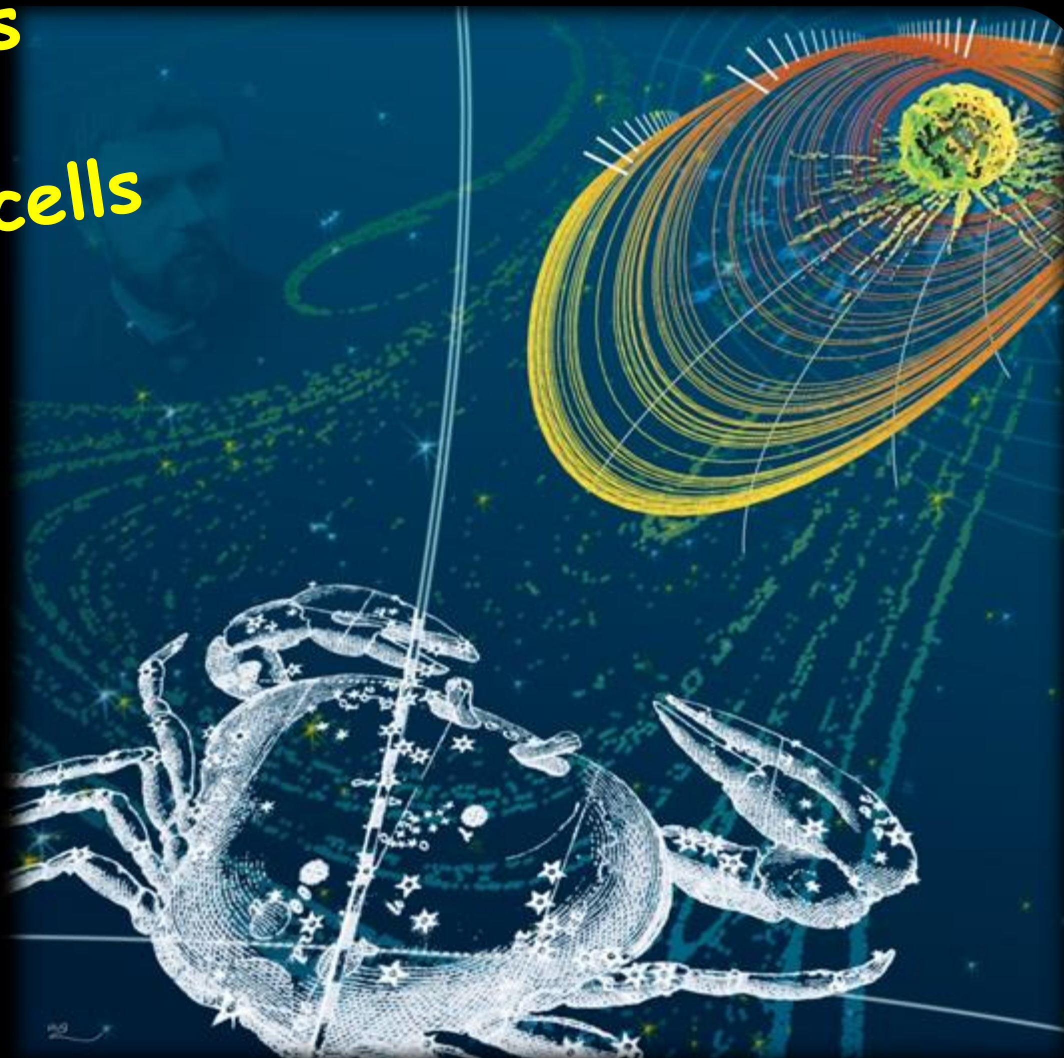
Math-Cancer, Marseille, 5-10 December 2015

How the dynamics between the populations of cells affects tumor growth



Christophe Letellier

Fabrice Denis

Louise Viger

Clément Draghi

A short introduction to chaos

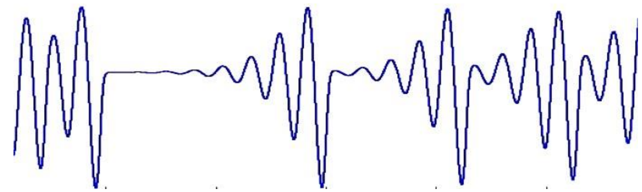
Required properties

✓ Determinism

$$\dot{x} = f(x)$$

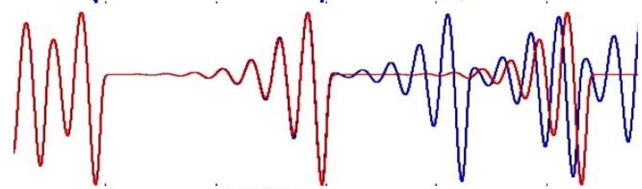
Hard

✓ Aperiodicity



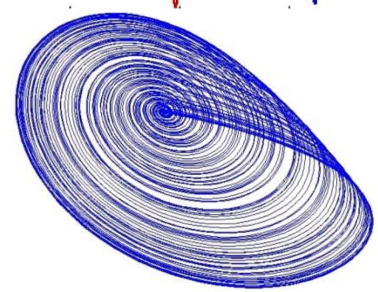
Easy

✓ Sensibility to initial conditions



Easy

✓ Recurrent (bounded trajectory)



Easy

Proc. R. Soc. Lond. A **413**, 9–26 (1987)
Printed in Great Britain

Nonlinear dynamics, chaos and complex cardiac arrhythmias

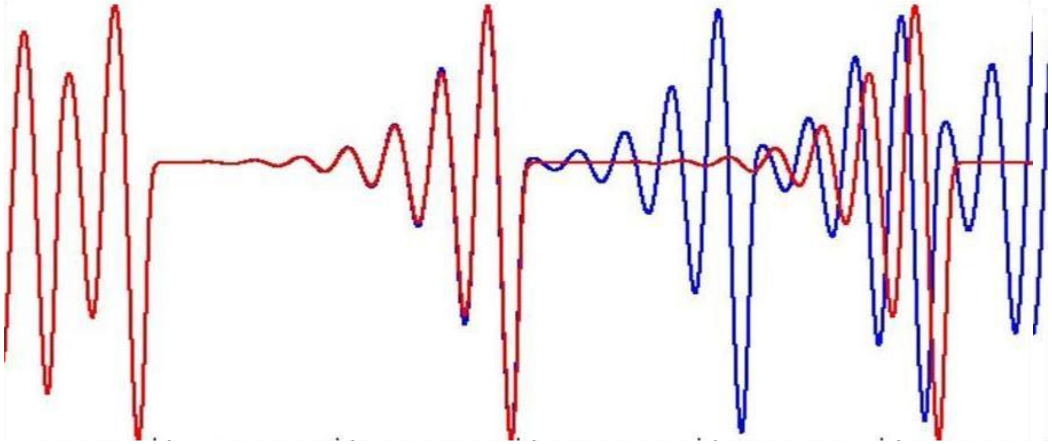
By L. Glass[1], A. L. Goldberger[2], M. Courtemanche[1] and A. Shrier[1]

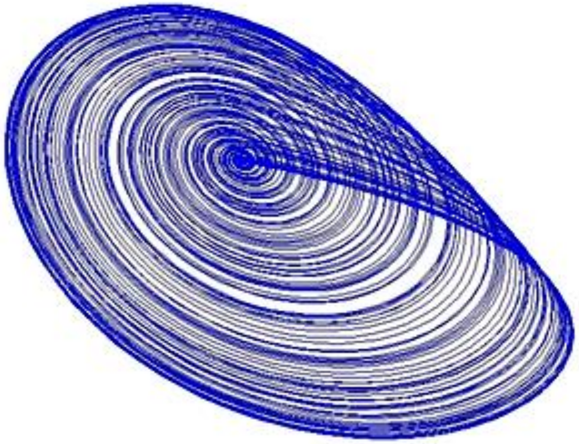
« The concept of chaos excludes **non-deterministic stochastic processes**»

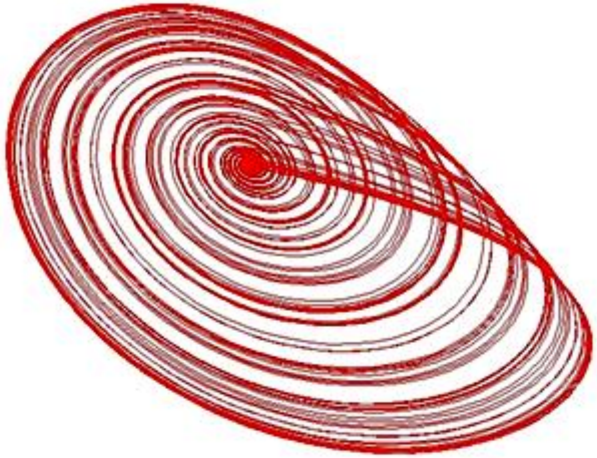
A short introduction to chaos

Stretching
Folding

Sensibility to initial conditions
+ mixing properties = **CHAOS**

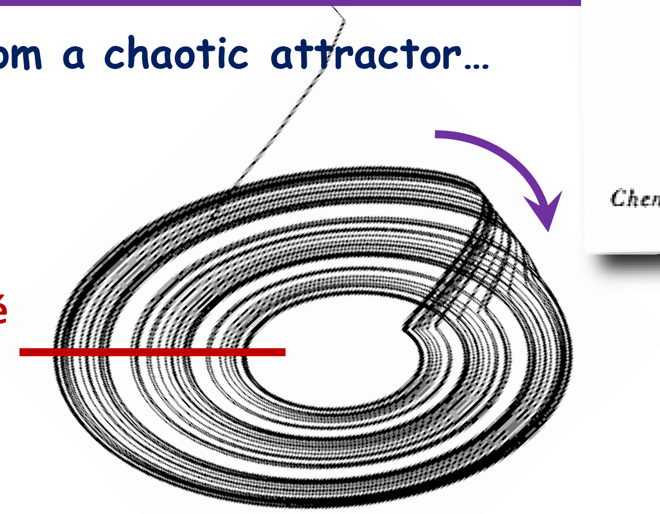




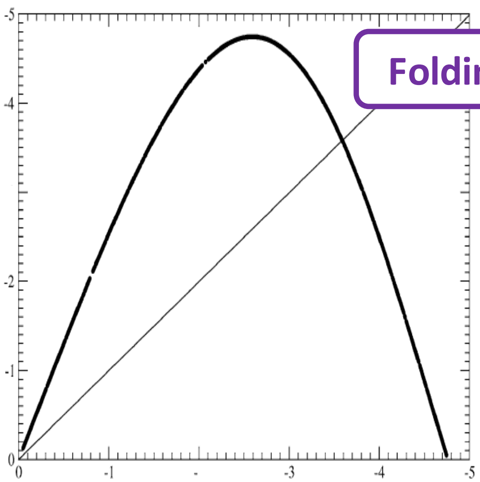


A short introduction to chaos

- From a chaotic attractor…



… to a first-return map to a Poincaré section



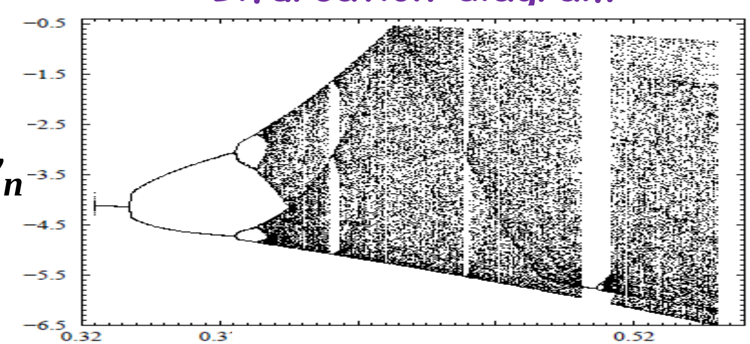
Chaotic Behavior in Simple Reaction Systems

Otto E. Rössler

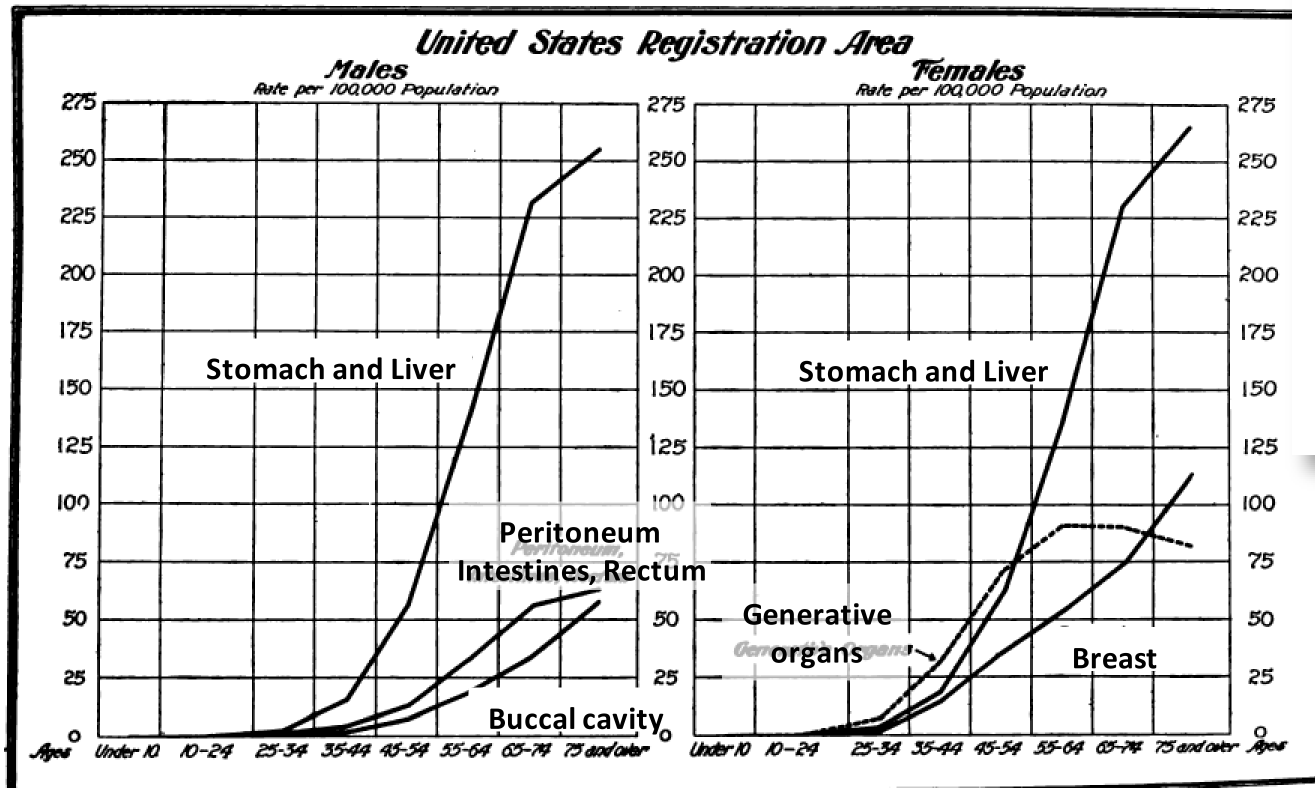
Institut für Physikalische und Theoretische Chemie der Universität Tübingen

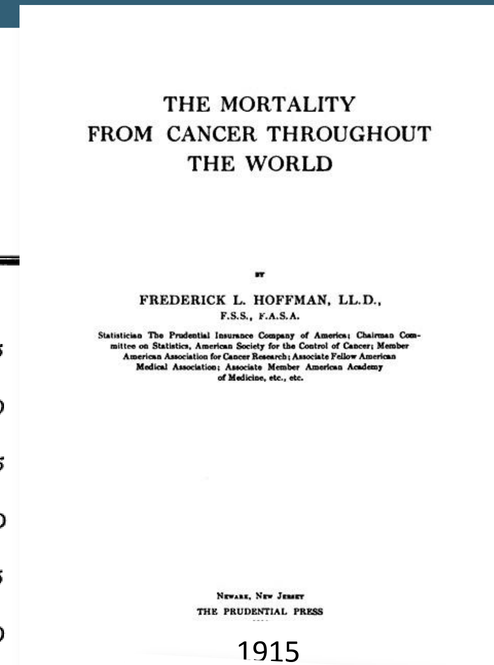
(Z. Naturforsch. 31 a, 259—264 [1976]; received January 5, 1976)

Chemical system theory, exotic kineti



Cancer mortality by age and organs




THE MORTALITY
FROM CANCER THROUGHOUT
THE WORLD

BY

FREDERICK L. HOFFMAN, LL.D.,
F.S.S., F.A.S.A.

Statistician The Prudential Insurance Company of America; Chairman Committee on Statistics, American Society for the Control of Cancer; Member American Association for Cancer Research; Associate Fellow American Medical Association; Associate Member American Academy of Medicine, etc., etc.

NEWARK, NEW JERSEY
THE PRUDENTIAL PRESS

1915

Frederick Hoffman
(1865-1945)

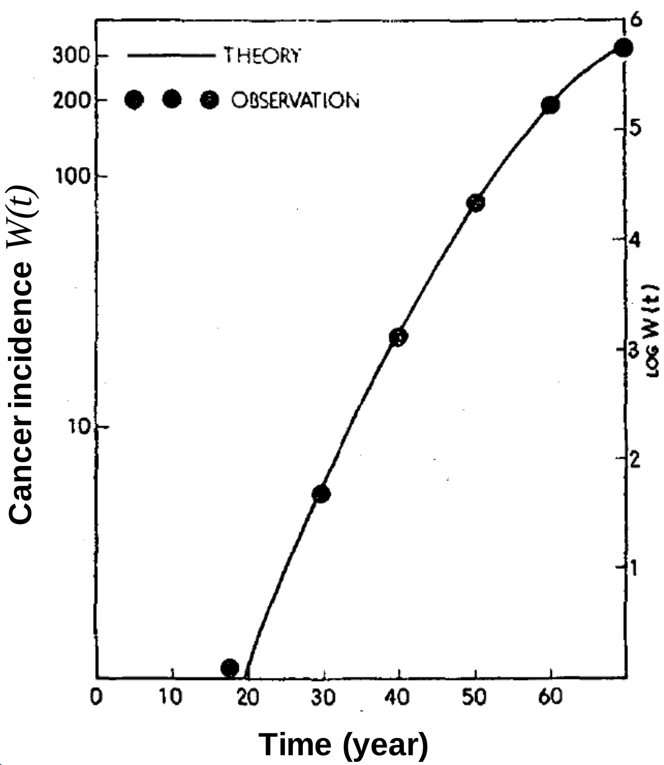
First mathematical model in cancer problem

Nicolas Rashevsky
(1899-1972)

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 7, 1945

OUTLINE OF A MATHEMATICAL APPROACH TO THE CANCER PROBLEM

N. RASHEVSKY
THE UNIVERSITY OF CHICAGO



Cancer incidence $W(t)$ for 100,000 males for all organs

$$\log W(t) = \log A_3 + \alpha t - \tfrac{1}{2}\alpha c t^2$$

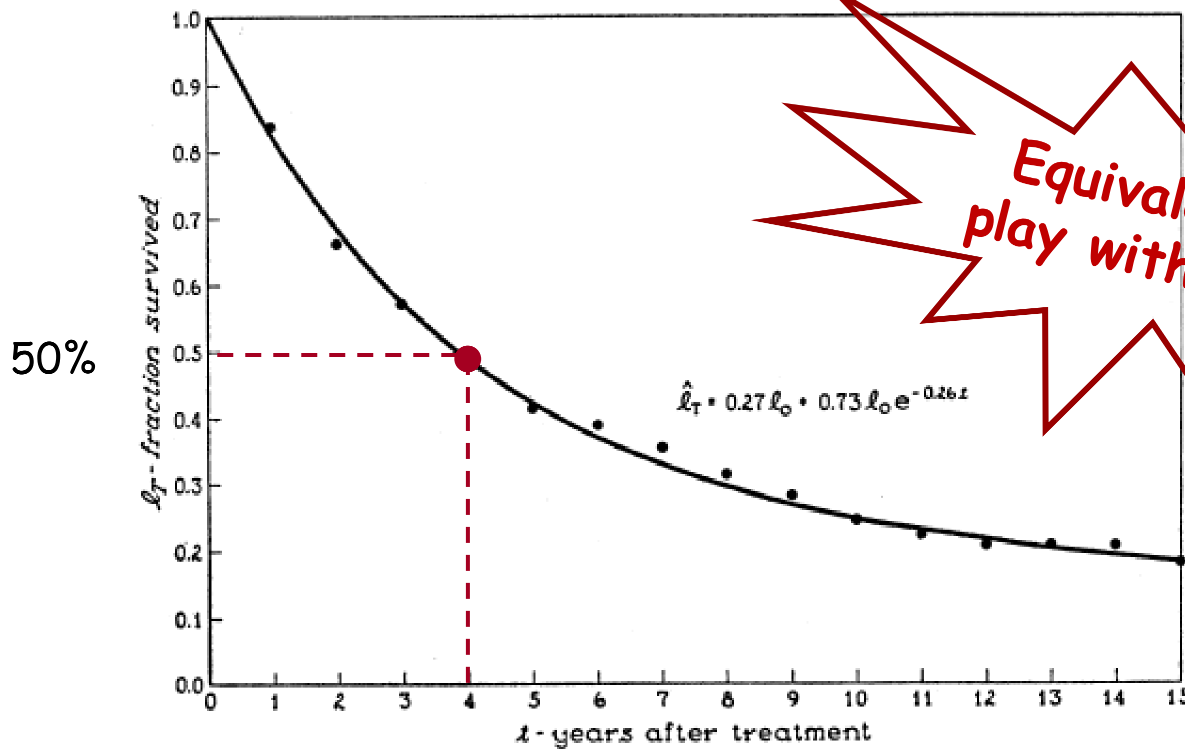
Log A_3 = -4.2
α = 0.236 year^{-1}
c =0.01 year^{-1}

Normal longevity $\dfrac{1}{c} = 88$ ans

« we thus can correctly compute the human normal longevity from data on cancer incidence. »

Survival curves

Survival curves for women with breast cancer

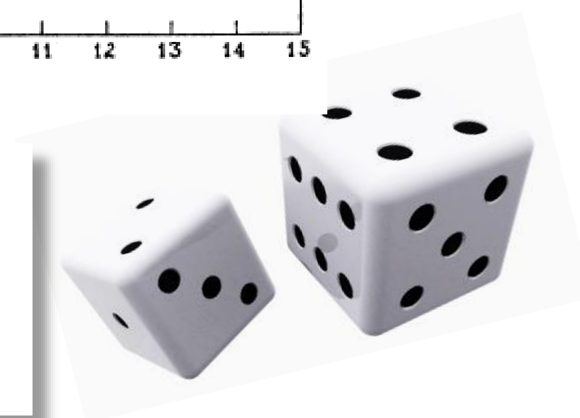


Equivalent to play with dices!

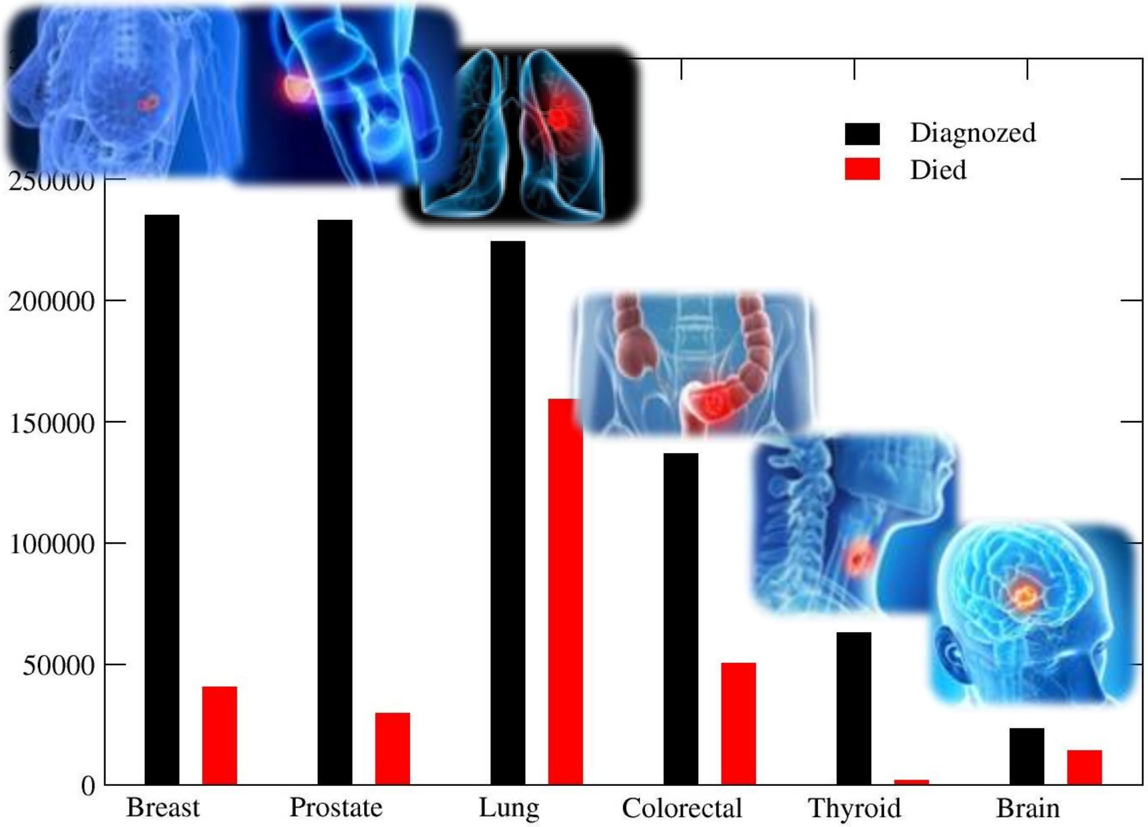
SURVIVAL CURVE FOR CANCER PATIENTS FOLLOWING TREATMENT

JOSEPH BERKSON AND ROBERT P. GAGE

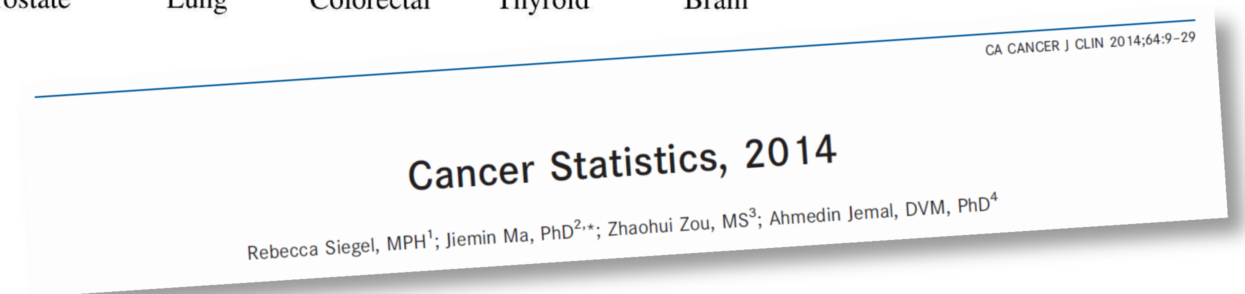
502 AMERICAN STATISTICAL ASSOCIATION JOURNAL, SEPTEMBER 1952



Number of cancers in US during 2014



Cancer risk strongly depends on the organ

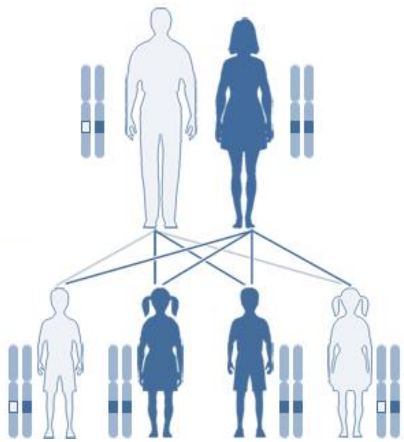

CA CANCER J CLIN 2014;64:9–29

Cancer Statistics, 2014

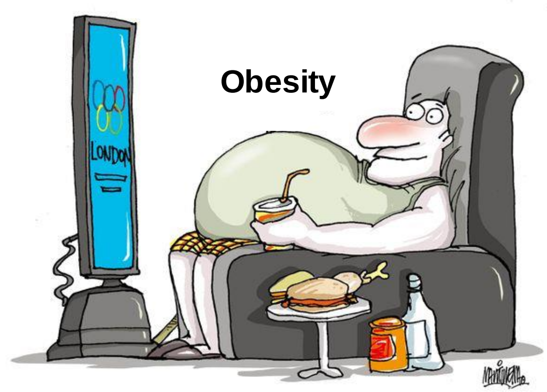
Rebecca Siegel, MPH[1]; Jiemin Ma, PhD[2,*]; Zhaohui Zou, MS[3]; Ahmedin Jemal, DVM, PhD[4]

Factors affecting the lifetime risk

Hereditary Syndrome
(gene mutation)



Obesity



Physical
inactivity

Red meat
Processed meat

Alcohol

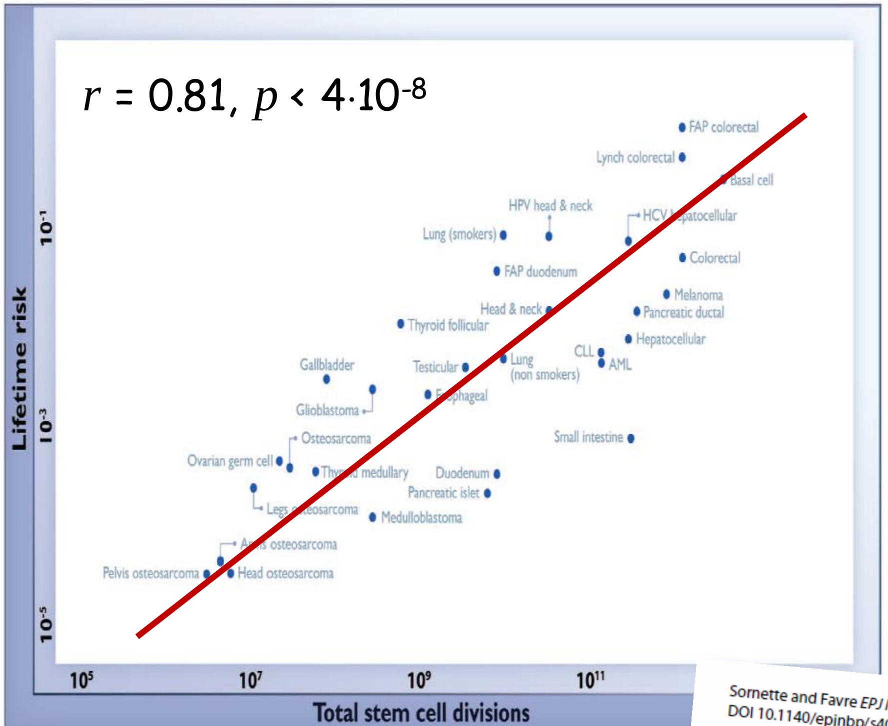
Smoking

10%

Tissue status

Tissue dynamics
=
Cell interactions

Lifetime risk: "bad luck" or not?



Lifetime risk of different types of cancer is strongly correlated to the total number of division of normal self-renewing cells

« Variation in cancer risk is due to **bad luck**, that is, to **random mutations** arising during DNA replication in normal cells. »

Wrong!

CANCER ETIOLOGY

Variation in cancer risk among tissues can be explained by the number of stem cell divisions

Cristian Tomasetti[1*] and Bert Vogelstein[2*]

2 JANUARY 2015 • VOL 347 ISSUE 6217

SCIENCE sciencemag.org

Sornette and Favre *EPJ Nonlinear Biomedical Physics* (2015) 3:10
DOI 10.1140/epjnbp/s40366-015-0026-0

EPJ.org

EPJ Nonlinear Biomedical Physics
a SpringerOpen Journal

LETTER

Open Access

Debunking mathematically the logical fallacy that cancer risk is just "bad luck"

D. Sornette and M. Favre*

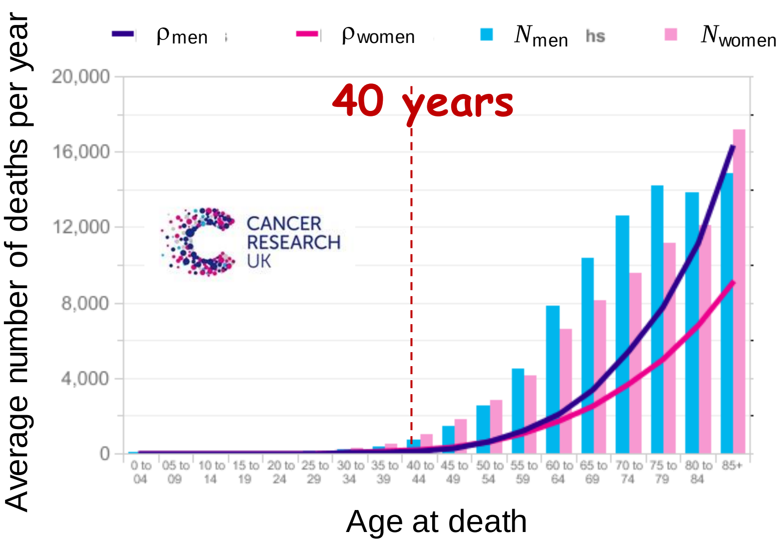
Peto's paradox

Hypothesis: the probability for presenting malignant cells depends on the number of cell divisions during the lifetime

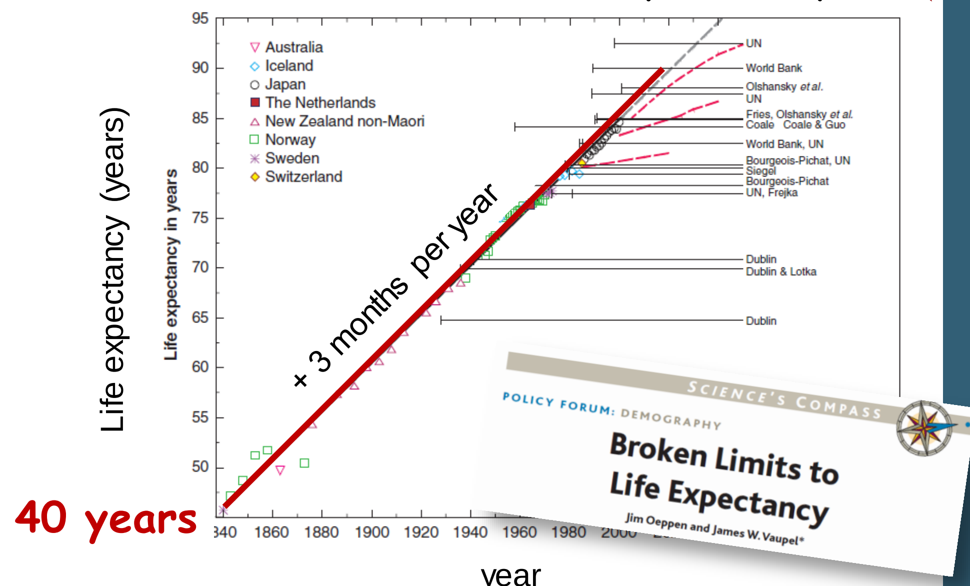
Corollary 1: longer the lifetime, larger the lifetime risk for a cancer…

True but…

In the United Kingdom
(all types of cancer included)



Evolution of the life expectancy



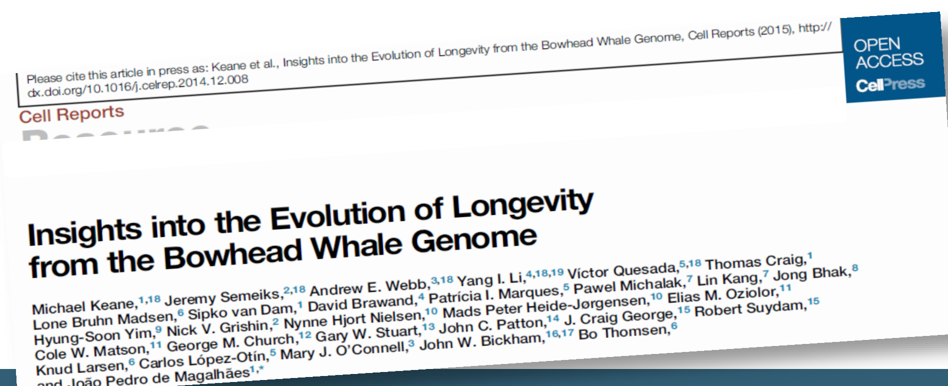
➢ **The probability does not linearly increase with the age…**

Peto's paradox

Hypothesis: the probability to observe a malignant cell depends on the cell division during the lifetime

Corollary: Bowhead whale should present much more cancers than humans

- Most likely live up to 250 years without cancer!
- Immune system 4 times more efficient!



Please cite this article in press as: Keane et al., Insights into the Evolution of Longevity from the Bowhead Whale Genome, Cell Reports (2015), http://dx.doi.org/10.1016/j.celrep.2014.12.008

OPEN ACCESS CellPress

Cell Reports

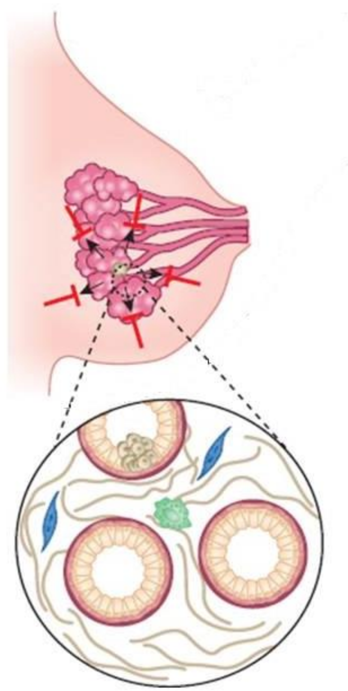
Insights into the Evolution of Longevity from the Bowhead Whale Genome

Michael Keane,[1,18] Jeremy Semeiks,[2,18] Andrew E. Webb,[3,18] Yang I. Li,[4,18,19] Víctor Quesada,[5,18] Thomas Craig,[1] Lone Bruhn Madsen,[6] Sipko van Dam,[1] David Brawand,[4] Patrícia I. Marques,[5] Pawel Michalak,[7] Lin Kang,[7] Jong Bhak,[8] Hyung-Soon Yim,[9] Nick V. Grishin,[2] Nynne Hjort Nielsen,[10] Mads Peter Heide-Jørgensen,[10] Elias M. Oziolor,[11] Cole W. Matson,[11] George M. Church,[12] Gary W. Stuart,[13] John C. Patton,[14] J. Craig George,[15] Robert Suydam,[15] Knud Larsen,[6] Carlos López-Otín,[5] Mary J. O'Connell,[3] John W. Bickham,[16,17] Bo Thomsen,[6] and João Pedro de Magalhães[1,*]

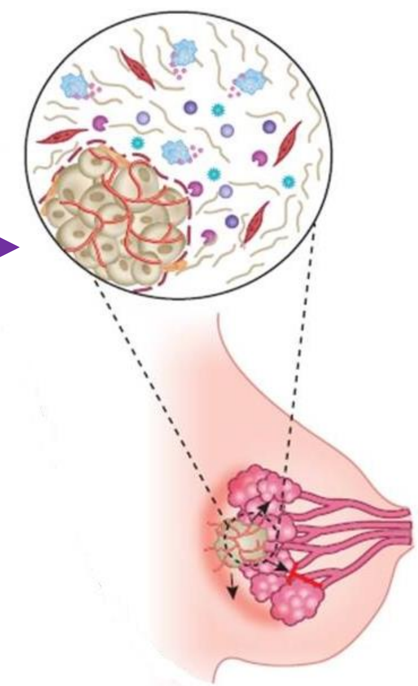
Role of the microenvironment

Hypothesis: the probability for presenting malignant cells depends on the number of cell divisions during the lifetime but diagnozing a tumor depends more on the **barriers in the microenvironment**

Corollary 3: the probability to initiate a cancer depends more on the status of the microenvironment than on the presence of malignant cells



Modification of the microenvironment




REVIEW

FOCUS ON CANCER

nature medicine

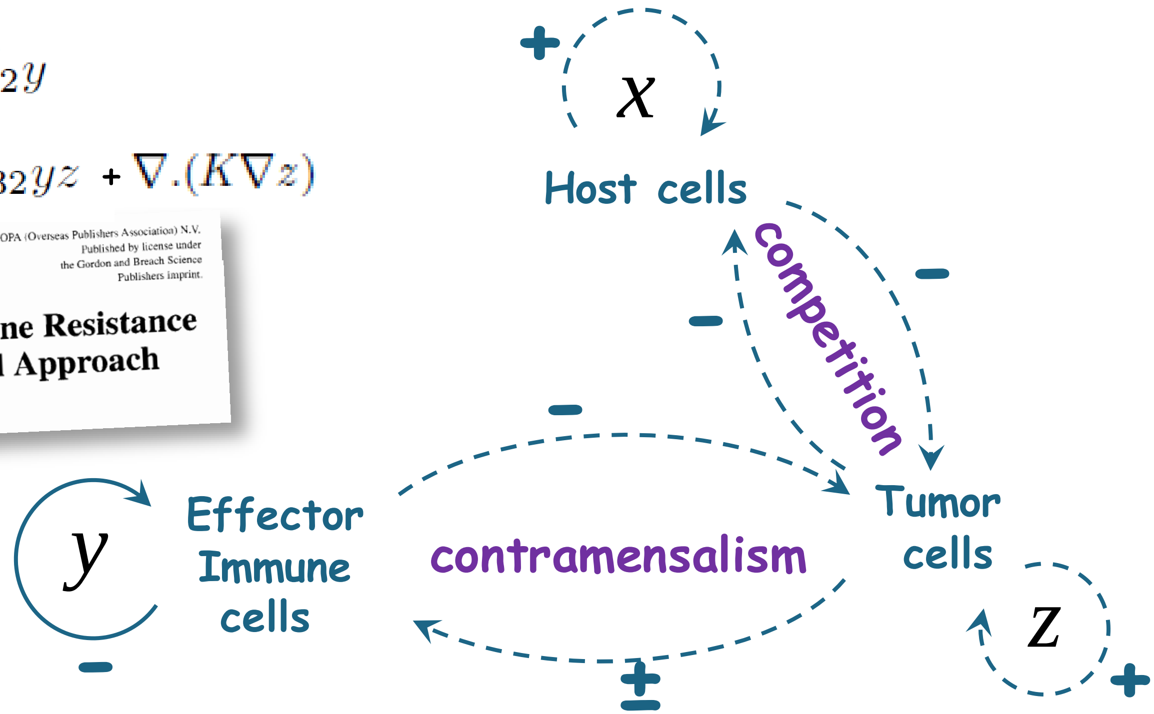
Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression

Mina J Bissell & William C Hines

A simple cancer model

Interactions between the populations of cells in a single tumoral site

$$\begin{cases} \dot{x} = \rho_1 x(1-x) - \alpha_{13} xz \\ \dot{y} = \dfrac{\rho_2 yz}{1+z} - \alpha_{23} yz - \delta_2 y \\ \dot{z} = z(1-z) - xz - \alpha_{32} yz + \nabla.(K\nabla z) \end{cases}$$



Journal of Theoretical Medicine, Vol. 3, pp. 79-100
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A Mathematical Tumor Model with Immune Resistance and Drug Therapy: an Optimal Control Approach

L.G. DE PILLIS[a,*,†] and A. RADUNSKAYA[b,‡]

OIKOS 77:2 (1996) 371

Contramensal interactions between species

Simon Hodge and Wallace Arthur, The Ecology Centre, Univ. of Sunderland, Sunderland, UK SR1 3SD.

Realistic parameter values?

Cancer origin	ID	Average doubling time (days)	Average doubling time (days)		Average doubling time (days)
Colons	SW480	5.4	3.4	x 100	391
	CaCO-2	[illegible]			
	SW620	3.2			
	Colo205	1.0			
	HCT-116				
Prostate	DU145	1.2	3.4	x 65	219
	PC-3	[illegible]			
Breast	HCC1954	1.3	5.6		152
	MDA-MB-468	1.3			
	MCF7	1.2			
	BT474	1.2			
	MDA-MB-231	1.2			
Skin	MM8.1	0.8	5.4		147
	A375	0.5			
	A375				
Lung	SNU-371	4.1	4.4	x 26	114
	H2126	[illegible]			
	SNU-1330	1.6			
	H1299	1.0			
	A549	0.9			

Citation: Cell Death and Disease (2012) 3, e411; doi:10.1038/cddis.2012.148

www.nature.com/cddis

Review

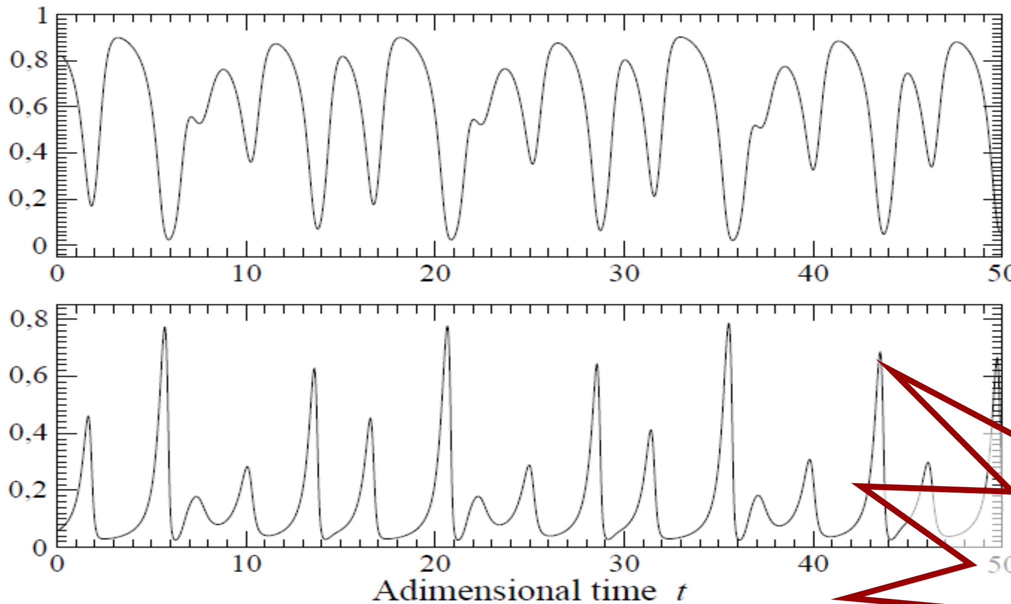
Mitosis-targeted anti-cancer therapies: where they stand

K-S Chan[1], C-G Koh[*,1] and H-Y Li[*,1]

Chaotic oscillations in this cancer model

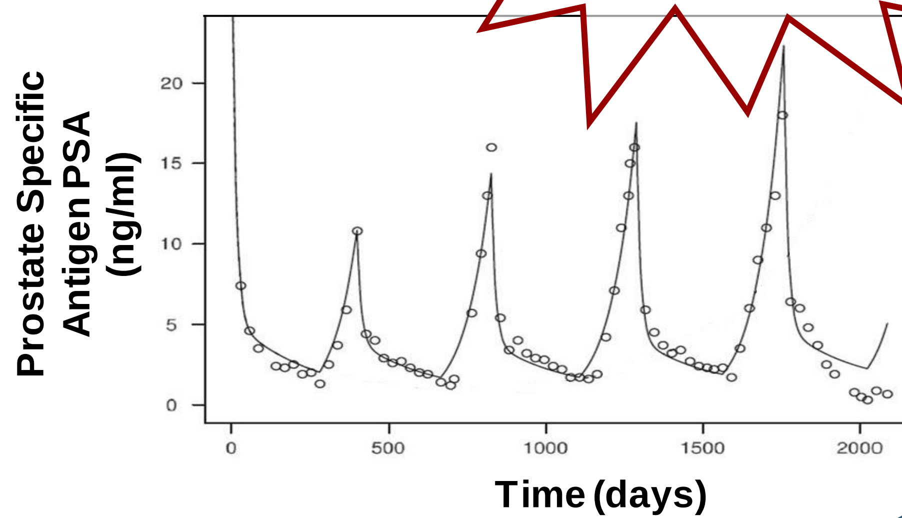
Host cells

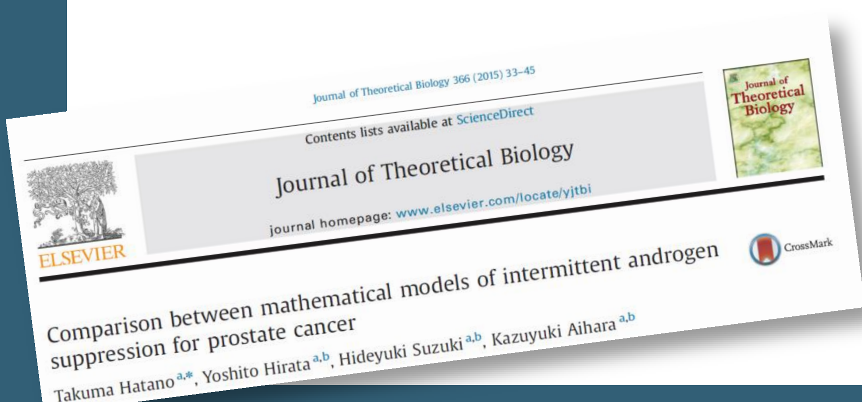
Tumor cells



Growth rate
ρ_x = 0.54

Oscillations in patients




Journal of Theoretical Biology 366 (2015) 33–45

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

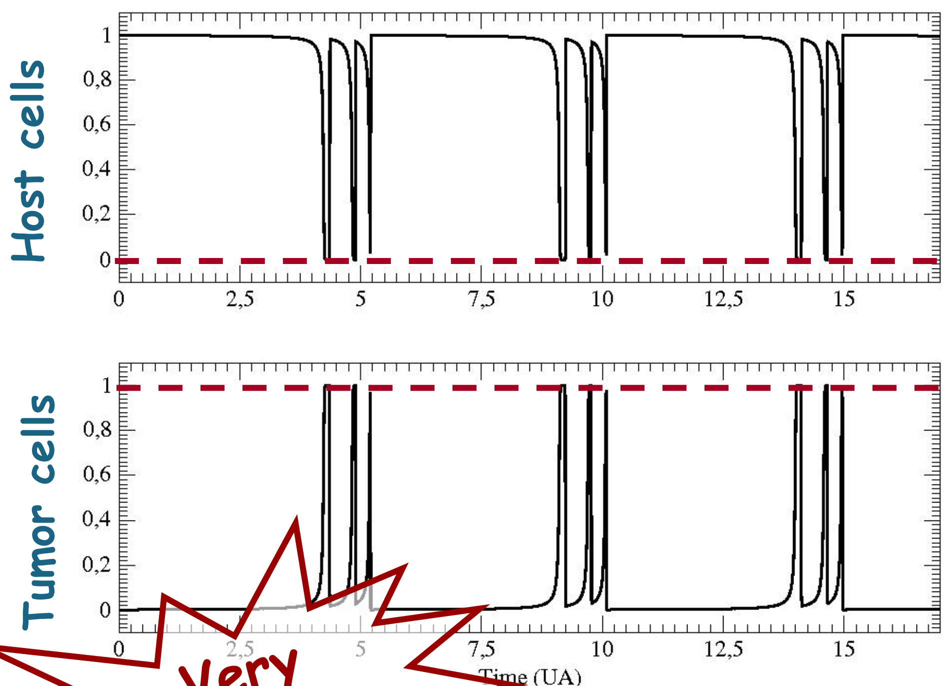
ELSEVIER

Comparison between mathematical models of intermittent androgen suppression for prostate cancer

Takuma Hatano [a,*], Yoshito Hirata [a,b], Hideyuki Suzuki [a,b], Kazuyuki Aihara [a,b]

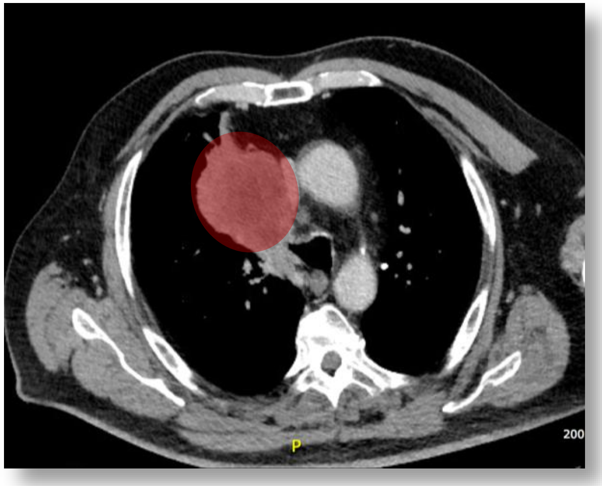
… but induces aggressive cancer

Growth rate ρ_1 =1.45



Very deleterous

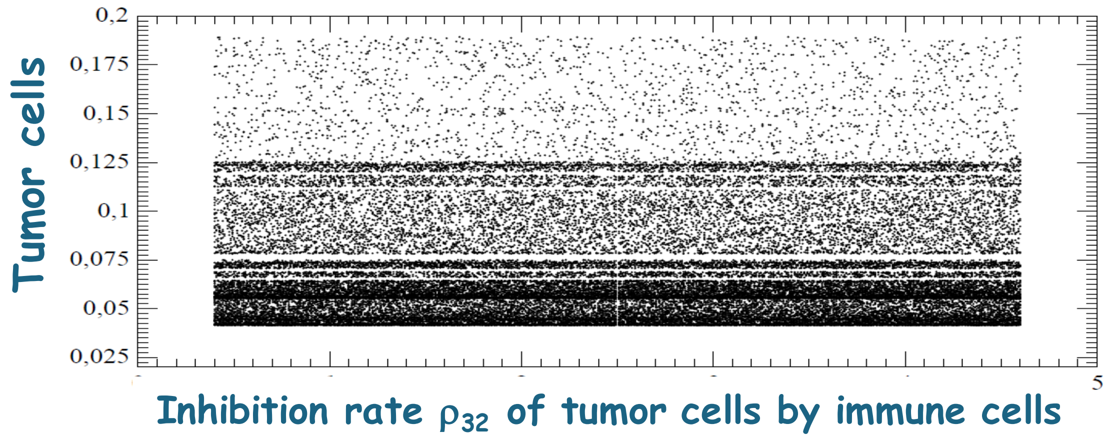
A clinical example



Man, 67 years
Smoker
Pulmonary adenocarcinoma

Role of immune cells

Influence of the inhibition of tumor cells by immune

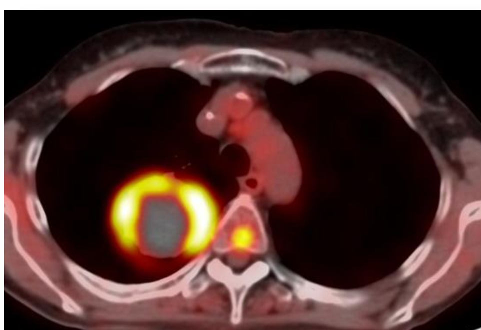


The action of immune cells does not affect the dynamics

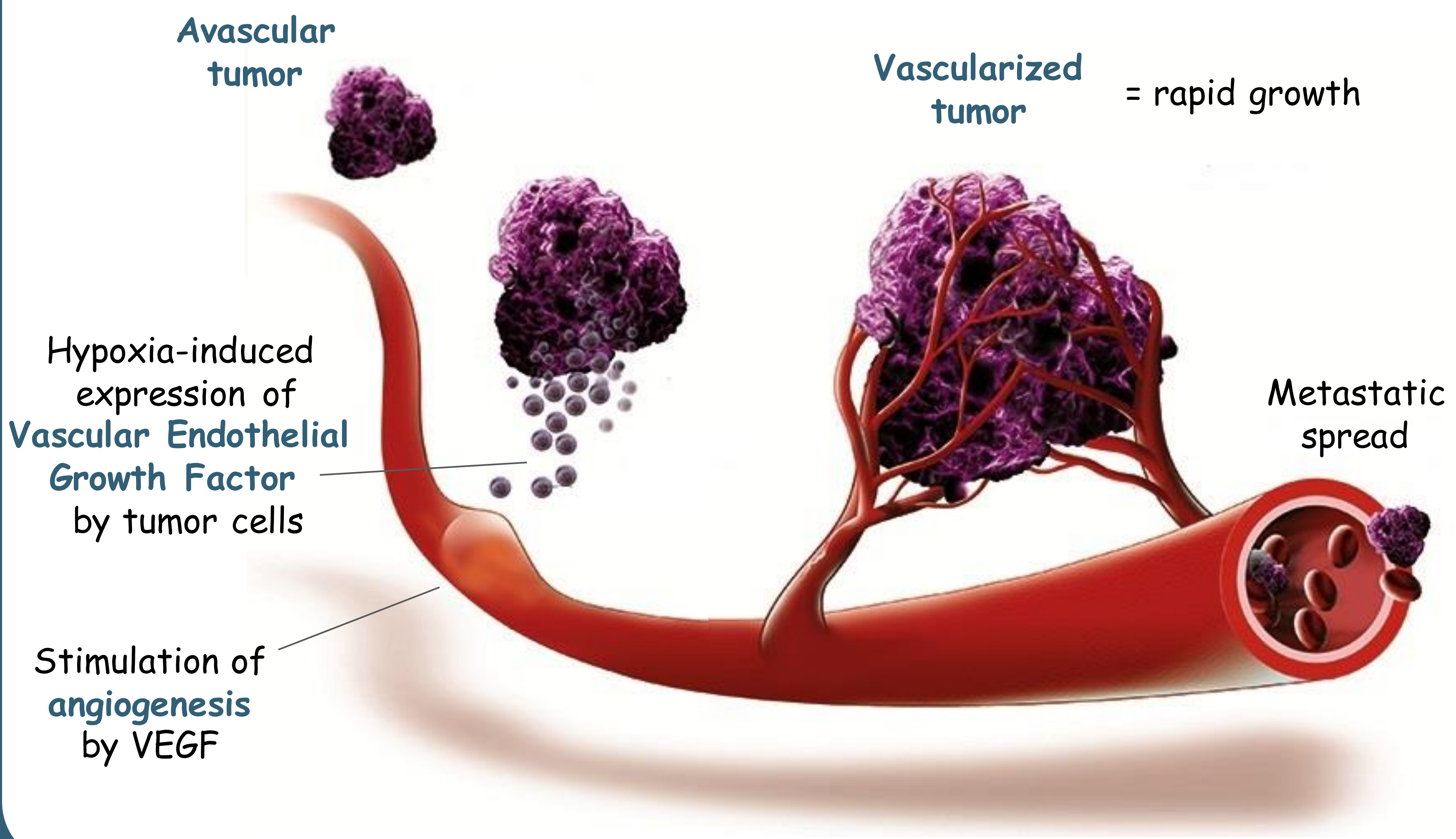
- Sometimes from a limited interest for a therapy

Anti PD-1 immunotherapy (Nivolumab)

Woman, 64 years
Smoker
Adenocarcinoma
with a bone metastasis



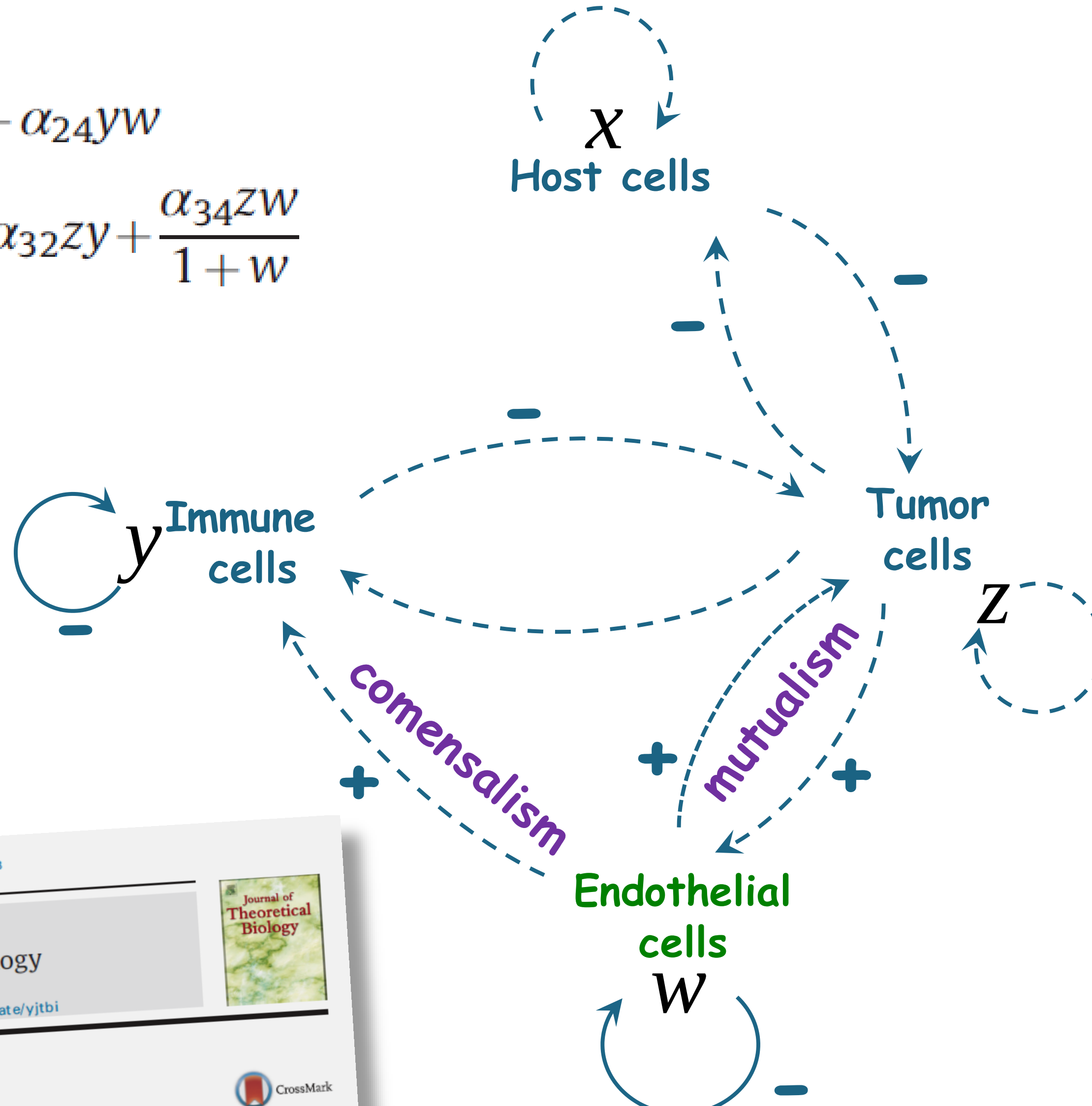
Tumor-induced angiogenesis

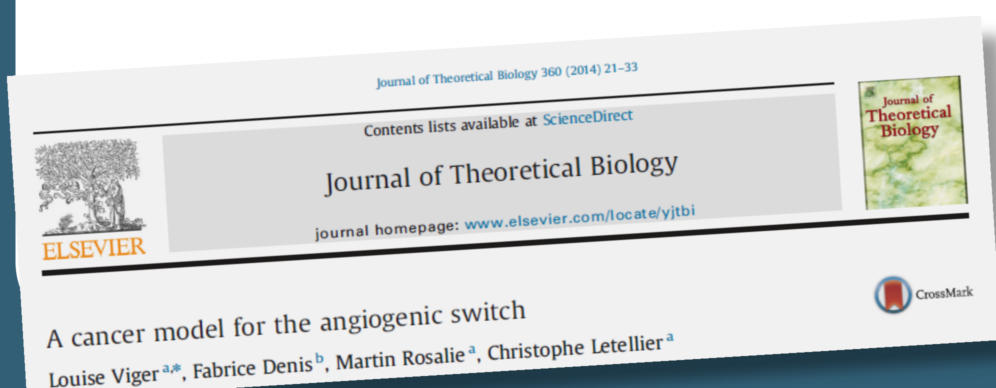


A cancer model for the angiogenic switch

$$
\begin{cases}
\dot{x} = \rho_1 x(1-x) - \alpha_{13} x z \\
\dot{y} = \dfrac{\rho_2 y z}{1+z} - \alpha_{23} y z - \delta_2 y + \alpha_{24} y w \\
\dot{z} = \rho_3 z(1-z) - \alpha_{31} z x - \alpha_{32} z y + \dfrac{\alpha_{34} z w}{1+w} \\
\dot{w} = \dfrac{\rho_4 w z}{1+z} - \delta_4 w
\end{cases}
$$

Cell interactions within a single tumoral site



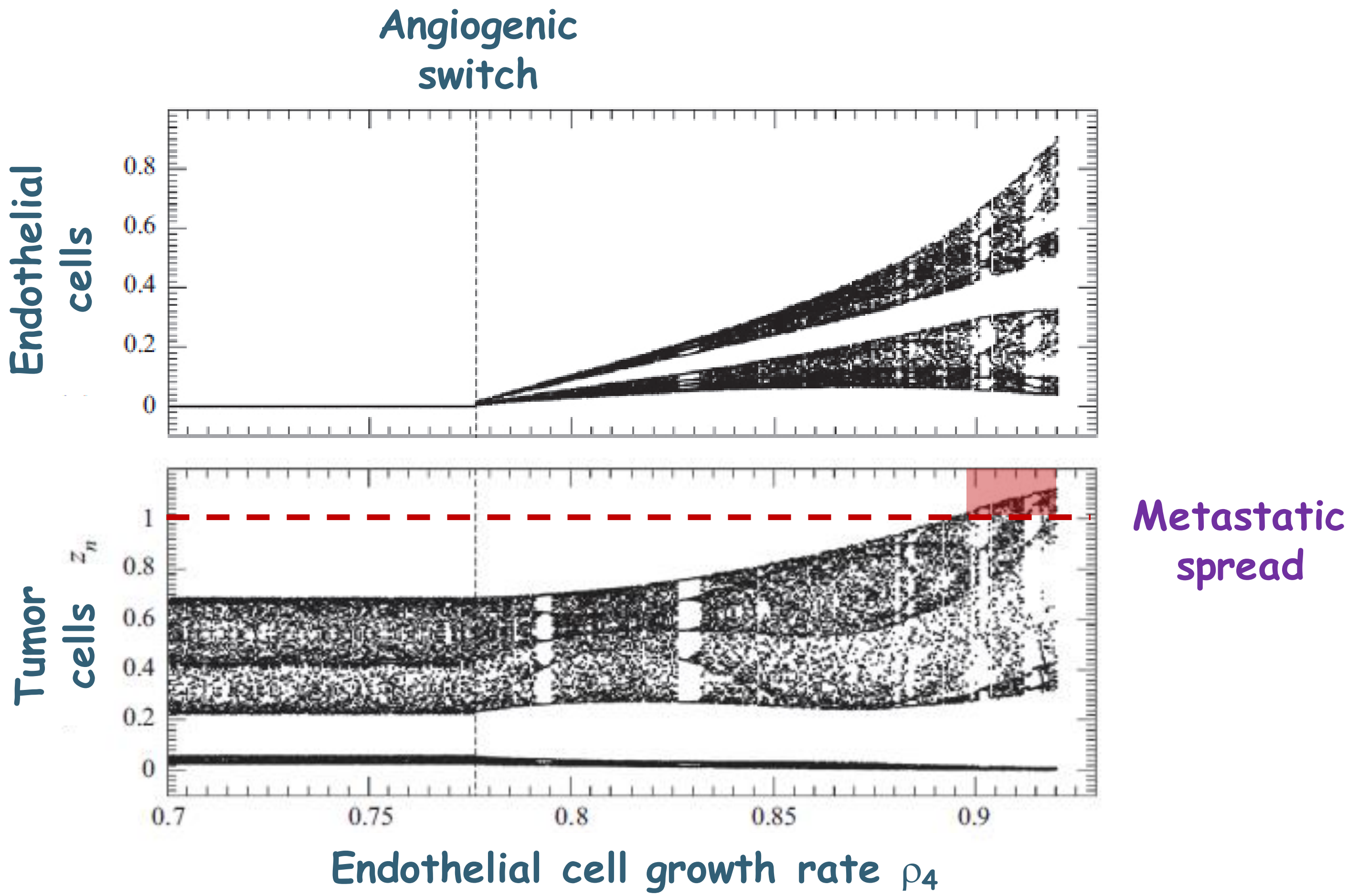


Journal of Theoretical Biology 360 (2014) 21–33
Contents lists available at ScienceDirect
Journal of Theoretical Biology
journal homepage: www.elsevier.com/locate/yjtbi

A cancer model for the angiogenic switch

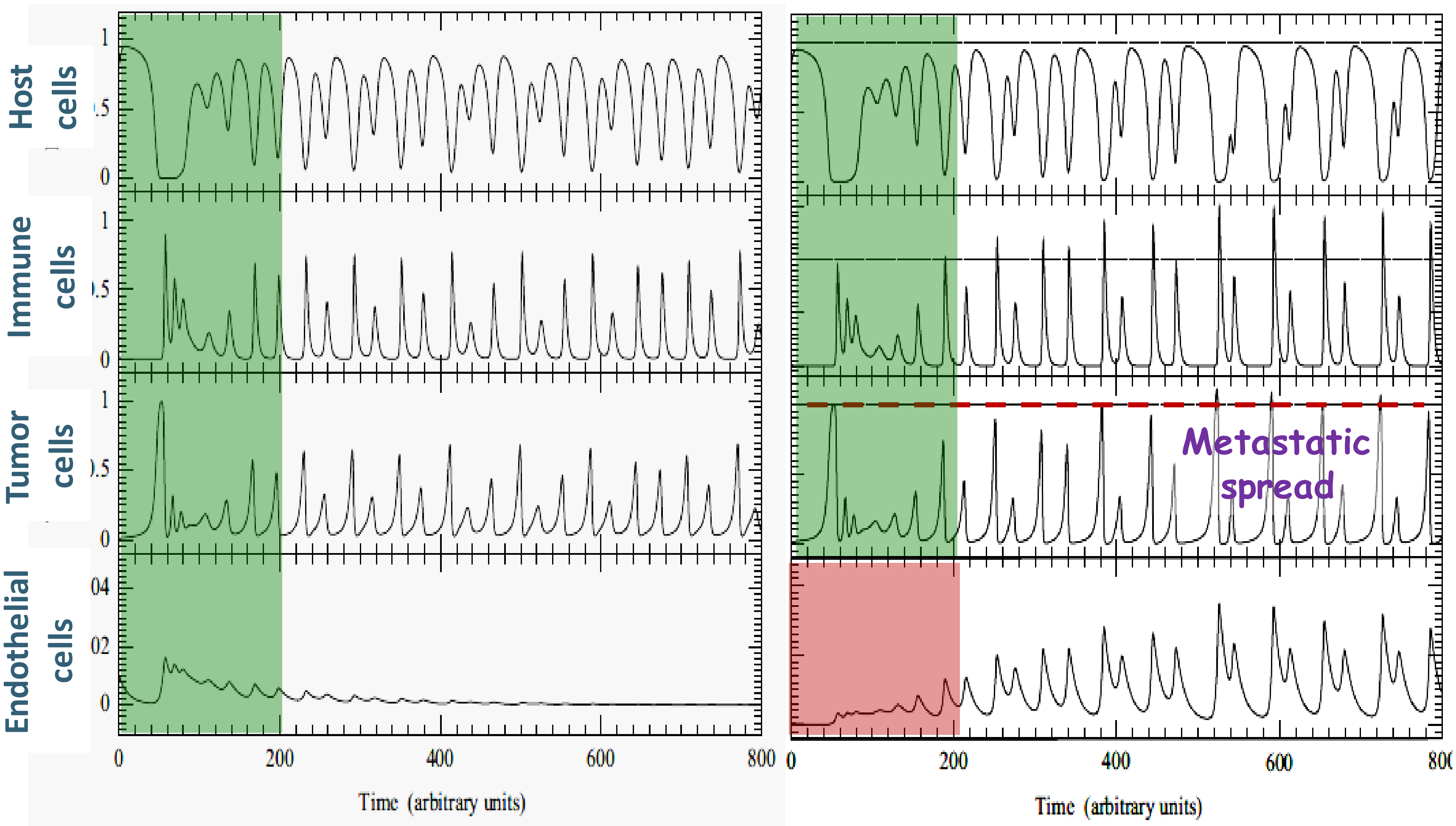
Louise Viger [a,*], Fabrice Denis [b], Martin Rosalie [a], Christophe Letellier [a]

A cancer model for the angiogenic switch



A cancer model for the angiogenic switch

- **Same** initial tumor
- **Different** values of the endothelial cell growth rate ρ_4



- Explain why a cancer evolution cannot be predicted

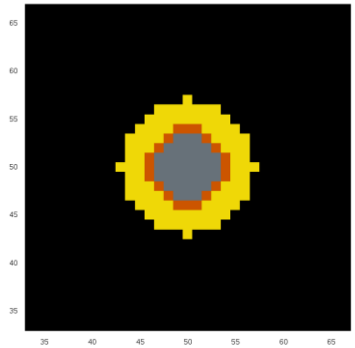
Spatial simulations of tumor growth

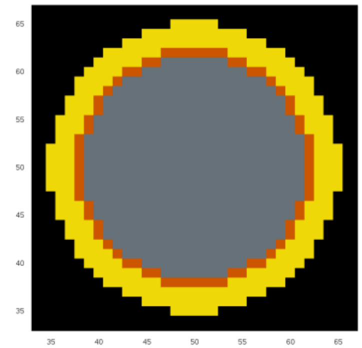
- Depends on the inhibition rate of immune cells by tumor cells

$\alpha_{yz} = 1.9$
$\varnothing_T \approx 1.3$ mm

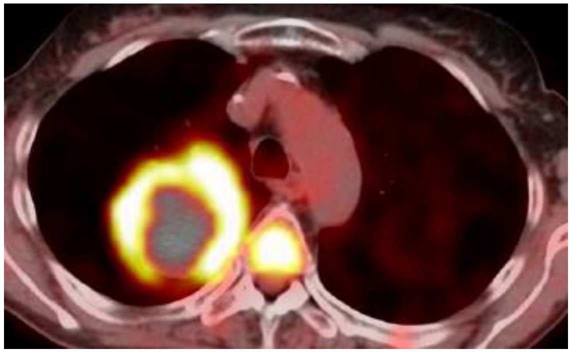
$\alpha_{yz} = 3.0$
$\varnothing_T \approx 2.9$ mm

Duration
6000 a.u.t.



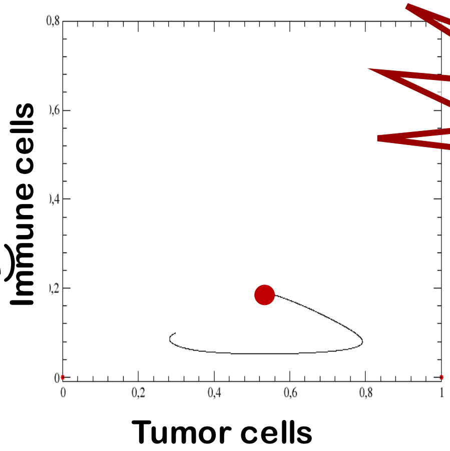


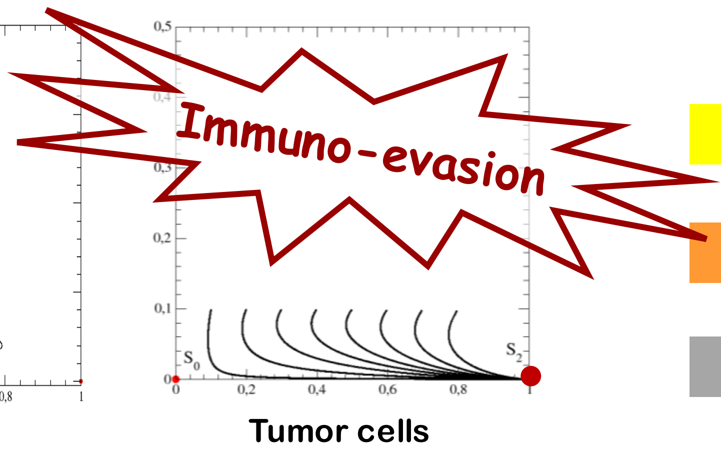
in the lung of a women



64 years, smoker, adenocarcinoma with a bone metastasis

Local
dynamics
(proliferation)





Proliferation

Quiescent

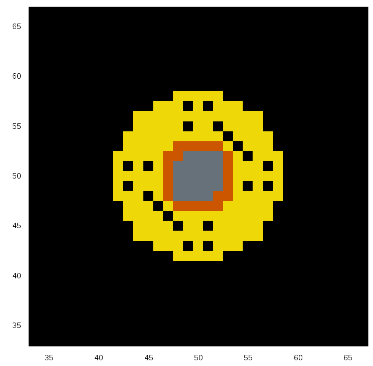
Necrotic

Spatial simulations of tumor growth

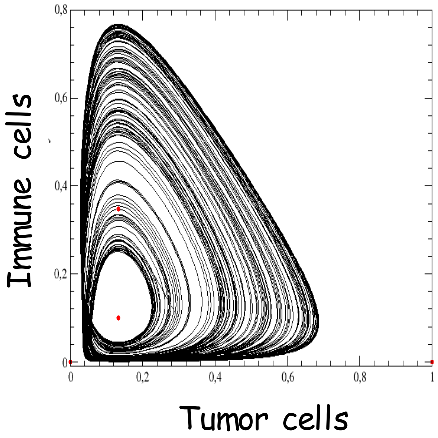
- The tumor growth depends on the inhibition rate of immune cells by tumor cells

Duration
74 800 a.u.t.

$\alpha_{yz} = 0{,}3015$
$\rho_y = 5{,}05$
$D \approx 1.7$ mm



Dynamics
in each site



Proliferation

Quiescent

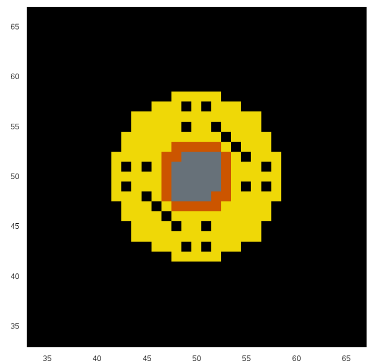
Necrotic

- **Chaotic dynamics in each site**
- **Very few sites have tumor cells**
- **Very slow tumor growth**

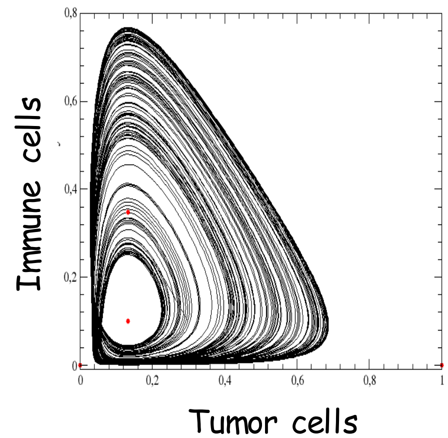
Spatial simulations of tumor growth

- When there is a local chaotic dynamics

t = 74 800 a.u.t.

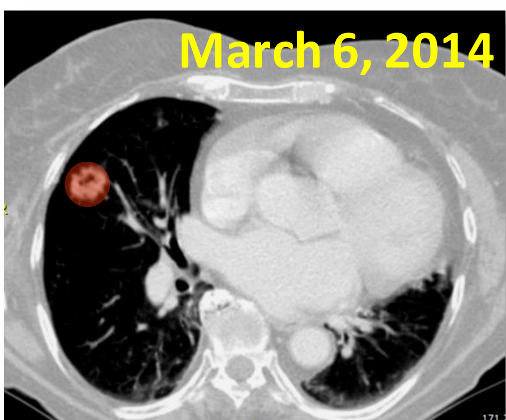


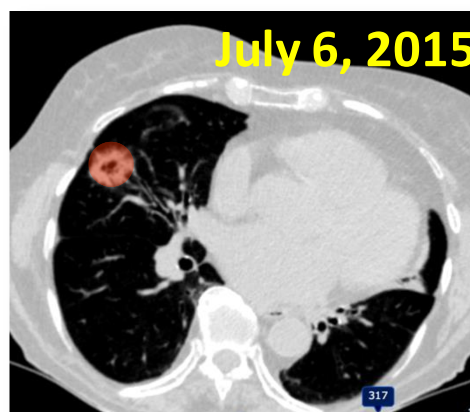
Local dynamics



- Heterogeneous
- Thick proliferation zone
- Very slow tumor growth

- Woman, 80 years, smoker up to 60 years, weakly evolutive nodule



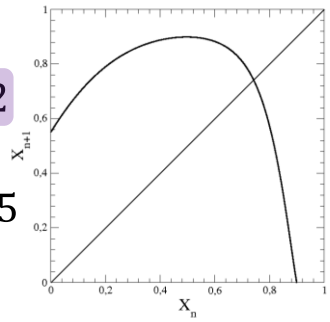


Adenocarcinoma

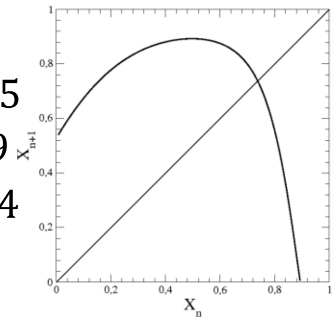
Dynamics more important than cell interactions

- Equivalent dynamics but different parameter values

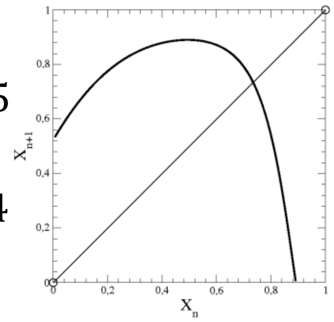
$\rho_x = 0{,}4862$
$\rho_y = 5{,}05$
$\alpha_{yz} = 0{,}3015$

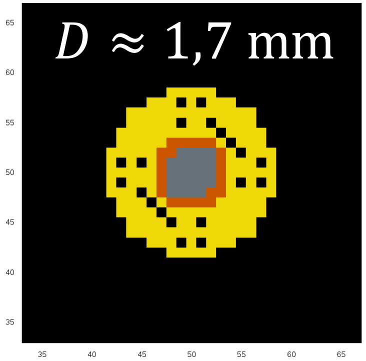


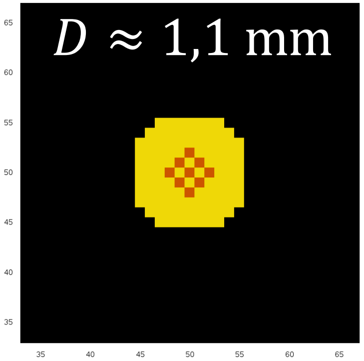
$\rho_x = 0{,}5015$
$\rho_y = 5{,}119$
$\alpha_{yz} = 0{,}624$

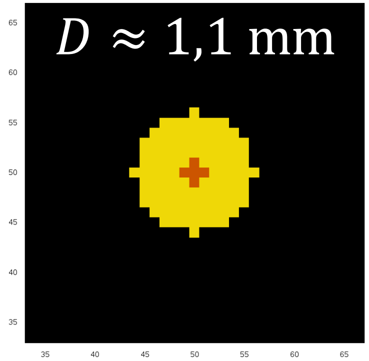


$\rho_x = 0{,}5015$
$\rho_y = 5{,}007$
$\alpha_{yz} = 0{,}504$









- **For equivalent dynamics, the host cell growth rate is the most influent parameter…**
- **Relevance of the micro-environment**

Why is observability so important?

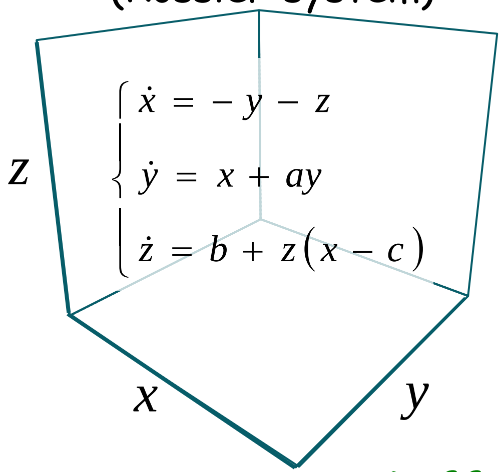
- The full description of the states of a system requires *a priori* the **knowledge of the full set of variables** spanning the state space

  - **Experimentally, only a few variables are measured…**
  - **Are we ensured by our ability to correctly define the states of the system?**

Conditions for a full observability

Original state space

(Rössler system)

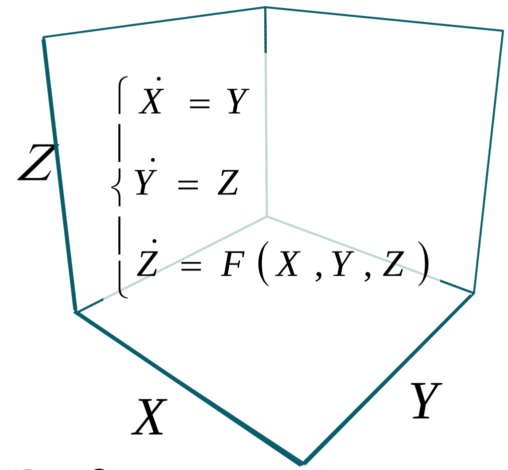


$$\begin{cases} \dot{x} = -y - z \\ \dot{y} = x + ay \\ \dot{z} = b + z(x - c) \end{cases}$$

Change of coordinates

$$\Phi_y = \left| \begin{array}{l} X = y \\ Y = \dot{y} = x + ay \\ Z = \ddot{y} = ax + \left(a^2 - 1\right)y - z \end{array} \right.$$

Differential embedding



$$\begin{cases} \dot{X} = Y \\ \dot{Y} = Z \\ \dot{Z} = F(X, Y, Z) \end{cases}$$

Diffeomorphic equivalence if **Det** $J_\Phi \neq 0$

$$\text{Det } J_{\Phi_y} = \text{Det} \begin{bmatrix} 0 & 1 & 0 \\ 1 & a & 0 \\ a & a^2 - 1 & -1 \end{bmatrix} = 1$$

This is the case of the Rössler system observed from variable $y(t)$

$\Rightarrow$ The system is thus **fully observable**

Observability from different variables

PHYSICAL REVIEW E 71, 066213 (2005)

Relation between observability and differential embeddi

Christophe Letellier,[1] Luis A. Aguirre,[2] and Jea

J. Phys. A: Math. Gen. 31 (1998) 7913–7927. Printed in the UK PII: S0305-4470(98)93312-1

On the non-equivalence of observables in phase-space reconstructions from recorded time series

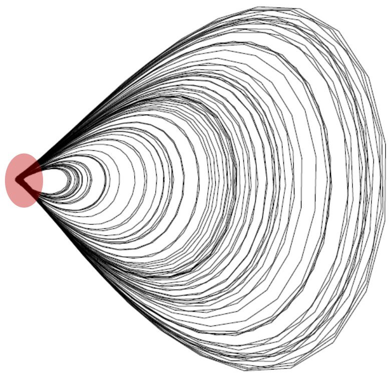
C Letellier†§, J Maquet†, L Le Sceller†, G Gouesbet† and L A Aguirre‡

PHYSICAL REVIEW E 79, 066210 (2009)

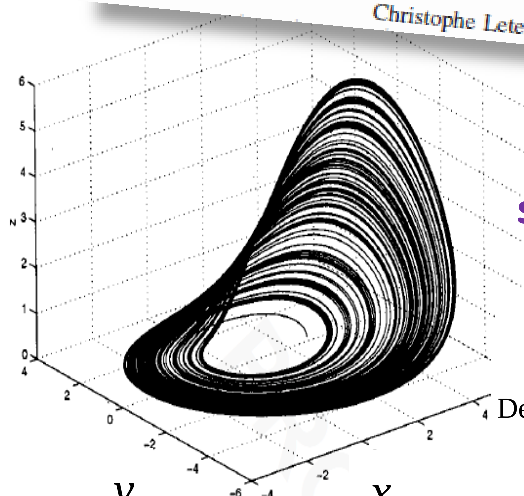
Symbolic observability coefficients for univariate and multivariate analysis

Christophe Letellier[1] and Luis A. Aguirre[2]

$$\mathrm{Det}\begin{bmatrix} 0 & 0 & 1 \\ z & 0 & x-c \\ b+2z(x-c) & -z & -y-2z+(x-c)^2 \end{bmatrix} = -z^2$$



$\delta_z = 0.44$ z



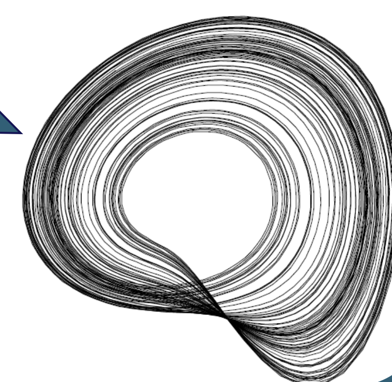
$$\mathrm{Det}\begin{bmatrix} 1 & 0 & 0 \\ 0 & -1 & -1 \\ -1-z & -a & c-x \end{bmatrix} = x-(a+c)$$

y x

$\delta_y = 1.0$

$$\mathrm{Det}\begin{bmatrix} 0 & 1 & 0 \\ 1 & a & 0 \\ a & a^2-1 & -1 \end{bmatrix} = 1$$

$\delta_x = 0.88$



Singular observability manifold

PHYSICAL REVIEW E **86**, 026205 (2012)

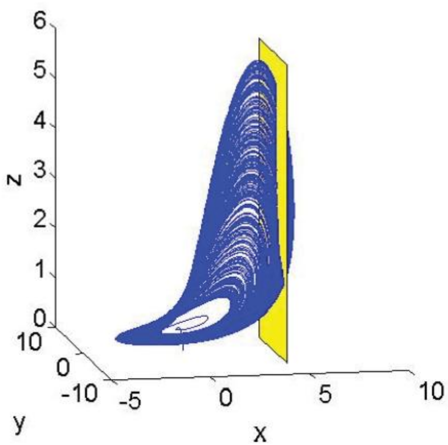
Influence of the singular manifold of nonobservable states in reconstructing chaotic attractors

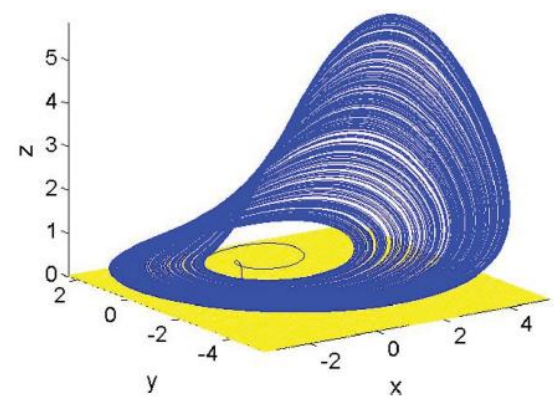
Madalin Frunzete,[1] Jean-Pierre Barbot,[1] and Christophe Letellier[2]

- Definition of a neighborhood to the singular observability manifold

$$\mathcal{U}_{\mathcal{M}_s^{\text{obs}}} = \{(x,y,z) \in \mathbb{R}^3 | \text{Det}\, \mathcal{J}_{\Phi_s}| < \epsilon\}$$

  - **Assessing the probability to have** $x \in \mathcal{A} \bigcap \mathcal{M}_s^{\text{obs}}$





$\mathcal{M}_x^{\text{obs}} = \{(x,y,z) \in \mathbb{R}^3 \mid x = a + c\}$ $\qquad$ $\mathcal{M}_y^{\text{obs}} = \emptyset$ $\qquad$ $\mathcal{M}_z^{\text{obs}} = \{(x,y,z) \in \mathbb{R}^3 \mid z = 0\}$

$\eta_x^{\mathcal{M}} = 0.86$ $\qquad$ $\eta_y^{M} = 1.00$ $\qquad$ $\eta_z^{\mathcal{M}} = 0.10$

Observability of a cancer model

Journal of Theoretical Biology 322 (2013) 7–16

Contents lists available at SciVerse ScienceDirect

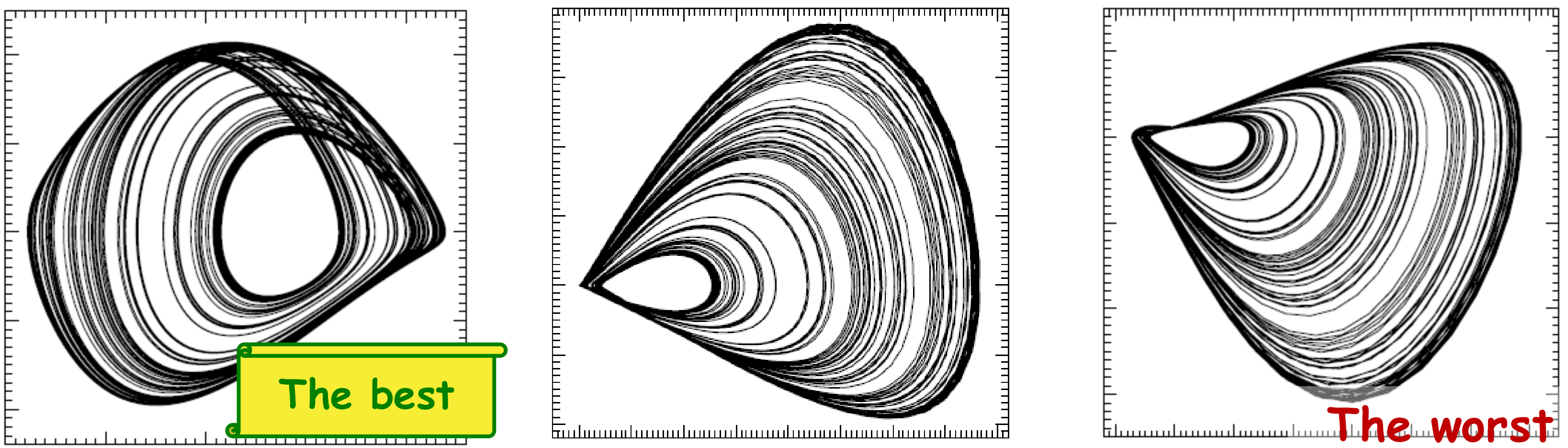
Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

What can be learned from a chaotic cancer model?

C. Letellier[a,*], F. Denis[b], L.A. Aguirre[c]

$$\eta_{x^3} = 0.56 \quad > \quad \eta_{z^3} = 0.36 \quad > \quad \eta_{y^3} = 0.30$$



Host cells | Tumor cells | Immune cells

It should be more efficient to track the environment
of the tumor rather than the tumor itself!

Lung Cancer

Non smoker | Smoker

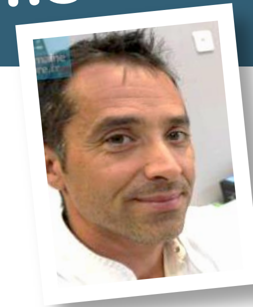
A follow-up weekly filled at home

Support Care Cancer
DOI 10.1007/s00520-013-1954-9

ORIGINAL ARTICLE

Detecting lung cancer relapse using self-evaluation forms weekly filled at home: the sentinel follow-up

Fabrice Denis · Louise Viger · Alexandre Charron · Eric Voog · Christophe Letellier



Fabrice Denis

Louise Viger

ILC Institut inter-régionaL de Cancérologie

- Rationale: since host cells provide the better observability of the tumor dynamics, could we track the environment of the tumor rather than the tumor itself ?

Environment = global state of the patient weekly self-evaluated

1. Weight
2. Lack of appetite
3. Fatigue
4. Pain
5. Cough
6. Breathlessness

- A cohort of 43 patients treated for a lung cancer

1. Pulmonary carcinoma (grade 3-4)
2. Internet access

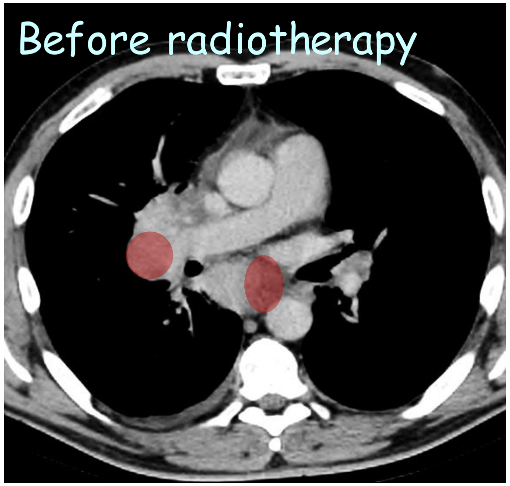
A follow-up weekly filled at home

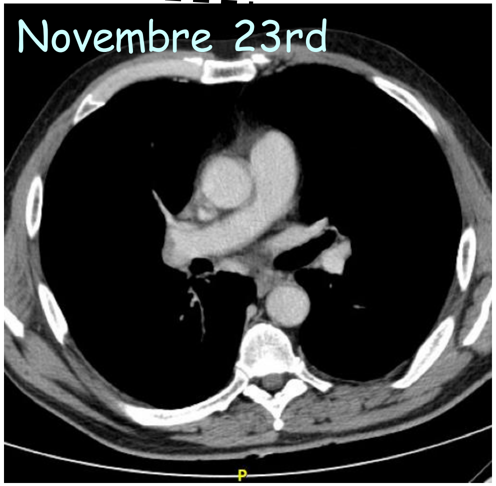
- Patient **with no relapse**

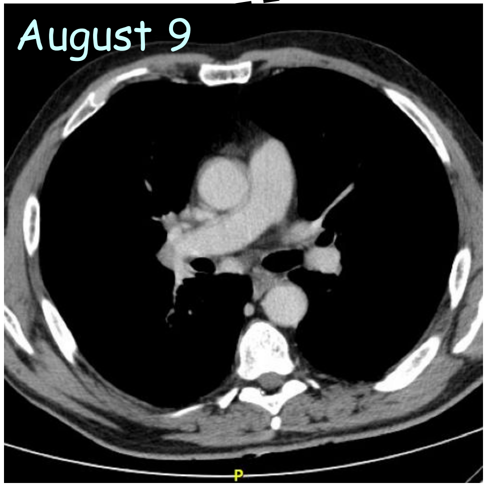
Man, 63 years
Smoker, 90 kg, non sporty
Treated by radiotherapy
Relapse probability = 75 %

jj|mm	23|11	30|11	07|12	15|12	21|12	28|12	04|01	11|01	18|01	25|01	02|02	08|02	15|02	22|02	01|03	08|03	15|03	22|03	29|03
aa	12	12	12	12	12	12	13	13	13	13	13	13	13	13	13	13	13	13	13
POIDS	89	89.5	90	91	91	92	92	91.5	91.5	91.5	91.5	91.5	91.5	91.5	92	92	92	93	93.5
DELTA POIDS	0	-0.5	-1	-2	-2	-3	-3	-2.5	-2.5	-2.5	-2.5	-2.5	-2.5	-2	-2	-1	-1	-1	-1.5
APPETIT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FAIBLESSE	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
DOULEUR	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TOUX	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ESSOUFFLEMENT	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
DEPRIME	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

jj|mm	05|04	12|04	19|04	26|04	03|05	10|05	17|05	24|05	31|05	07|06	14|06	21|06	28|06	05|07	13|07	19|07	26|07	02|08	09|08
aa	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
POIDS	93.5	94	95	95	95.5	96	95	95	95.5	95	95	95	96.5	97	97	96	96	97	95
DELTA POIDS	-2	-2.5	-3.5	-3.5	-4	-4.5	-3.5	-3	-3.5	-3	-2	-1.5	-3	-3	-2	-1	-0.5	-1	0
APPETIT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FAIBLESSE	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
DOULEUR	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TOUX	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ESSOUFFLEMENT	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
DEPRIME	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0





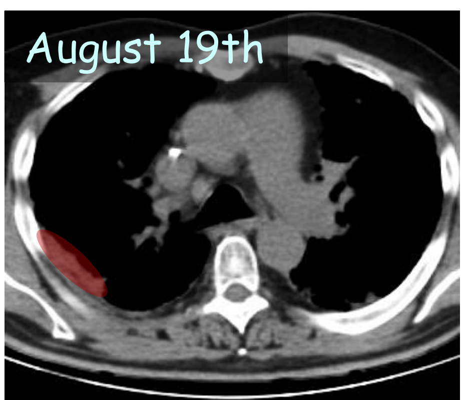


A follow-up weekly filled at home

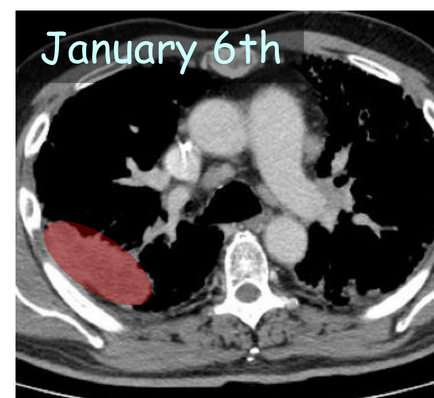
- Patient with **relapse**

Man, 65 years
Smoker, 86 kg, non sporty
Treated by chemiotherapy
Relapse probability = 75 %

jj|mm	19|08	26|08	02|09	09|09	19|09	23|09	30|09	07|10	14|10	21|10	28|10	04|11	11|11	18|11	25|11	16	[illegible]	12	06|01
aa	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	1	[illegible]	[illegible]	14
POIDS	86	86.9	87.2	86.9	87.2	87.4	87.8	87.5	87.9	88.1	88.1	87.7	87.5	88.3	87.5	86.2	86.6	85.8	86
DELTA POIDS	0	-0.9	-1.2	-0.9	-1.2	-1.4	-1.8	-1.5	-1.9	-2.1	-2.1	-1.7	-1.5	-1.4	-0.3	0.7	0.6	1.8	1.8
APPETIT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FAIBLESSE	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2
DOULEUR	0	1	1	0	0	1	1	0	0	1	0	1	0	0	2	3	3	3	3
TOUX	0	0	0	0	0	0	0	1	1	1	1	1	0	1	1	1	1	1	0
ESSOUFFLEMENT	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
DEPRIME	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1


August 19th

- 2 months before the routine scan


January 6th

A follow-up weekly filled at home

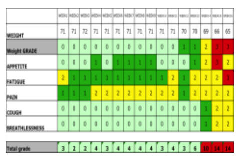
- Table of confusion

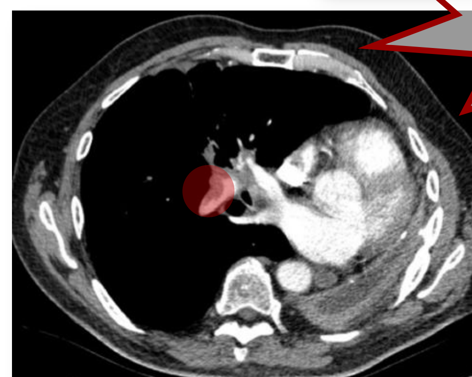
	Relapse	No relapse
Sentinel positive	13	3
Sentinel negative	0	25

Other diseases

jj|mm	24|03	30|03	07|04	13|04	22|04
aa	15	15	15	15	15
POIDS	92	92	92	90.5	86
DELTA POIDS	0	0	0	1.5	6
APPETIT	0	0	1	2	2
FAIBLESSE	0	1	2	2	1
DOULEUR	0	0	0	0	0
TOUX	0	0	0	0	0
Breathlessness	2	1	3	3	1
DEPRIME	0	0	1	1	0
FIEVRE	0	0	0	0	0
VISAGE	0	0	0	0	0
PEAU	0	0	0	0	0
VOIX	0	[illegible]	0	0	0
CRACHATS	0	[illegible]	[illegible]	0	0

Pulmonary embolism



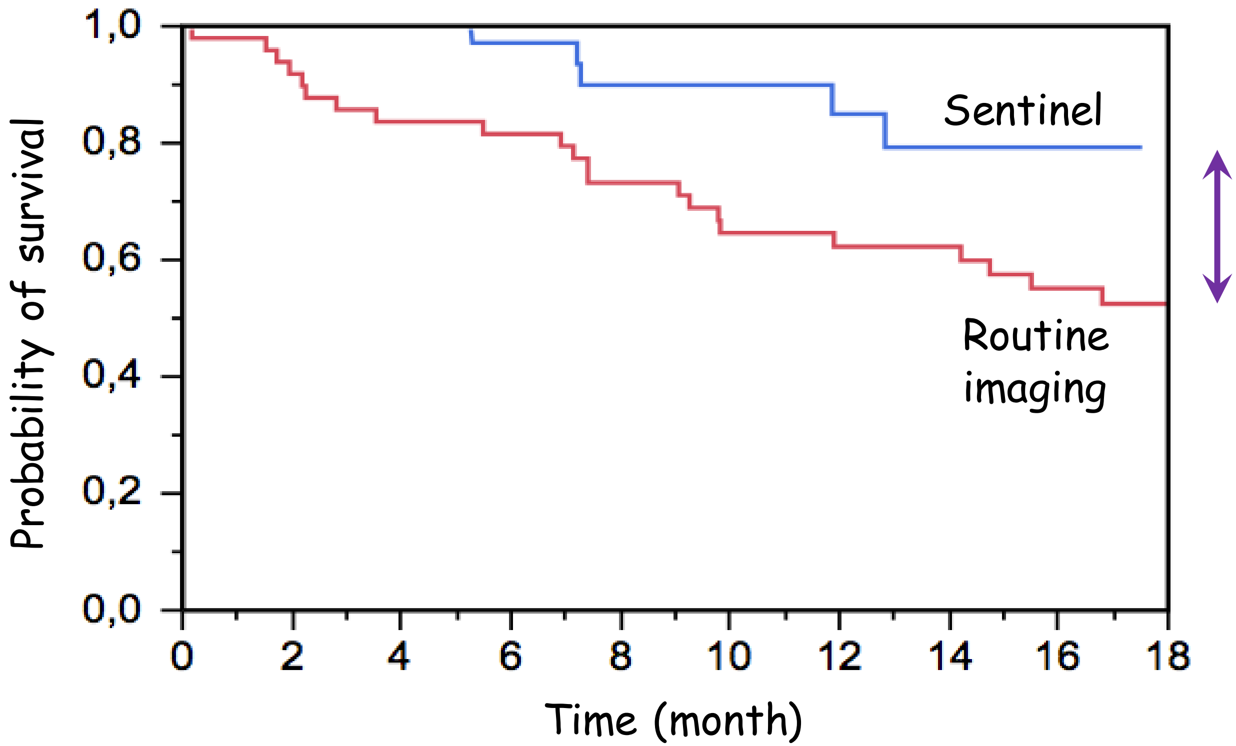


- Sensibility 100% 85%
- Spécificity 89% 96%

- **Detection of cancer relapse advanced by five weeks with respect to the routine scan…**
- **Reliability equivalent to a routine follow-up!**

A follow-up weekly filled at home

- First study (phase II) : survival curve



- **More than 20% gained at 18 months…**
- **Cancer relapse treated earlier (5 weeks), better life quality (less stressed, less pain, …)**

A follow-up weekly filled at home

Le Mans. Cancer du poumon : un logiciel capable de détecter les rechutes

Cancer du poumon : les atouts de l'autosurveillance

Un questionnaire hebdomadaire permet de détecter les rechutes plus précocement que le scanner, selon des travaux français

Sandrine Cabut

Des systèmes simples d'autosurveillance peuvent-ils améliorer le suivi de patients atteints de cancers, comme c'est déjà le cas pour des maladies chroniques telles que l'hypertension artérielle et le diabète ?

L'expérience semble en tout cas concluante dans le domaine des tumeurs du poumon, selon les données d'une équipe française. Une étude pilote menée par le docteur Fabrice Denis (cancérologue au Mans et chercheur associé à l'université de Rouen) auprès de 43 malades conclut qu'un autocontrôle hebdomadaire de six paramètres cliniques (poids, fatigue, perte d'appétit, douleur, essoufflement, toux) est un outil fiable de surveillance des cancers du poumon.

Cette stratégie a même permis de repérer des rechutes en moyenne six semaines plus tôt que les examens d'imagerie programmés (scanner ou tomographie à émission de positons), soulignent les auteurs dans un article publié le 1er septembre en ligne dans la revue Support Care Cancer.

En France, les cancers du poumon représentent plus de 40 000 nouveaux cas par an et environ 30 000 décès. Le suivi après traitement, qui n'est pas standardisé, repose sur des consultations tous les trois à six mois, avec examen clinique et analyses complémentaires, en particulier d'imagerie. La survenue d'une perte de poids ou d'autres signes tels une toux, un essoufflement ou des douleurs peut témoigner d'une rechute, mais n'amène pas forcément les malades à consulter, même si ces signes sont sévères.

Cinq signes cliniques

Dans une première étude, les chercheurs français ont sélectionné cinq signes cliniques fréquents, que les patients ont cotés chaque semaine de 0 à 3 selon leur intensité. L'éventuelle perte de poids était également mesurée : 1 pour une perte de 1 kg, 2 pour 2 kg... Les résultats étaient transmis à l'équipe médicale et lui ont permis d'élaborer un algorithme d'alerte.

« *Nos données suggèrent que les symptômes cliniques sont plus sensibles que le scanner*, résume le docteur Denis. *Nous n'avons pas la preuve que cette stratégie dynamique, que nous avons appelée "sentinel", peut améliorer le pronostic en cas de rechute. Mais ce suivi personnalisé est rassurant pour les patients, et simple à mettre en œuvre puisqu'il ne nécessite qu'un accès Internet.* »

Une analyse partagée par les principaux intéressés. « *Il suffit d'aller sur un site, de taper son code et de remplir le questionnaire. Au total, cela prend moins de cinq minutes par semaine et permet d'être en liaison plus étroite avec le médecin, c'est un atout* », témoigne ainsi Alain Maillard, qui a participé à l'étude.

Depuis, l'équipe a encore amélioré les performances de son test, en incluant au total douze paramètres. Les résultats d'une deuxième étude sont en cours de publication. Fabrice Denis et ses collègues proposent désormais cette autosurveillance systématiquement à leurs patients et espèrent bientôt rencontrer les autorités de santé pour les convaincre de son utilité.

« *Nous prévoyons de mener des essais avec une approche comparable pour des cancers dans d'autres localisations : œsophage, vessie, côlon-rectum, ovaire. A ce stade, nous cherchons à valider les symptômes les plus pertinents* », précise Fabrice Denis.

Une analyse économique du système sentinel est en cours. Globalement, le déploiement de la santé mobile (m-santé) pourrait générer jusqu'à 11,5 milliards d'euros d'économies en France d'ici à 2017, selon une estimation récente du cabinet d'audit PriceWaterhouseCooper. ■

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

American Society of Clinical Oncology 2013 Top Five List in Oncology

Lowell E. Schnipper, Gary H. Lyman, Douglas W. Blayney, J. Russell Hoverman, Derek Raghavan, Dana S. Wollins, and Richard L. Schilsky

3. Avoid using PET or PET-CT scanning as part of routine follow-up care to monitor for a cancer recurrence in patients who have finished initial treatment to eleminate the cancer unless there is high-level evidence that such imaging will change the outcome.

Conclusion

- Based on a deterministic model describing cell interactions, we showed that the micro-environment is relevant for **understanding tumor dynamics**

- We are already able to reproduce **qualitatively** some clinical facts

- **Chaotic** local dynamics provide **strong barriers** against tumor growth

- Tracking the environment rather than the tumor is as reliable (if not more) as a routine imaging
  - Randomized study (phase III) in progress (and very promising)

WORLD SCIENTIFIC SERIES ON NONLINEAR SCIENCE Series A Vol. 00

Series Editor: Leon O. Chua

CHAOS IN NATURE

Christophe Letellier

World Scientific