介绍和综合评语：

博士生夏小华同志经过三年的学习与论文工作 成绩优秀 已达到博士水平

指导教师签名：高为炳 年 2月 26日



Acknowledgement

- Train team
  - A. Veldsman, S. Scott, M. Howthorn, M. S. Chou, S. J. Wang, 专祥涛, M. Stempel, C. Kayser
- HIV team
  - I. Craig, C. Gray, C. H. Moog, M. Jeffrey, R. Filter, E. du Toit, C. Williamson, H. Bredell, A. Puren, L. Zijenah, H. Cao, L. Morries, E. Vardas, M. Colvin, J. McIntyre, R. Musonda, S. Allen, D. Katzenstein, M. Mbizo, N. Kumwenda, T. Taha, S. A. Karim, J. Flores, H. W. Sheppard, H. Miao, A. S. Perelson, H. Wu, A. M. Elaiw, P. S. Rivadeneira, G.B. Stan, V. Costanza, C. Brunet, F. Raffi, V. Ferre, M. J. Mhawej, F. Biafore, D. A. Ouattara, D. Ernst, R. Fonteneau, 张江峰
- Energy team
  - 张江峰，叶先明，王博，梅俊，范玉玲，张李军，王楠，伍洲，诸兵，E. M. Malatjie, Z. Olinga, H. Tazvinga, D. Setlhaolu, N. Nwulu, T. Mathaba, P. Numbi, H. Carsten, U. Ekpenyong, S. Sichlalu, E. Wanjiru, F. Wamalwa, M. Michael, S. Ntsaluba, A. Chatterjee