Developing Mathematical Models in Cancer Biology: Some Personal Reflections

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(Note to self: learn PowerPoint this summer...)

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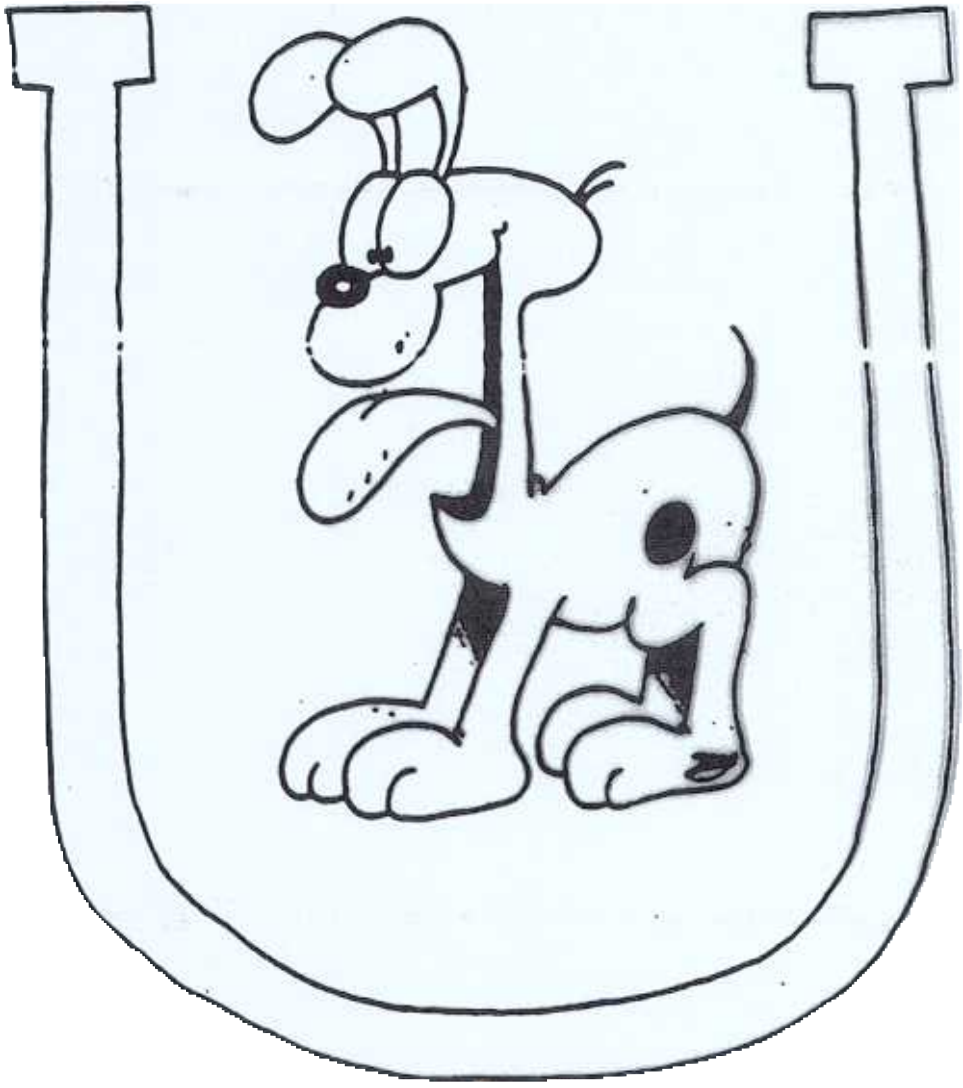


SUMMARY

Pertinent Quotes (well, I think so)

What is a Mathematical Model? (comments on its nature and methodology)

Categories of Tumor Models

Important considerations for realism in Tumor Modeling

Totally inadequate comments about Catastrophe Theory

A "Toy" Model for Tumor/Immune System Interaction based on Catastrophe Theory

So what's Quantum Mechanics got to do with it? An even more speculative metaphor…

Mathematical Modeling according to The Far Side (time permitting)

"As in many hierarchies of scientific models, the virtues of a simpler theory can, under the right circumstances, outweigh its vices."

Raymond L. Lee, Jr., and Alistair B. Fraser, in

The Rainbow Bridge: Rainbows in Art, Myth, and Science

"It is better to have an approximate answer to the right question than an exact answer to the wrong one"

- John Tukey

"The purpose of models is not (necessarily) to fit the data, but to sharpen the questions..."

S. Karlin, 1983

"The careful use of models holds as much promise as the careless use holds danger. The difference between realizing the promise and encountering the danger lies in genuine acknowledgement of limitations and productive interplay of knowledge and imagination, of discipline and adventure, of seriousness and humor."

A. Rescigno & J.S. Beck, 1972

"...This model will be a simplification and an idealization, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge."

A.M. Turing, 1953

What *is* a mathematical model?

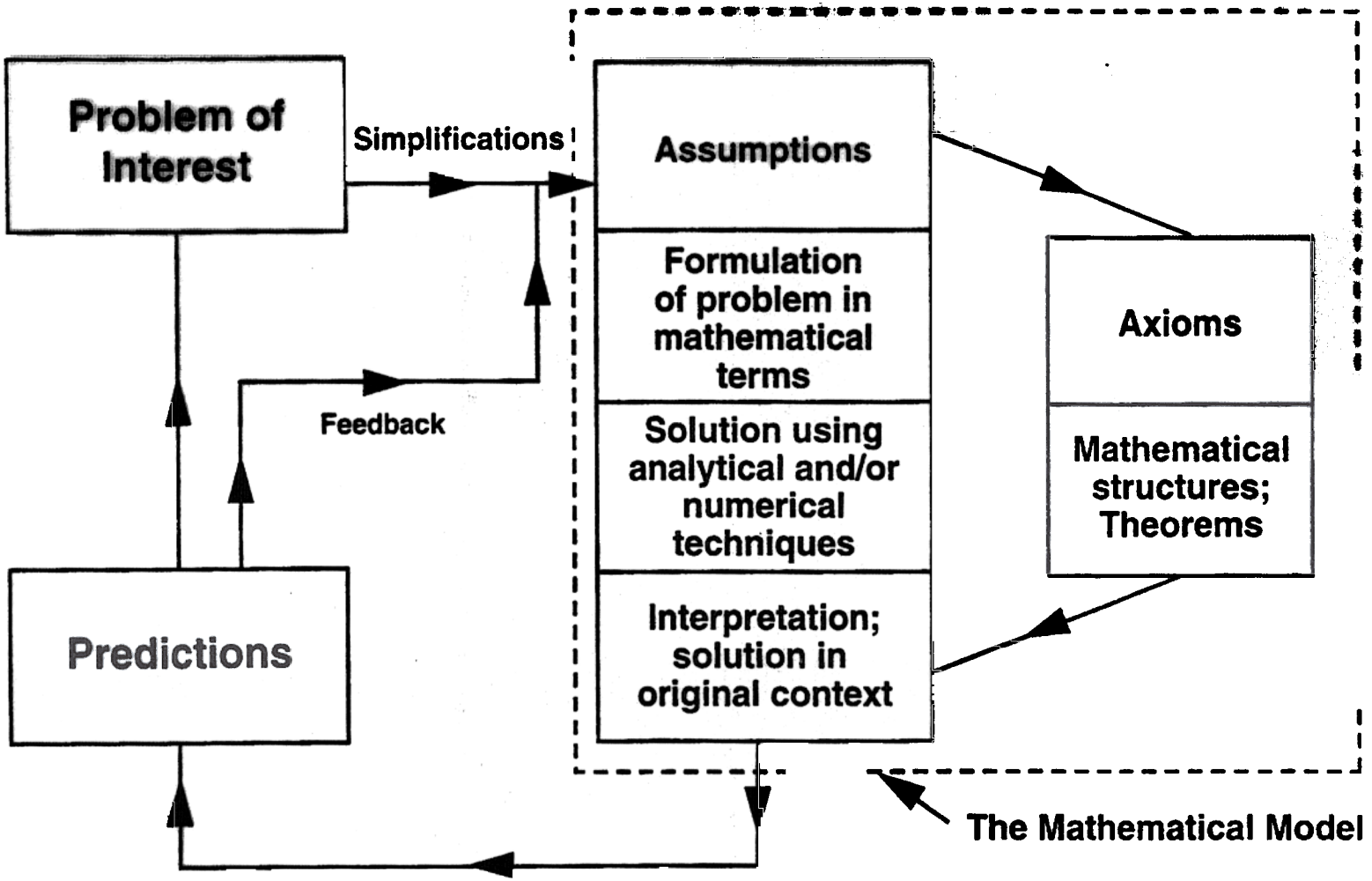
The formulation in mathematical terms of the assumptions and their consequences believed to underlie a particular "real world" problem.

The aim of mathematical modeling is the practical application of mathematical models to help unravel the underlying mechanisms involved in biological (or other) processes.

Common pitfalls include the indiscriminate, naive or uninformed use of models, but when developed and interpreted thoughtfully, mathematical models can

(i) provide insight into the nature of the problem;
(ii) be useful in interpreting data; and
(iii) stimulate experiments.

Figure 1


Problem of Interest
Simplifications
Assumptions
Formulation of problem in mathematical terms
Solution using analytical and/or numerical techniques
Interpretation; solution in original context
Axioms
Mathematical structures; Theorems
Feedback
Predictions
The Mathematical Model

The art of good modeling relies on

(i) a sound understanding and appreciation of the biological problem;

(ii) a realistic mathematical representation of the important biological phenomena;

(iii) finding useful solutions, preferably quantitative ones, and

(iv) biological interpretation of the mathematical results - insights, predictions, etc.

There is not necessarily a "right" model; obtaining results which are consistent with observations is only a first step and does not imply that the model is the only one that applies, or even that it is "correct".

Furthermore, mathematical descriptions are not *explanations*, and never on their own can they provide a complete solution to the biological problem – often there may be complementary levels of description possible within the particular scientific paradigm.

Collaboration with biologists is needed for realism and help in modifying the model mechanisms to reflect the biology more accurately.

On the other hand, workers in the biological sciences (for example) need to appreciate what mathematics (and its practitioners) can and cannot do! (The mathematician needs to do the educating here; good communication is necessary.)

The mathematics is dictated by the biology and not, in general, vice versa, however tempting that may be! Sometimes the mathematics used can be very simple. The usefulness of a mathematical model should not be judged by the sophistication of the mathematics, but by different (and no less demanding) criteria.

Some categories of tumor models

(selected)

"Demographic": - exponential, logistic, Gompertz, generalized logistic

Diffusion: - "generic", deterministic (time evolutionary)

Reaction-diffusion: - angiogenesis, vascularization, invasion

"Elasticity": - invasion, classification

"Speculative/metaphorical": -

Can we usefully think about cancer in different terms?

(See references in "A Survey of Models for Tumor-Immune System Dynamics", Adam, Bellomo, Eds.)

- Mechanical/Pressure Effects
- Oxygen Distribution
- Nutrient Distribution
- Generalized Growth Inhibitor Distribution
- Destructive Enzyme Action
- Metabolic Activity
- Blood Vessel and Capillary Distribution
- Cell Adhesiveness
- pH
- Immune System Response
- Growth Inhibition due to Radiation Treatment

What is a tumor?

According to Greller et al. (Invasion & Metastasis, **16**:177-208;1996):

A tumor is an assembly of cellular subpopulations exhibiting diverse traits at several levels of biological organization:

genetic, phenotypic, cellular, physiological

Cellular heterogeneity:

genotypic, phenotypic, spatial, temporal

Includes variable patterns of:

gene expression, enzymatic activity, cell surface properties, metabolic control, hormonal dependencies, tissue invasiveness, metastatic competencies, host immune responses, resistance to treatment modalities

PROGRESSION:

an aggregate phenomenological property

an irreversible qualitative change in one or more characters of the neoplastic cells

"...different from a mere extension in space and time without qualitative change..."

(Foulds,L., 1954, Cancer Research,**14**:327-339)

does not necessarily correlate uniformly with actual elapsed chronological time

"indicates development of a tumor by way of permanent, irreversible qualitative change in one or more of its characters" (Foulds)

We therefore identify "**progression state**" with "**degree of malignancy**"

WHAT CHARACTERISTICS "DEFINE" CANCER AS A DISEASE?

- a tumor's exploitation of cellular heterogeneity, vis-a-vis

increasing growth autonomy

loss of proliferative constraints

invasion of neighboring tissues

aquisition of metastatic potential

Certain phenotypic traits in tumor cells appear to be primarily progression-driven, as opposed to growth-driven, e.g.

drug resistance

genetic instability

invasiveness

metastatic potential

The following are probably more growth-driven:

tumor mass and growth rate

vascularization

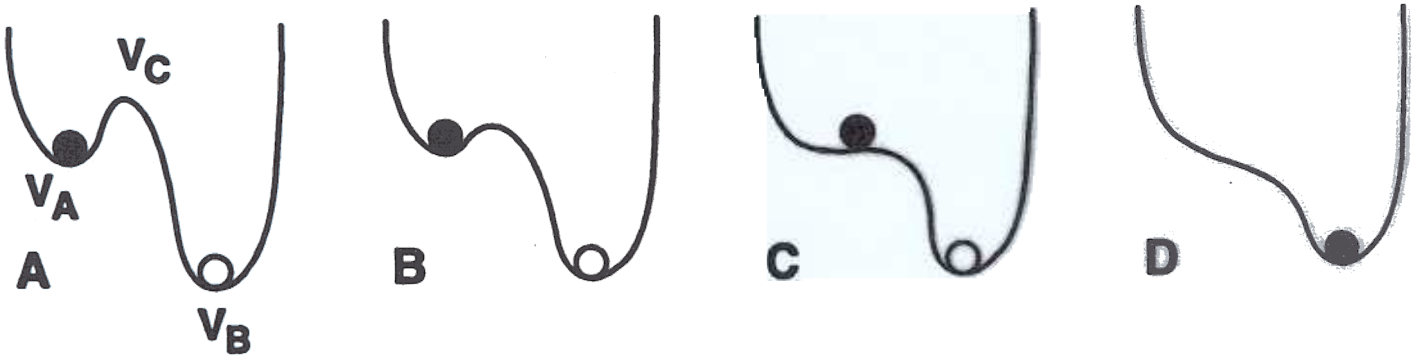
For a mechanistic or physical model, frequently there exists a direct connection between the system of interest and its mathematical representation (e.g. struts and springs vs. catastrophe theory)

For a metaphor, no such connection may be known, though the system behavior may well imply its existence. Surely this applies to some biological systems…

Are there any intermediate levels of description?

May one such level for studying aspects of cancer growth and remission be found in *catastrophe theory*?

Figure 6



Catastrophe Theory

(with apologies to Rene Thom and Christopher Zeeman)

- **The phenomenon of interest is assumed to be governed by a potential function of some kind: here $V = V(a,b;x)$ with control parameters *a* and *b***

- **For the cusp catastrophe, $V = \frac{1}{4}x^4 + \frac{a}{2}x^2 + bx$**

- **Stable states are regarded as minima of *V***

- **More than one such state may be accessible to the system: normal/cancerous, benign/malignant, good prognosis/bad prognosis**

- **Changing the control parameters *a* and *b* may alter the form of *V* so as to change the positions, relative heights or total number of local maxima**

- **The cusp catastrophe exhibits *bimodality, discontinuity, hysteresis, divergence***

Figure

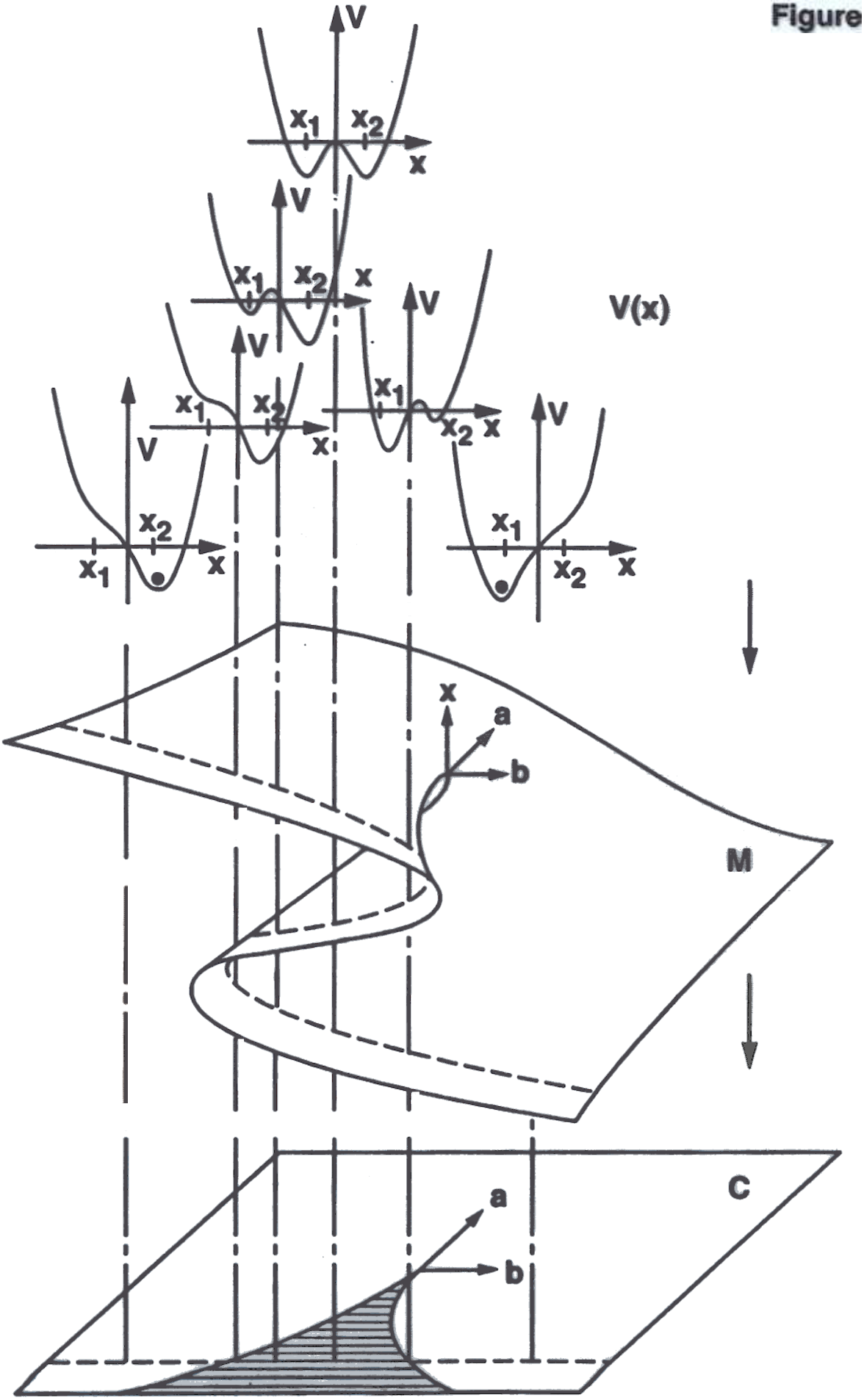


Figure 7c

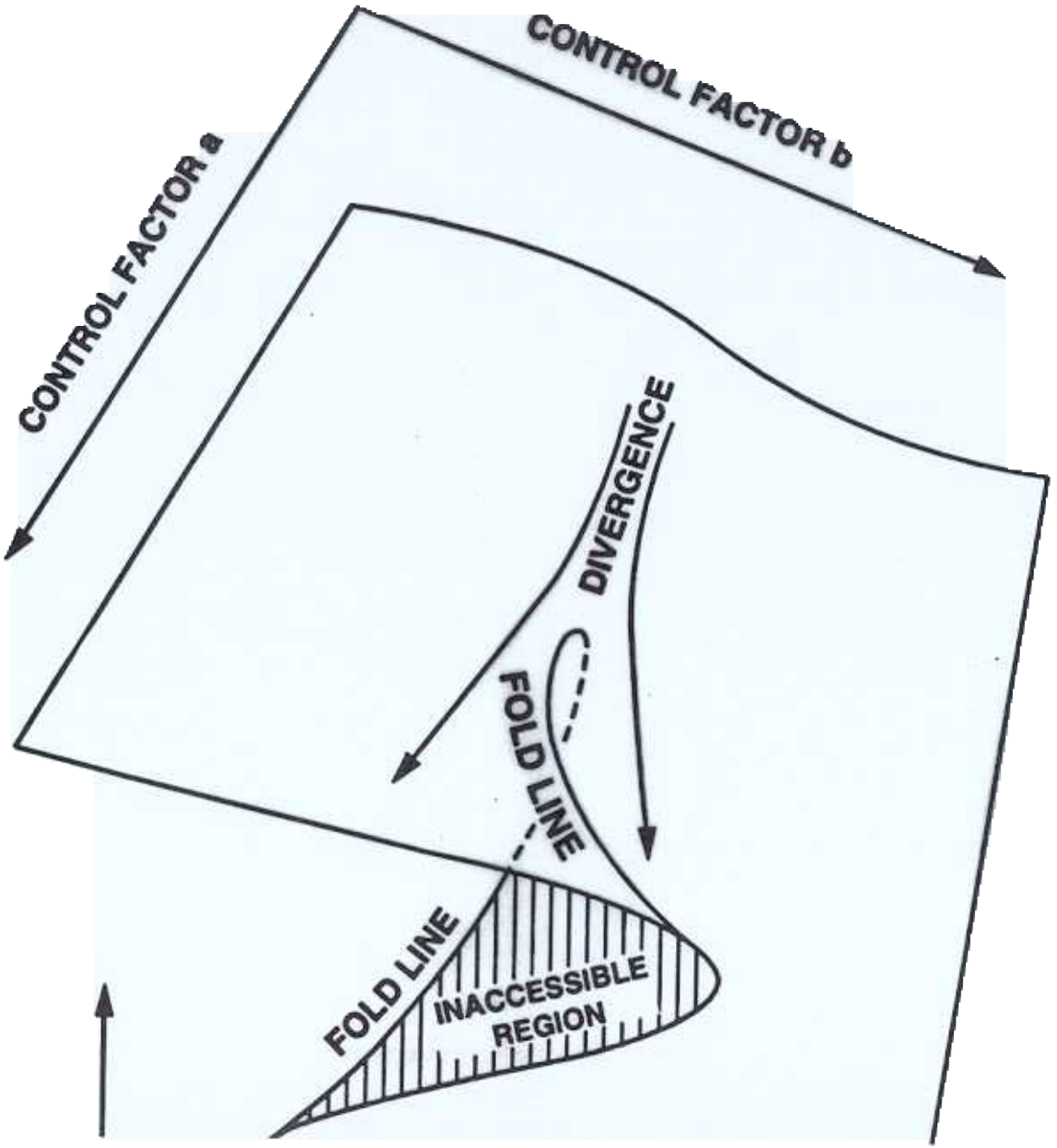
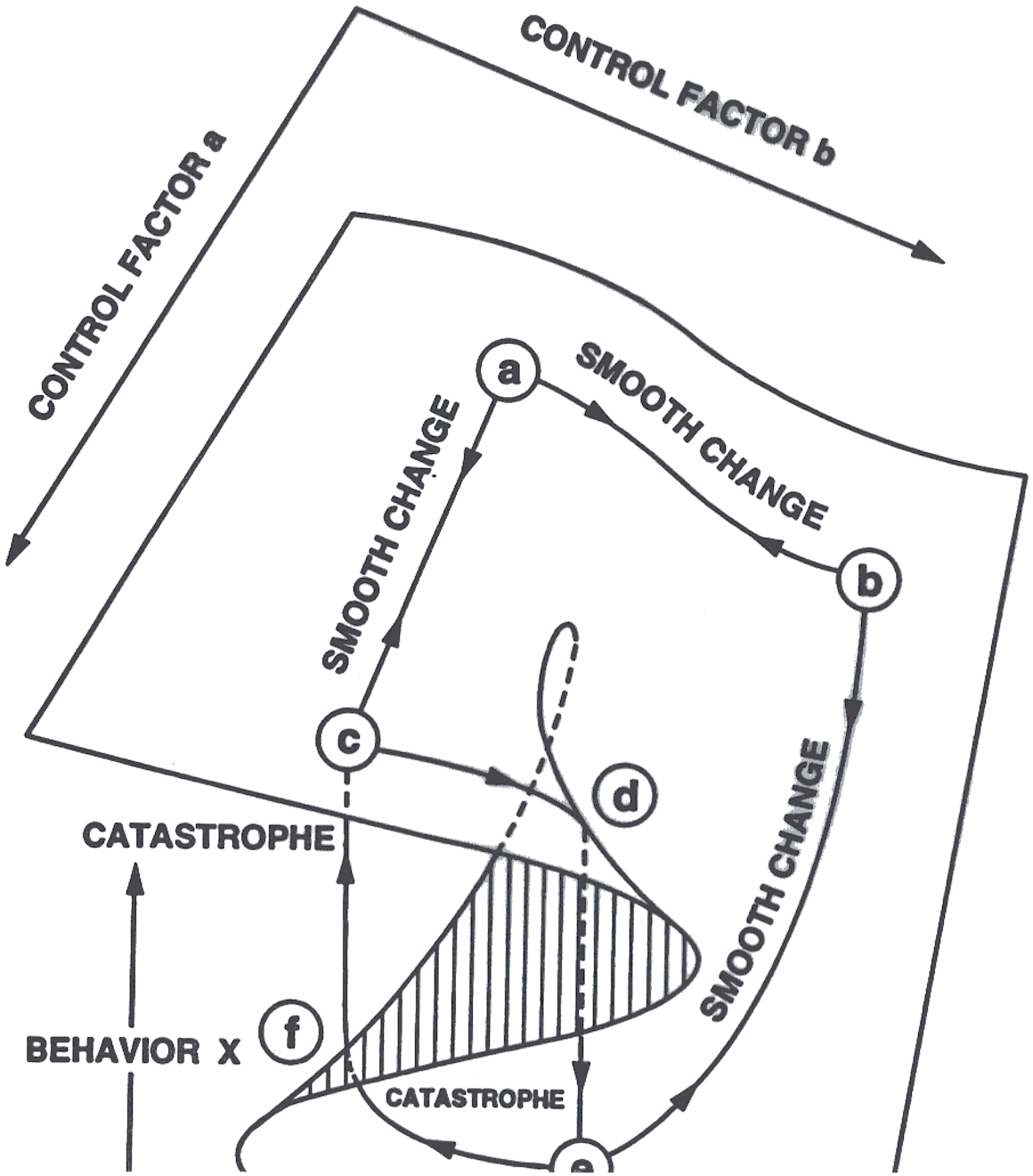

CONTROL FACTOR b
CONTROL FACTOR a
DIVERGENCE
FOLD LINE
FOLD LINE
INACCESSIBLE
REGION

Figure 7b


CONTROL FACTOR b
CONTROL FACTOR a
a
SMOOTH CHANGE
SMOOTH CHANGE
b
c
d
CATASTROPHE
SMOOTH CHANGE
BEHAVIOR X
f
CATASTROPHE
e

Introduction: *a toy model of immune system/cancer interaction*:

In dimensionless form the governing ODE is

$$\frac{dx}{dt} = \alpha + x(1 - \theta x) - \frac{\beta x}{1 + x}$$

where α, β and θ^{-1} are respectively measures of the mutation rate of normal cells to neoplastic cells, the efficiency of the cell-mediated immune response to the presence of tumor cells (x = cell number), and the local saturation limit for cancer cells.

Steady states of the system are defined by

$$-\theta x^3 + (1 - \theta)x^2 + (1 + \alpha - \beta)x + \alpha = 0$$

or in canonical form

$$+ aX + b = 0$$

where

$$X = x - x_c, \qquad x_c = \frac{1 - \theta}{3\theta}$$

$$a = -3x_c^2 - \left(\frac{1 + \alpha - \beta}{\theta}\right)$$

$$b = -2x_c^3 - x_c\left(\frac{1+\alpha-\beta}{\theta}\right) - \frac{\alpha}{\theta}$$

The **cusp catastrophe surface** is defined by

$$\boldsymbol{X} = X(a,b)$$

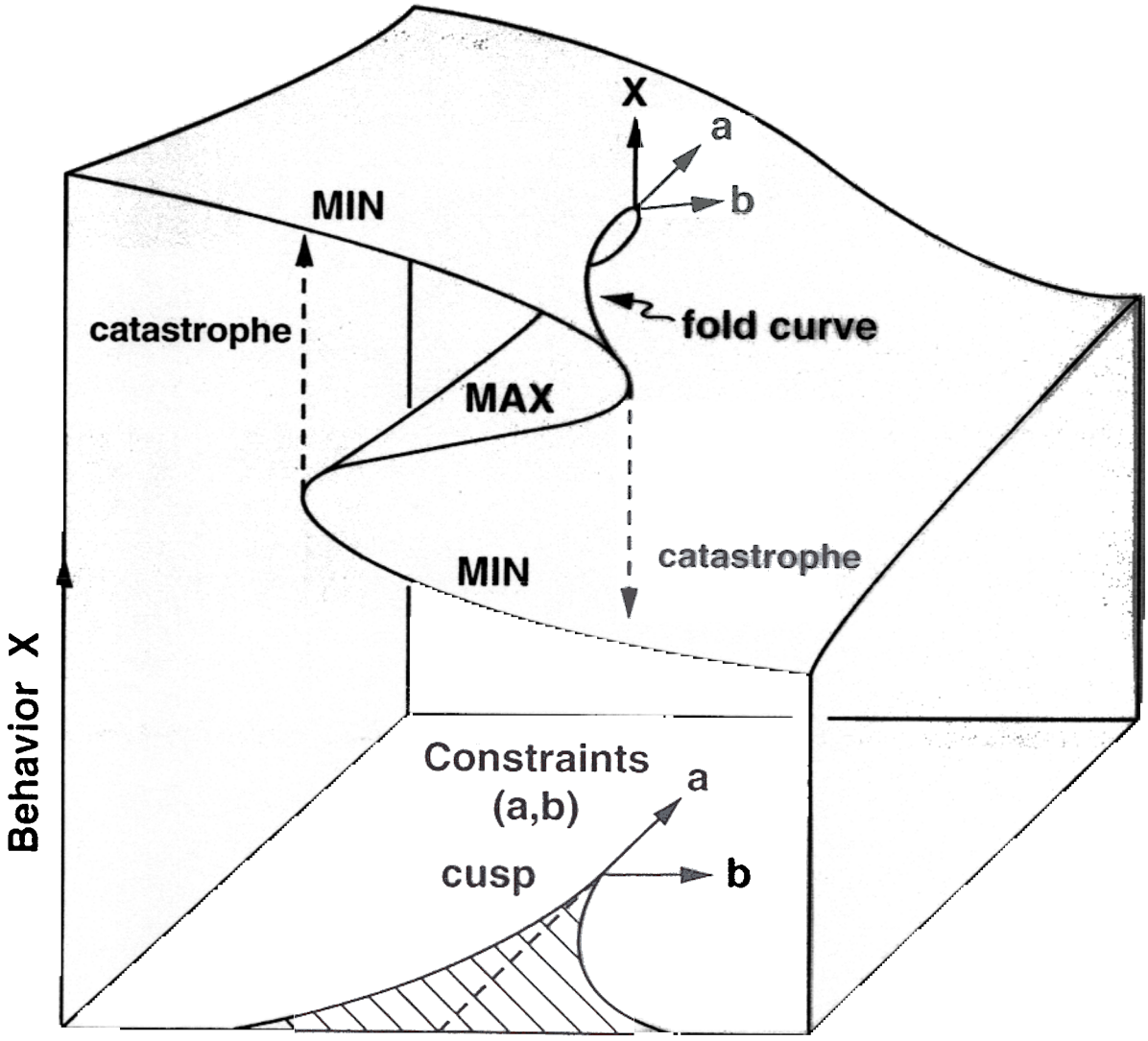
The projection of this surface on the (b,a) plane defines the **catastrophe set**: a cusped region, on the boundary of which

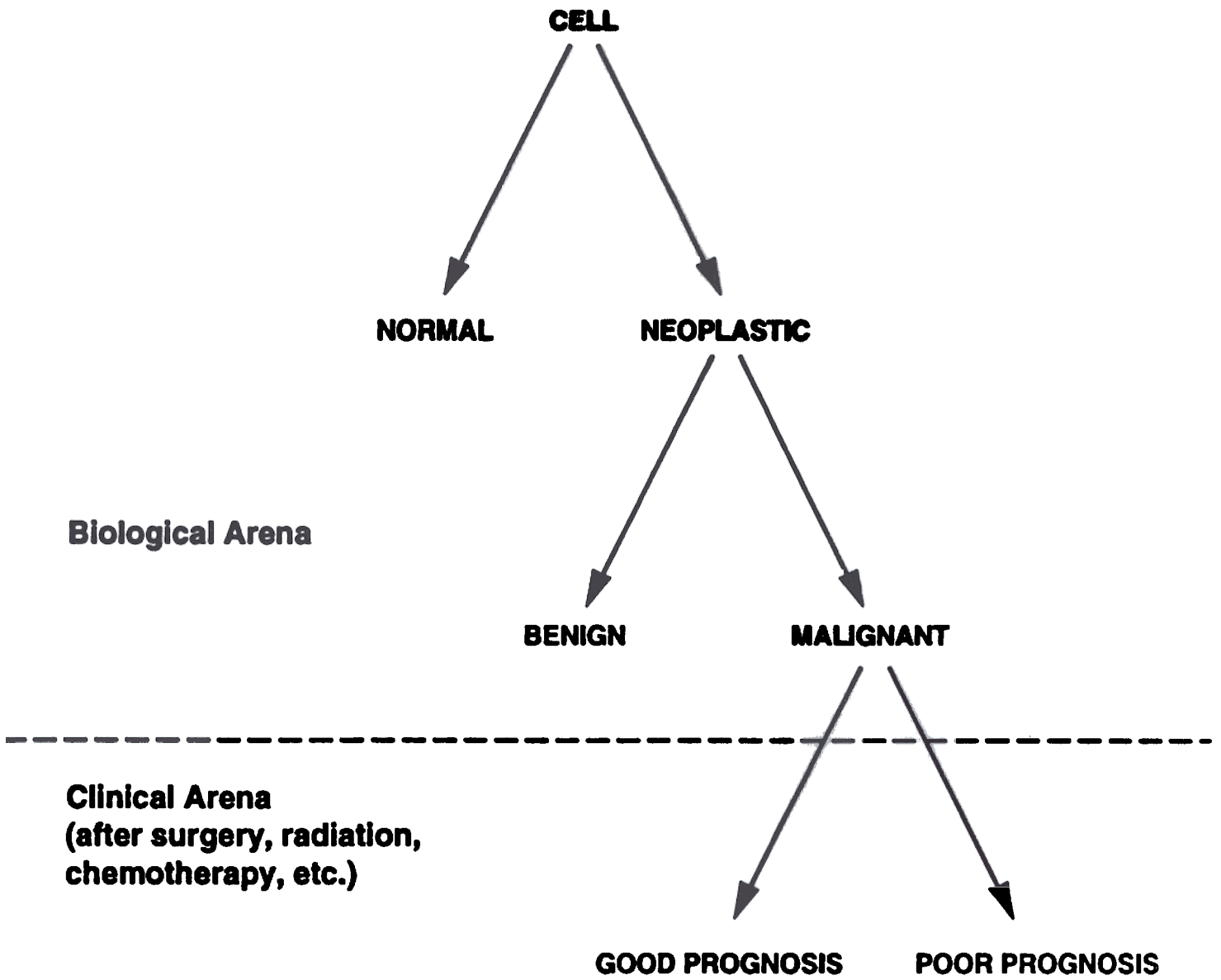
$$b = \pm\left(-\frac{4}{27}a^3\right)^{\frac{1}{2}}$$

For appropriate variations in a and b (and hence in the biological parameters α, β and θ), it may be shown that both **high** $X \rightarrow$ **low** X (remission) and **low** $X \rightarrow$ **high** X (metastatic growth) rapid transitions (**catastrophes**) are possible.

(Invasion & Metastasis, **16**:247-267;1996)

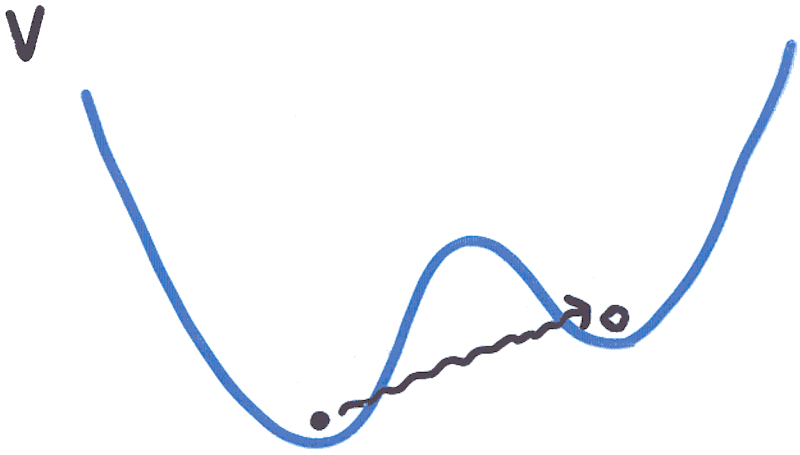
Figure 2


X
a
b
MIN
catastrophe
fold curve
MAX
MIN
catastrophe
Behavior X
Constraints
(a,b)
a
cusp
b


CELL
NORMAL
NEOPLASTIC
Biological Arena
BENIGN
MALIGNANT
Clinical Arena
(after surgery, radiation,
chemotherapy, etc.)
GOOD PROGNOSIS
POOR PROGNOSIS

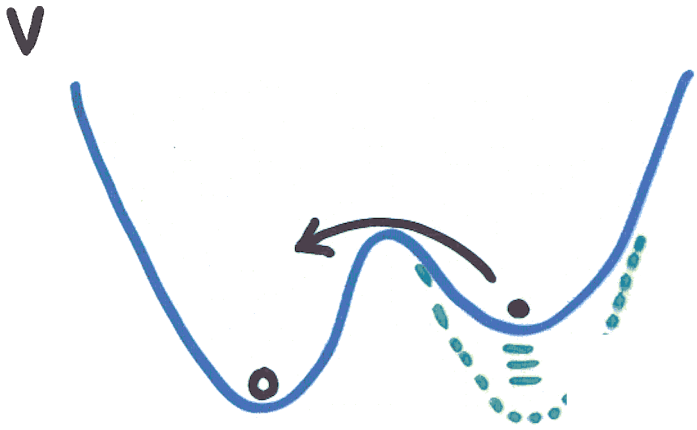
- **What physiological, genetic or environmental parameters – or combinations of them – comprise "*a*" and "*b*"?**
- **How do we find them?**
- **Lots of raw data?**
- **If we can solve this "inverse problem" for the control parameters, then we may have a potentially valuable prognostic tool…**
- **It is likely that *a* and *b* are unique to each individual…**
- **Could we formulate a personalized catastrophe surface? (Sounds silly, but…)**

- Can such a catastrophe potential $V(a,b;x)$ serve as a metaphor for the immune system?
- The quantum mechanical connection? Tunneling?
- Stochastic resonance?
- Lifetime of state (probability of escape



Tunneling

or



Stochastic fluctuations

Metastable states?

Lifetime ~ (Prob of "escape")$^{-}$

Immune system metaphor?

STOCHASTIC RESONANCE

"Stochastic resonance has become widely recognized as a paradigm for noise-induced effects in driven nonlinear dynamic systems."

Bulsara & Gammaitoni (1996)

Necessary requirements for SR:

(i) a bistable system

(ii) a periodic driving signal - e.g. normal daily variations or periodicity of chemotherapeutic or other regimens.

(iii) a noise signal

Why the Schrödinger Equation anyway?

Suppose that $[y(x)]^2$ is the probability of the "system" (neoplastic cell, tumor, metastasis, etc.) being in progression state x), and $[\varepsilon y'(x)]^2$ is a measure of the *propensity* of the system to "progress" (i.e. to move higher in progression space x).

This is measured relative to the effectiveness of the immune system to inhibit such progression, denoted by the "immune potential" $V(x)$.

Consider the Lagrange density ***L*** (by analogy with classical mechanics)

$$\boldsymbol{L} = \{\varepsilon^2[y'(x)]^2 + V(x)[y(x)]^2\}$$
$$\sim \text{“}K.E.\text{”} + \text{“}P.E.\text{”}$$

In accordance with a Hamilton-type principle (if it applies) we may wish to examine extrema of the "action" integral

$$\mathbf{I} = \int_{D} \boldsymbol{L}\, dx$$

over some appropriate domain ***D***, subject to the constraint

$$\int_{D} |y(x)|^2 dx = 1.$$

Let

$$\boldsymbol{H} = \boldsymbol{L} - \lambda|y|^2 = \{\varepsilon^2[y'(x)]^2 + (V(x) - \lambda)[y(x)]^2\}$$

where λ is a Lagrange multiplier, which will be identified below with the "free energy" (metastatic or "invasive" energy?) of the system.

From the Euler-Lagrange equation

$$\frac{\partial \boldsymbol{H}}{\partial y} - \frac{\partial}{\partial x}\left(\frac{\partial \boldsymbol{H}}{\partial y'}\right) = 0$$

we obtain a time-independent Schrödinger "look-alike" equation

$$\varepsilon^2 \frac{d^2y}{dx^2} + \{\lambda - V(x)\}y = 0$$

In a simple case (a rectangular barrier of height $V_0 > \lambda$ and width a), the *transmission coeffient* is

$$T = \left[1 + \frac{V_0^2 \sinh^2[(a\sqrt{V_0 - \lambda})/\varepsilon]}{4\lambda(V_0 - \lambda)} \right]^{-}$$

If $\varepsilon \to \infty$, $T \to 1^{-}$; this indicates that (i) for extremely aggressive tumors, the immune system becomes swamped, or (ii) for very weak immune systems, tumor progression may occur even for relatively low-aggression types of cancer.

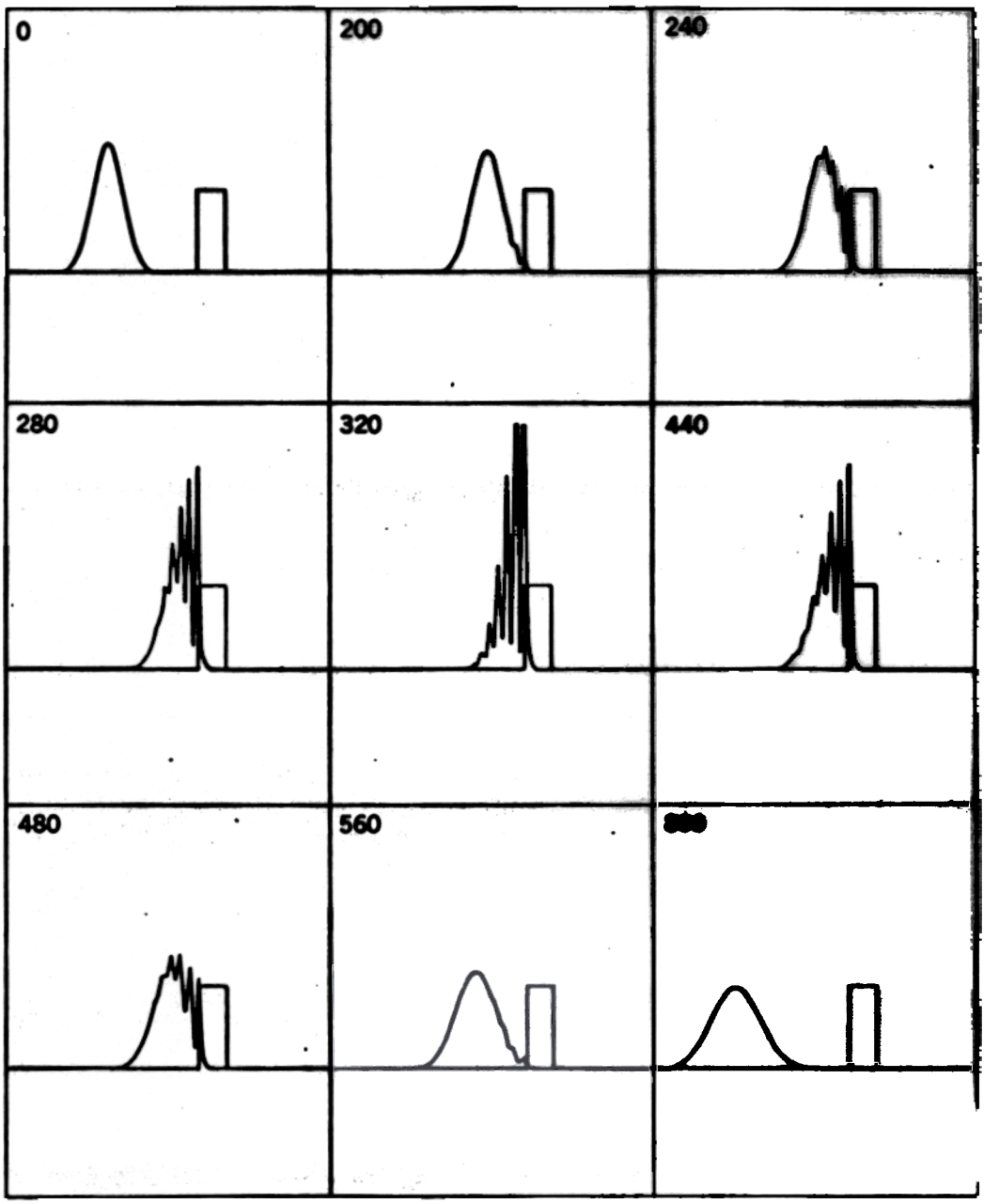


Fig. 16 Gaussian wave-packet scattering from a square barrier when the mean energy of the packet is half the barrier height.

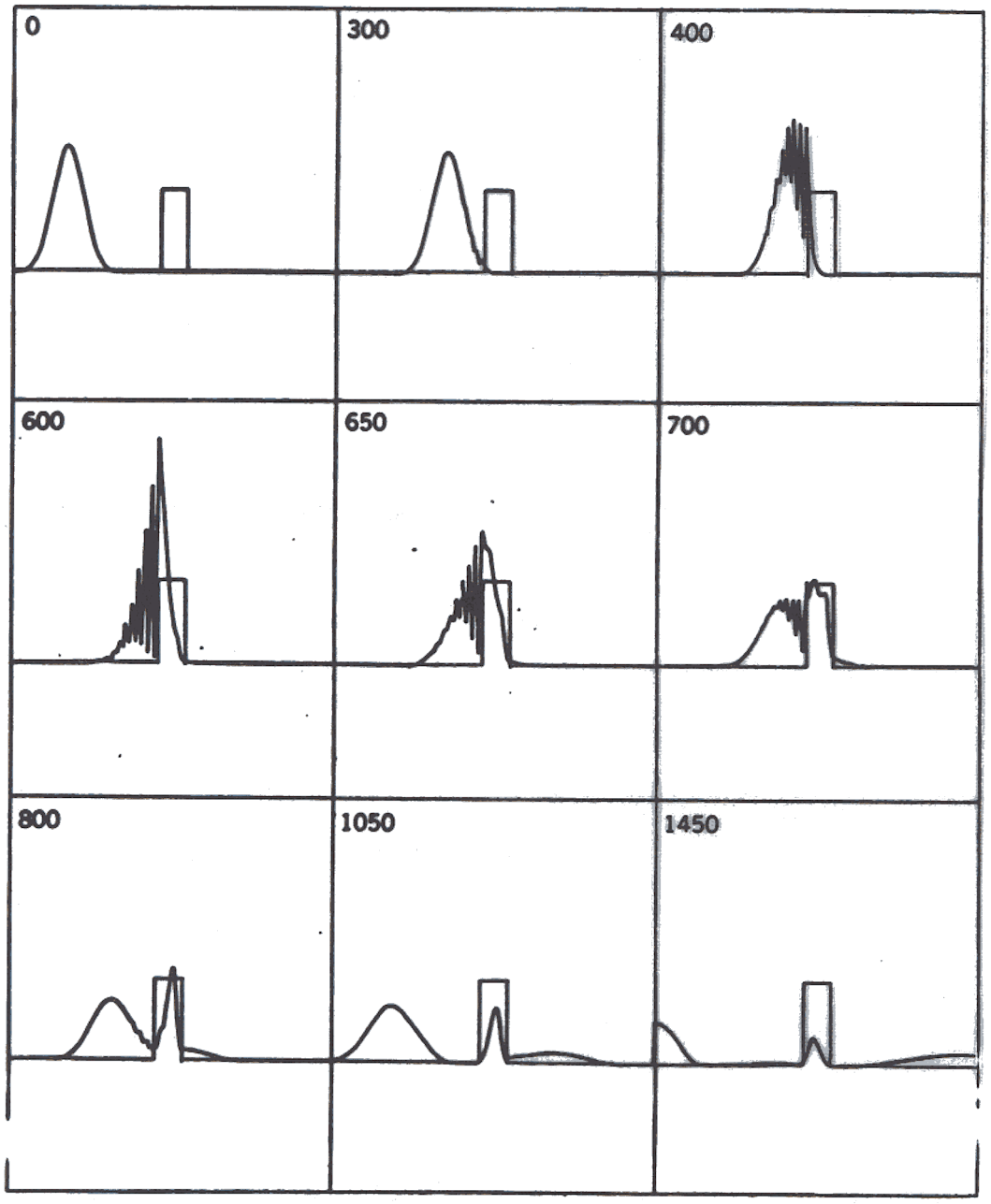


Fig. 17 Same as Fig. 16, with the mean energy equal to barrier height.